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# **The Alkaloids**

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# The Alkaloids

Volume 7

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A Review of the Literature Published  
between July 1975 and June 1976

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# Foreword

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The seventh volume of *The Alkaloids* follows the policy and format adopted in previous volumes. Most sections are concerned with literature published during July 1975—June 1976, but the three Chapters on Amaryllidaceae and Related Alkaloids, *Erythrina* and Related Alkaloids, and Miscellaneous Alkaloids cover the two-year period up to June 1976.

The dedication of the Chapter on Indole Alkaloids to Professor R. B. Woodward acknowledges his contributions to alkaloid chemistry during more than thirty years.

My editorial work has been made so much easier by the ready co-operation and understanding of the contributors and it is a pleasure to record my appreciation.

June 1976

M. F. GRUNDON



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## 1 Introduction

For ease of access to previous Reports in this series the practice introduced last year of listing them as the first references<sup>1-6</sup> is continued as is the reference to the earlier comprehensive reviews.<sup>7,8</sup> (As the volume of published work on alkaloid biosynthesis grows so too does the need for a new comprehensive treatise.)

The use of incorporation efficiencies as a measure of the relative importance of various precursors within a biosynthetic pathway must often be subject to considerable uncertainty<sup>9</sup> since it is difficult to achieve identical conditions in successive feeding experiments. This problem is overcome<sup>10</sup> if the precursors are fed together to the same plant (or culture), distinction between them being made by use of different isotopic labels *e.g.* <sup>14</sup>C and <sup>3</sup>H. A problem with this approach is that, particularly, tritium (or deuterium) may be lost from one of the precursors, leading to a false result. An ingenious solution to this difficulty is to run a second experiment in which only the substrate which bears the tritium label in the first experiment is fed, but labelled now with <sup>14</sup>C and <sup>3</sup>H. The <sup>14</sup>C:<sup>3</sup>H ratio observed in the metabolite then allows one to make adjustment for any tritium loss in the first experiment; one is in effect then comparing two sets of <sup>14</sup>C incorporation data.<sup>11</sup> [This method has been successfully applied in a study of pyrrolizidine biosynthesis where there was a quite spectacular variation in relative incorporation efficiencies but a fairly constant

<sup>1</sup> R. B. Herbert, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1971, Vol. 1.

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

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

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

<sup>5</sup> R. B. Herbert, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1975, Vol. 5.

<sup>6</sup> R. B. Herbert, in 'The Alkaloids', ed. M. F. Grundon (Specialist Periodical Reports), The Chemical Society, London, 1976, Vol. 6.

<sup>7</sup> 'Biosynthese der Alkaloide', ed. K. Mothes and H. R. Schütte, VEB Deutscher Verlag der Wissenschaften, Berlin, 1969.

<sup>8</sup> I. D. Spenser, in 'Comprehensive Biochemistry', ed. M. Florkin and E. H. Stotz, Elsevier, Amsterdam, 1968, Vol. 20, p. 231.

<sup>9</sup> S. A. Brown, in 'Biosynthesis', ed. T. A. Geissman (Specialist Periodical Reports), The Chemical Society, London, 1972, Vol. 1, p. 1.

<sup>10</sup> E. Leistner, R. N. Gupta, and I. D. Spenser, *J. Amer. Chem. Soc.*, 1973, **95**, 4040; R. B. Herbert, in *ref.* 5, p. 5.

<sup>11</sup> N. M. Bale and D. H. G. Crout, *Phytochemistry*, 1975, **14**, 2617.

isotope ratio between the substrates examined (see p. 18)]. Further difficulties which these approaches do not, of course, overcome are uncertainties associated with the absorption and transport of a substrate to the site of biosynthesis. Normally the specific labelling of a metabolite by a precursor is taken as a firm indication that the substrate is involved in the biosynthesis of the metabolite. However, particularly with complex molecules, the specific labelling observed may be the result of fragmentation of the precursor and subsequent incorporation of a labelled fragment. This problem may be overcome very successfully if doubly labelled precursors are used (*cf.* ref. 12). It is worth noting that in experiments with precursors labelled with both  $^{14}\text{C}$  and  $^3\text{H}$  (normally made by mixing two samples) the  $^3\text{H}:^{14}\text{C}$  ratio found for the metabolite may be higher (up to 20% has been observed) than that expected because of preferential utilization of molecules labelled with  $^{14}\text{C}$  along other pathways<sup>13</sup> (which may include faster conversion of  $^{14}\text{C}$ -labelled material through to the alkaloid and subsequent metabolism, so that at the end of the feeding experiment the more slowly metabolized  $^3\text{H}$ -labelled material is present in greater amount).

## 2 Piperidine, Pyridine, and Pyrrolidine Alkaloids

**Securinine.**—The eight carbon unit (normal bonding) of the *Securinega* alkaloid, securinine (3), is derived from tyrosine.<sup>14-16</sup> The remaining  $\text{C}_5\text{N}$  unit (heavy bonding) can be formed from labelled cadaverine in the expected manner.<sup>15</sup> Lysine (1) was also found to be incorporated<sup>15</sup> but the derived alkaloid was not degraded to determine whether securinine falls into the group of alkaloids which are derived from lysine in unsymmetrical fashion or those which have an obligatory genesis through a symmetrical intermediate (cadaverine).<sup>17</sup> Recent work has established, however, that securinine falls into the former group and that  $\Delta^1$ -piperideine (2) is also implicated in its biosynthesis.<sup>18</sup>

DL-[2- $^{14}\text{C}$ ]Lysine [as (1)] and [2- $^{14}\text{C}$ ]- $\Delta^1$ -piperideine [as (2)] afforded securinine (3) in which the label was confined essentially to the asterisked carbon atom. Further, [RS-6- $^3\text{H}$ ; 6- $^{14}\text{C}$ ]-DL-lysine [as (1)] gave securinine without loss of tritium. Consequently C-6 of lysine does not undergo oxidation in the course of securinine biosynthesis and so the  $\epsilon$ -amino-group of (1) must be retained whilst the  $\alpha$ -amino-group and carboxy-function are lost. The combined results<sup>14,15,18</sup> are consistent with the hypothetical route to securinine shown in Scheme 1.<sup>18</sup> This pathway will now gain more validity if alkaloids with structures similar to those of the proposed intermediates can be found in *Securinega* or related plants.

It is interesting to note that securinine (3) is the first among those alkaloids with a nitrogen atom common to two rings which is known to avoid a symmetrical intermediate (*cf.* ref. 17).

<sup>12</sup> P. W. Jeffs, H. F. Campbell, D. S. Farrier, G. Ganguli, N. H. Martin, and G. Molina, *Phytochemistry*, 1974, **13**, 933; R. B. Herbert, in ref. 5, p. 22.

<sup>13</sup> (a) A. R. Battersby, R. J. Francis, M. Hirst, E. A. Ruveda, and J. Staunton, *J.C.S. Perkin I*, 1975, 1140; (b) A. R. Battersby, J. Staunton, H. R. Wiltshire, R. J. Francis, and R. Southgate, *ibid.*, 1147.

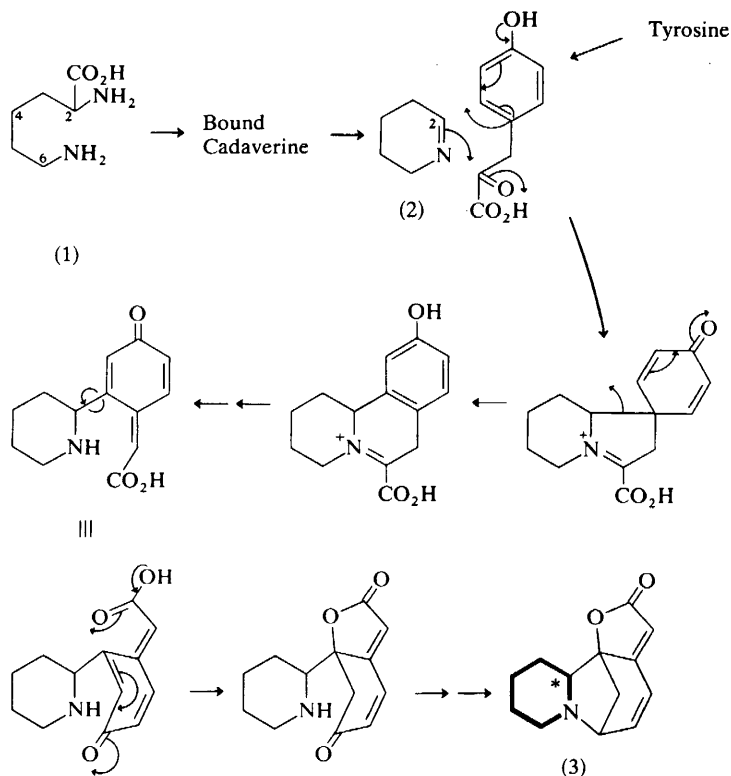
<sup>14</sup> R. J. Parry, *Tetrahedron Letters*, 1974, 307.

<sup>15</sup> U. Sankawa, K. Yamasaki, and Y. Ebizuka, *Tetrahedron Letters*, 1974, 1867.

<sup>16</sup> R. B. Herbert, in ref. 5, p. 10; in ref. 6, p. 40.

<sup>17</sup> R. B. Herbert, in ref. 5, p. 5, and refs. cited therein.

<sup>18</sup> W. M. Golebiewski, P. Horsewood, and I. D. Spenser, *J.C.S. Chem. Comm.*, 1976, 217.



Scheme 1

**Lycopodine.**—Lycopodine (4) is formed in *Lycopodium tristachyum* from lysine [via  $\Delta^1$ -piperidine (2)] and acetic acid.<sup>19–22</sup> The labelling pattern observed with these precursors suggests that lycopodine (4) could be formed simply from two molecules of pelletierine (5) but in this case ‘Occam’s Razor’ does not apply since radioactive pelletierine (5) labels only one of these ‘pelletierine’ units in lycopodine (4).<sup>22,23</sup> The hypothetical pathway proposed<sup>21</sup> to take account of these results has been tested in further experiments.<sup>24</sup> Piperidine-2-acetic acid (6), as its CoA ester, is one of the hypothetical intermediates but the evidence obtained most strongly points to it not being involved in lycopodine biosynthesis. [*carboxy*-<sup>14</sup>C]Piperidine-2-acetic acid fed in admixture with DL-[4-<sup>3</sup>H]lysine [as (1)] gave lycopodine with a <sup>3</sup>H:<sup>14</sup>C ratio

<sup>19</sup> R. N. Gupta, M. Castillo, D. B. MacLean, I. D. Spenser, and J. T. Wrobel, *J. Amer. Chem. Soc.*, 1968, **90**, 1360; R. B. Herbert, in ref. 1, p. 5.

<sup>20</sup> M. Castillo, R. N. Gupta, D. B. MacLean, and I. D. Spenser, *Canad. J. Chem.*, 1970, **48**, 1893.

<sup>21</sup> J.-C. Brækman, R. N. Gupta, D. B. MacLean, and I. D. Spenser, *Canad. J. Chem.*, 1972, **50**, 2591; R. B. Herbert, in ref. 4, p. 1.

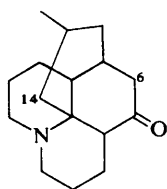
<sup>22</sup> M. Castillo, R. N. Gupta, Y. K. Ho, D. B. MacLean, and I. D. Spenser, *Canad. J. Chem.*, 1970, **48**, 2911; R. B. Herbert, in ref. 3, p. 28.

<sup>23</sup> M. Castillo, R. N. Gupta, Y. K. Ho, D. B. MacLean, and I. D. Spenser, *J. Amer. Chem. Soc.*, 1970, **92**, 1074; R. B. Herbert, in ref. 1, p. 5.

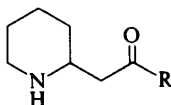
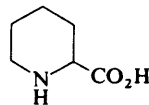
<sup>24</sup> W. D. Marshall, T. T. Nguyen, D. B. MacLean, and I. D. Spenser, *Canad. J. Chem.*, 1975, **53**, 41.

indicating that lysine is *ca.* 17 times more efficient as a precursor than (6) thus casting doubt on a biosynthetic role for (6). (This experiment is a further application of the useful procedure described on p. 1.) As expected  $[2-^{14}\text{C}]$ malonic acid is incorporated in the same way as  $[2-^{14}\text{C}]$ acetic acid (and *ca.* 14 times more efficiently than lysine, measured in a similar way to the above). Attempted trapping of piperidine-2-acetic acid (6) during metabolism of a mixture of  $[^3\text{H}]$ lysine and  $[^{14}\text{C}]$ malonate by also feeding inactive (6) gave material containing only tritium whereas the lycopodine was labelled by both precursors. [If (6) were an intermediate then it should have shown the same  $^3\text{H}:^{14}\text{C}$  ratio as that observed for the lycopodine.] Finally an attempt to dilute the incorporation of  $[2-^{14}\text{C}]$ malonate into C-6 and C-14 of lycopodine (4) with inactive (6) [in the hypothetical pathway these two carbons are derived from C-2 of malonate-acetate *via* the side-chain of (6)] also failed. It is a consequence of these results that the hypothetical pathway<sup>21</sup> to lycopodine (4) must now be modified.

DL-[4,5- $^3\text{H}_2$ , 6- $^{14}\text{C}$ ]Lysine [as (1)] has been found to give lycopodine (4) with 22% loss of tritium.<sup>20,24</sup> This was rationalized in terms of a route in which half the tritium is lost from C-5, and confirmed when it was shown<sup>24</sup> that DL-[4- $^3\text{H}$ , 6- $^{14}\text{C}$ ]lysine was incorporated without tritium loss. The results of further experiments<sup>24</sup> with doubly labelled samples of lysine (DL-[4,5- $^3\text{H}_2$ ]/D-[6- $^{14}\text{C}$ ]-lysine and L-[4,5- $^3\text{H}_2$ ]/DL-[6- $^{14}\text{C}$ ]-lysine) have demonstrated that in *L. tristachyum* lycopodine (4) is derived from L-lysine whereas pipelicolic acid (7) is derived largely, if not exclusively, from D-lysine. These results are analogous to those obtained in other plant species for piperidine alkaloids on the one hand and pipelicolic acid on the other.<sup>10,25</sup>

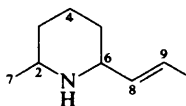


(4)

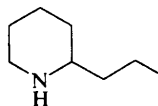
(5) R = Me  
(6) R = OH

(7)

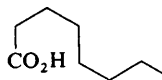
**Pinidine and Coniine.**—Pinidine (8) and the hemlock alkaloid coniine (9) are unusual among simple piperidine alkaloids in being derived exclusively from acetate units. The combination is in each case a simple linear one and proceeds either *via* polyketide intermediates or, arguably in the case of coniine, *via* the fatty acid (10). Strong evidence from tracer<sup>26</sup> and enzyme<sup>27</sup> studies points to (11) as an intermediate



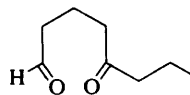
(8)



(9)



(10)



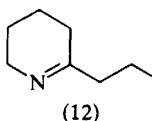
(11)

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

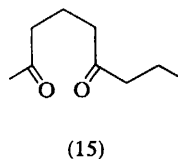
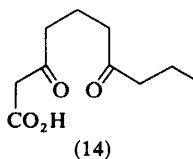
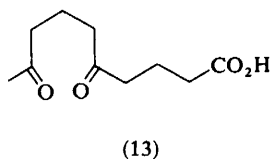
<sup>26</sup> E. Leete and J. O. Olsen, *J. Amer. Chem. Soc.*, 1972, **94**, 5472; R. B. Herbert, in ref. 4, p. 10; J. Staunton, in ref. 2, p. 26.

<sup>27</sup> M. F. Roberts, *Phytochemistry*, 1971, **10**, 3057; R. B. Herbert, in ref. 4, p. 10.

in coniine biosynthesis. Further enzyme studies relate to the *N*-methylation of coniine (9)<sup>28</sup> and most recently to the conversion of  $\gamma$ -coniceine (12) into coniine (9).<sup>29</sup> An enzyme which effects this step,  $\gamma$ -coniceine reductase, has been isolated from *Conium maculatum* leaves. It was found that it has an absolute requirement for NADPH and that hydride transfer occurs from the  $\beta$  (pro-*S*) face of the dihydropyridine nucleotide.



[1-<sup>14</sup>C]Acetate labels the alternate carbon atoms, C-2, C-4, C-6, and C-9 of pinidine (8).<sup>30</sup> This, by analogy with the biosynthesis of coniine, leads to (13) or (14) as likely intermediates in the formation of this alkaloid. However, neither [10-<sup>14</sup>C]-5,9-dioxodecanoic acid [as (13)]<sup>31</sup> nor [1-<sup>14</sup>C]nonadione [as (15)],<sup>32</sup> the decarboxylation product of (14), labelled pinidine significantly. The *in vivo* transformation of octanoic acid into coniine suggested that decanoic acid might be a precursor for pinidine but [9-<sup>14</sup>C] and [10-<sup>14</sup>C]-labelled materials were not significantly incorporated.<sup>32</sup>



More positive information was obtained, however, when diethyl [1-<sup>14</sup>C]malonate was fed to *Pinus jeffreyi* together with inactive sodium acetate.<sup>32</sup> The activity at C-2 (9%) in the derived pinidine was much lower than that at C-9 (30%) from which it follows that C-2 and C-7 of pinidine (8) represent the 'starter' acetate unit and the carboxy-function lost in the course of biosynthesis must therefore be sited as in (13) rather than as in (14). It was suggested that the failure of (13) to act as a precursor might indicate that biosynthesis only proceeds *via* a  $\Delta^{3,4}$ -derivative of this acid.

**Coccinelline.**—Coccinelline (16) is an alkaloid isolated from the defensive secretion of the Coccinellidae.<sup>33</sup> [1-<sup>14</sup>C]Acetate has been found to be incorporated into this arthropod alkaloid with 16% of the activity confined to C-2 plus C-10.<sup>34</sup> This is consistent with derivation *via* the polyketide (17) (or the alternative with the carboxy-group at what becomes C-10 of coccinelline).

**Tropane Alkaloids.**—It is clearly established that the tropic acid moiety (19), found in alkaloids such as hyoscyamine (20), is derived from all the carbon atoms of

<sup>28</sup> M. F. Roberts, *Phytochemistry*, 1974, **13**, 1847; R. B. Herbert, in ref. 6, p. 7.

<sup>29</sup> M. F. Roberts, *Phytochemistry*, 1975, **14**, 2393; *J. Pharm. Pharmacol.*, 1975, **27S**, 86P.

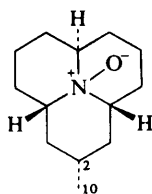
<sup>30</sup> E. Leete and K. N. Juneau, *J. Amer. Chem. Soc.*, 1969, **91**, 5614; R. B. Herbert, in ref. 1, p. 1.

<sup>31</sup> E. Leete and R. A. Carver, *J. Org. Chem.*, 1975, **40**, 2151.

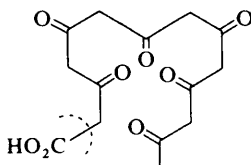
<sup>32</sup> E. Leete, J. C. Lechleiter, and R. A. Carver, *Tetrahedron Letters*, 1975, 3779.

<sup>33</sup> R. Karlsson and D. Losman, *J.C.S. Chem. Comm.*, 1972, 626, and refs. cited therein.

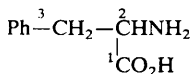
<sup>34</sup> B. Tursch, D. Daloze, J. C. Braekman, C. Hootele, and J. M. Pasteels, *Tetrahedron*, 1975, **31**, 1541.



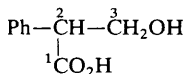
(16)



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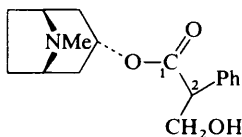


(18)

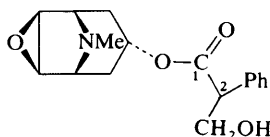


(19)

phenylalanine (for reviews see refs. 35 and 36). Important proof that the conversion of phenylalanine (18) into tropic acid (19) involves an intramolecular 1,2-shift of the carboxy-group of (18) or derivative, has come from the results of feeding [1,3-<sup>13</sup>C<sub>2</sub>]phenylalanine [as (18)], containing 81% of doubly labelled species, to *Datura innoxia*.<sup>37</sup> (A <sup>14</sup>C label was also included to facilitate the measurement of incorporation.) The scopolamine (21) and hyoscyamine (20) isolated both showed satellite



(20)



(21)

resonances, corresponding to C-1 and C-2, with <sup>13</sup>C—<sup>13</sup>C coupling. This coupling demands the presence of two contiguous <sup>13</sup>C atoms and can only have arisen as the result of intra-molecular rearrangement in the course of the transformation of phenylalanine into tropic acid. (Because of the inevitable dilution of isotopically labelled precursors in the plant with unlabelled endogenous material, inter-molecular rearrangement would have given tropic acid with essentially only one <sup>13</sup>C label per molecule—at either C-1 or C-2.)

Cinnamic acid (24), a metabolite of phenylalanine, has been linked with tropic acid biosynthesis *via* its epoxide on chemical grounds but neither of these compounds have previously been found to act as a tropic acid precursor.<sup>36,38,39</sup> Results with cinnamoyltropine were similarly negative.<sup>40</sup> More recently examination of [2-<sup>14</sup>C]cinnamic acid [as (24)] as a precursor for the acid moieties of hyoscyamine (20), scopolamine (21), apohyoscyne (22), and littorine (23) also gave negative results

<sup>35</sup> E. Leete, in 'Biosynthesis', ed. T. A. Geissman (Specialist Periodical Reports), The Chemical Society, London, 1973, Vol. 2, p. 115.

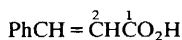
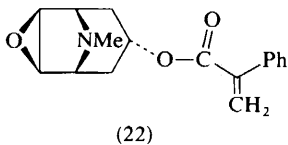
<sup>36</sup> R. B. Herbert, in ref. 6, p. 8.

<sup>37</sup> E. Leete, N. Kowanko, and R. A. Newmark, *J. Amer. Chem. Soc.*, 1975, **97**, 6826.

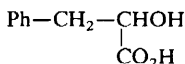
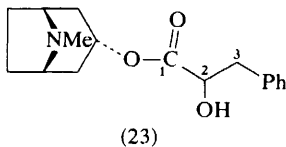
<sup>38</sup> H. W. Liebisch, 'Abstracts 7th Internat. Symp. on The Chemistry of Natural Products', Riga, U.S.S.R., 1970, p. 557; E. Leete and J. D. Braunstein, unpublished work (both quoted in ref. 40).

<sup>39</sup> W. C. Evans, J. G. Woolley, and V. A. Woolley, in 'Biochemie und Physiologie der Alkaloide', 4th Internat. Symp., 1969, ed. K. Mothes, K. Schreiber, and H. R. Schütte, Akademie-Verlag, Berlin, p. 227.

<sup>40</sup> E. Leete and E. P. Kirven, *Phytochemistry*, 1974, **13**, 1501.



(24)



(25)

under conditions when other precursors were incorporated.<sup>41</sup> However, an incorporation<sup>42</sup> of [2-<sup>14</sup>C]cinnamic acid into atropine (20) at a level comparable with that of phenylalanine,<sup>43,44</sup> has recently been recorded. Moreover the label was confined to C-3 of the tropic acid moiety as expected if phenylalanine was utilized *via* cinnamic acid. This is an important result not least in regard to the mechanism of the rearrangement involved in the conversion of (18) into (19), which is still unknown. No doubt workers in this field will re-examine the previous negative results in the light of this strikingly positive one. One point which may be of significance is that the tropic acid moiety of atropine (20) is racemic (the latest experiment) whereas the earlier experiments were with alkaloids containing optically active tropic acid residues.

Fuller details on the incorporation of phenyllactic acid (25) into tropane alkaloids have been published.<sup>41</sup> This acid is a better precursor than phenylalanine for the acid fragments of (20), (21), and (22). The significance of this difference is doubtful; it may be the result of several causes, the simplest being more effective diversion of phenylalanine into other biosynthetic pathways. None the less phenyllactic acid (25) is clearly a precursor for tropic acid (19) and atropic acid [as (22)] since it is specifically incorporated and moreover labels the alkaloids in the same way as phenylalanine does.

It is known from labelling studies that C-1 and C-3 of phenylalanine (18) appear at C-1 and C-3 respectively of littorine (23).<sup>45</sup> Not unexpectedly label from C-2 of (18) appears at C-2 of (25).<sup>41</sup>

Phenylacetic acid has been reported as a precursor of tropic acid (19),<sup>44,46</sup> but in a recent experiment it was found not to label hyoscyamine (20) or scopolamine (21).<sup>37</sup> Nor was phenylalanine labelled which excludes incorporation of phenylacetic acid through this amino-acid.

The sequence by which the tropane nucleus as in (26) becomes hydroxylated to give alkaloids like meteloidine (27) and 3 $\alpha$ -tigloyloxy-tropane-7 $\beta$ -ol is unknown. The most recent evidence is conflicting. On the one hand 3 $\alpha$ -tigloyloxytropane, doubly labelled as shown in (26), was found to be an intact and specific precursor for meteloidine (27) in *Datura innoxia*, although both the 3 $\alpha$ -tigloyloxytropane (26) and

<sup>41</sup> W. C. Evans and J. G. Woolley, *Phytochemistry*, 1976, **15**, 287.

<sup>42</sup> B. V. Prabhu, C. A. Gibson, and L. C. Schramm, *Lloydia*, 1976, **39**, 79.

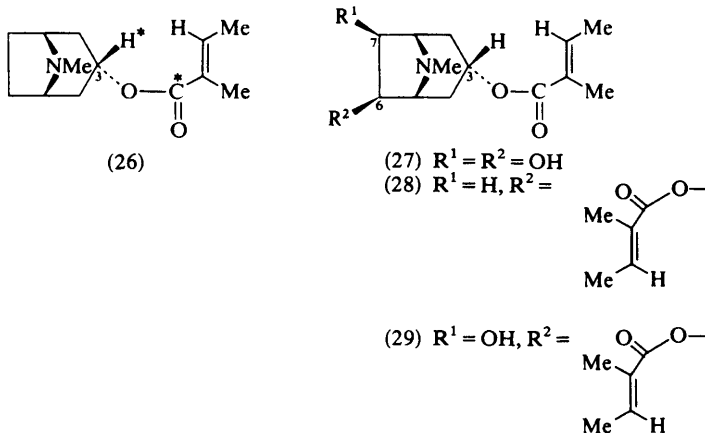
<sup>43</sup> C. A. Gibson and H. W. Youngken jun., *J. Pharm. Sci.*, 1967, **56**, 854; D. Gross and H. R. Schütte, *Arch. Pharm.*, 1963, **296**, 1.

<sup>44</sup> E. W. Underhill and H. W. Youngken jun., *J. Pharm. Sci.*, 1962, **51**, 121.

<sup>45</sup> W. C. Evans and V. A. Woolley, *Phytochemistry*, 1969, **8**, 2183; R. B. Herbert, in ref. 1, p. 9.

<sup>46</sup> N. W. Hamon and J. L. Eyolfson, *J. Pharm. Sci.*, 1972, **61**, 2006; R. B. Herbert in ref. 4, p. 13.

the  $3\alpha,6\beta$ -ditigloyloxytropene (28) isolated at the end of the experiment had suffered extensive hydrolysis and re-esterification.<sup>47</sup> On the other hand, and in agreement with the observations on (26) and (28), neither  $3\alpha$ -tigloyloxytropene (26) nor valtropene (26; with saturated double bond) (2-methylbutanoic acid is a precursor for tiglic acid in *Datura*<sup>48</sup>) were incorporated intact into (26), (28) and (29) in *D. innoxia* under apparently very similar conditions.<sup>49</sup> This was followed by a different approach in which the sequence of hydroxylation and esterification was deduced by observing the relative activities of the tigloyl moieties of (26), (27), (28), and (29)



after feeding tiglic acid in a short-term experiment.<sup>50</sup> Interpretation of the results has led to the proposal of a possible sequence of reactions in which di- and tri-hydroxytropenes are formed by different pathways. However, the conclusions reached must be subject to considerable doubt since they depend on the tacit assumption that ester formation is not significantly reversible. Clearly this is not so in longer term experiments at least and a further complication may be that the rates of hydrolysis-esterification vary from compound to compound.

A mutual interconversion between scopolamine (21) and hyoscyamine (20) has been observed in *D. innoxia*.<sup>51</sup>

**Pyrrolizidine Alkaloids.**—Both ornithine (30)<sup>52,53</sup> and putrescine (31)<sup>53</sup> are specific precursors of retronecine (34) and it is thus a reasonable assumption that arginine (32) might be an alternative source for the pyrrolizidine ring system either through hydrolysis to ornithine or by way of agmatine (33) to putrescine. Rigorous comparison of the relative efficiencies of incorporation of ornithine and arginine have shown that the assumption is correct: arginine is a specific precursor for the retronecine (34)

<sup>47</sup> E. Leete and D. H. Lucast, *Phytochemistry*, 1975, **14**, 2199.

<sup>48</sup> K. Basey and J. G. Woolley, *Phytochemistry*, 1973, **12**, 2197; E. Leete, *Phytochemistry*, 1973, **12**, 2203; R. B. Herbert, in ref. 5, p. 13.

<sup>49</sup> K. Basey and J. G. Woolley, *Phytochemistry*, 1975, **14**, 2201.

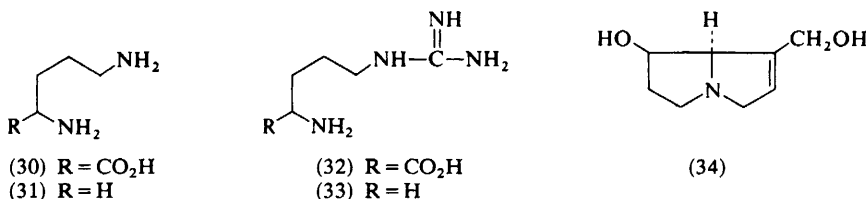
<sup>50</sup> P. J. Beresford and J. G. Woolley, *Phytochemistry*, 1975, **14**, 2205.

<sup>51</sup> G. Verzar-Petri, F. Soti, and L. Horvath, *Herba Hung.*, 1974, **13**, 77 (*Chem. Abs.*, 1975, **83**, 40238).

<sup>52</sup> E. Nowacki and R. U. Byerrum, *Life Sciences*, 1962, **1**, 157; C. A. Hughes, R. Letcher, and F. L. Warren, *J. Chem. Soc.*, 1964, 4974.

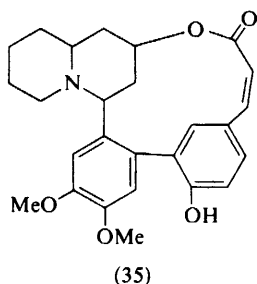
<sup>53</sup> W. Bottomley and T. A. Geissman, *Phytochemistry*, 1964, **3**, 357.



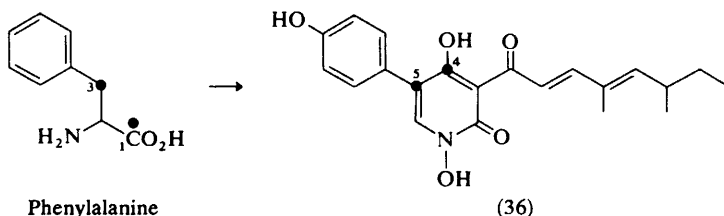


moiety of senecionine in *Senecio magnificus* but it is slightly less efficiently incorporated than ornithine.<sup>11</sup>

**Lythraceae Alkaloids.**—The rate at which quinolizidine alkaloids of the cryogenine (35) type are synthesized and degraded in *Heimia salicifolia* has been studied as has their sequence of appearance in growing plants.<sup>54</sup> The results do not yet add to the preliminary data so far obtained on these alkaloids.<sup>55</sup>



**Tenellin.**—Tenellin (36), produced by the fungi *Beauveria tenella* and *B. bassiana*, has its genesis in acetate, methionine, and phenylalanine.<sup>56</sup> Of particular interest is the observation that the incorporation of phenylalanine involves a skeletal rearrangement similar to the one which affords tropic acid (see above). It has recently been shown that tropic acid arises by an intra-molecular 1,2-shift of C-1 (phenylalanine numbering).<sup>37</sup> In the same way DL-[1,3-<sup>13</sup>C<sub>2</sub>]phenylalanine containing 81% of doubly labelled species afforded tenellin (36) which showed <sup>13</sup>C—<sup>13</sup>C coupling between C-4 and C-5.<sup>57</sup> Since an inter-molecular rearrangement would



<sup>54</sup> R. H. Dobberstein, J. M. Edwards, and A. E. Schwarting, *Phytochemistry*, 1975, **14**, 1769.

<sup>55</sup> S. H. Koo, R. N. Gupta, I. D. Spenser, and J. T. Wrobel, *Chem. Comm.*, 1970, 396; S. H. Koo, F. Comer, and I. D. Spenser, *Chem. Comm.*, 1970, 897; A. Rother and A. E. Schwarting, *Phytochemistry*, 1972, **11**, 2475; R. B. Herbert, in ref. 1, p. 6; in ref. 4, p. 13; J. Staunton, in ref. 2, p. 24.

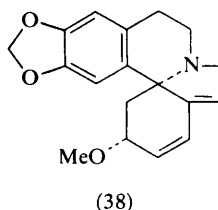
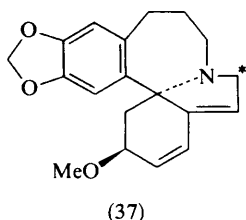
<sup>56</sup> A. G. McInnes, D. G. Smith, J. A. Walter, L. C. Vining, and J. L. C. Wright, *J.C.S. Chem. Comm.*, 1974, 282; R. B. Herbert, in ref. 5, p. 11.

<sup>57</sup> E. Leete, N. Kowanko, R. A. Newmark, L. C. Vining, A. G. McInnes, and J. L. C. Wright, *Tetrahedron Letters*, 1975, 4103.

have resulted in separation of the two  $^{13}\text{C}$  labels present in each molecule, the rearrangement must be an intra-molecular one.<sup>57</sup> The apparently close resemblance of the rearrangements which afford tropic acid in plants and tenellin in fungi argues for a common rearrangement step in phenylalanine metabolism in plants and fungi and one which is not essentially related to the structure of the ultimate product. It is likely that information gathered on the biosynthesis of one of these metabolites will be of value in elucidating the biosynthesis of the other. In this regard one wonders if cinnamic acid is a precursor for tenellin in the light of the conflicting evidence on tropic acid biosynthesis discussed above.

### 3 Isoquinoline Alkaloids

**Schelhammeridine.**—Schelhammeridine (37), a major alkaloid of *Schelhammera pedunculata*, is structurally related to the *Erythrina* alkaloids, e.g. erythraline (38),



which contain one less skeletal carbon atom. These latter alkaloids are known to be derived from a 1-benzylisoquinoline.<sup>58</sup> Aporphine alkaloids likewise derive from this type of precursor<sup>59</sup> whereas the homo-aporphines derive from 1-phenethylisoquinolines.<sup>60</sup> It is thus reasonable to expect that schelhammeridine (37) will also be generated from a 1-phenethylisoquinoline [as (39)], and results of preliminary experiments support this view.<sup>61</sup> DL-[2- $^{14}\text{C}$ ]Tyrosine specifically labelled the asterisked site of (37) as required by this hypothesis and phenylalanine, dopamine, and cinnamic acid were also incorporated (these results in particular parallel the findings on the biosynthesis of colchicine,<sup>62</sup> which is also elaborated from a 1-phenethylisoquinoline). It must be noted, however, that different results have been obtained<sup>63</sup> for cephalotaxine (40) which is structurally similar to schelhammeridine (37). Moreover both these structural types are found together in *Cephalotaxus wilsoniana*.<sup>64</sup>

**Reticuline.**—Reticuline (41) is a pivotal intermediate in the biosynthesis of many alkaloids based on the benzylisoquinoline skeleton, and by association with these

<sup>58</sup> D. H. R. Barton, R. B. Boar, and D. A. Widdowson, *J. Chem. Soc.*, (C), 1970, 1213, and refs. cited therein; R. B. Herbert, in ref. 5, p. 24; in ref. 1, p. 22.

<sup>59</sup> H. R. Schütte in ref. 7, p. 390; R. B. Herbert, in ref. 1, p. 19; in ref. 3, p. 17; in ref. 4, p. 17; in ref. 5, p. 15; in ref. 6, p. 19; J. Staunton, in ref. 2, p. 12.

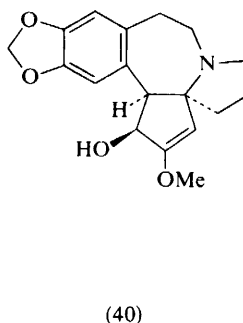
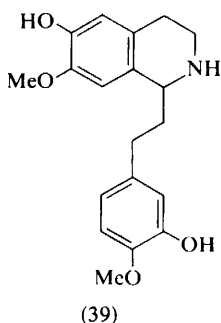
<sup>60</sup> A. R. Battersby, P. Böhler, M. H. G. Munro, and R. Ramage, *J.C.S. Perkin I*, 1974, 1399; R. B. Herbert, in ref. 1, p. 22; in ref. 5, p. 18.

<sup>61</sup> A. R. Battersby, E. McDonald, J. A. Milner, S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Tetrahedron Letters*, 1975, 3419.

<sup>62</sup> R. B. Herbert, in ref. 4, p. 19 and refs. cited therein.

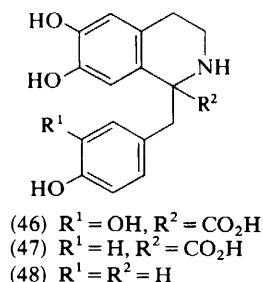
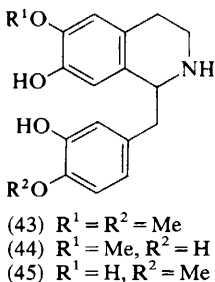
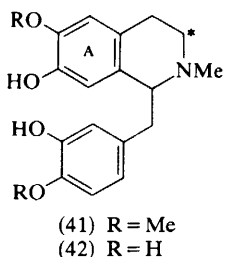
<sup>63</sup> R. J. Parry and J. M. Schwab, *J. Amer. Chem. Soc.*, 1975, **97**, 2555; R. B. Herbert, in ref. 6, p. 27.

<sup>64</sup> R. G. Powell, K. L. Mikolajczak, D. Weisleder, and C. R. Smith, jun., *Phytochemistry*, 1972, **11**, 3317.



alkaloids much is known about its biosynthesis too. Recently its derivation has been subject to further scrutiny in *Litsea glutinosa*.<sup>65</sup> Whereas radioactive tyrosine (49) labelled both Ar-C<sub>2</sub> units of (41) the label from DL-[2-<sup>14</sup>C]dopa [as (50)] was located only at one site [the asterisked carbon in (41)], consonant with findings on morphine biosynthesis in *Papaver orientale*<sup>66,67</sup> and on aporphine biosynthesis in *Decentra eximia*,<sup>68</sup> but differing slightly from observations on the biosynthesis of norlaudanosoline in *P. orientale*.<sup>67,69</sup> Together these results point to the implication of dopa in benzyloquinoline biosynthesis very largely through dopamine (53) which is the source<sup>70</sup> of ring A [as (41)] and attached C<sub>2</sub> unit.

In support of earlier work<sup>66,67,69</sup> where convincing evidence was obtained that (46), but most probably not (47), was an intermediate in benzyloquinoline biosynthesis, (47) [and (48)] was incorporated into reticuline (41) to an insignificant



extent.<sup>65</sup> Thus the benzyloquinoline skeleton must be formed from two dihydroxy-aromatic fragments, probably (53) and (52). If the latter cannot be formed by transamination from dopa, as the tracer results perhaps imply, then it must arise by the sequence (49) → (51) → (52).

Examination of the relative incorporations of (42), (43), (44), and (45) into reticuline (41) suggest that *O*-methylation precedes *N*-methylation.<sup>65</sup>

<sup>65</sup> S. Tewari, D. S. Bhakuni, and R. S. Kapil, *J.C.S. Chem. Comm.*, 1975, 554.

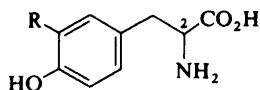
<sup>66</sup> A. R. Battersby, R. C. F. Jones, and R. Kazlauskas, *Tetrahedron Letters*, 1975, 1873.

<sup>67</sup> R. B. Herbert, in ref. 6, p. 17.

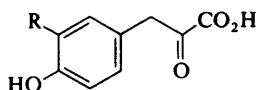
<sup>68</sup> A. R. Battersby, J. L. McHugh, J. Staunton, and M. Todd, *Chem. Comm.*, 1971, 985.

<sup>69</sup> M. L. Wilson and C. J. Coscia, *J. Amer. Chem. Soc.*, 1975, **97**, 431.

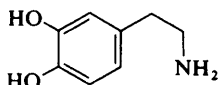
<sup>70</sup> H. R. Schütte, in ref. 7, p. 367; I. D. Spenser in ref. 8, p. 309.



(49) R = H  
(50) R = OH



(51) R = H  
(52) R = OH



(53)

**Papaverine.**—Recent evidence<sup>71,72</sup> has added to the knowledge that papaverine (62) is biosynthesized by way of norlaudanosoline (54)<sup>73</sup> and nor-reticuline (55)<sup>74</sup> in *Papaver somniferum*. A high and specific incorporation of tetrahydropapaverine (59) marks this base down as an important intermediate.<sup>71,72</sup> All four isomeric *O,O*-dimethylaudanosolines were specifically incorporated, and at a similar level, into papaverine (62), but the observation that (57) and (58) labelled tetrahydropapaverine (59) at a much lower level than (55) and (56) did, suggested that the former pair was implicated *via* a route which does not involve (59) and which may be an aberrant one.<sup>71</sup> This route may involve the trimethyl ether (61) since a high level of label was observed in this alkaloid in the experiment with norprotosinomenine (57). Two of the remaining trimethyl ethers, (63) and (64), were poorly incorporated and the dimethyl ether (65) failed to act as a precursor.

These results, summarized in Scheme 2, indicate that the methylation pattern can be important in deciding the metabolic fate of precursors at this particular stage of biosynthesis (*cf.* ref. 75) as well as during oxidative phenol coupling. In addition *in vivo* *O*- and *N*-methylation in *P. somniferum* was found to be dependent, and variably so, on the configuration of the substrate.<sup>71</sup> Further, dehydrogenation of (59) depends on the stereochemistry at C-1 since only the (–)-isomer affords papaverine (62). Moreover it is (–)-norreticuline [as (55)] rather than the (+)-isomer which is implicated.<sup>71,72</sup> Finally it is to be noted that norlaudandine (66) is as efficient a precursor for papaverine as is (59).<sup>72</sup>

**Stylopine, Chelidionine, and Related Alkaloids.**—Full details<sup>13</sup> have been published on a study of the biosynthesis of stylopine (71) and chelidionine (76) in *Chelidonium majus*. The original publications<sup>76</sup> predate these reports so it is fitting that the work be summarized here. In any case some of the results are new and the work is notable for the rigour of its approach and the elegant application of tritium labelling as a probe for the course of the reactions involved. The results obtained with the *R* and *S* isomers of multiple labelled reticuline [as (67)] and scoulerine [as (68)] establish the biosynthetic sequence as (67) → (68) → (71) → (76); (–)-(*S*)-scoulerine was shown to be a natural constituent of *C. majus*. (Stylopine isolated from the plant in these experiments was partially racemic but this does not materially affect the conclusions.)

<sup>71</sup> E. Brochmann-Hanssen, C. C. Chen, C. R. Chen, H. Chiang, A. Y. Leung, and K. McMurtrey, *J.C.S. Perkin I*, 1975, 1531.

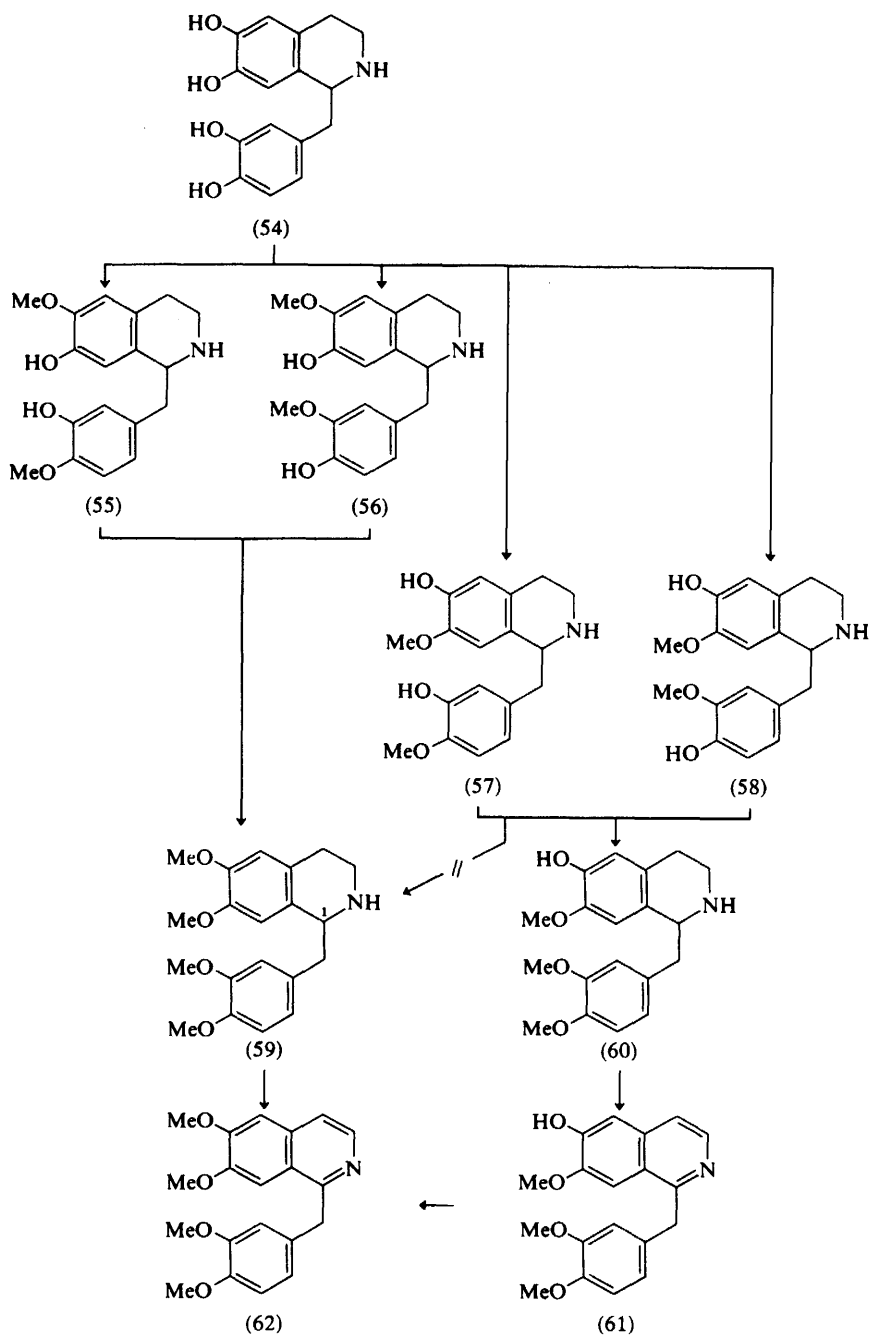
<sup>72</sup> H. Upreti, D. S. Bhakuni, and R. S. Kapil, *Phytochemistry*, 1975, **14**, 1535.

<sup>73</sup> A. R. Battersby, R. Binks, R. J. Francis, D. J. McCaldin, and H. Ramuz, *J. Chem. Soc.*, 1964, 3600.

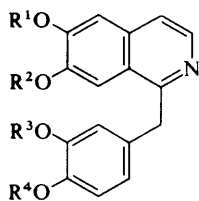
<sup>74</sup> E. Brochmann-Hanssen, C.-C. Fu, A. Y. Leung, and G. Zanati, *J. Pharm. Sci.*, 1971, **60**, 1672; R. B. Herbert, in ref. 3, p. 20.

<sup>75</sup> J. Lundström, *Acta Pharm. Suecica*, 1971, **8**, 275; R. B. Herbert, in ref. 3, p. 16; in ref. 1, p. 16.

<sup>76</sup> A. R. Battersby, R. J. Francis, E. A. Ruveda, and J. Staunton, *Chem. Comm.*, 1965, 89; A. R. Battersby, R. J. Francis, M. Hirst, R. Southgate, and J. Staunton, *ibid.*, 1967, 602.



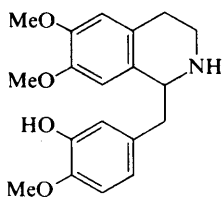
Scheme 2



(63)  $R^1 = R^2 = R^4 = \text{Me}, R^3 = \text{H}$

(64)  $R^1 = R^3 = R^4 = \text{Me}, R^2 = \text{H}$

(65)  $R^1 = R^4 = \text{Me}, R^2 = R^3 = \text{H}$



(66)

The methylenedioxy-group on ring *D* of stylophine was shown to arise from the *ortho*-hydroxy-methoxy-system of reticuline as in other cases (*e.g.* refs. 77 and 78).

The tritium labelling results establish that C-1 and C-9 of reticuline are unaffected by transformation through scoulerine into stylophine. The transformation of the *N*-methyl group of reticuline into the 'berberine-bridge' atom<sup>77,79</sup> (C-8) of stylophine, which necessarily involves loss of one hydrogen/tritium atom, was found to occur with very high tritium retention consonant with a tritium isotope effect.<sup>80</sup> Subsequent reaction to give chelidonine (76) results in retention of tritium at C-8, and also at C-5, but loss of the tritium atom at C-14.<sup>13</sup> Further, loss of the pro-*S* hydrogen atom from C-13 with retention of the pro-*R* atom occurs in the course of this conversion<sup>81</sup> (simple double labelling results were misleading; see Section 1). This is consistent with enzyme-mediated proton removal from C-13 at a stage after (71), and taken with the observed loss of hydrogen from C-1, gives credence to the possibility of an enamine intermediate [see (74) and (75)] between (71) and (76) [in this last experiment extensive non-stereospecific loss of hydrogen was observed for (73), (72), and (84)].

Additional results<sup>13</sup> are that (–)-(*S*)-scoulerine (68) is a precursor for sanguinarine (77) and chelerythrine (78) and labelled (–)-(*S*)-stylophine (71) is incorporated into coptisine (72). [*N*-methyl-<sup>14</sup>C, 8-<sup>3</sup>H]Stylophine methochloride [as (70)] afforded chelidonine (76) and protopine (73) essentially without change in isotope ratio and must thus be considered as implicated on the pathway to both alkaloids. (The same conclusion for protopine has been reached independently.<sup>82</sup>) On the other hand radioactive nandinine (79) failed to label chelidonine, stylophine, or protopine, suggesting that the alternative (69) may be an intermediate instead. In agreement with other work<sup>77</sup> (*S*)-reticuline (67) and (*S*)-scoulerine (68) were much better precursors than the *R*-isomers for protopine (73), and incorporation of (68) resulted in complete loss of tritium label from C-14. Allocryptopine (81) was well labelled by radioactive isocorypalmine (82) (which also serves as a precursor for narcotine: see below). The combined results lead to the pathways shown in Scheme 3.

<sup>77</sup> D. H. R. Barton, R. H. Hesse, and G. W. Kirby, *J. Chem. Soc.*, 1965, 6379.

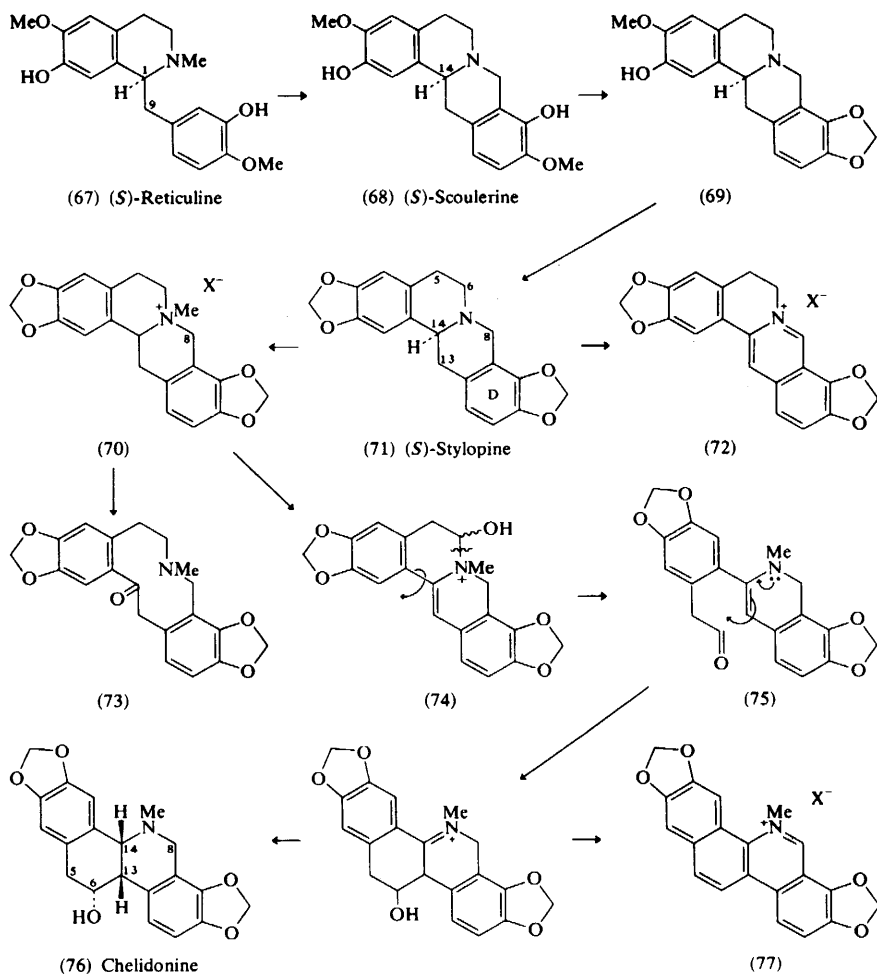
<sup>78</sup> A. R. Battersby and M. Hirst, *Tetrahedron Letters*, 1965, 669.

<sup>79</sup> A. R. Battersby, R. J. Francis, M. Hirst, and J. Staunton, *Proc. Chem. Soc.*, 1963, 268; experimental in ref. 13a.

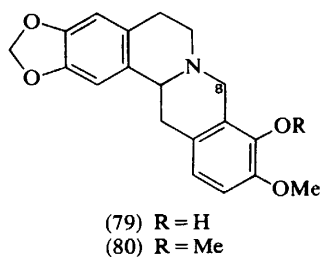
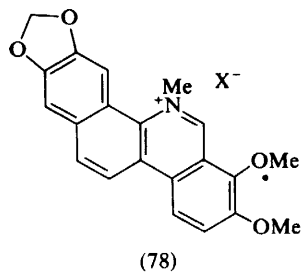
<sup>80</sup> R. B. Herbert, in ref. 6, p. 23.

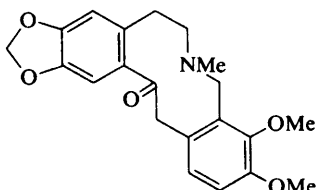
<sup>81</sup> A. R. Battersby, J. Staunton, H. R. Wiltshire, B. J. Bircher, and C. Fuganti, *J.C.S. Perkin I*, 1975, 1162.

<sup>82</sup> C. Tani and K. Tagahara, *Chem. Pharm. Bull. (Japan)*, 1974, 22, 2457; R. B. Herbert, in ref. 6, p. 22.

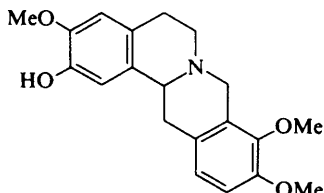


Scheme 3



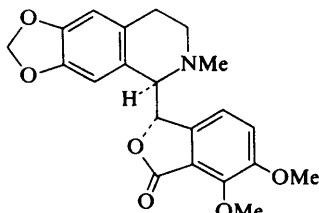


(81)

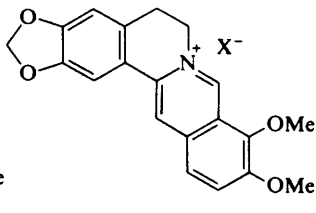


(82)

**Narcotine.**—Previous results<sup>83</sup> had allowed the biosynthetic route to narcotine (83) to be traced as far as (–)-(*S*)-scoulerine (68). Further results<sup>13b</sup> show that isocorypalmine (82) and canadine (80) are effective precursors for (83) in *Papaver somniferum*. The biosynthesis of narcotine may thus be further defined as (68) → (82) → (80) → (83). [It appears that aromatization of canadine (80) to give berberine (84) involves stereospecific removal of hydrogen from C-8 of (80).] As in



(83)



(84)

the transformation of scoulerine into chelidonine (76) (see above), its conversion into narcotine (83) involves removal of the 13-*pro-S* hydrogen atom.<sup>81</sup> Introduction of the oxygen atom thus proceeds with the expected retention of configuration.

#### 4 Alkaloids Derived from Tryptophan

**Indolmycin.**—Previous evidence<sup>84</sup> on the biosynthesis of indolmycin (88) in *Streptomyces griseus* cultures accords with the pathway shown in Scheme 4. The first two steps in the pathway have been carried out using cell-free extracts of *S. griseus*<sup>84,85</sup> and recent work has led to the isolation of two enzymes which can effect these transformations.<sup>86</sup> The first, tryptophan transaminase, catalysed the pyridoxal phosphate-dependent transamination of L-tryptophan, but not D-tryptophan, and in common with some other microbial transaminases,<sup>87</sup>  $\alpha$ -ketoglutarate was an efficient amino-group acceptor. L-Phenylalanine, tyrosine, and 3-methyltryptophan (this compound inhibited enzyme function) also underwent transamination.

<sup>83</sup> A. R. Battersby, M. Hirst, D. J. McCaldin, R. Southgate, and J. Staunton, *J. Chem. Soc. (C)*, 1968, 2163.

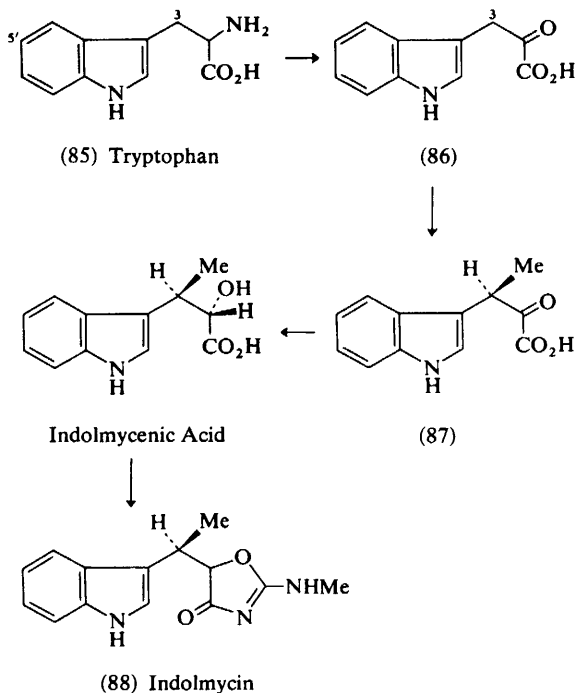
<sup>84</sup> U. Hornemann, L. H. Hurley, M. K. Speedie, and H. G. Floss, *J. Amer. Chem. Soc.*, 1971, **93**, 3028; R. B. Herbert in ref. 3, p. 10.

<sup>85</sup> U. Hornemann, M. K. Speedie, L. H. Hurley, and H. G. Floss, *Biochem. Biophys. Res. Comm.*, 1970, **39**, 594.

<sup>86</sup> M. K. Speedie, U. Hornemann, and H. G. Floss, *J. Biol. Chem.*, 1975, **250**, 7819.

<sup>87</sup> D. Rudman and A. Meister, *J. Biol. Chem.*, 1953, **200**, 591; R. H. Collier and G. Kohlhaw, *J. Bacteriol.*, 1972, **112**, 365; T. Hartmann and K. Glombitza, *Arch. Mikrobiol.*, 1967, **56**, 1; S. R. O'Neil and R. D. DeMoss, *Arch. Biochem. Biophys.*, 1968, **127**, 361.

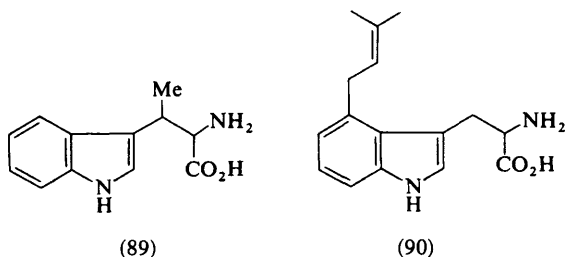




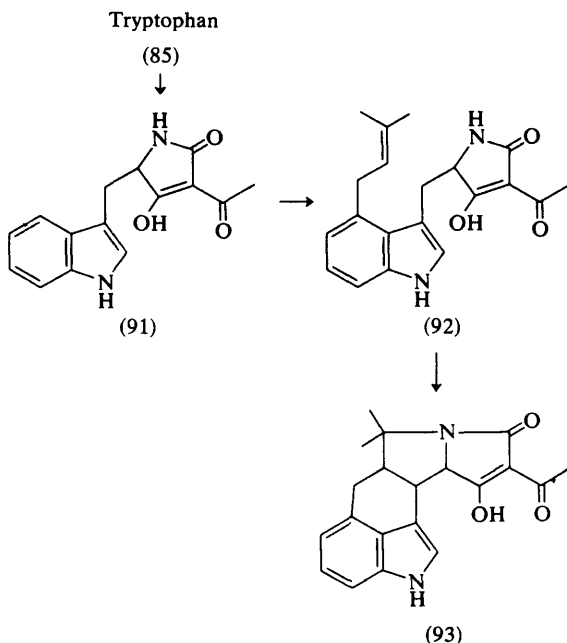
Scheme 4

The second enzyme isolated, indolepyruvate *C*-methyltransferase, is more interesting since the mechanism of *C*-methylation is fascinating<sup>88</sup> and this enzyme may play a role in initiating indolmycin biosynthesis. The transferase catalysed the transfer of a methyl group from *S*-adenosylmethionine to the 3-position of indolepyruvic acid (86); no co-factors were found to be required. Crude enzyme catalysed the methylation of phenylpyruvate and *p*-hydroxyphenylpyruvate as well as (86) but this activity was lost with purification. It was concluded that either the enzyme is non-specific in its natural form and undergoes conformational or other changes during purification with consequent loss of activity towards phenylpyruvate or two enzymes are present in the crude extract and the phenylpyruvate enzyme is denatured during purification. Crude enzyme did not methylate L-tryptophan and so although 3-methyltryptophan (89) is an efficient precursor of indolmycin it is unlikely to be a natural intermediate. This is supported by the failure to identify (89) in *S. griseus* cultures. The observation that (89) undergoes transamination in the presence of the first enzyme isolated suggests that exogenous material enters the pathway to indolmycin at this point. The results obtained with these enzymes strongly support then the early part of the pathway shown in Scheme 4.

<sup>88</sup> E. Lederer, *Quart. Rev.*, 1969, **23**, 453; see also, R. B. Herbert, *Tetrahedron Letters*, 1974, 4525; R. B. Herbert, in ref. 6, p. 42.



**Cyclopiazonic Acid.**— $\alpha$ -Cyclopiazonic acid (93) is formed in *Penicillium cyclopium* from tryptophan *via* (91) and  $\beta$ -cyclopiazonic acid (92) (Scheme 5).<sup>89</sup> Further



**Scheme 5**

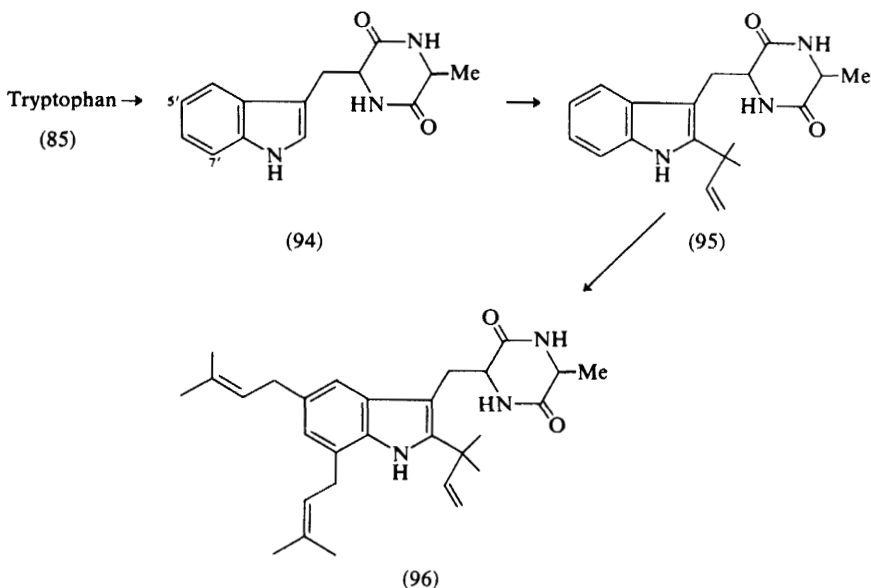
support for this pathway comes from the results of additional experiments,<sup>90</sup> which relate to the postulated intermediate (91). The observation that (91) accumulates in the culture and that exogenous material is transformed together with dimethylallylpyrophosphate into  $\beta$ -cyclopiazonic acid (92) substantiates its role as an intermediate. Moreover,  $\gamma,\gamma$ -dimethylallyltryptophan (90) is not a precursor of (93). Dimethylallylpyrophosphate is not only a better precursor for the cyclopiazonic acids than either the parent alcohol or the monophosphate as might be expected, but was also found to stimulate production of the acids.<sup>90</sup> By contrast tryptophan,

<sup>89</sup> P. S. Steyn, R. Vlegaar, N. P. Ferreira, G. W. Kirby, and M. J. Varley, *J.C.S. Chem. Comm.*, 1975, 465, and refs. cited therein; R. B. Herbert, in ref. 6, p. 30.

<sup>90</sup> R. M. McGrath, P. S. Steyn, N. P. Ferreira, and D. C. Neethling, *Bioorg. Chem.*, 1976, **4**, 11.

although a specific precursor,<sup>90,91</sup> inhibited production of the metabolites.<sup>90</sup> (It was noted that the pool size of tryptophan was extremely small compared to the other amino-acids.)

**Echinulin.**—Most convincing evidence has been obtained for the biosynthesis of echinulin (96) proceeding as shown in Scheme 6.<sup>92</sup> The cyclic dipeptide (94) has also



Scheme 6

been shown to be a precursor for neoechinulins A (97), B (99), C (100), and D (98) and neoechinulin (101) in *Aspergillus amstelodami*.<sup>93</sup> *cyclo*-L-[U-<sup>14</sup>C]Alanyl-L-[5',7'-<sup>3</sup>H<sub>2</sub>]tryptophyl [as (94)] was efficiently incorporated and without change in isotope ratio, thus establishing intact incorporation. By contrast, *cyclo*-L-alanyl-D-tryptophyl is unlikely to be a direct precursor since it was poorly incorporated and the original <sup>3</sup>H: <sup>14</sup>C ratio was lost.

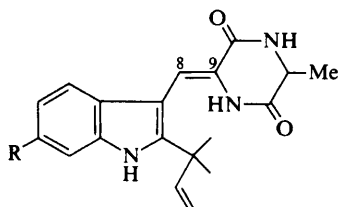
The steps of prenylation and dehydrogenation which follow (94) in the biosynthesis of these neoechinulins is unknown but from knowledge of echinulin biosynthesis (Scheme 6) introduction of the side chain at C-2 may be the next step. Prenylation of the benzene unit seems, by inspection of structures (97) through (101), to depend on C-8—C-9 unsaturation rather than the structure of the dioxopiperazine ring. The stereochemistry of the desaturation reaction has been explored<sup>94</sup> with L-tryptophan (85) samples stereospecifically labelled with tritium at

<sup>91</sup> C. W. Holzappel and D. C. Wilkins, *Phytochemistry*, 1971, **10**, 351.

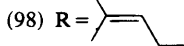
<sup>92</sup> G. P. Slater, J. C. MacDonald, and R. Nakashima, *Biochemistry*, 1970, **9**, 2886; C. M. Allen, jun., *Biochemistry*, 1972, **11**, 2154; *J. Amer. Chem. Soc.*, 1973, **95**, 2386; R. B. Herbert, in ref. 4, p. 29; in ref. 6, p. 29.

<sup>93</sup> R. Marchelli, A. Dossena, and G. Casnati, *J.C.S. Chem. Comm.*, 1975, 779.

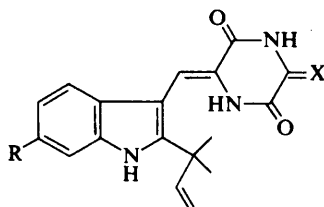
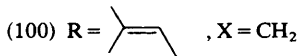
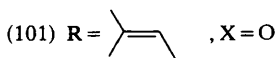
<sup>94</sup> R. Cardillo, C. Fuganti, D. Ghiringhelli, P. Grasselli, and G. Gatti, *J.C.S. Chem. Comm.*, 1975, 778.



(97) R = H



(98) R =

(99) R = H, X = CH<sub>2</sub>(100) R = , X = CH<sub>2</sub>

(101) R = , X = O

C-3. The results show that the 3-*pro-S* hydrogen is lost on formation of cryp-  
toechinulin A (100). From the stereochemistry of the double bond in (100) it follows  
that hydrogen loss occurs with formal *cis* stereochemistry. [The incorporation of the  
[3-<sup>3</sup>H]tryptophan samples into echinulin (96) occurred without tritium loss which,  
although expected, contrasts with the observation of partial loss of 3-*R*-tritium in the  
transformation of phenylalanine into gliotoxin<sup>95,96</sup> and of tyrosine into  
mycelianamide.<sup>96</sup>]

**Ergot Alkaloids.**—The biosynthesis of these alkaloids, elaborated by species of the  
parasitic fungus *Claviceps*, has been authoritatively and comprehensively  
reviewed.<sup>97</sup>

A fascinating problem in the biosynthesis of ergot alkaloids is the mechanism by  
which dimethylallyltryptophan (102) is transformed through chanoclavine-I (103) to  
agroclavine (104) and elymoclavine (106), a reaction sequence which involves two  
*cis-trans* isomerizations in the side-chain double bond.<sup>98</sup> Further evidence on the  
course of biosynthesis comes from feeding dimethylallyltryptophan labelled as  
shown in (102), to *Claviceps penniseti*.<sup>99</sup> The alkaloids (103), (104), and (106) were  
isolated and the sites of labelling were determined to be as shown in Scheme 7. Thus  
the first double bond isomerization occurs between (102) and (103) and the second  
between (103) and (104).

The possibility that allylic alcohols [as (105)] might be intermediates in the  
sequence (102) to (106) was examined by feeding (105) and (107) labelled as  
shown.<sup>99</sup> Essentially in agreement with earlier work<sup>100</sup> only the elymoclavine (106)  
isolated was radioactive (label as shown). Since (103) and (104) were not labelled it  
was concluded that (105) and (107) were unnatural precursors for (106), being  
transformed into the alkaloid by an aberrant pathway.<sup>99</sup>

<sup>95</sup> J. D. Bu'Lock, A. P. Ryles, N. Johns, and G. W. Kirby, *J.C.S. Chem. Comm.*, 1972, 100; R. B. Herbert, in  
ref. 3, p. 12.

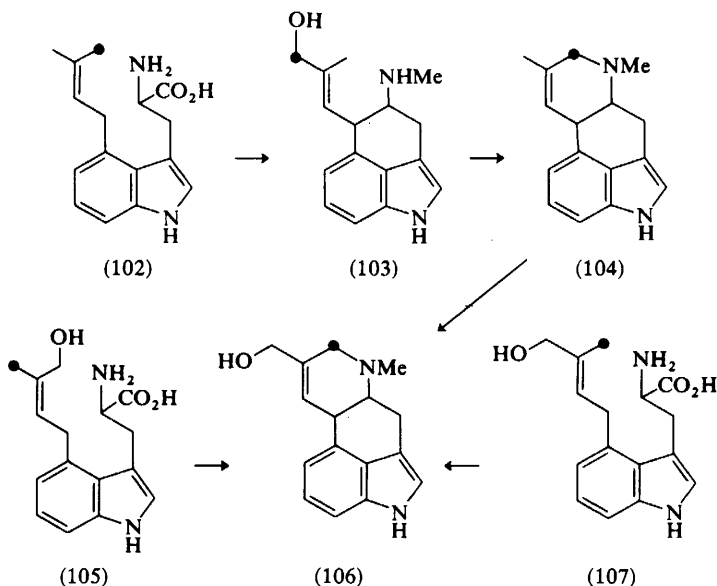
<sup>96</sup> G. W. Kirby and S. Nayaranaswami, *J.C.S. Chem. Comm.*, 1973, 322; R. B. Herbert, in ref. 4, p. 42.

<sup>97</sup> H. G. Floss, *Tetrahedron*, 1976, **32**, 873.

<sup>98</sup> T. Fehr, W. Acklin, and D. Arigoni, *Chem. Comm.*, 1966, 801; see also H. G. Floss, M. Tcheng-Lin, C.  
Chang, B. Naidoo, G. E. Blair, C. I. Abou-Chaar, and J. M. Cassady, *J. Amer. Chem. Soc.*, 1974, **96**,  
1898; R. B. Herbert, in ref. 5, p. 27, and refs. cited therein.

<sup>99</sup> P. Pachlatko, C. Taback, W. Acklin, and D. Arigoni, *Chimia (Switz.)*, 1975, **29**, 526.

<sup>100</sup> H. Plieninger, C. Wagner, and H. Immel, *Annalen*, 1971, **743**, 95; J. Staunton in ref. 2, p. 8; R. B.  
Herbert in ref. 5, p. 31; but see ref. 97 for fuller details of unpublished work.

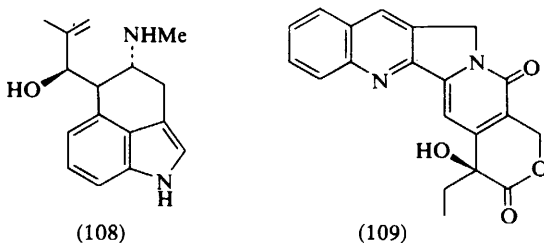


Scheme 7

The naturally occurring allylic alcohol, paliclavine (108), has been tested as a precursor for ergot alkaloids, and found not to be incorporated into the main alkaloids, paspalic acid, agroclavine, and elymoclavine.<sup>101</sup> The conclusion that it is not involved in the biosynthesis of these alkaloids is strengthened by the observation that in parallel experiments [ $N$ - $^{14}\text{CH}_3$ ]chanoclavine-I was efficiently utilized. Examination of the minor alkaloids isolated in these experiments showed further that paliclavine (108) does not arise from chanoclavine-I (103) and it is not converted into either this alkaloid or isochanoclavine-I (the conversion of chanoclavine-I to isochanoclavine-I was established).

Previous evidence pointing to induction of ergot biosynthesis by tryptophan has been further supported in a recent study.<sup>102</sup>

**Camptothecin.**—Convincing evidence has been obtained that camptothecin (109) is derived along a pathway which for most of its length closely resembles that which

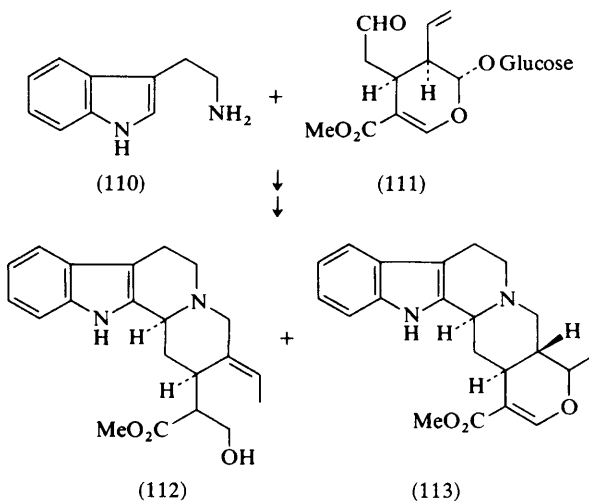


<sup>101</sup> W. Acklin, T. Fehr, and P. A. Stadler, *Helv. Chim. Acta*, 1975, **58**, 2492.

<sup>102</sup> V. M. Krupinski, J. E. Robbers, and H. G. Floss, *J. Bacteriol.*, 1976, **125**, 158.

affords the terpenoid indole alkaloids.<sup>103</sup> Results obtained by other workers<sup>104</sup> are less complete, but are in agreement with this conclusion. Additional points of interest are that (i) [*aryl*-<sup>3</sup>H<sub>4</sub>, 2-<sup>14</sup>C]tryptophan is incorporated without change in isotope ratio so no hydrogen (tritium) is lost from the aromatic ring during biosynthesis and the tryptophan skeleton, apart from C-1, is incorporated intact, and (ii) tryptamine (110) and geraniol-nerol are also incorporated.

**Terpenoid Indole Alkaloids.**—Crude preparations from *Catharanthus roseus* seedlings and from tissue cultures have been shown to be capable of synthesizing in good yield from tryptamine (110) and secologanin (111) with added co-factors, geissoschizine (112) and ajmalicine (113), representatives of the first major class of terpenoid indole alkaloids (Corynanthé).<sup>105</sup> Geissoschizine was metabolized to ajmalicine and several other unidentified alkaloids (for reviews of biosynthesis in intact plants see ref. 106). The catabolic turnover of vindoline and catharanthine in *C. roseus* has been studied.<sup>107</sup>



Research on the biosynthesis of uleine (114) and apparicine (115)<sup>108</sup> has been reviewed.<sup>109</sup> The review includes unpublished results of preliminary studies in *Aspidosperma australe* on olivacine, apparicine, uleine, and guatamine. As the author points out these results are in need of substantiation.

<sup>103</sup> C. R. Hutchinson, A. H. Heckendorf, P. E. Daddona, E. Hagaman, and E. Wenkert, *J. Amer. Chem. Soc.*, 1974, **96**, 5609; R. B. Herbert, in ref. 6, p. 36.

<sup>104</sup> G. M. Sheriha and H. Rapoport, *Phytochemistry*, 1976, **15**, 505.

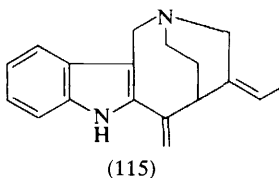
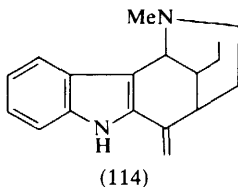
<sup>105</sup> A. I. Scott and S.-L. Lee, *J. Amer. Chem. Soc.*, 1975, **97**, 6906.

<sup>106</sup> A. R. Battersby, in ref. 1, p. 31 (see also refs. 2-6); A. I. Scott, *Accounts Chem. Res.*, 1970, **3**, 151; G. A. Cordell, *Lloydia*, 1974, **37**, 219; B. Gabetta, *Fitoterapia*, 1975, **46**, 147; J. P. Kutney, *Heterocycles*, 1976, **4**, 169.

<sup>107</sup> P. E. Daddona, J. L. Wright, and C. R. Hutchinson, *Phytochemistry*, 1976, **15**, 941.

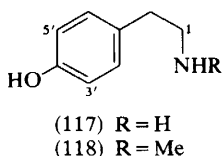
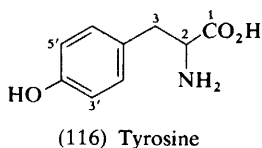
<sup>108</sup> J. P. Kutney, J. F. Beck, C. Ehret, G. Poulton, R. S. Sood, and N. D. Westcott, *Bioorg. Chem.*, 1971, **1**, 194; J. P. Kutney, V. R. Nelson, and D. C. Wigfield, *J. Amer. Chem. Soc.*, 1969, **91**, 4278; *ibid.*, 4279; A. R. Battersby, in ref. 1, p. 47; R. B. Herbert, in ref. 3, p. 3.

<sup>109</sup> J. P. Kutney, *Heterocycles*, 1976, **4**, 429.

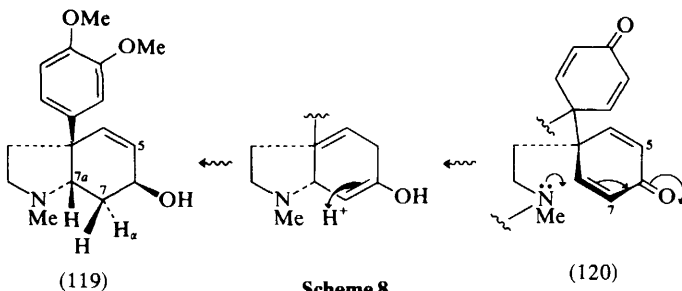


### 5 Miscellaneous Bases of Aromatic Origin

**Mesembrine Alkaloids.**—The way in which tyrosine, labelled in the side-chain, is incorporated into mesembrine alkaloids suggests that it is the source of all the carbon atoms of the octahydroindole moiety (phenylalanine provides the remaining C<sub>6</sub> unit).<sup>110</sup> The incorporation of L-[3',5'-<sup>3</sup>H<sub>2</sub>, U-<sup>14</sup>C]tyrosine [as (116)] into mesembrenol (119) with retention of both labels (incomplete in the case of tritium: see below) proves that this is so.<sup>111</sup> Further, similar incorporations were recorded for [3',5'-<sup>3</sup>H<sub>2</sub>, 1-<sup>14</sup>C]tyramine [as (117)], [3',5'-<sup>3</sup>H<sub>2</sub>, 1-<sup>14</sup>C]-*N*-methyltyramine [as (118)], and [3',5'-<sup>3</sup>H<sub>2</sub>, *N*-methyl-<sup>14</sup>C]-*N*-methyltyramine thus defining the sequence tyrosine (116) → tyramine (117) → *N*-methyltyramine (118) → (119) as a major pathway in the biosynthesis of mesembrine alkaloids.



Unexpectedly, however, each of the precursors examined showed a 50% tritium loss on incorporation into mesembrenol (119), the residual tritium being equally distributed between H-5 and H-7 $\alpha$ . On the basis of the generalized bis-spirodienone intermediate (120)<sup>12,112</sup> the results are consistent with an internal conjugate addition of nitrogen followed by stereospecific  $\beta$ -protonation of the resulting enolate at C-7 (Scheme 8). Since tritium is equally distributed between H-5 and H-7 $\alpha$  in (119)



<sup>110</sup> P. W. Jeffs, W. C. Archie, R. L. Hawks, and D. S. Farrier, *J. Amer. Chem. Soc.*, 1971, **93**, 3752; R. B. Herbert, in ref. 3, p. 23.

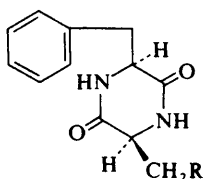
<sup>111</sup> P. W. Jeffs, D. B. Johnson, N. H. Martin, B. S. Rauckman, *J.C.S. Chem. Comm.*, 1976, 82.

<sup>112</sup> P. W. Jeffs, T. Capps, D. B. Johnson, J. M. Karle, N. H. Martin, and B. Rauckman, *J. Org. Chem.*, 1974, **39**, 2703.

tritium loss most probably occurs whilst the ring is still aromatic (on dienone formation these positions become non-equivalent) and it is suggested<sup>111</sup> that tritium is lost by substitution with a group X which is later replaced by hydrogen.

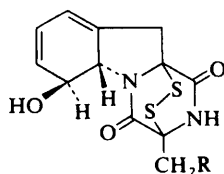
**Gliotoxin.**—In contrast to the recent report that the cyclic dipeptide (121) is not incorporated into gliotoxin (123) in *Penicillium terlikowskii*,<sup>113</sup> it has recently been found that this cyclic dipeptide, with both constituent amino-acids labelled, is efficiently incorporated into gliotoxin (123) in *Trichoderma viride*<sup>114</sup> and without alteration in isotope ratio. Thus, (123), like brevianamide A<sup>115</sup> and echinulin,<sup>116</sup> originates from a cyclic dipeptide. The difference in the two results could be due to the different organisms used in the two experiments, but it was suggested<sup>114</sup> that the probable reason was associated with the large excess of (121) used in the first experiment.

The cyclic peptide (122) has been found to serve as a substrate in *T. viride*, the gliotoxin analogue (124) being synthesized *de novo* from it.<sup>117</sup>



(121) R = OH

(122) R = H



(123) R = OH

(124) R = H

**Benzodiazepine Bases.**—Tracer experiments have shown that cyclophenin (127) and cyclophenol (128) are formed *via* cycloheptene (126) and its dehydro-derivative (125) in *Penicillium cyclopium*. These intermediates, (125) and (126), are reversibly transformed into each other *in vivo*.<sup>118,119</sup> The enzyme, cycloheptene dehydrogenase, which catalyses this reaction has been identified recently in *P. cyclopium* cultures.<sup>120</sup> Cycloheptene dehydrogenase activity in the cultures increased at the beginning of the alkaloid production phase, indicating that the enzyme is involved in alkaloid production. The enzyme showed a high degree of substrate specificity and since cycloheptene (126), *m*-hydroxylated in ring B, was not dehydrogenated it follows that introduction of the hydroxy-group characteristic of cyclophenol (128) must occur after dehydrogenation, in accord with the observation that cyclophenin (127) is a precursor of cyclophenol (128).<sup>119,120</sup> Furthermore, cyclophenin *m*-hydroxylase which catalyses this step has also been identified in *P. cyclopium* cultures.<sup>121</sup> Like most mixed function oxidases it needs both oxygen and a hydrogen

<sup>113</sup> J. C. MacDonald and G. P. Slater, *Canad. J. Biochem.*, 1975, **53**, 475; R. B. Herbert, in ref. 6, p. 37.

<sup>114</sup> J. D. Bu'Lock and C. Leigh, *J.C.S. Chem. Comm.*, 1975, 628.

<sup>115</sup> J. Baldas, A. J. Birch, and R. A. Russell, *J.C.S. Perkin I*, 1974, 50; R. B. Herbert, in ref. 5, p. 26.

<sup>116</sup> G. P. Slater, J. C. MacDonald, and R. Nakashima, *Biochemistry*, 1970, **9**, 2886; R. B. Herbert, in ref. 4, p. 29.

<sup>117</sup> G. W. Kirby and D. J. Robins, *J.C.S. Chem. Comm.*, 1976, 354.

<sup>118</sup> J. Framm, L. Nover, A. El Azzouny, H. Richter, K. Winter, S. Werner, and M. Luckner, *European J. Biochem.*, 1973, **37**, 78.

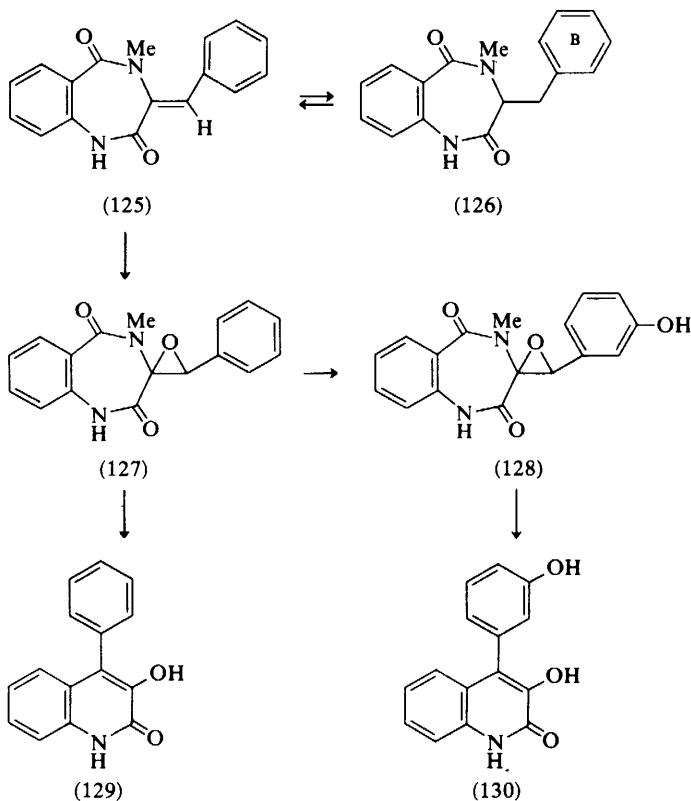
<sup>119</sup> R. B. Herbert, in ref. 5, p. 39.

<sup>120</sup> E. A. Aboutabl and M. Luckner, *Phytochemistry*, 1975, **14**, 2573.

<sup>121</sup> I. Richter and M. Luckner, *Phytochemistry*, 1976, **15**, 67.



donor as co-substrates (an earlier *in vivo* study had shown that oxygen was required and that hydroxylation occurred with a partial 'NIH' shift).<sup>119-123</sup> Compounds related to cyclopenin were found, with the exception of viridicatin (129), to be hydroxylated in the presence of the hydroxylase [cyclopenin (127) and cyclopenol (128) are known to be precursors of viridicatin (129) and viridicatinol (130) respectively, and cyclopenase, the enzyme responsible for this step has been identified<sup>119,124</sup>].



**Anthramycin and Related Antibiotics.**—Results of a study on the biosynthesis of anthramycin (131) have appeared in full.<sup>125</sup> Data additional to those in the preliminary communication,<sup>126</sup> already reviewed,<sup>127</sup> are as follows. L-[3',5'-<sup>2</sup>H<sub>2</sub>]Tyrosine [as (116)] gave anthramycin (131) with retention of one of the two deuterium atoms, as expected from results with tritiated material. The deuterium atom was located at C-13 of (131), thus substantiating the conclusion that the conversion of tyrosine into

<sup>122</sup> L. Nover and M. Luckner, in ref. 39, p. 535.

<sup>123</sup> L. Nover and M. Luckner, *F.E.B.S. Letters*, 1969, **3**, 292.

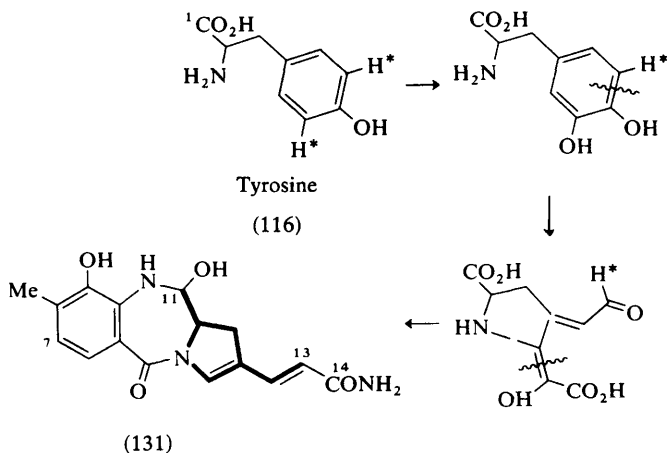
<sup>124</sup> M. Luckner, *European J. Biochem.*, 1967, **2**, 74; M. Luckner, K. Winter, and J. Reisch, *ibid.*, 1969, **7**, 380; M. Luckner and L. Nover, in ref. 39, p. 525.

<sup>125</sup> L. H. Hurley, M. Zmijewski, and C.-J. Chang, *J. Amer. Chem. Soc.*, 1975, **97**, 4372.

<sup>126</sup> L. H. Hurley and M. Zmijewski, *J.C.S. Chem. Comm.*, 1974, 337.

<sup>127</sup> R. B. Herbert, in ref. 5, p. 40.

the acrylamide-proline residue of anthramycin (heavy bonding in 131) proceeds along the pathway shown in Scheme 9 (an alternative pathway was thereby excluded). Important confirmation of the mode of incorporation of tyrosine and also of methionine came with the determination of the fate of the  $^{13}\text{C}$  labels of [*methyl*- $^{13}\text{C}$ ]methionine and [ $1\text{-}^{13}\text{C}$ ]tyrosine on transformation into anthramycin (131). Label from the former precursor appeared at the aromatic methyl and, more importantly, at C-14, thus confirming the  $^{14}\text{C}$  results. The tyrosine label appeared in accord with hypothesis (Scheme 9) at C-11.



**Scheme 9**

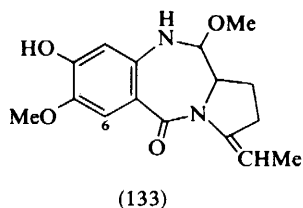
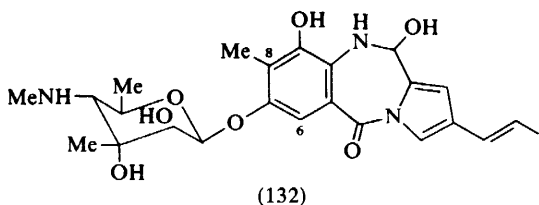
Preliminary results indicate that a cyclic compound related to those involved in cyclopenin biosynthesis (see above) could be involved in anthramycin biosynthesis, with modification of the tyrosine moiety taking place after formation of this cyclic compound.<sup>125</sup>

A 1,2-shift of hydrogen in the course of aromatic hydroxylation *in vivo* leading to preferential retention of isotopic hydrogen in accord with primary isotope effects is widespread. Known as the 'NIH' shift it is observed only with entry of the first of two adjacent aromatic hydroxy-groups (for example, [ $4\text{'-}^3\text{H}$ ] phenylalanine is transformed into tyrosine with 'NIH' shift of the C-4' tritium equally to C-3' and C-5' and retention of most of it at these sites in preference to hydrogen by primary isotope effect. Subsequent conversion into dopa involves hydroxylation at C-3'/C-5' and, not being accompanied by an 'NIH' shift, loss of half of the tritium present in the tyrosine is observed).<sup>128</sup>

The incorporation of DL-[ $5\text{'-}^3\text{H}$ ;  $7\text{'a-}^{14}\text{C}$ ]tryptophan [as (85)] into anthramycin (131) was expected to occur without loss of tritium since C-7, the position corresponding to C-5' of tryptophan, is unsubstituted and this was found to be correct.<sup>129</sup> On the other hand, sibiromycin (132) and tomaymycin (133), antibiotics related to anthramycin, were expected to be more interesting since they are

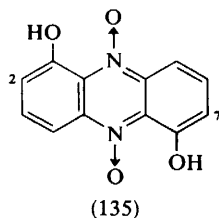
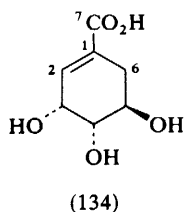
<sup>128</sup> J. W. Daly, D. M. Jerina, and B. Witkop, *Experientia*, 1972, **28**, 1129, and refs. cited therein.

<sup>129</sup> L. Hurley, N. Das, C. Gairola, and M. Zmijewski, *Tetrahedron Letters*, 1976, 1419.

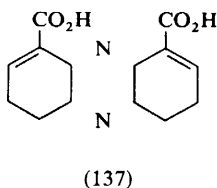
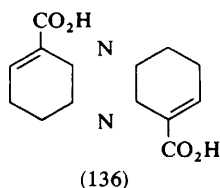


oxygenated at C-7. Sibiromycin (132) showed almost complete retention of tritium, which is probably located at C-6 (regrettably this was not established). Clearly an 'NIH' shift has occurred either selectively to C-6 (rather than C-8) or after entry of the C-8 methyl group. In contrast tomaymycin (133) showed only 16% retention of tritium which cannot be explained by operation of a single sequence of hydroxylation unless tritium is lost by exchange in the course of biosynthesis. However, before this result can be rationalized it is important to establish whether the residual tritium is at C-6, as expected.

**Phenazines.**—Shikimic acid (134) is clearly implicated as a precursor for microbial phenazines,<sup>130</sup> e.g. iodinin (135), and it can act as the sole source of the carbon skeleton.<sup>131</sup> Essential proof that two molecules of shikimic acid are involved in phenazine biosynthesis was provided<sup>132</sup> when it was shown that on incorporation of DL-[1,6-<sup>14</sup>C<sub>2</sub>, 2-<sup>2</sup>H]shikimic acid [as (134)] into iodinin (135) in *Brevibacterium iodinum*, some (7.5%) of the molecules of (135) produced were dideuteriated. [The shikimic acid was incorporated with the usual high efficiency (similar values for <sup>14</sup>C and <sup>2</sup>H) and the deuterium label was confined to the expected positions (see below).]



It follows from this result<sup>132</sup> and the <sup>14</sup>C labelling studies<sup>130</sup> that phenazine biosynthesis proceeds from two shikimic acid units linked as in (136) or (137). By determining that the sites of deuterium labelling in the iodinin (135) derived from



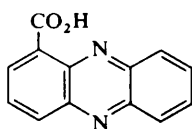
<sup>130</sup> R. B. Herbert, F. G. Holliman, and J. B. Sheridan, *Tetrahedron Letters*, 1974, 4201; U. Hollstein and D. A. McCamey, *J. Org. Chem.*, 1973, **38**, 3415; U. Hollstein and L. G. Marshall, *J. Org. Chem.*, 1972, **37**, 3510; R. B. Herbert, in ref. 5, p. 44; in ref. 4, p. 46, and refs. cited therein.

<sup>131</sup> W. M. Ingledew and J. J. R. Campbell, *Canad. J. Microbiol.*, 1969, **15**, 535.

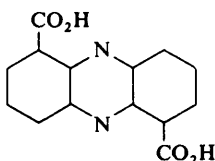
<sup>132</sup> R. B. Herbert, F. G. Holliman, and J. B. Sheridan, *Tetrahedron Letters*, 1976, 639.

[2-<sup>2</sup>H]shikimic acid were exclusively at C-2 and C-7, it followed that the biosynthesis of iodinin (135), and most probably other phenazines, was according to pattern (136) and not pattern (137). This accords with the structures of other naturally occurring phenazines like the griseolutesins, e.g. griseolutein A (140).

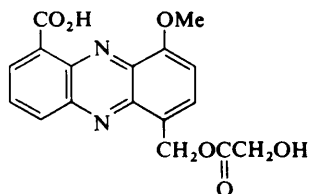
Further support<sup>132</sup> for the conclusion that two molecules of shikimic acid are involved in phenazine biosynthesis comes from the incorporation of *D*-[1,6,7-<sup>14</sup>C<sub>3</sub>]shikimic acid [as (134)] into phenazine-1-carboxylic acid (138) in *Pseudomonas aureofaciens* with close to a fifth of the activity present in the carboxy-group, as required if two molecules of shikimic acid are involved [however, the same result would have been obtained if only one molecule of shikimic acid was implicated provided that a symmetrical intermediate of type (139) was also involved in the elaboration of (138)].



(138)



(139)



(140)

**Dolichotheline.**—The unusual alkaloid, dolichotheline (144), is elaborated in the cactus *Dolichothele sphaerica* from isovaleric acid (143) (presumably *via* its CoA ester) and histamine (142), formed by decarboxylation of histidine (141).<sup>133</sup> *D. sphaerica* is also able to synthesize unnatural analogues of dolichotheline, e.g. (146), from substrates related to (142) and (143).<sup>134</sup> This property is a potentially useful one in general, in that it could be applied to the synthesis of biologically useful molecules which are accessible only with difficulty by chemical means. However, such usefulness will depend on the yield in which the analogue can be obtained. One factor affecting this is competition between natural and unnatural substrate for the appropriate enzyme(s). The yield of unnatural metabolite should be improved then if the competition is reduced.

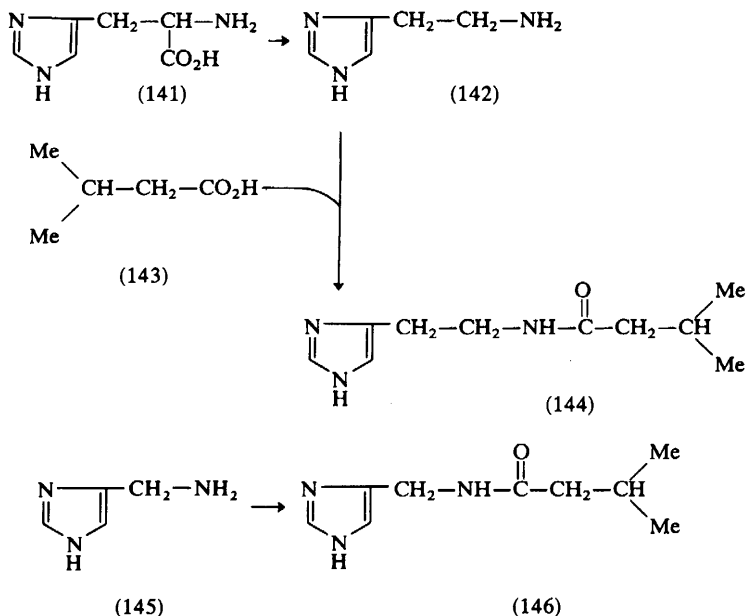
This has been achieved for the production of (146) in *D. sphaerica* by means of histidine decarboxylase inhibitors.<sup>135</sup> Both  $\alpha$ -methylhistidine and  $\alpha$ -hydrazinohistidine (inhibitors for mammalian 'specific' histidine decarboxylase)<sup>136</sup> inhibited formation of histamine with the result that more (146) was synthesized at the expense of (144) (based on the radioactivity of the products after feeding [<sup>3</sup>H]histidine, [<sup>14</sup>C]isovaleric acid and inactive animomethylimidazole [145]).  $\alpha$ -Methyldopa, an inhibitor of mammalian 'non-specific' decarboxylase,<sup>136</sup> was without effect on the proportions of the products formed.

<sup>133</sup> H. Horan and D. G. O'Donovan, *J. Chem. Soc. (C)*, 1971, 2083; J. Staunton, in ref. 2, p. 32; H. Rosenberg and A. G. Paul, *Lloydia*, 1971, **34**, 372; R. B. Herbert, in ref. 3, p. 17.

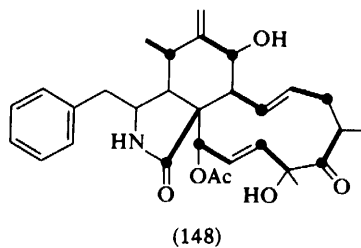
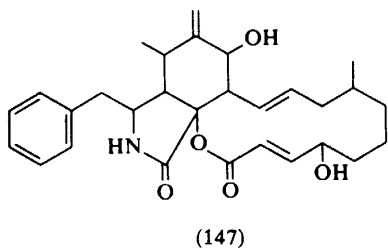
<sup>134</sup> H. Rosenberg and A. G. Paul, *J. Pharm. Sci.*, 1973, **62**, 403; R. B. Herbert, in ref. 4, p. 42; H. Rosenberg, S. J. Stohs, and A. G. Paul, *Phytochemistry*, 1974, **13**, 823; H. Rosenberg and S. J. Stohs, *Lloydia*, 1974, **37**, 313; R. B. Herbert, in ref. 5, p. 48.

<sup>135</sup> H. Rosenberg and S. J. Stohs, *Phytochemistry*, 1976, **15**, 501.

<sup>136</sup> G. Kahlson and E. Rosengran, 'Biogenesis and Physiology of Histamine', Williams and Wilkins, Baltimore, 1971, p. 31.



**Cytochalasins.**—The genesis of both cytochalasin B (147) and cytochalasin D (148) is from phenylalanine (complete carbon skeleton) and acetate-malonate (*via* C<sub>18</sub> and



C<sub>16</sub> polyketides respectively) with methionine providing, respectively, two and three C<sub>1</sub> units.<sup>137</sup> Results with [1,2-<sup>13</sup>C<sub>2</sub>]acetate more rigorously defined the constitution of the polyketide fragment of cytochalasin D as that shown in (148).<sup>138</sup> The reported<sup>139</sup> intact incorporation of palmitic acid into brefeldin A (subsequently refuted)<sup>140</sup> prompted the examination of 1-<sup>13</sup>C/<sup>14</sup>C-labelled palmitic and myristic acids together with butyric acid as cytochalasin D precursors.<sup>138</sup> In each case incorporation was through C-1 labelled acetate resulting from fragmentation by way

<sup>137</sup> M. Binder, J.-R. Kiechel, and C. Tamm, *Helv. Chim. Acta*, 1970, **53**, 1797; C.-R. Lebet and C. Tamm, *Helv. Chim. Acta*, 1974, **57**, 1785; W. Graf, J.-L. Robert, J. C. Vederas, C. Tamm, P. H. Solomon, I. Miura, and K. Nakanishi, *ibid.*, p. 1801; R. B. Herbert, in ref. 6, p. 44.

<sup>138</sup> J. C. Vederas, W. Graf, L. David, and C. Tamm, *Helv. Chim. Acta*, 1975, **58**, 1886.

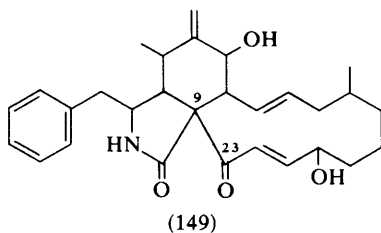
<sup>139</sup> J. D. Bu'Lock and P. T. Clay, *Chem. Comm.*, 1969, 237.

<sup>140</sup> B. E. Cross and P. Hendley, *J.C.S. Chem. Comm.*, 1975, 124.

of the common degradative path<sup>141a</sup> involving  $\beta$ -oxidation. Propionic acid was implicated in cytochalasin biosynthesis, on the one hand by fragmentation to acetate (loss of label from C-1 but retention of that at C-2 was observed, consonant with degradation to acetate through the path involving  $\alpha$ -oxidation)<sup>141b</sup> and on the other, incorporation (of C-1 label) into the phenylalanine residue of cytochalasin D (148) apparently as the result of metabolism<sup>141c</sup> *via* phosphoenol pyruvate.

Although the phenylalanine-derived fragment of cytochalasin D (148) possesses the configuration of the L-amino-acid both D- and L-phenylalanine are equally effective precursors. Incorporation occurs with complete loss of tritium and <sup>15</sup>N from C-2 and extensive loss of tritium from both diastereotopic hydrogens at C-3.<sup>142</sup> These losses could be explained as occurring in part during the course of transamination and phenylpyruvic acid may then be implicated. This acid depressed the incorporation of D-phenylalanine as measured relative to the L-isomer[(2*S*)-[4'-<sup>3</sup>H]- and (2*RS*)-[2-<sup>14</sup>C]-phenylalanine were fed; the cytochalasin isolated showed an increased <sup>3</sup>H:<sup>14</sup>C ratio, *cf.* discussion on p. 1}. It follows that L-phenylalanine rather than the D-isomer is the primary precursor of cytochalasin D (148).

Efficient incorporation of [4'-<sup>3</sup>H, U-<sup>14</sup>C]phenylalanine into deoxaphomin (149) without change in ratio indicates that this amino-acid is an intact precursor for (149) as it is for the other cytochalasins.<sup>143</sup> More importantly radioactive deoxaphomin obtained in this way was used to see if it was a precursor for cytochalasin B (147). A highly efficient incorporation was obtained and without change in isotope ratio thus establishing that cytochalasin B (147) is derived from (149) manifestly by introduction of an oxygen atom between C-9 and C-23. A similar oxygenation has been observed<sup>144</sup> in the *in vivo* transformation of rifamycin W to rifamycin B.



## 6 Miscellaneous Bases of Aliphatic Origin

**$\beta$ -Lactam Antibiotics.**—A wealth of detail is now available on the fates of individual carbon and hydrogen atoms of valine (150) and cysteine (152) on transformation into the penicillins [as (151)].<sup>145</sup> It has been confirmed recently that cysteine gives penicillin with loss of the 3-*pro-S* hydrogen<sup>146</sup> and it was pointed out that if oxidation of the C-3 thio-group to say a thioaldehyde occurs in the course of biosynthesis, then

<sup>141</sup> (a) H. R. Mahler and E. H. Cordes, 'Biological Chemistry', Harper and Row, New York, 2nd edn., 1971, p. 593; (b) *ibid.*, p. 601; (c) *ibid.*, p. 787.

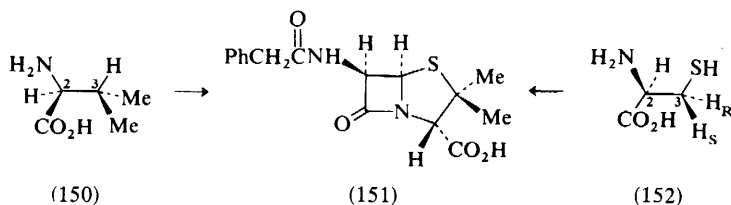
<sup>142</sup> J. C. Vederas and C. Tamm, *Helv. Chim. Acta*, 1976, **59**, 558.

<sup>143</sup> J.-L. Robert and C. Tamm, *Helv. Chim. Acta*, 1975, **58**, 2501.

<sup>144</sup> R. J. White, E. Martinelli, and G. Lancini, *Proc. Nat. Acad. Sci., U.S.A.*, 1974, **71**, 3260; R. B. Herbert, in *ref.* 6, p. 45.

<sup>145</sup> R. B. Herbert, in *ref.* 5, p. 51; in *ref.* 6, p. 49; and *refs. cited therein*.

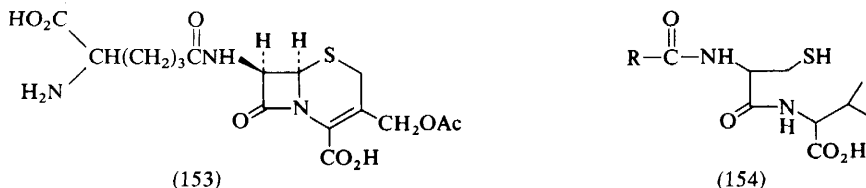
<sup>146</sup> D. J. Aberhart, L. J. Lin and J. Y.-R. Chu, *J.C.S. Perkin I*, 1975, 2517.



the stereochemistry of the reaction is of the opposite sense to that normally observed<sup>147</sup> in the enzymatic conversion of primary alcohols into aldehydes. Although L-valine is well established as a precursor of the D-valine part of penicillins there has been uncertainty on the role of D-valine.<sup>148</sup> Recent experiments have shown however, that although the uptake of D-valine was considerably slower than that of the L-isomer in a high-producing strain of *Penicillium chrysogenum* they were both similarly effective precursors of penicillin G (151);<sup>149</sup> both isomers of [2-<sup>3</sup>H]valine were incorporated with loss of tritium. In an extension of this work L-[U-<sup>14</sup>C, <sup>15</sup>N]valine was examined as a penicillin precursor in cultures of this strain.<sup>150</sup> The <sup>15</sup>N was assayed by a new quantitative application of <sup>15</sup>N pulsed Fourier transform n.m.r. spectroscopy and was found to be incorporated to almost the same extent as the carbon label. This confirms that the inversion of configuration at C-2 of L-valine (152) on transformation into penicillin does not involve the loss of the nitrogen atom.

Evidence additional to that already reported,<sup>151</sup> which strongly points to O-acetylation being the terminal step in the biosynthesis of cephalosporin C (153), has been published.<sup>152,153</sup> In particular the relevant acetyl-transferase has been isolated from *Cephalosporium acremonium* cultures.<sup>152</sup>

The mechanism by which the tripeptide (154), thought to be a precursor for the  $\beta$ -lactam antibiotics,<sup>148</sup> is converted to the cyclic system is unknown but it has been



suggested that the  $\beta$ -lactam ring may be formed by nucleophilic attack of amide nitrogen on the  $sp^2$  carbon of a thioaldehyde or its  $sp^3$  receptor equivalent.<sup>154</sup> An

<sup>147</sup> R. Bentley, 'Molecular Asymmetry in Biology', Academic Press, New York, 1970, Vol. II, p. 14.

<sup>148</sup> P. A. Lemke and D. R. Brannon, in 'Cephalosporins and Penicillins', ed. E. H. Flynn, Academic Press, New York, 1972, p. 370.

<sup>149</sup> B. W. Bycroft, C. M. Wels, K. Corbett, A. P. Maloney, and D. A. Lowe, *J.C.S. Chem. Comm.*, 1975, 923.

<sup>150</sup> H. Booth, B. W. Bycroft, C. M. Wels, K. Corbett, and A. P. Maloney, *J.C.S. Chem. Comm.*, 1976, 110.

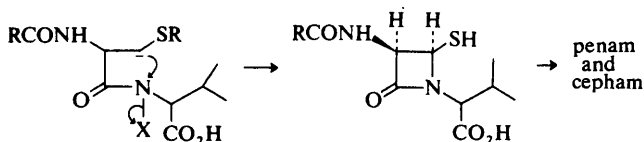
<sup>151</sup> Y. Fujisawa, H. Shirafuji, M. Kida, and K. Nara, *Nature New Biol.*, 1973, **246**, 154; R. B. Herbert, in ref. 5, p. 51.

<sup>152</sup> Y. Fujisawa and T. Kanzaki, *Agric. and Biol. Chem. (Japan)*, 1975, **39**, 2043.

<sup>153</sup> Y. Fujisawa, H. Shirafuji, M. Kida, K. Nara, M. Yoneda, and T. Kanzaki, *Agric. and Biol. Chem. (Japan)*, 1975, **39**, 1295; Y. Fujisawa, H. Shirafuji, and T. Kanzaki, *ibid.*, p. 1303.

<sup>154</sup> H. R. V. Arnstein and J. C. Crawhall, *Biochem. J.*, 1957, **67**, 180; H. R. V. Arnstein, *Ann. Reports*, 1957, 339.

intriguing alternative suggestion<sup>155</sup> is that cyclization is associated with oxidation of the amide nitrogen; nucleophilic displacement at this centre by an anion generated at the  $\beta$ -carbon of the cysteine fragment then follows (Scheme 10). A chemical synthesis of a  $\beta$ -lactam system employing these ideas provides attractive support for them.



Scheme 10

**Streptovaricins and Mitomycins.**—Consideration of the structures deduced for metabolites with the streptovaricin skeleton which lack in particular the extensive oxygenation of say streptovaricin D, has allowed a reasonable sequence of events for streptovaricin biosynthesis to be proposed.<sup>156</sup> (The streptovaricins belong to the class of ansamycins.<sup>157</sup> For earlier reviews on ansamycin biosynthesis see ref. 5, p. 52, and ref. 6, p. 45.)

Both citrulline (156) and arginine (157) serve as efficient precursors for mitomycins (155).<sup>158</sup> An efficient incorporation of L-[NH<sub>2</sub>CO-<sup>15</sup>N,<sup>13</sup>C]citrulline with high retention of both labels as doubly labelled mitomycin rather than a mixture of singly labelled species establishes an intact incorporation of this precursor.<sup>159</sup> Moreover, citrulline is not converted into arginine (157) or urea prior to incorporation since this would have resulted in a loss of half the <sup>15</sup>N by interchange with the <sup>14</sup>N in either compound.

**Azetidine-2-carboxylic Acid.**—DL-[1-<sup>14</sup>C]methionine has been found to be a specific precursor for azetidine-2-carboxylic acid (158) in *Nicotiana tabacum*<sup>160</sup> as it is in other species.<sup>161</sup> The label was located on the carboxy-group, the expected site.

**Steroid and Terpenoid Alkaloids.**—Following upon earlier work on the biosynthesis of steroidal alkaloids<sup>162</sup> it has been shown that (25*S*)-5 $\alpha$ -cholestan-3 $\beta$ ,26-diol (159), but not the corresponding furostan derivative (160), is a precursor for tomatidine (162) in *Lycopersicon pimpinellifolium*.<sup>163</sup> [This contrasts with the observation that the (25*S*)-sapogenin, neotigogenin (163), was labelled by both precursors in these experiments.] If these results are taken together with the observation that

<sup>155</sup> A. I. Scott, S. E. Yoo, S.-K. Chung, and J. A. Lacadie, *Tetrahedron Letters*, 1976, 1137.

<sup>156</sup> P. V. Deshmukh, K. Kakinuma, J. J. Ameal, K. L. Rinehart, jun., P. F. Wiley, and L. H. Li, *J. Amer. Chem. Soc.*, 1976, **98**, 870.

<sup>157</sup> K. L. Rinehart, jun., *Accounts Chem. Res.*, 1972, **5**, 57.

<sup>158</sup> U. Hornemann and J. C. Cloyd, *Chem. Comm.*, 1971, 301; U. Hornemann, J. P. Kehrer, C. S. Nunez, and R. L. Ranieri, *J. Amer. Chem. Soc.*, 1974, **96**, 320; R. B. Herbert, in ref. 4, p. 40; in ref. 5, p. 52.

<sup>159</sup> U. Hornemann and J. H. Eggert, *J. Antibiotics*, 1975, **28**, 841.

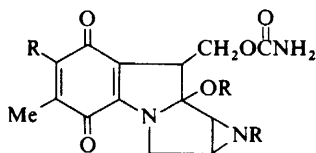
<sup>160</sup> E. Leete, *Phytochemistry*, 1975, **14**, 1983.

<sup>161</sup> E. Leete, G. E. Davis, C. R. Hutchinson, K. W. Woo, and M. R. Chedekel, *Phytochemistry*, 1974, **13**, 427 and refs. cited therein; R. B. Herbert, in ref. 5, p. 50.

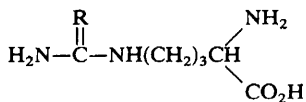
<sup>162</sup> K. Schreiber, in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1968, Vol. 10, p. 115; H. Ripberger, W. Moritz, and K. Schreiber, *Phytochemistry*, 1971, **10**, 2699; E. Heftmann, E. R. Lieber, and R. D. Bennett, *Phytochemistry*, 1967, **6**, 225; R. Tschesche, and H. Hulpke, *Z. Naturforsch.*, 1966, **21b**, 893; F. Ronchetti and G. Russo, *J.C.S. Chem. Comm.*, 1974, 785; R. B. Herbert, in ref. 6, p. 53; in ref. 3, p. 40.

<sup>163</sup> F. Ronchetti, G. Russo, G. Ferrara, and G. Vecchio, *Phytochemistry*, 1975, **14**, 2423.





(155)



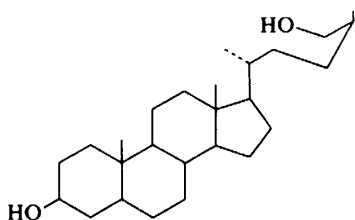
(156) R = O

(157) R = NH

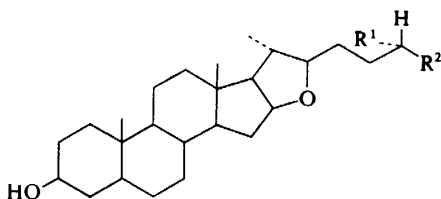
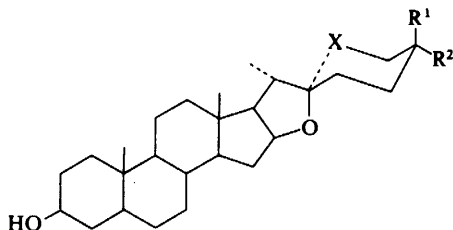


(158)

the 26-amino compound (161) is a precursor for solasodine (164),<sup>164</sup> then it follows that introduction of the amino-group occurs before formation of the tetrahydrofuran ring (it is assumed that the biosynthesis of (25*R*)- and (25*S*)-spirosolanones is similar).<sup>163</sup>



(159)

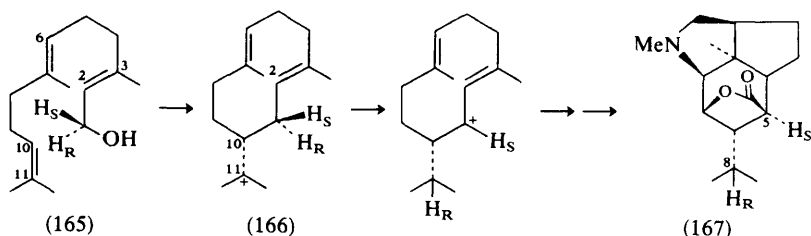
(160) R<sup>1</sup> = Me, R<sup>2</sup> = CH<sub>2</sub>OH(161) Δ<sup>5</sup>, R<sup>1</sup> = CH<sub>2</sub>NH<sub>2</sub>, R<sup>2</sup> = Me(162) X = NH, R<sup>1</sup> = Me, R<sup>2</sup> = H(163) X = O, R<sup>1</sup> = Me, R<sup>2</sup> = H(164) Δ<sup>5</sup>, X = NH, R<sup>1</sup> = H, R<sup>2</sup> = Me

Results<sup>165</sup> with [5-<sup>3</sup>H<sub>2</sub>]mevalonate indicate that both of the tritium atoms which would appear at an intermediate stage at C-1 of farnesol (165) are retained in the formation of the sesquiterpenoid alkaloid dendrobine (167). One of the tritium atoms appears unexceptionally at C-5 whereas the other undergoes a 1,3-shift in an intermediate which may be represented as (166),<sup>165,166</sup> and thus appears at C-8. Incorporation of (1*RS*)-[1-<sup>3</sup>H<sub>2</sub>]- and (1*S*)-[1-<sup>3</sup>H]-2-*trans*,6-*trans*farnesol [as (165)] but not the corresponding 2-*cis*-isomer (similarly labelled) points to the 10-membered ring intermediate (166) being as shown rather than having the 2-*cis* geometry.<sup>166</sup> The results further show that the hydrogen migration is stereospecific

<sup>164</sup> R. Tschesche, 'Euchem Conference on Chemistry and Biosynthesis of Steroids and Terpenoids', La Laguna, Canary Isles, Spain, 1972, quoted in ref. 163.

<sup>165</sup> A. Corbella, P. Gariboldi, and G. Jommi, *J.C.S. Chem. Comm.*, 1973, 729.

<sup>166</sup> A. Corbella, P. Gariboldi, G. Jommi, and M. Sisti, *J.C.S. Chem. Comm.*, 1975, 288.



and involves the *pro-R* atom at C-1. (Similar conclusions have been reached from results with (5*R*)- and (5*S*)-[5-<sup>3</sup>H]mevalonic acid).<sup>167</sup> Interestingly the biosynthesis of the related sesquiterpene, culmorin, involves migration of the *pro-S* hydrogen from C-1 to C-10 (farnesol numbering).<sup>168</sup> Accepting related biosynthetic pathways for the two compounds, a modification to the reactions surrounding (166) has been proposed which allows for the shift of different hydrogens in the course of the formation of 10- and 11-membered ring intermediates for dendrobine and culmorin respectively.

<sup>167</sup> D. Arigoni, '9th IUPAC Symposium of Natural Products', Ottawa, 1974, quoted in ref. 166.

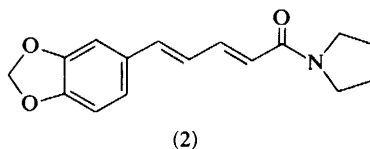
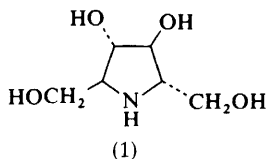
<sup>168</sup> J. R. Hanson and R. Nyfeler, *J.C.S. Chem. Comm.*, 1975, 171; *ibid.*, 824.

## Pyrrolidine, Piperidine, and Pyridine Alkaloids

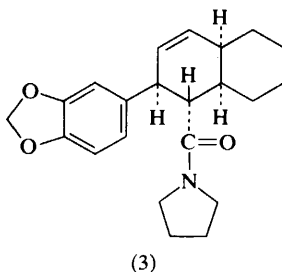
BY A. R. PINDER

### 1 Pyrrolidine Alkaloids

A new natural imino-alcohol, 3,4-dihydroxy-2,5-dihydroxymethylpyrrolidine (1) has been isolated from the roots and leaves of *Derris elliptica*. Its structure and configuration have been settled principally by n.m.r. and mass spectrometry.<sup>1</sup> It appears to be the first example of the occurrence of an iminopolyol in the vegetable kingdom. Trichostachine (2) has been found in the fruit of *Piper guineense* Schum.



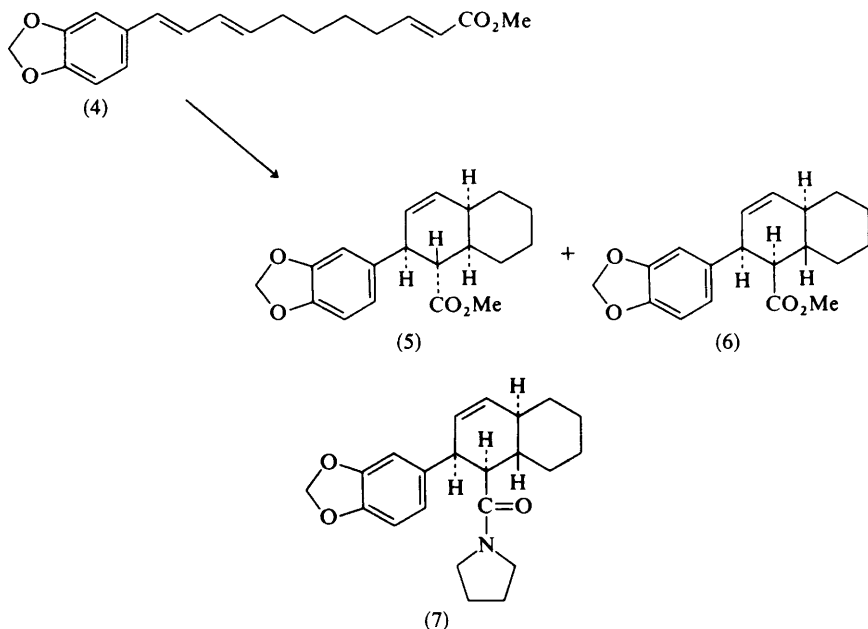
and Thonn. and also in the roots.<sup>2</sup> New Piperaceae alkaloids include cyclostachine-A, occurring in the stems of *P. trichostachyon*. Hydrolysis afforded pyrrolidine, and catalytic hydrogenation yielded a dihydro-derivative, osmylation confirming the presence of a double bond, which proved to be disubstituted since a dialdehyde was formed on periodate cleavage of the diol. Lithium aluminium hydride reduction of the alkaloid generated an amine, the sulphate of which was subjected to X-ray diffraction analysis. These investigations and n.m.r. and mass spectral studies pointed to structure (3) for cyclostachine-A, confirmed by synthesis *via* intramolecu-



<sup>1</sup> A. Welter, J. Jadot, G. Dardenne, M. Marlier, and J. Casimir, *Phytochemistry*, 1976, **15**, 747.

<sup>2</sup> D. Dwuma-Badu, J. S. K. Ayim, T. T. Dabra, H. N. ElSohly, J. E. Knapp, D. J. Slatkin, and R. I. Schiff, jun., *Lloydia*, 1976, **39**, 60.

lar Diels–Alder reaction of the ester (4), which furnished (5) and (6), separable by chromatography. Hydrolysis of the former yielded the corresponding acid, which when converted into its chloride and treated with pyrrolidine gave (3).<sup>3,4</sup> A second alkaloid from the same source is cyclostachine-B (7), a stereoisomer of (3) with a *trans* ring fusion. It was synthesized from ester (6) by the same route.<sup>4</sup>



Two new syntheses of racemic mesembrine have been described. In the first,<sup>5</sup> outlined in Scheme 1, an improved synthesis of the penultimate 2-pyrroline (8) was achieved; annelation of this afforded (±)-mesembrine (9). The second (Scheme 2) incorporates a regioselective borohydride imide reduction.<sup>6</sup> Investigations on the biosynthesis of mesembrine alkaloids have revealed that a stereospecific protonation occurs at C-7 [see formula (9)] as one of the late stages.<sup>7</sup>

**Dendrobium Alkaloids.**—8-Epidendrobine (14) has been synthesized employing a route involving a diene isomerization in a Diels–Alder reaction (Scheme 3).<sup>8</sup> To account for the unexpected stereochemical result of the latter addition [(12) → (13) and epimeride] it is proposed that ester (15) assumes a very hindered conformation in the transition state, involving no secondary orbital overlap between diene and ester groups. However isomerization of the trisubstituted double bond to give (16) leads

<sup>3</sup> B. S. Joshi, N. Viswanathan, D. H. Gawad, V. Balakrishnan, W. von Philipsborn, and A. Quick, *Experientia*, 1975, **31**, 880.

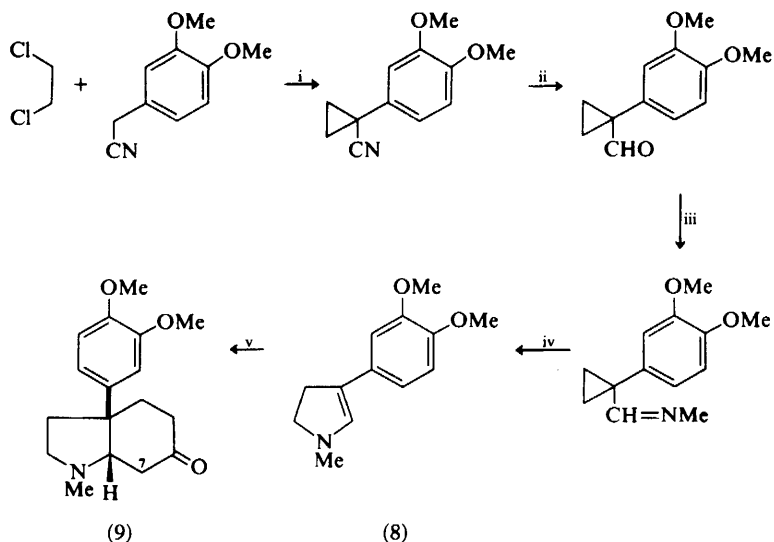
<sup>4</sup> B. S. Joshi, N. Viswanathan, D. H. Gawad, V. Balakrishnan, and W. von Philipsborn, *Helv. Chim. Acta*, 1975, **58**, 2295.

<sup>5</sup> R. V. Stevens, P. M. Lesko, and R. Lapalme, *J. Org. Chem.*, 1975, **40**, 3495.

<sup>6</sup> J. B. P. A. Wijnberg and W. N. Speckamp, *Tetrahedron Letters*, 1975, 3963.

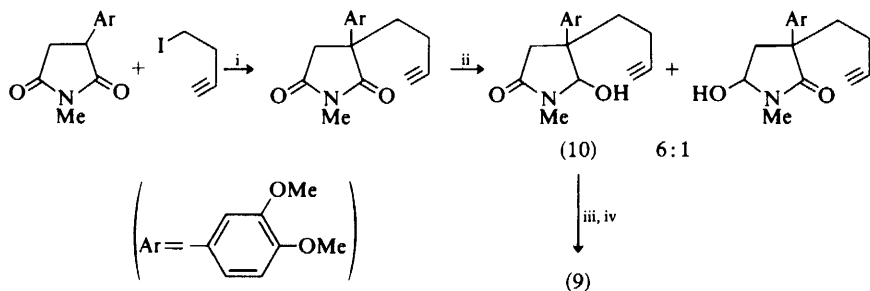
<sup>7</sup> P. W. Jeffs, D. B. Johnson, N. H. Martin, and B. S. Rauckman, *J.C.S. Chem. Comm.*, 1976, 82.

<sup>8</sup> R. F. Borch, A. J. Evans, and J. J. Wade, *J. Amer. Chem. Soc.*, 1975, **97**, 6282.



Reagents: i,  $\text{LiN}(\text{CHMe}_2)_2$ ; ii,  $(\text{Me}_2\text{CHCH}_2)_2\text{AlH}$ ; iii,  $\text{MeNH}_2$ ; iv,  $\text{NH}_4\text{I}$ ; v.  $\text{MeCOCH}=\text{CH}_2$ ,  $\text{HCl}$ .

**Scheme 1**



Reagents: i,  $\text{NaH}$ ; ii,  $\text{NaBH}_4$ ; iii,  $\text{HCO}_2\text{H}$ ; iv,  $\text{MeCOCH}=\text{CH}_2$ .

**Scheme 2**

to a more favourable situation in the transition state, which would lead to the  $\alpha$ -configuration for the isopropyl group as depicted in (14).

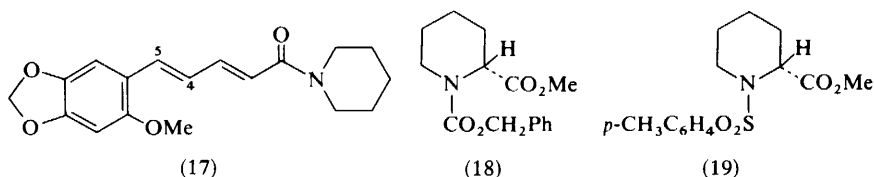
## 2 Piperidine Alkaloids

Piperine has been isolated from the fruits and roots of *Piper guineense* Schum. and Thonn., along with 4,5-dihydropiperine. Both show marked antimicrobial activity against *Mycobacterium smegmatis*, and the former against *Candida albicans* and the latter against *Klebsiella pneumoniae*.<sup>2</sup> Wisanine is a new pepper alkaloid found in



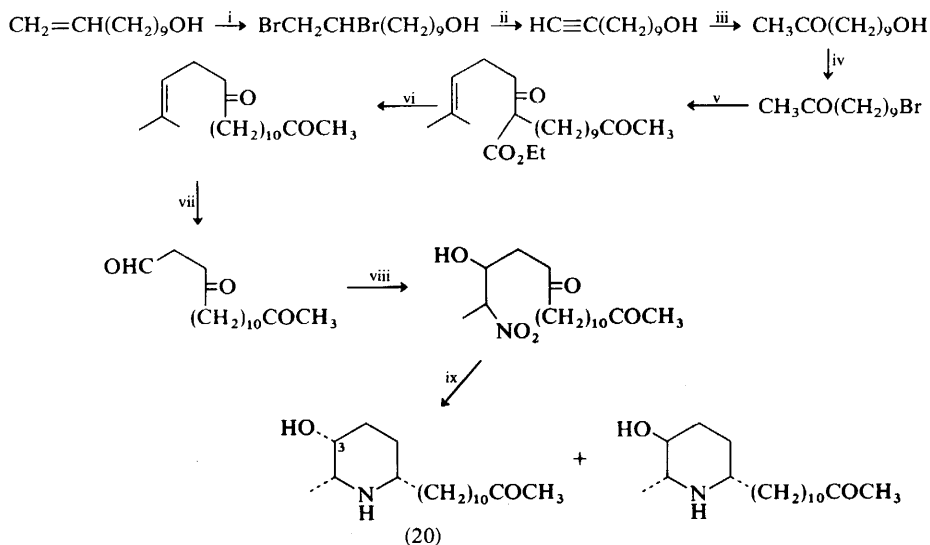
the roots of the same plant; its structure (17) has been settled mainly by u.v., i.r., n.m.r., and mass spectral study.<sup>9</sup>

$\gamma$ -Coniceine reductase, isolated from leaves and fruit of several *Conium maculatum* varieties, is NADPH dependent. Hydride transfer occurs from the B(*pro-S*) side of the pyridine nucleotide to  $\gamma$ -coniceine to yield coniine.<sup>10</sup> (*S*)-(+)-Coniine, almost optically pure, has been prepared from L-lysine hydrochloride *via* D-pipecolic acid and the (*R*)-(+)-compounds (18) and (19).<sup>11</sup> Coniine has been



found to occur in the leaves of the pitcher plant, *Sarracenia flava*, which employs it as a paralyzing agent in connection with its insectivorous behaviour.<sup>12</sup>

Total syntheses of racemic cassine (20), an alkaloid of the leaves of *Cassia exdelsa* Shrad., and of its 3-epimeride have been disclosed (Scheme 4).<sup>13</sup>



Reagents: i,  $\text{Br}_2$ ; ii,  $\text{NaNH}_2$ ; iii,  $\text{Hg}^{++}$ ,  $\text{H}^+$ ; iv,  $\text{PBr}_3$ ; v,  $\text{Me}_2\text{C}=\text{CHCH}_2\text{CH}_2\text{COCH}_2\text{CO}_2\text{Et}$ ; vi, hydrolysis and decarboxylation [ $\text{Ba}(\text{OH})_2$ ]; vii,  $\text{O}_3$ , then  $\text{Zn}$ ,  $\text{AcOH}$ ; viii,  $\text{EtNO}_2$ ,  $\text{NaOEt}$ ; ix,  $\text{H}_2$ ,  $\text{Pd-C}$ .

**Scheme 4**

<sup>9</sup> I. Addae-Mensah, F. G. Torto, and I. Baxter, *Tetrahedron Letters*, 1976, 3049.

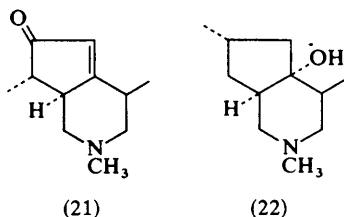
<sup>10</sup> M. F. Roberts, *Phytochemistry*, 1975, **14**, 2393.

<sup>11</sup> K. Areta, S. Terashima, and S. Yamada, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 621.

<sup>12</sup> N. V. Mody, R. Henson, P. A. Hedin, U. Korpel, and D. H. Miles, *Experientia*, 1976, **32**, 829.

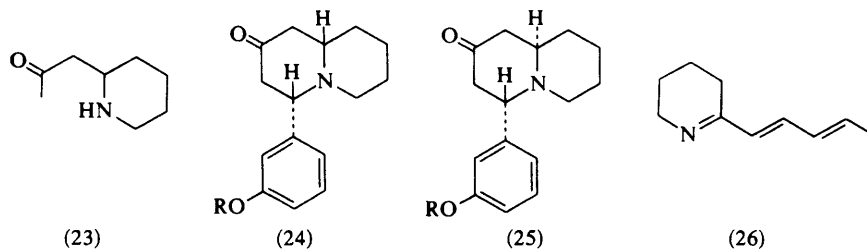
<sup>13</sup> E. Brown and A. Bonte, *Tetrahedron Letters*, 1975, 2881.

The crystal structures and absolute stereochemistry of tecomanine (21) and alkaloid-C (22), occurring in *Tecoma stans*, have been settled by *X*-ray diffraction analysis of their respective methoperchlorate and methiodide salts. In the latter case the results reveal the position of the angular hydroxy-group, hitherto not known with certainty.<sup>14</sup>



Isopelletierine (23) undergoes a Mannich reaction with both *m*-methoxy- and *m*-hydroxy-benzaldehyde, to give respectively a mixture of the *cis* (24; R = Me) and *trans* (25; R = Me) quinolizidines, and exclusively the *trans*-quinolizidine (25; R = H). The ratio of stereoisomers in the former reaction varies widely with solvent used.<sup>15</sup>

The structure of an alkaloid isolated from *Streptomyces* sp. NA-337 has been revised to (E,E)-2-pentadienyl-3,4,5,6-tetrahydropyridine (26). The absence of optical activity in the base hydrochloride precluded an earlier structure derived from a methylpyrrolidine and containing an asymmetric centre.<sup>16</sup>



**Spiropiperidine Alkaloids.**—A new synthetic pathway to (±)-perhydrohistrionicotoxin (27) (Scheme 5) has been elaborated.<sup>17</sup> The final product is the intermediate (28), convertible to (27) as described earlier.<sup>18</sup> A further synthetic entry into this ring system uses a Mannich-type spiro cyclization as key step and leads ultimately to racemic 2,7-epiperhydrohistrionicotoxin (29) (Scheme 6). The structure and stereochemistry of the urethane intermediate (30) were ascertained by *X*-ray diffraction analysis.<sup>19</sup>

<sup>14</sup> G. Ferguson and W. C. Marsh, *J.C.S. Perkin II*, 1975, 1124.

<sup>15</sup> M. Hanaoka, N. Ogawa, K. Shimizu, and Y. Arata, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 1573.

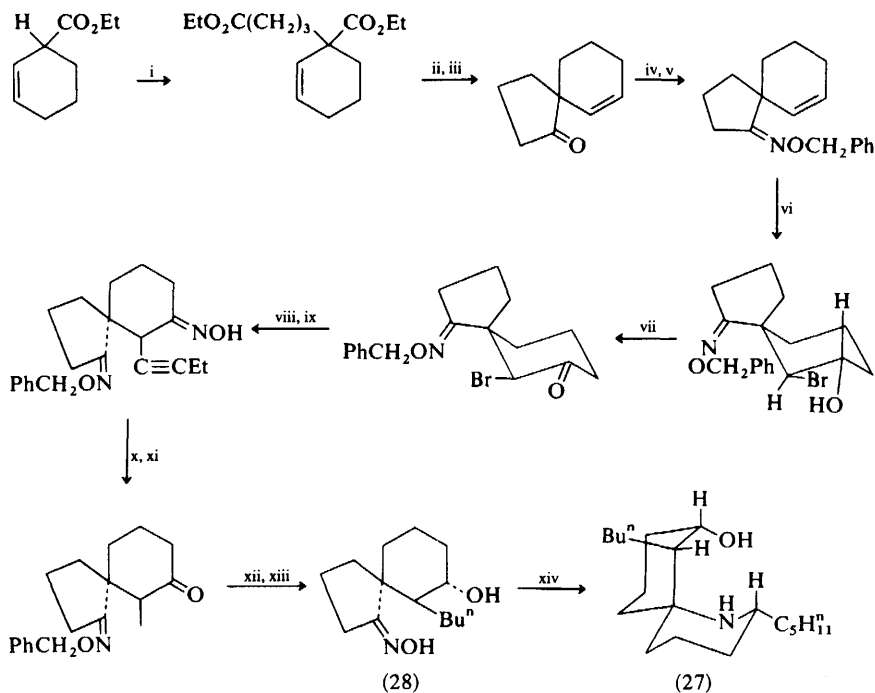
<sup>16</sup> M. Onda, Y. Konda, Y. Narimatsu, H. Tanaka, J. Awaya, and S. Omura, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 2462.

<sup>17</sup> E. J. Corey, M. Petrzilka, and Y. Ueda, *Tetrahedron Letters*, 1975, 4343.

<sup>18</sup> E. J. Corey, J. F. Arnett, and G. N. Widiger, *J. Amer. Chem. Soc.*, 1975, **97**, 430; M. Aratani, L. V. Dunkerton, T. Fukuyama, Y. Kishi, H. Kakoi, S. Sugiura, and S. Inoue, *J. Org. Chem.*, **40**, 2009 (1975); T. Fukuyama, L. V. Dunkerton, M. Aratani, and Y. Kishi, *ibid.*, p. 2011.

<sup>19</sup> E. J. Corey, Y. Uyeda, and R. A. Ruden, *Tetrahedron Letters*, 1975, 4347.





Reagents: i,  $\text{Br}(\text{CH}_2)_3\text{CO}_2\text{Et}$ ,  $\text{LiN}(\text{CHMe}_2)_2$ , HMPA, THF; ii, NaH, THF; iii, hydrolysis and decarboxylation; iv,  $\text{NH}_2\text{OH} \cdot \text{HCl}$ , py; v,  $\text{PhCH}_2\text{Br}$  on K salt; vi, NBS-DME- $\text{H}_2\text{O}$ ; vii, Jones oxidation; viii,  $\text{NH}_2\text{OH} \cdot \text{HCl}$ , NaOAc, AcOH; ix,  $\text{EtC}\equiv\text{CLi}$ ; x,  $\text{H}_2$ , Pd-C; xi,  $\text{TiCl}_3$ , MeOH, NaOAc; xii,  $\text{H}_2$ , Pd-C; xiii, Na- $\text{NH}_3$ ; xiv, several steps.<sup>18</sup>

Scheme 5

**Decahydroquinoline Alkaloids.**—Full details of a synthesis of ( $\pm$ )-pumiliotoxin-C hydrochloride and of its X-ray diffraction analysis, described briefly earlier,<sup>20</sup> have been published.<sup>21</sup> Two new syntheses of the racemic free base (31) have been described; the first is outlined in Scheme 7. The final hydrogenation afforded the desired base (31) as major product, a consequence of a high order of stereoselectivity in this step.<sup>22</sup> The second approach (Schemes 8 and 9) uses 1,3-bis(trimethylsilyloxy)-1,3-dienes as intermediates.<sup>23</sup> In both of the latter pathways the final product is the lactam (32), the conversion of which to ( $\pm$ )-pumiliotoxin-C has already been documented.<sup>21</sup>

### 3 Pyridine Alkaloids

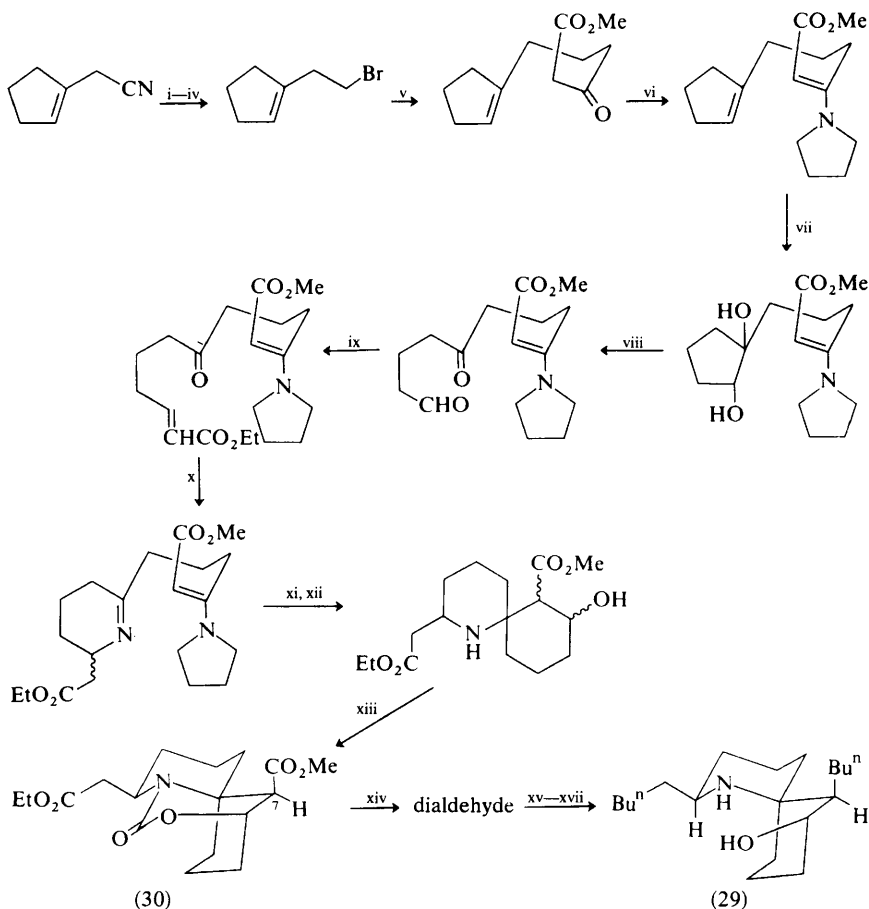
The leaves of *Duboisia myoporoides* from New Caledonia contain nicotine and nornicotine; the alkaloid content of this plant is very different from the same species

<sup>20</sup> T. Ibuka, Y. Inubushi, I. Saji, K. Tanaka, and N. Masaki, *Tetrahedron Letters*, 1975, 323.

<sup>21</sup> T. Ibuka, N. Masaki, I. Saji, K. Tanaka, and Y. Inubushi, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 2779.

<sup>22</sup> G. Habermehl, H. Andres, and B. Witkop, *Naturwiss.*, 1975, **62**, 345.

<sup>23</sup> T. Ibuka, Y. Mori, and Y. Inubushi, *Tetrahedron Letters*, 1976, 3169.



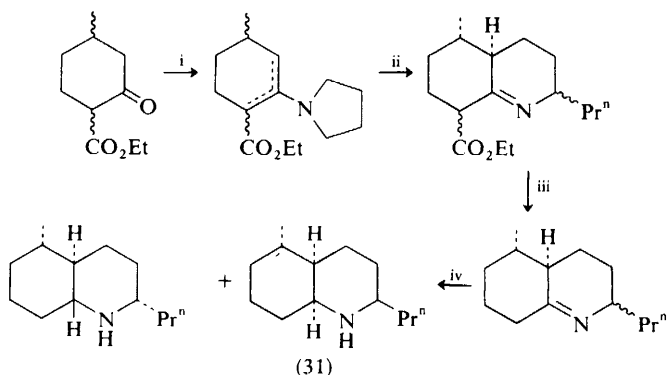
Reagents: i-iv, standard procedures; v,  $\text{CH}_3\text{COCH}_2\text{CO}_2\text{Me}$  dianion, HMPA, THF; vi, pyrrolidine, AcOH; vii,  $\text{OsO}_4$ , then aq.  $\text{NaHSO}_3$ ; viii,  $\text{Ag}_2\text{CO}_3$ ; ix,  $(\text{EtO})_2\text{PCH}_2\text{CO}_2\text{Et}$  anion, THF; x,  $\text{NH}_3$ , sealed tube; xi, toluene-*p*-sulfonic acid monohydrate; xii,  $\text{NaBH}_4$ ; xiii,  $\text{COCl}_2$ , pyridine; xiv,  $(\text{Me}_2\text{CHCH}_2)_2\text{AlH}$ ; xv,  $\text{CH}_2=\text{CHCH}_2\text{P}^+\text{Me}_2\text{Ph Br}^-$ ,  $\text{CH}_3\text{SOCH}_2$ ; xvi,  $\text{H}_2$ , Pd-C; xvii, Li,  $\text{MeNH}_2$ .

Scheme 6

growing in Australia.<sup>24</sup> The configuration of nicotine has been investigated by n.m.r. study. In trifluoroacetic acid solution signals for the *N*-methyl group at 3.13 and 2.82 p.p.m. are attributed to contributions from structures in which the group is respectively *trans* and *cis* to the pyridine ring. It is estimated that in the free base the same group is about 91% *trans* to the ring.<sup>25</sup> The various possible *N*-oxides of nicotine have been prepared and their n.m.r. and mass spectra recorded. The *cis*- and *trans*-isomers of nicotine 1'-*N*-oxide have been found to occur in the leaves,

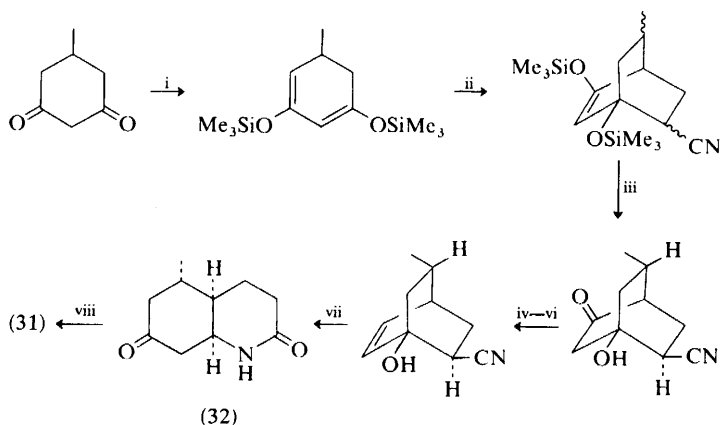
<sup>24</sup> L. Cosson and J.-C. Vaillant, *Phytochemistry*, 1976, **15**, 818.

<sup>25</sup> J. F. Whidby and J. I. Seeman, *J. Org. Chem.*, 1976, **41**, 1585.



Reagents: i, pyrrolidine; ii,  $\text{Me}(\text{CH}_2)_2\text{CH}(\text{NH}_2)(\text{CH}_2)_2\text{Br}$ , DMF; iii,  $\text{HCl}$ ,  $\text{H}_2\text{O}$ ; iv,  $\text{H}_2$ ,  $\text{Pd-C}$ .

Scheme 7

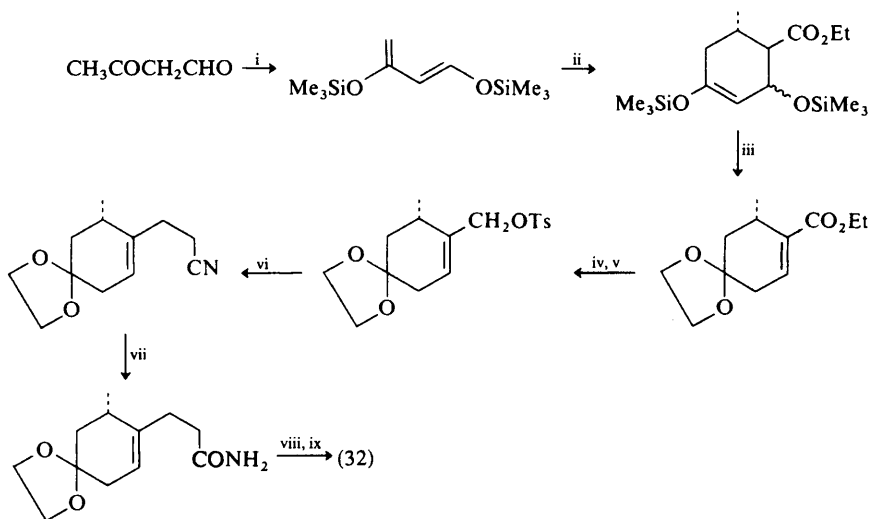


Reagents: i,  $\text{Me}_3\text{SiCl}$ ; ii,  $\text{CH}_2=\text{CHCN}$ ; iii,  $\text{HCl aq.}$ ; iv,  $\text{C}_5\text{H}_5\text{NH}^+\text{B}_3^-$ ; v,  $\text{NaBH}_4$ ; vi,  $\text{Zn}$ ,  $\text{AcOH}$ ; vii,  $\text{HClO}_4$ ,  $\text{AcOH}$  (retro-aldol cleavage); viii, ref. 21.

Scheme 8

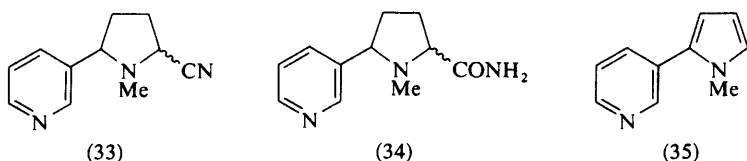
stems, and roots of *Nicotiana tabacum*, *N. affinis*, and *N. glauca*. These, the 1-*N*-oxide, and the *cis*- and *trans*-dioxides are all reduced by  $\text{TiCl}_3$  to nicotine.<sup>26</sup> The dye-sensitized photochemical oxidations of nicotine and *N*-methylanabasine have been studied. The former, irradiated in the presence of oxygen, methylene blue, and potassium cyanide, afforded epimeric mixtures of the cyanides (33) and amides (34), whereas in the presence of eosin, under nitrogen, nicotyrine (35) results, mixed with

<sup>26</sup> J. D. Phillipson and S. S. Handa, *Phytochemistry*, 1975, **14**, 2683.

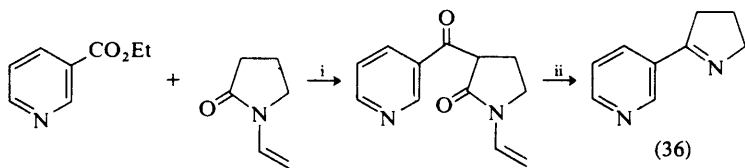


Reagents: i,  $\text{Me}_3\text{SiCl}$  on Na salt; ii,  $\text{MeCH}=\text{CHCO}_2\text{Et}$ ,  $170^\circ$ ; iii,  $(\text{CH}_2\text{OH})_2$ ,  $\text{H}^+$ ; iv,  $\text{LiAlH}_4$ ; v,  $\text{TsCl}$ ; vi,  $\text{CuMeCN}$ ; vii,  $\text{H}_2\text{O}_2$ ,  $^-\text{OH}$ ; viii,  $\text{H}^+$ ,  $\text{H}_2\text{O}$ ; ix,  $\text{NaOMe}$ ,  $\text{MeOH}$  (cyclization).

Scheme 9



the nitriles. Under some conditions the *N*-methyl group is oxidized off.<sup>27</sup> A new synthesis of myosmine (36) has been achieved (Scheme 10).<sup>28</sup>



Reagents: i,  $\text{NaH}$  in toluene; ii,  $\text{H}^+$ ,  $\text{H}_2\text{O}$ , then  $^-\text{OH}$ ,  $\text{H}_2\text{O}$ .

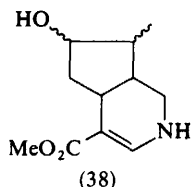
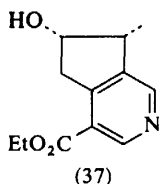
Scheme 10

The compounds cantleyine (37) and tetrahydrocantleyine (38) are artefacts formed during extraction of the tree *Lasianthera austrocaledonica* in the presence of ammonia. They are formed by dismutation of an intermediate dihydropyridine.<sup>29</sup>

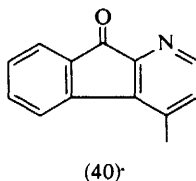
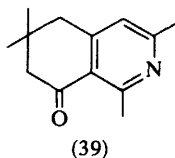
<sup>27</sup> Y. Hubert-Brierre, D. Herlem, and F. Khuong-Huu, *Tetrahedron*, 1975, **31**, 3049.

<sup>28</sup> S. Brandänge and L. Lindblom, *Acta Chem. Scand.*, 1976, **30B**, 93.

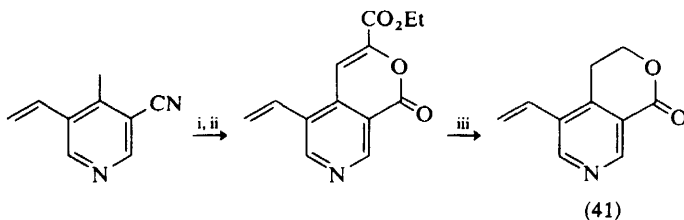
<sup>29</sup> T. Sévenet, A. Husson, and H.-P. Husson, *Phytochemistry*, 1976, **16**, 576.



1,3,6,6-Tetramethyl-5,6,7,8-tetrahydroisoquinoline-8-one (39) has been identified as one of the many basic components of the scent gland of the Canadian beaver, *Castor fiber* L.<sup>30</sup> Onychine, a new base occurring in the trunk wood of *Onychopetalum amazonicum*, native to the Amazon basin, is to be formulated as (40), chiefly on spectral evidence.<sup>31</sup>



A new synthesis of gentianine (41) has been described (Scheme 11); it is an intermediate in a synthesis of certain *Strychnos* alkaloids.<sup>32</sup>



Reagents: i,  $(\text{CO}_2\text{Et})_2$ , NaH; ii,  $\text{H}^+$ ,  $\text{H}_2\text{O}$ ; iii,  $\Delta$ , DMF, NaCl.

Scheme 11

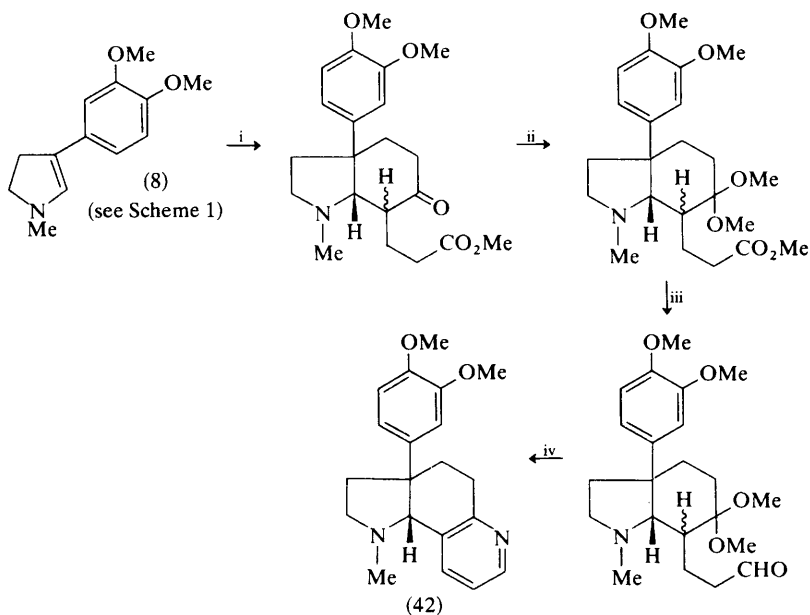
Two total syntheses of sceletium alkaloid A4 (42) have been reported. The first, which involves a rearrangement of a cyclopropylimine to a pyrroline, is condensed in Scheme 12.<sup>5</sup> The general pattern of the second (Scheme 13) is similar.<sup>33</sup>

<sup>30</sup> B. Maurer and G. Ohloff, *Helv. Chim. Acta*, 1976, **59**, 1169.

<sup>31</sup> M. E. L. de Almeida, R. Braz, M. V. von Bülow, O. R. Gottlieb, and J. G. S. Maia, *Phytochemistry*, 1976, **15**, 1186.

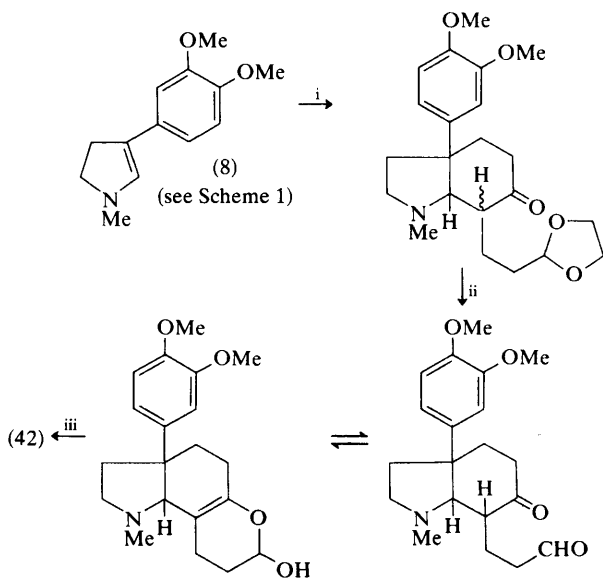
<sup>32</sup> T. Kametani, M. Takeshita, M. Ihara, and K. Fukumoto, *Heterocycles*, 1975, **3**, 627; *J. Org. Chem.*, 1976, **41**, 2542.

<sup>33</sup> C. P. Forbes, J. D. Michau, T. van Ree, A. Wiechers, and M. Woudenberg, *Tetrahedron Letters*, 1976, 935.



Reagents: i,  $\text{MeO}_2\text{C}(\text{CH}_2)_3\text{COCH}=\text{CH}_2$ ,  $\text{MeCN}$ ; ii,  $(\text{MeO})_3\text{CH}$ ,  $\text{H}^+$ ; iii,  $(\text{Me}_2\text{CHCH}_2)_2\text{AlH}$ ; iv,  $\text{NH}_2\text{OH} \cdot \text{HCl}$ ,  $\text{EtOH}$ .

Scheme 12

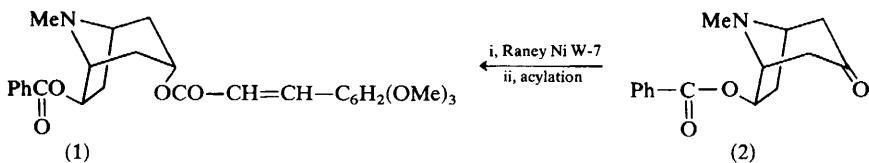


Reagents: i,  $\text{1,3-dioxane}-(\text{CH}_2)_3\text{COCH}=\text{CH}_2$ ,  $\text{MeCN}$ ; ii,  $\text{H}^+$ , dioxan; iii,  $\text{NH}_2\text{OH} \cdot \text{HCl}$ ,  $\text{EtOH}$ .

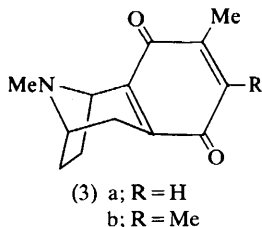
Scheme 13

### 1 Occurrence and Isolation of New Alkaloids

A new tropane heterodiester, tropan-6 $\beta$ -yl-benzoate-3 $\alpha$ -yl-3',4',5'-trimethoxycinnamate (1) has been isolated<sup>1</sup> from the rootbark of *Erythroxylum monogynum*. The relative positions of the ester groups were established by mass spectrometry which by loss of C-6 and C-7 atoms gave rise to an ion  $m/e$  333, corresponding to a 4-(3',4',5'-trimethoxycinnamoyloxy)piperidenium ion that identified the C-3 substituent. The ease of this type of cleavage is also indicative<sup>2</sup> of C-6 and/or C-7 substituted tropanes. Synthesis, from 6 $\beta$ -benzoyloxytropan-3-one (2) by reduction and subsequent acylation led to ( $\pm$ )-(1).



A novel tropane alkaloid, ferrugine (3b),<sup>3</sup> has been isolated from *Darlingia ferrugine* and *Datura darlingiana*, two Queensland plants. The structure (3b) was established by its spectral resemblance with bellendine (3a),<sup>4</sup> isolated from a



Tasmanian plant of the family *Proteaceae*. In addition, the same plant extract afforded a minor alkaloid, C<sub>15</sub>H<sub>19</sub>NO; high-resolution mass spectrometry showed the molecular ion, which by subsequent cleavage lost a benzoyl group, besides the

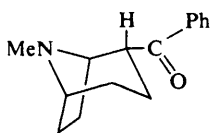
<sup>1</sup> J. T. H. Agar and W. C. Evans, *J. Pharm. Pharmacol.*, 1975, **27**, Suppl., 85P.

<sup>2</sup> E. C. Blossy, H. Budzikiewicz, M. Ohashi, G. Fodor, and C. Djerassi, *Tetrahedron*, 1964, **20**, 585.

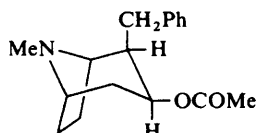
<sup>3</sup> I. R. C. Bick, J. W. Gillard, and M. Woodruff, *Chem. and Ind.*, 1975, 794.

<sup>4</sup> W. D. S. Motherwell, N. W. Isaacs, O. Kennard, I. R. C. Bick, J. B. Brenner, and J. W. Gillard, *Chem. Comm.*, 1971, 133.

usual<sup>2</sup> tropane fragments  $C_5H_8N$  and  $C_6H_9N$ . However, the base peak  $C_6H_{10}N$  indicated the presence of a monosubstituted piperidine ring. The presence of a *C*-benzoyl group was also demonstrated by the u.v., i.r., and  $^1H$  n.m.r. spectra: the latter revealed the appropriate multiplets in the aromatic region. The C-2 proton at  $\delta$  3.25 was an unresolved multiplet which, together with the  $^{13}C$  n.m.r. spectrum, is in agreement with the structure of 2 $\alpha$ -benzoyl-tropane (4). This seems to be closely related to 2-benzyl-3 $\beta$ -acetoxytropane (5) found in the New Caledonian plant,<sup>5</sup> *Knightia deplanchei*, with five other alkaloids; the relative configurations of the first four had been established<sup>6</sup> by  $^{13}C$  n.m.r. spectroscopy.

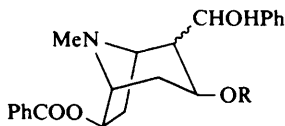


(4)



(5)

Two further representatives (6a and b) of this class have been recently reported both containing a benzhydryl, instead of the benzyl group in position 2 of the tropane skeleton. The structural evidence for (6b) rests on mass spectroscopic data:  $M^+ = 497$  corresponds to  $C_{31}H_{31}NO_5$ . The base peak,  $m/e$  94, is formed either through the loss of  $PhCH(OH)$  from the ion  $m/e$  201 ( $C_{13}H_{15}NO^+$ ) or by loss of cinnamic acid from the ion  $m/e$  242 ( $C_{15}H_{16}NO_2^+$ ), which must itself arise through the molecular ion losing  $PhCOOCH=CH_2$ , again a typical tropane fragmentation of the pyrrolidine ring.



(6) a; R = H  
b; R = cinnamoyl

The 6-hydroxyhyoscyamine which occurs in low concentration (0.005%) in *Datura* species<sup>7</sup> is an intermediate<sup>8</sup> in the *in vivo* conversion of hyoscyamine into hyoscyne. This has now been isolated<sup>9</sup> in a relatively high yield (0.5%) from a *Duboisia* hybrid.

Both *N*-diastereoisomers of hyoscyamine *N*-oxide, (7) and (8), have now been isolated<sup>10</sup> from *Atropa belladonna*. A chemical and mainly  $^1H$  n.m.r. study of those same *N*-oxides has again been undertaken.<sup>11</sup>

<sup>5</sup> M. Lounasmaa, *Planta Med.*, 1975, **27**, 83.

<sup>6</sup> M. Lounasmaa, P. H. Wokulich, and E. Wenkert, *J. Org. Chem.*, 1975, **40**, 3694; *cf.* this series, 1975, Vol. 6, p. 67.

<sup>7</sup> A. Romeike, *Naturwiss.*, 1962, **49**, 476.

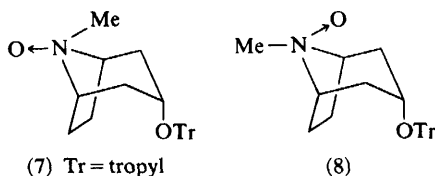
<sup>8</sup> A. Romeike and G. Fodor, *Tetrahedron Letters*, 1960, **22**, 1.

<sup>9</sup> W. J. Griffin, *Naturwiss.*, 1975, **65**, 97.

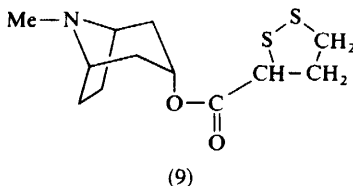
<sup>10</sup> J. D. Phillipson and S. S. Handa, *Phytochemistry*, 1976, **15**, 605.

<sup>11</sup> G. Werner, M. Wiechmann, P. Schreiber, A. Gieren, Th. Fischer, and W. Hoppe, *Annalen*, 1976, 617; *cf.* this series, 1975, Vol. 6, p. 68.





Brugine (9), another unusual tropane alkaloid, was originally discovered in and isolated<sup>12</sup> from the stem bark of *Bruguiera sexangular* Lour in New Guinea. It has now been found<sup>13</sup> in Malaya in *Bruguiera cylindrica* (L.).

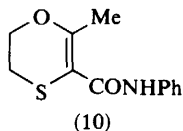


A new patent<sup>14</sup> claims more appropriate extraction of scopolamine and hyoscyamine from *Duboisia Leichardtia*, *D. alba*, and *Scopolia carniolica* by solvent naphtha.

*Duboisia myoporoides* from New Caledonia<sup>15</sup> proved to have the same tropane constituents as the Australian *Duboisia* but in an entirely different proportion: here scopolamine is the major alkaloid, not hyoscyamine.

Mineral fertilization<sup>16</sup> has no apparent effect on alkaloid formation.

Two non-identified tropane alkaloids have been isolated<sup>17</sup> from aerial parts of *Scopolia tangutica*. Correlation between total alkaloid content in *Belladonna* leaves and roots has been made.<sup>18</sup> Regional differences in tropane alkaloid formation of atropine and scopolamine have been studied,<sup>19</sup> using *Atropa belladonna*. Uptake of Vitavax-6 (10) via the <sup>14</sup>C-labelled species was followed in *Datura innoxia*, a



medicinal plant. Only growth was stimulated, however, while alkaloid contents decreased.<sup>20</sup>

<sup>12</sup> J. W. Loden and G. B. Russell, *Tetrahedron Letters*, 1966, 6327.

<sup>13</sup> A. Kato, *Phytochemistry*, 1975, **14**, 1458.

<sup>14</sup> Japan Kokai 75 19 412 (*Chem. Abs.*, 1975, **83**, 65 453).

<sup>15</sup> L. Cosson and J.-C. Vaillant, *Phytochemistry*, 1975, **14**, 818.

<sup>16</sup> L. Stecka, A. Munk-Luczkiewica, and S. Wilk, *Herba Pol.*, 1975, **21**, 17 (*Chem. Abs.*, 1975, **83**, 130 525).

<sup>17</sup> S. A. Minina, T. V. Astakhova, and V. Borisnyuk, *Rastit. Resur.*, 1975, **11**, 493 (*Chem. Abs.*, 1975, **84**, 56 479).

<sup>18</sup> S. Gwiazdzinska and Z. Zakrzewski, *Herba Pol.*, 1975, **21**, 24 (*Chem. Abs.*, 1975, **83**, 20 722).

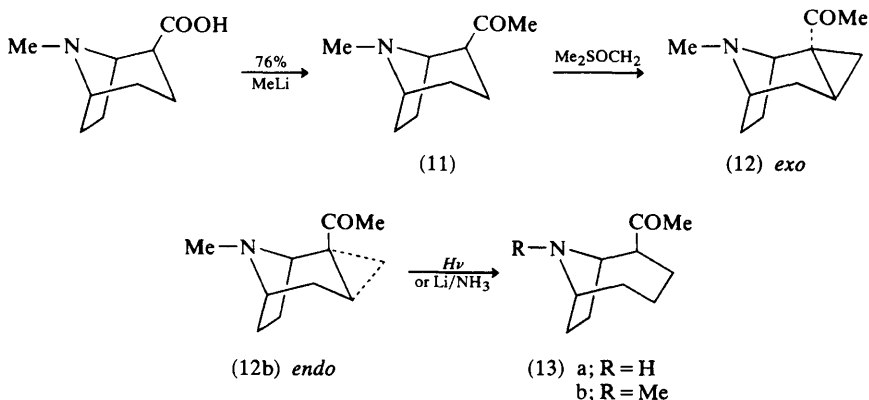
<sup>19</sup> G. Seifert, *Herba Hung.*, 1975, **14**, 23.

<sup>20</sup> G. Verzár-Petri, M. Vincze-Vermes, I. Bálint-Ambró, and T. Szarvas, *Acta Pharm. Hung.*, 1975, **45**, 167.

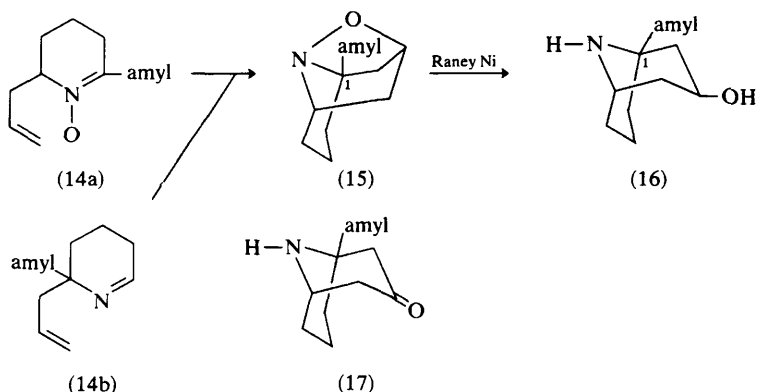
## 2 Synthetic, Chemical, and Pharmacological Studies

The fascinating intramolecular mechanism<sup>21</sup> of 3 $\alpha$ -tropanol (but *not* of 3 $\beta$ ) with benzoyl chloride involving H-transfer has now been published in detail.

Cocaine served as an intermediate in the synthesis<sup>22</sup> of the homotropane anatoxin-a (13b). Anhydroecgonine was converted into the methylketone (11), which was treated with trimethylsulphoxonium methylide; the resultant *endo*-cyclopropane (12b) was subsequently photolysed. Ring cleavage could also be



achieved by reductive fission. *N*-Demethylation with phosgene<sup>23</sup> failed. However, diethyl azodicarboxylate gave the toxic natural product (13b). The alcohol (16) related to another natural homotropane, adaline (17) has been synthesized<sup>24</sup> in several steps. In essence, two isomeric nitrones (14a and b) were cyclized to a bridged hydroxylamine ether (15) and the latter then reductively cleaved into the alcohol (16).



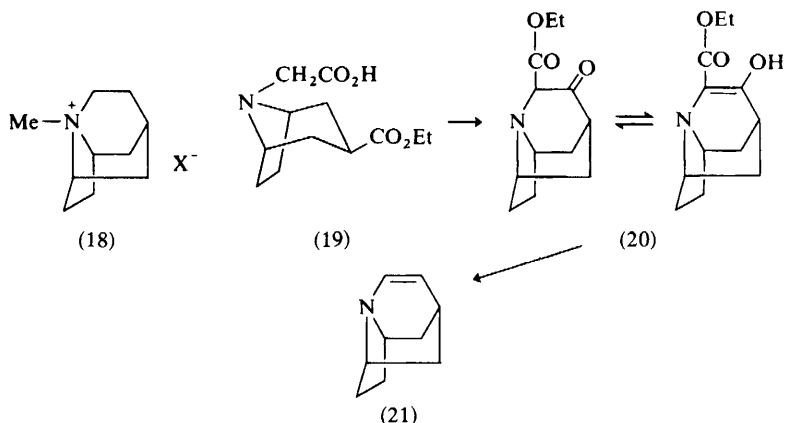
<sup>21</sup> P. J. Kocienski and M. Kirkup, *J. Org. Chem.*, 1975, **40**, 2988.

<sup>22</sup> H. F. Campbell, O. E. Edwards, and R. Kolt, *Canad. J. Chem.*, (in press); private communication to B. Witkop.

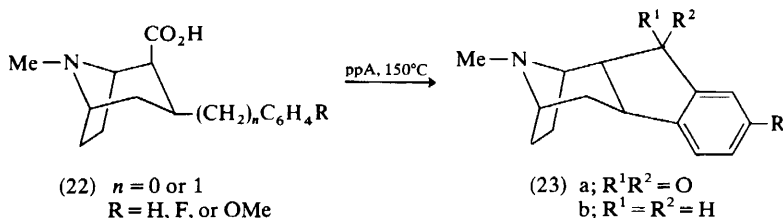
<sup>23</sup> R. Banholzer, A. Heusner, and W. Schulz, *Annalen.*, 1975, 2227.

<sup>24</sup> E. Gossinger, personal communication to B. Witkop.

Tropaquinuclidine (18) has been synthesized<sup>25</sup> from 3-tropanecarboxylic acid *via* 3β-tropanylmethylchloride. Tropanehydroquinuclidine (21) was obtained by keto-ester condensation of (19) to (20) and subsequent deoxygenation of the ring to (21).



Cyclization of the carboxylic acids (22) gave ketones (23a) which, through reaction of the dithioketals with diborane, gave rise to local anesthetic activity.<sup>26</sup>



Preferred quaternization of selected heterocycles<sup>27</sup> was studied by  $^1\text{H}$ ,  $^2\text{H}$ , and  $^{13}\text{C}$  n.m.r. spectroscopy which indicated that the negative  $\Delta G$  value is consistent with equatorial attack in tropanes, in agreement with previous  $^1\text{H}$ <sup>28</sup> and  $^{13}\text{C}$ <sup>29</sup> n.m.r. studies.

The stability<sup>30</sup> of tropic acid amide has been investigated; tropic acid itself is a major esterifying acid in many natural tropanes.

The first thiadesazatropane was synthesized from 3-tropanone methiodide,<sup>31</sup> and now the addition of sulphur dichloride<sup>32</sup> to cycloheptadienol (24) has given 6α,7α-dichloro-8-thiabicyclo[3,2,1]octan-3-ol (25). However, the diene acetal (26a) and the dienone (26b) gave rise to thiabicyclo[3,2,1]octanes (27) and not to the tropane isologues.

<sup>25</sup> W. Schneider, B. Lang, and F. Schumann, *Arch. Pharm.*, 1976, **309**, 447.

<sup>26</sup> R. L. Clarke and S. J. Daun, U.S. P. 3 901 892 (*Chem. Abs.*, 1975, **84**, 5227).

<sup>27</sup> A. J. Jones, C. P. Beeman, A. F. Casy, and M. Hasan, *Canad. J. Chem.*, 1976, **54**, 126.

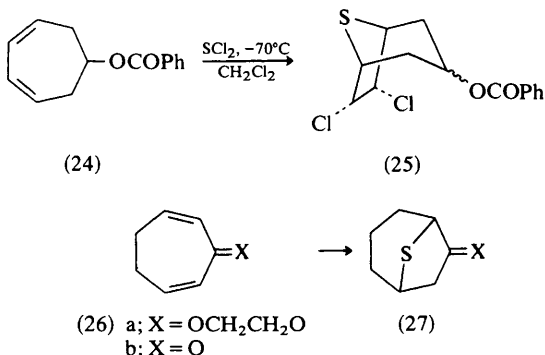
<sup>28</sup> G. Fodor, G. V. Chartain, jun., D. Frehel, M. J. Cooper, N. Mandava, and E. L. Gooden, *J. Amer. Chem. Soc.*, 1971, **93**, 403.

<sup>29</sup> E. Wenkert, private communication to this Reporter.

<sup>30</sup> A. Goeber, U. Timm, S. Wendtland, S. Pfeifer, and R. Kraft, *Pharmazie*, 1975, **30**, 610.

<sup>31</sup> V. Horak, J. Zavada, and A. Piskala, *Chem. and Ind.*, 1958, 1113.

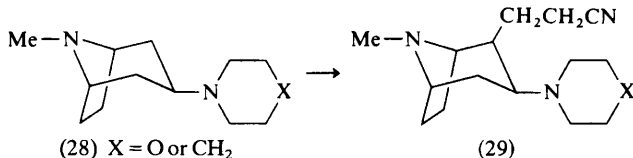
<sup>32</sup> P. H. McCabe and W. Routledge, *Tetrahedron Letters*, 1976, 85.



A number of quaternary tropanium salts have been synthesized<sup>33,34</sup> in order to find new pharmacokinetic effects. Bronchoselectivity of *N*-isopropylatropinium bromide is very pronounced,<sup>33</sup> and it also causes a fall in blood pressure.<sup>34</sup>

Active benzhydrylethers of sterically hindered amino-alcohols, *e.g.* of tropanols, have been obtained by a new technique.<sup>35</sup>

Tropinone enamines (28) have been prepared,<sup>36</sup> with morpholine and piperidine respectively, and cyanoethylation of (28) gives the 2- $\beta$ -cyanoethyl derivative (29). On the other hand, quaternization with methyl iodide of (28) gave the quaternary salt showing adrenolytic and antihistaminic activity.



Labelled tropanes, particularly ring radiolabelled cocaines,<sup>37</sup> have been described. A technical synthesis of some tropane derivatives from agricultural waste *via* 2,5-dimethoxyfuran,<sup>38</sup> followed by hydrogenation to 2,5-dimethoxytetrahydrofuran, has been elaborated.

### 3 Analytical

A charge-transfer spectrophotometric method<sup>39</sup> has been developed for unit-dose assay of the tropane alkaloids and some of their synthetic analogues. The high molar adsorptivities of the charge-transfer bands of the alkaloids with iodine in ethylene chloride give high precision even at low doses, such as in hypodermic and pediatric tablets.

<sup>33</sup> W. Deckers, *Postgrad. Med. J.*, 1975, **51** (Suppl. 7), 76.

<sup>34</sup> A. Engelhardt and H. Klupp, *Postgrad. Med. J.*, 1975, **51** (Suppl. 7), 82.

<sup>35</sup> O.-E. Schultz, D. Haber, and P. Kiessner, *Arch. Pharm.*, 1976, **309**, 234.

<sup>36</sup> R. G. Glushkov, N. I. Koretskaya, A. I. Ermanov, G. Shwartz, and M. D. Mashkovskii, *Khim.-Farm. Zhur.*, 1975, **9**, 6.

<sup>37</sup> H. M. Grotta, A. F. Fentiman, jun., and B. G. Sherwood, *U.S. NTTS AD Report*, 1974, No. 008434 (*Chem. Abs.*, 1975, **83**, 17 9342).

<sup>38</sup> M. P. Jain, R. S. Takur, and P.R. Rao, *Res. Ind.* 1975, **20**, 3 (*Chem. Abs.*, 1975, **83**, 193 562).

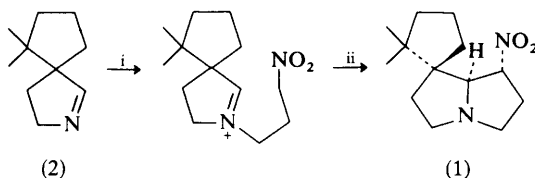
<sup>39</sup> C. Goma and A. Taha, *J. Pharm. Sci.*, 1976, **65**, 1398.

*Duboisia* samples have been analysed<sup>40</sup> for scopolamine and hyoscyamine, using g.l.c. by a slope ratio method and by methods employing homatropine, tetraphenylethylene, and phenylacetyltropine as internal standards. The alkaloids were converted into their trimethylsilyl ethers with hexamethyldisilazane; scopolamine was the major component, followed by hyoscyamine and norhyoscyamine, meteloidine, phenylacetyltropeine, and valeroidine, tigloidine, valtropine, butropine, and acetyltropine, together with some anabasine and nicotine as non-tropane bases.

<sup>40</sup> W. J. Griffin, H. P. Arand, and J. G. Dare, *J. Pharm. Sci.*, 1975, **64**, 1822.

### 1 The Necine Bases

The structure and absolute configuration of nitropolizonamine (1), a component of the defensive secretion of the millipede *Polyzonium rosalbum* has been elucidated by X-ray crystallography.<sup>1</sup> Nitropolizonamine (1) occurs together with polyzonimine (2) from which it was synthesized by alkylation with 1-iodo-3-nitropropane followed by cyclization in boiling pyridine (Scheme 1). Since polyzonimine is clearly monoterpenoid, the obvious biogenetic relationship between nitropolizonamine (1) and polyzonimine (2) places the former in a biogenetic class distinct from that of the majority of pyrrolizidine bases of plant origin, which are derived from ornithine.



Reagents: i,  $\text{O}_2\text{NCH}_2\text{CH}_2\text{I}$ ; ii,  $\text{C}_5\text{H}_5\text{N}$ .

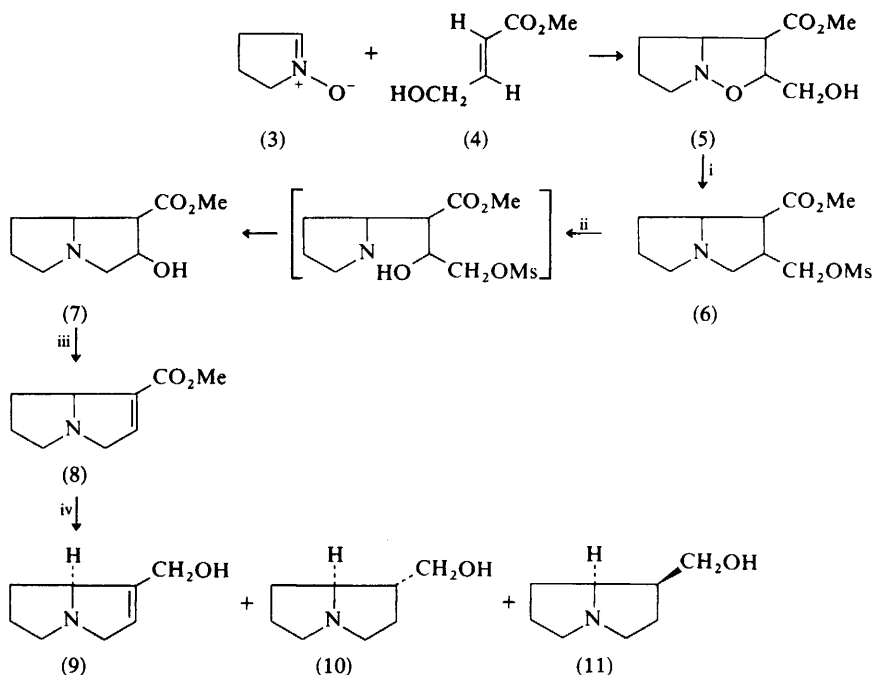
**Scheme 1**

Tufariello and Tette<sup>2</sup> have used the 1,3-dipolar reactivity of 1-pyrroline-1-oxide (3) in an elegant synthesis of supinidine (9). The adduct (5) with the hydroxycrotonate ester (4) was formed in 80% yield. Hydrogenolysis of the corresponding mesylate (6) gave the hydroxypyrrolizidine (7) from which  $(\pm)$ -supinidine (9) was obtained by dehydration to the ester (8) followed by reduction (Scheme 2). In addition to  $(\pm)$ -supinidine, two other compounds were produced in the final step. These were provisionally identified as  $(\pm)$ -trachelanthamidine (10) and  $(\pm)$ -isoretronecanol (11).  $(\pm)$ -[6- $^3\text{H}_2$ ]Dehydroheliotridine (13) has been synthesized<sup>3</sup> by base-catalysed exchange of the C-6 protons in the dihydropyrrolizine ketone (12) followed by borohydride reduction (Scheme 3). The labelled necine (13) was used to investigate the binding of dehydroheliotridine to macromolecules (see below).

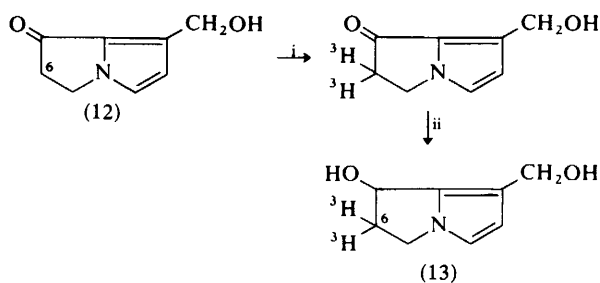
<sup>1</sup> J. Meinwald, T. Smolanoff, A. T. McPhail, R. W. Miller, T. Eisner, and K. Hicks, *Tetrahedron Letters*, 1975, 2367.

<sup>2</sup> J. F. Tufariello and J. P. Tette, *J. Org. Chem.*, 1975, **40**, 3866.

<sup>3</sup> C. C. Curtain and J. A. Edgar, *Chem.-Biol. Interactions*, 1976, **13**, 243.



Scheme 2

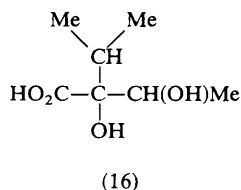
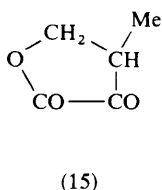


Reagents: i,  $^3\text{H}_2\text{O}$ ,  $\text{K}_2\text{CO}_3$ ; ii,  $\text{NaBH}_4$ .

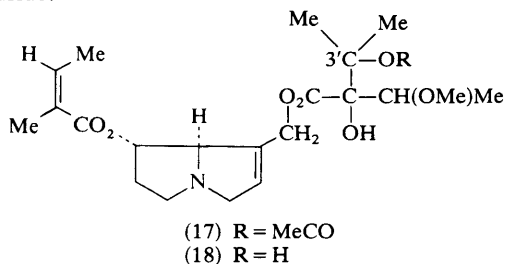
Scheme 3

## 2 The Necic Acids

Male butterflies of the nymphalid subfamilies Ithomiinae and Danainae produce hairpencil secretions which often contain pyrrolizidine derivatives derived from pyrrolizidine alkaloid containing plants on which the butterflies feed. The hairpencils are used during courtship to subdue and seduce females. Most Ithomiinae also possess an erectile fringe of hairs on the costal margins of their hindwings which

$$\begin{array}{c}
 \text{Me} \\
 | \\
 \text{CH}_2 - \text{C} - \text{CH(OH)Me} \\
 / \quad | \quad | \\
 \text{O} \quad \text{CO} \quad \text{OH}
 \end{array}
 \quad (14)$$


Re-examination of the alkaloids of *Heliotropium europaeum* has revealed the presence of a new alkaloid, acetylasiocarpine (17) as a minor component.<sup>5</sup> The alkaloid could not be crystallized, but gave lasiocarpine (18) on partial hydrolysis. Proof that the acetoxy group was attached to C-3' was obtained from the <sup>13</sup>C n.m.r. spectrum, which showed a downfield acylation shift of approximately 12 p.p.m. for C-3' by comparison with the corresponding signal in the spectrum of lasiocarpine (18). Acetylasiocarpine (17) was regenerated from lasiocarpine (18) by acetylation with acetic anhydride.



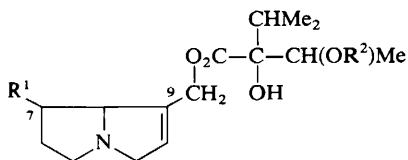
<sup>4</sup> J. A. Edgar, C. C. J. Culvenor, and T. E. Pliske, *J. Chem. Ecol.*, 1976, **2**, 263.

<sup>5</sup> C. C. J. Culvenor, S. R. Johns, and L. W. Smith, *Austral. J. Chem.*, 1975, **28**, 2319.

<sup>6</sup> E. Pedersen, *Arch. Pharm. Chem. Sci. Ed.*, 1975, **3**, 55.



data which may be obtained by the application of this technique include the constitution of the necine base, the constitutions of simple necic acids that may be present and identification of the hydroxy group usually at C-7 or C-9, [cf. (19)] to which the necic acids are attached. Unambiguous evidence as to stereochemistry cannot, however, be obtained using this technique alone. Within the limitations of this approach, Pedersen has demonstrated the presence of alkaloids with constitutions (19)–(25) in various combinations in the species examined (Table 1). Of

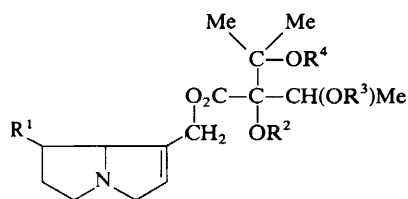


(19)  $R^1 = H$ ,  $R^2 = H$  (i.e. supinine or stereoisomer)

(20)  $R^1 = OH$ ,  $R^2 = H$  (i.e. echinatine or stereoisomer)

(21)  $R^1 = MeCO_2$ ,  $R^2 = H$

(22)  $R^1 = (Z)\text{-MeCH=C(Me)CO}_2$ ,  $R^2 = H$



(23)  $R^1 = OH$ , either  $R^2$  or  $R^3$  or  $R^4 = MeCO$

(24)  $R^1 = (Z)\text{-MeCH=C(Me)CO}_2$ ,  $R^2 = R^3 = R^4 = OH$  (i.e. heliosupine or a stereoisomer)

(25)  $R^1 = (Z)\text{-MeCH=C(Me)CO}_2$ , either  $R^2$  or  $R^3$  or  $R^4 = MeCO$

**Table 1** Alkaloids of Danish species of the Boraginaceae

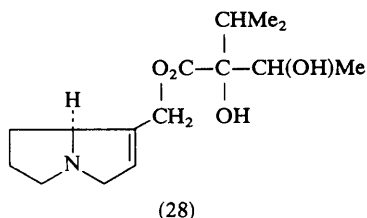
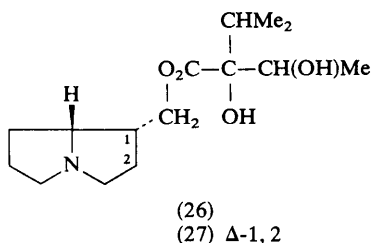
Species	Alkaloid <sup>a</sup>						
	19	20	21	22	23	24	25
<i>Asperugo procumbens</i> L.	+	+					
<i>Anchusa arvensis</i> (L.) Bieb		+					
<i>Anchusa officinalis</i> L.		+	+				
<i>Cynoglossum officinale</i> L.		+				+	+
<i>Echium vulgare</i> L.		+				+	+
<i>Symphytum officinale</i> L.		+	+	+			
var. <i>ochroleucum</i> DC							
<i>Symphytum</i> × <i>uplandicum</i> Nyman			+	+		+	
<i>Symphytum asperum</i> Lepechin			+			+	+
<i>Symphytum officinale</i> L.			+	+		+	
<i>Lithospermum officinale</i> L.					+		

<sup>a</sup> Constitutional formulae only, stereoisomers were not distinguished.

interest is the common occurrence of acetylated derivatives. The alkaloids occurred as mixtures of the free base and corresponding *N*-oxide. From the Indian species *Cynoglossum lanceolatum* Forsk., cynaustaline (26) and cynaustine (27) have been isolated, whereas *C. glochidiatum* Wall. ex Lindl yielded amabiline (28). Amabaline (28) was also isolated from another Boraginaceous species, *Lindelofia angustifolia* (Schrenk) A. Brand. together with echinatine (20).<sup>7</sup> From *Eupatorium cannabinum* L., echinatine (20) and supinine (19) have been isolated.<sup>8</sup> *Eupatorium* belongs to the family Compositae but, as in the present example, species of this genus have consistently been found to contain alkaloids typical of those occurring in alkaloid-

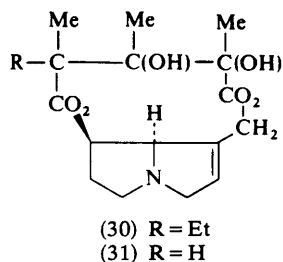
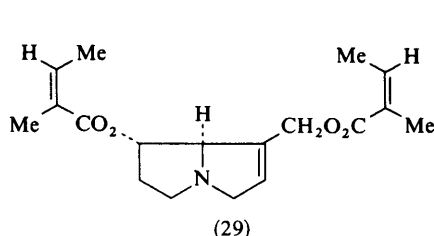
<sup>7</sup> K. A. Suri, R. S. Sawhney, and C. K. Atal, *Indian J. Pharm.*, 1975, **37**, 69.

<sup>8</sup> E. Pedersen, *Phytochemistry*, 1975, **14**, 2086.

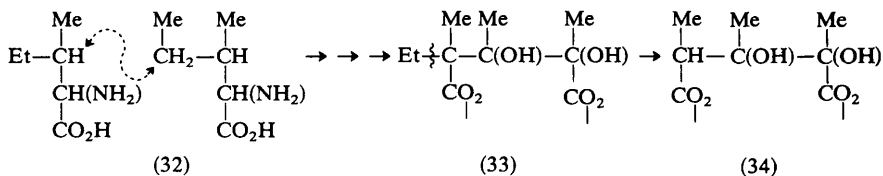


producing genera of the family Boraginaceae; the macrocyclic diester alkaloids characteristic of the taxonomically more closely related genus *Senecio* are absent. Asperumine (29) and its *N*-oxide have been isolated from *Echium vulgare* in addition to the previously identified heliosupine.<sup>9</sup>

In last year's report the occurrence of a new alkaloid, crotalarine (30), from *Crotalaria burhia* Buch.-Ham., was reported. Atal *et al.*<sup>10</sup> have also reported the presence in this species of an alkaloid, croburhine, which is clearly identical with crotalarine (30). The observation<sup>10</sup> that monocrotaline (31) also occurs in *C. burhia*



is biogenetically significant in that all eight carbon atoms of monocrotalic acid, (34) the necic acid component of monocrotaline (31), are derived from isoleucine (32), an observation that would be readily accommodated by a biogenesis from isoleucine (32) *via* the necic acid from crotalarine (33) with reductive loss of the ethyl group (Scheme 4).

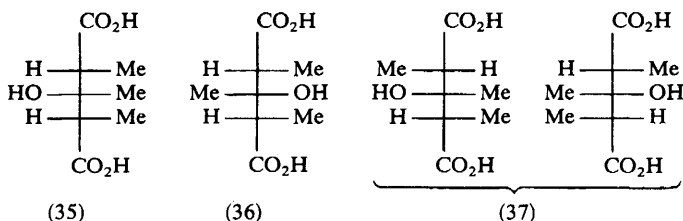


Scheme 4

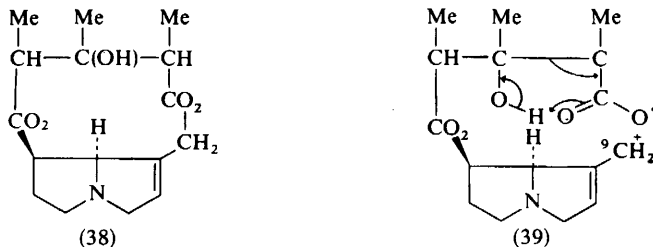
There are four stereoisomers of 3-hydroxy-2,3,4-trimethylglutaric acid [(35)—(37)]. The two *meso* forms, fulvinic (35) and crispatic (36) acids are the esterifying acids of the alkaloids fulvine and crispatine respectively. Now the two remaining

<sup>9</sup> A. Karimov, M. V. Telezhenetskaya, K. L. Lutfullin, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, **11**, 433.

<sup>10</sup> P. G. Rao, R. S. Sawhney, and C. K. Atal, *Indian J. Chem.*, 1975, **13**, 835.



isomers, the enantiomers (37), have been found as the necic acid components of two new *Crotalaria* alkaloids cromadurine<sup>11</sup> and isocromadurine<sup>12</sup> from *Crotalaria madurensis* R. Wight. As in fulvine and crispatine, the necic acids are esterified to retronecine. All four isomers thus have the constitution (38). The absolute configurations of cromaduric and isocromaduric acids (37) and their mode of esterification to retronecine in cromadurine and isocromadurine remain to be elucidated. The proposed constitutions of cromadurine and isocromadurine were fully supported by analytical and spectroscopic data. In the mass spectrometer the molecular ions underwent the usual cleavage at the C-9 allylic ester function followed by the characteristic McLafferty rearrangement (39) to give an abundant ion of  $m/e$  236 as in the mass spectra of structurally related alkaloids. Alkaline hydrolysis of the alkaloids gave retronecine, and cromaduric and isocromaduric acids (37) respectively. The necic acids had identical melting points, n.m.r. and i.r. spectra, but opposite optical rotations.



The mode of attachment of the necic acid in crotastratine (from *Crotalaria striata*) to the necine (retronecine) has been investigated.<sup>13</sup> Hydrogenolysis of crotastratine gave a product, presumably the zwitterion (41) the i.r. spectrum of which indicated the presence of an intact  $\alpha\beta$ -unsaturated ester function, confirming the mode of attachment as in (40). Crotastratine (40) is the acetate of nilgirine (42) which has also been found in *Crotalaria striata* (= *C. mucronata*). Acetylation of nilgirine (42) with acetic anhydride-perchloric acid gave crotastratine (40).

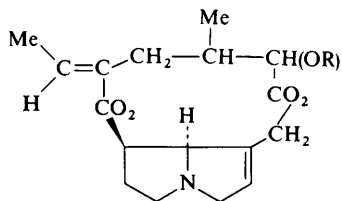
A further isomer of senkirkine (43), crotaverrine, has been isolated from *Crotalaria verrucosa* Linn.<sup>14</sup> The spectroscopic properties and analytical data were consistent with a constitution for crotaverrine isomeric with that of senkirkine (43). The configuration about the C-15=C-16 double bond could not be determined unambiguously from the n.m.r. spectrum since the chemical shift of the C-16 vinyl

<sup>11</sup> P. G. Rao, R. S. Sawhney, and C. K. Atal, *Indian J. Chem.*, 1975, **13**, 870.

<sup>12</sup> P. G. Rao, R. S. Sawhney, and C. K. Atal, *Experientia*, 1975, **31**, 878.

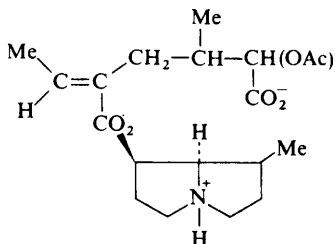
<sup>13</sup> V. Batra, R. N. Gandhi, and T. Rajagopalan, *Indian J. Chem.*, 1975, **13**, 989.

<sup>14</sup> O. P. Suri, R. S. Sawhney, M. S. Bhatia, and C. K. Atal, *Phytochemistry*, 1976, **15**, 1061.

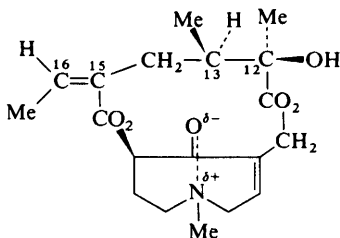


(40) R = MeCO

(42) R = H

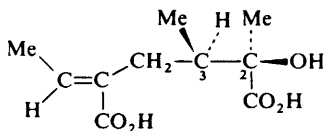


(41)

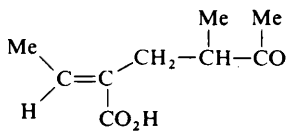


(43)

proton signal at  $\tau$  3.9 was intermediate between the normally observed values for analogous alkaloids having either the E- or Z-configuration. However, in the n.m.r. spectrum of the necic acid obtained on mild alkaline hydrolysis of crotaverrine, this proton gave a signal at  $\tau$  2.96 thereby establishing the E-configuration about the C-15=C-16 double bond. The necic acid and the corresponding lactone obtained on acid hydrolysis of crotaverrine differed from integerrineic acid (44) and its lactone respectively. However, lead tetra-acetate oxidation of the necic acid gave a keto acid (45) the 2,4-dinitrophenylhydrazone of which had the same i.r. spectrum and melting



44



(45)

point as the corresponding derivative prepared from integerrineic acid. The mixed melting point showed no depression. The necic acid from crotaverrine and the corresponding lactone had properties closely similar to those reported for a synthetic diastereoisomer of integerrineic acid which had either the 2*R*,3*S*- or the 2*S*,3*R*-configuration.<sup>15</sup> It was concluded that crotaverrine differed from senkirine (43) in having the E-configuration about the C-15=C-16 double bond and in having the opposite absolute configuration at either C-12 or C-13. The absence of a depression or elevation of the mixed melting point of the 2,5-dinitrophenylhydrazones mentioned above, makes the former alternative the more probable. Acid hydrolysis of

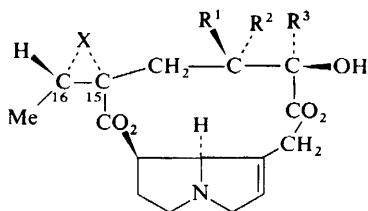
<sup>15</sup> J. D. Edwards and T. Matsumoto, *J. Org. Chem.*, 1967, **32**, 1837.

crotaverrine gave otonecine hydrochloride. Crotaverrine was accompanied in *C. verrucosa* by *O*-acetylcrotaverrine, the structure of which was confirmed by its formation on acetylation of crotaverrine.

Neosenkirkine, a new alkaloid isolated from *Senecio auricola* Bourg. has been shown to differ from senkirkine (43) in the configuration about the C-15=C-16 double bond.<sup>16</sup> This assignment, made on the basis of the chemical shift ( $\tau$  3.22) of the C-16 vinyl proton, was confirmed by hydrolysis of neosenkirkine to integerrinic acid (44) and otonecine. Integerrimine (46) was detected as the sole alkaloid produced by *Senecio durieui* Gay.<sup>16</sup>

The alkaloids of *Senecio cineraria* DC of Czechoslovakian provenance have been examined.<sup>17</sup> In addition to the alkaloids jacobine (47), senecionine (48) and seneciphylline (49) previously reported as occurring in this species, retrorsine (50) was also found. Otosenine, previously found in an Egyptian collection of *S. cineraria*<sup>18</sup> was not present. *Tussilago farfara* L. (coltsfoot, family Compositae) has been used in medicine from antiquity. The young flowers, which are used medicinally in China and Japan, have been shown to contain the hepatotoxic alkaloid senkirkine (43) at levels of 0.015%.<sup>19</sup> Two-thirds of a group of rats fed on a diet containing 32% pre-blooming flowers of *T. farfara* developed liver tumours.<sup>20</sup>

Integerrimine (46) and usaramine (51) have been isolated from *Crotalaria intermedia* Kotschy.<sup>21</sup>



- (46) X = (*E*)- $\Delta^{15,16}$ ,  $R^1 = R^3 = \text{Me}$ ,  $R^2 = \text{H}$   
 (47) X = O,  $R^1 = R^3 = \text{Me}$ ,  $R^2 = \text{H}$   
 (48) X = (*Z*)- $\Delta^{15,16}$ ,  $R^1 = R^3 = \text{Me}$ ,  $R^2 = \text{H}$   
 (49) X = (*Z*)- $\Delta^{15,16}$ ,  $R^1, R^2 = \text{CH}_2$ ,  $R^3 = \text{Me}$   
 (50) X = (*Z*)- $\Delta^{15,16}$ ,  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ,  $R^3 = \text{CH}_2\text{OH}$   
 (51) X = (*E*)- $\Delta^{15,16}$ ,  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ,  $R^3 = \text{CH}_2\text{OH}$

#### 4 General Studies

Australian workers have prepared a number of semisynthetic pyrrolizidine esters as part of a major investigation of pyrrolizidine alkaloid toxicity.<sup>22</sup> 7,9-Diacetylheliotridine (52), 7-acetylheliotridine (53), 7,9-divalerylheliotridine (54), and 7-pivalyl-(55), 9-pivalyl-(56) and 7,9-dipivalylheliotridine (57) were prepared by acylation of heliotridine with the appropriate acid chloride. The three last-

<sup>16</sup> F. Martin Panizo and B. Rodriguez, *Anales de Quim.*, 1974, **70**, 1043.

<sup>17</sup> A. Klásek, V. A. Mnatskanyan, and F. Šantavý, *Coll. Czech. Chem. Comm.*, 1975, **40**, 2524.

<sup>18</sup> M. A. Habib, *Planta Med.*, 1974, **26**, 279.

<sup>19</sup> C. C. J. Culvenor, J. A. Edgar, L. W. Smith, and I. Hirono, *Austral. J. Chem.*, 1976, **29**, 229.

<sup>20</sup> I. Hirono, H. Mori, and C. C. J. Culvenor, *Gann*, 1976, **67**, 125.

<sup>21</sup> K. A. Suri, R. S. Sawhney, and C. K. Atal, *Indian J. Pharm.*, 1975, **37**, 96.

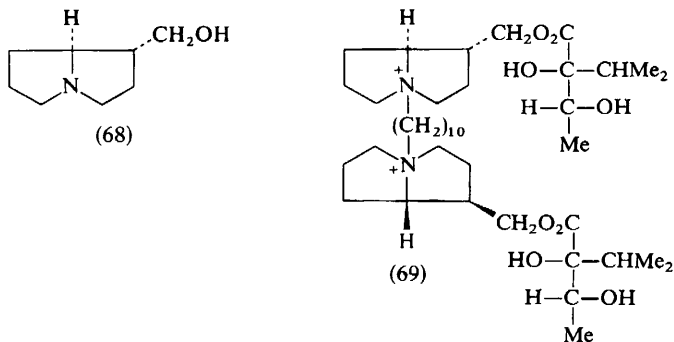
<sup>22</sup> C. C. J. Culvenor, J. A. Edgar, M. V. Jago, A. Outteridge, J. E. Peterson, and L. W. Smith, *Chem.-Biol. Interactions*, 1976, **12**, 299.



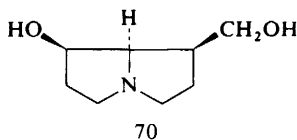
cyanide and methanol to the corresponding methyl ester, which was then reduced to  $[9\text{-}^3\text{H}_2]\text{retronecine}$  with  $[^3\text{H}]\text{lithium aluminium hydride}$ .

Semisynthetic amides of retronecine (66), itself prepared from retronecine (65) in three steps,<sup>24</sup> have been synthesized by coupling with the appropriate acid using  $NN'$ -dicyclohexylcarbodi-imide. Several of the compounds prepared, notably the *p*-hydroxybenzoyl-, cinnamoyl-, and benzoyl-retronecines, had marked hypotensive activity. The amides could not be crystallized and details of their characterization were not given. Atal and his co-workers have also prepared<sup>25,26</sup> a number of semisynthetic diesters of retronecine, heliotridine, and platynecine by esterification of the necine base with the appropriate acid chloride. Several of the compounds prepared had marked local anaesthetic activity.

Russian workers have prepared for pharmacological studies simple carbamates of trachelanthamidine (68) by treatment with the appropriate isocyanate.<sup>27</sup> Some cholinesterase inhibitors based on the standard decamethonium model have been prepared.<sup>28</sup> Decamethylene bistrachelanthamine dibromide (69) showed marked curare-like activity in cats and rabbits. New procedures for the iodometric determination of platyphylline bitartrate<sup>29</sup> and for the colorimetric determination<sup>30</sup> of trichodesmine and incanine in the organs of poisoned animals have been described.



The u.v. spectra of 20 pyrrolizidine mono- and diesters have been studied.<sup>31</sup> The semisynthetic esters were prepared by acylation of retronecine (65) and platynecine (70). Details of their characterization were not given. The necines in hexane showed



<sup>24</sup> P. G. Rao, R. S. Sawhney, O. P. Gupta, and C. K. Atal, *Indian J. Pharm.*, 1975, **37**, 127.

<sup>25</sup> O. P. Suri, R. S. Sawhney, and C. K. Atal, *Indian J. Pharm.*, 1975, **37**, 36.

<sup>26</sup> O. P. Gupta, M. Mohd, A. B. J. R. Ghatak, and C. K. Atal, *Indian J. Exp. Biol.*, 1976, **14**, 34.

<sup>27</sup> K. Sakhidoyatov, F. Kiyamitdinova, and C. S. Kadyrov, *Khim. prirod. Soedinenii*, 1975, **11**, 765.

<sup>28</sup> F. S. Sadritdinov, I. Khamdamov, and B. Rustamov, *Doklady Akad. Nauk Uz. S.S.R.*, 1974, **31**, 22.

<sup>29</sup> P. P. Suprun, *Farm. Zhur. (Kiev)*, 1975, **30**, 47.

<sup>30</sup> M. V. Ikramova, *Mater. Yubileinoi Resp. Nauchn. Konf. Farm., Posvyashch. 50-Letiye Obyaz. S.S.S.R.*, Sep. 1972, ed. Kh. Kh. Khalmatov, 1972 (*Chem. Abs.* 1975, **83**, 38336r).

<sup>31</sup> V. P. Gupta, S. K. Handoo, and R. S. Sawhney, *Indian J. Pure Appl. Physics*, 1975, **13**, 776.

three absorption bands, at 206, 225.6, and 266.9 nm for platynecine (70) and 206, 230.8, and 266.9 nm for retronecine (65). The long wavelength bands were much less intense than the short wavelength bands. In methanol, both necines gave a single band, which, in the case of retronecine (65) was concentration dependent, undergoing a hypsochromic shift on dilution. The limiting absorption maximum was found to lie near 210 nm. The conclusion that this blue shift was attributable to increased hydrogen bonding between solvent and the nitrogen atom of the base on changing the solute concentration from 2.27 to 0.1387 mmol is questionable. The observations are more reasonably attributable to decreasing solute-solute interaction on dilution. The spectra of the esters showed little perturbation of the bands attributable to the simple necines. Additional bands due to the acidic components were observed.

## 5 Pharmacological and Biological Studies

Mattocks<sup>32</sup> has reviewed the metabolic activation of pyrrolizidine alkaloids. Schoental<sup>33</sup> has amplified her hypothesis that the acute effects of pyrrolizidine alkaloid toxicity are due to the alkylation of coenzymes. A summary of the physiological activity and biosynthesis of the pyrrolizidine alkaloids has appeared.<sup>34</sup>

In a major investigation of pyrrolizidine alkaloid toxicity, Australian workers have used a test procedure in which single doses of alkaloid were administered to 14 day old rats.<sup>22</sup> Among the new findings emerging from this study were that diesters of retronecine (66) and its 7 $\alpha$ -stereoisomer heliotridine are about four times as toxic as their corresponding monoesters and that heliotridine esters are two to four times as toxic as corresponding retronecine esters (a quantitative statement of a qualitative relationship previously pointed out by Schoental). 9-Pivalyl- and 7,9-dipivalylheliotridine, the  $\alpha$ - and  $\beta$ -epoxides of monocrotaline, 7-angelyl-1-methylenepyrrolizidine and the methiodides of monocrotaline and senecionine were found to be non-toxic. Chronic lung lesions were produced by most of the hepatotoxic alkaloids.

The pulmonary oedema produced in rats by dehydromonocrotaline has been studied by electron microscopy.<sup>35</sup> Tritiated dehydroretronecine has been used in studies of the binding of this metabolite to macromolecules.<sup>36,37</sup> Studies *in vivo* with rhesus monkeys revealed preferential binding of dehydroretronecine to the protein of gastric mucosa. Much less radioactivity was found associated with RNA and DNA. Binding *in vitro* to calf thymus DNA and bovine serum albumin took place most readily under acidic conditions. Tritiated dehydroheliotridine has been used to study the preferential depression of satellite DNA synthesis by this metabolite in cultured sheep lymphocytes and ovine kidney cells.<sup>3</sup> The mechanism of the antimitotic action of lasiocarpine and dehydroheliotridine has been investigated in

<sup>32</sup> A. R. Mattocks, 'Proc. 11th Internat. Cancer Congr.', Florence, 1974, *Excerpta Med. Internat. Congr. Ser. No. 350*, Excerpta Medica, Amsterdam, 1975, Vol. 2, *Chem. Viral Oncogenesis*, p. 20.

<sup>33</sup> R. Schoental, *F.E.B.S. Letters*, 1976, **61**, 111.

<sup>34</sup> D. H. G. Crout, *Chimia (Switz.)*, 1976, **30**, 270.

<sup>35</sup> J. V. Hurley and M. V. Jago, *J. Path.*, 1975, **117**, 23.

<sup>36</sup> I. C. Hsu, K. A. Robertson, R. C. Shumaker, and J. R. Allen, *Res. Comm. Chem. Path. Pharmacol.*, 1975, **11**, 99.

<sup>37</sup> I. C. Hsu, K. A. Robertson, and J. R. Allen, *Chem.-Biol. Interactions* 1976, **12**, 19.



rat liver parenchymal cells and possible locations of the mitotic block identified.<sup>38</sup> Repair-deficient strains of *Escherichia coli* have been used to detect and characterize DNA damage caused by heliotrine and monocrotaline. These alkaloids were not mutagenic in bacteria.<sup>39</sup>

The continuing losses of cattle, sheep and horses in many countries, due to *Senecio* poisoning, have stimulated further investigations of the toxicity of various *Senecio* species towards cattle and sheep.<sup>40-42</sup> The persistent dangers arising from the contamination of flour by *Trichodesma incanum*,<sup>43</sup> the principal alkaloids of which trichodesmine and incanine, are potent hepatotoxins, has stimulated efforts in the Soviet Union to find sensitive analytical procedures for these alkaloids. It has now been shown<sup>44</sup> that guppies are very sensitive towards trichodesmine and extracts of *T. incanum* seeds, concentration of 0.001% being lethal within a few hours. This response has been proposed as a bioassay for *T. incanum* contamination of food-stuffs.

The complex relationship between certain genera of butterflies belonging to the nymphalid subfamilies Danainae and Ithomiinae, and pyrrolizidine alkaloid containing plants has been discussed.<sup>45</sup> As well as using alkaloids as precursors of pheromones, male butterflies are believed to use pyrrolizidine alkaloids to produce compounds used for territory marking (see above).

<sup>38</sup> A. Samuel and M. V. Jago, *Chem.-Biol. Interactions*, 1975, **10**, 185.

<sup>39</sup> M. H. L. Green and W. J. Muriel, *Mutation Res.*, 1975, **28**, 331.

<sup>40</sup> P. H. Mortimer and E. P. White, *Proc. New Zealand Weed Control Conf.*, 1975, **28**, 88.

<sup>41</sup> A. E. Johnson, *Amer. J. Vet. Res.*, 1976, **37**, 107.

<sup>42</sup> P. R. Cheeke and G. R. Garman, *Nutr. Rep. Internat.*, 1974, **9**, 197.

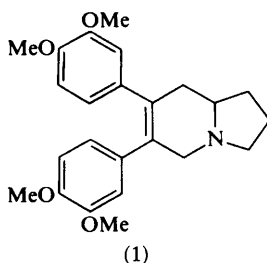
<sup>43</sup> M. V. Ikramova, *Med. Zhur. Uzbekistana*, 1972, **4**, 71.

<sup>44</sup> S. I. Arutyunyan, *Tr. Uzbesk. Nauchn. Vet. Inst.*, 1973, **23**, 47 (*Chem. Abs.*, 1975, **83**, 202578).

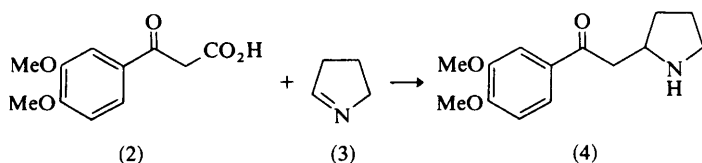
<sup>45</sup> J. A. Edgar, *Phil. Trans. B.*, 1975, **272**, 467.

### 1 *Tylophora* Alkaloids

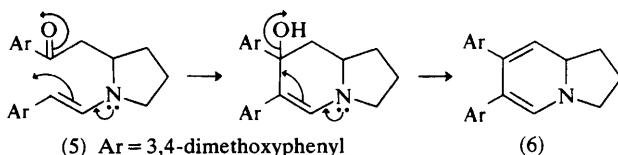
A convenient synthesis of the unsubstituted seco-phenanthroindolizidine ring system and of the alkaloid septicine (1) has been based on the probable biosynthetic



route to the phenanthroindolizidines of the *Tylophora* group.<sup>1</sup> Condensation of 3,4-dimethoxybenzoylacetic acid (2) with  $\Delta^1$ -pyrroline (3) gave (4) which, by reaction with 3,4-dimethoxyphenylacetaldehyde and reduction of the product with sodium borohydride, was converted into racemic septicine (24% yield). The reaction of (4)

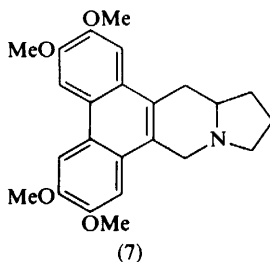


with 3,4-dimethoxyphenylacetaldehyde is considered to take place by formation of an enamine (5) which then undergoes cyclization to the intermediate (6) by addition of the enamine group to the carbonyl group.

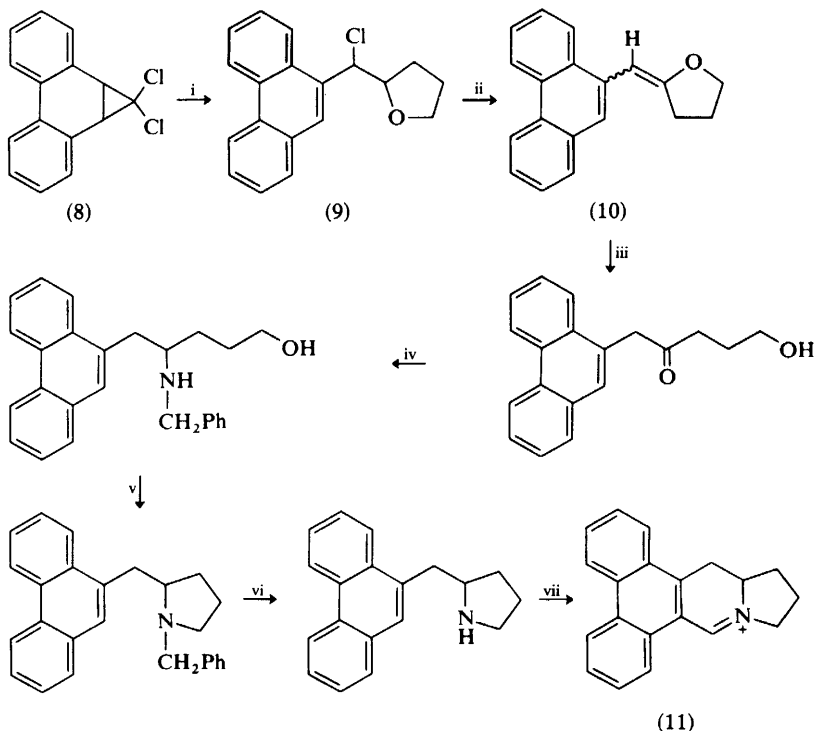


<sup>1</sup> R. B. Herbert, F. B. Jackson, and I. T. Nicolson, *J.C.S. Chem. Comm.*, 1976, 450.

A synthesis (Scheme)<sup>2</sup> of the phenanthroindolizidine skeleton itself has also been achieved, and in this instance the authors state their intention of applying this method to the synthesis of tylophorine (7). 7,7-Dichlorodibenzo[*a,c*]bicyclo[4,1,0]-



heptane (8), derived from phenanthrene and dichlorocarbene, was converted into 9-(chloro-2-tetrahydrofurylmethyl)phenanthrene (9), and thence into the mixture of



Reagents: i, Bu<sup>4</sup>OK, THF; ii, hot pyridine-DMF; iii, EtOH-HCl; iv, PhCH<sub>2</sub>NH<sub>2</sub>, NaBH<sub>4</sub>; v, SOCl<sub>2</sub>-CHCl<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>; vi, benzoxycarbonyl chloride-K<sub>2</sub>CO<sub>3</sub>, CHCl<sub>3</sub>, then EtOH-HCl, 120°C; vii, N-formylation, then cyclization with POCl<sub>3</sub>.

**Scheme**

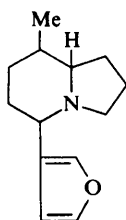
<sup>2</sup> S. Takano, K. Yuta, and K. Ogaswara, *Heterocycles*, 1976, 4, 947.

isomers represented by (10). The reaction sequence shown in the Scheme led to the quaternary product (11), which was reduced with sodium borohydride to give the required ring system.

Seventeen Indian *Tylophora* species have been surveyed for the presence of alkaloids,<sup>3</sup> and the seasonal variation of alkaloidal content of *T. asthmatica* has been studied. The proportion of tylophorine is comparatively high during flowering periods.<sup>3</sup>

## 2 Scent-gland Constituent of Canadian Beaver

5-(3-Furyl)-8-methyloctahydroindolizine (12) has been isolated from the scent-gland of the Canadian beaver (*Castor fiber* L.), together with (–)-castoramine and a series of related quinolizidines and other alkaloids.<sup>4</sup> The alkaloid (12) is only a minor



(12)

component, estimated to amount to *ca.* 0.0002% of the partly dried beaver gland, and its relative and absolute configuration are unknown.

<sup>3</sup> C. R. Karnick, *Planta Med.*, 1975, **27**, 333.

<sup>4</sup> B. Maurer and G. Ohloff, *Helv. Chim. Acta*, 1976, **59**, 1169.

Once again the azaphenalene, *Nuphar*, and *Lythraceae* alkaloids are included in this Chapter. Perhaps the most notable achievement of the year is the synthesis of azaphenalenes of ladybird beetles by Ayer and co-workers.<sup>1,2</sup> Amongst the new alkaloids, the novel pyridone quinolizidine, maminine (3) and its tetrahydro-derivative, pohakuline (5) are of special interest.<sup>3</sup>

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

**Occurrence.**—Alkaloid isolation is recorded in the Table.<sup>3–23</sup> A considerable number of new species have been studied, and although many contain the ubiquitous

- <sup>1</sup> W. A. Ayer, R. Dawe, R. A. Eisner, and K. Furuichi, *Canad. J. Chem.*, 1976, **54**, 473.
- <sup>2</sup> W. A. Ayer and K. Furuichi, *Canad. J. Chem.*, 1976, **54**, 1494.
- <sup>3</sup> M. M. Kadooka, M. Y. Chang, H. Fukami, P. J. Scheuer, J. Clardy, B. A. Solheim, and J. P. Springer, *Tetrahedron*, 1976, **32**, 919.
- <sup>4</sup> Yu. K. Kushmuradov, Kh. A. Aslanov, and S. Kuchkarov, *Khim. prirod. Soedinenii*, 1975, 377 (*Chem. Abs.*, 1976, **84**, 105 874).
- <sup>5</sup> M. H. Radema, *Planta Med.*, 1975, **28**, 143.
- <sup>6</sup> J. L. Van Eijk and M. H. Radema, *Planta Med.*, 1975, **28**, 139.
- <sup>7</sup> J. Santamaria and F. Khuong-Huu, *Phytochemistry*, 1975, **14**, 2501.
- <sup>8</sup> J. Adzet and J. L. Masso, *Trav. Soc. Pharm., Montpellier*, 1975, **35**, 329 (*Chem. Abs.*, 1976, **84**, 132 665).
- <sup>9</sup> A. Gulubov and A. Venkov, *Natura (Plovdiv, Bulg.)*, 1973, **6**, 97 (*Chem. Abs.*, 1976, **84**, 14 663).
- <sup>10</sup> J. Adzet and J. L. Musso, *Trav. Soc. Pharm., Montpellier*, 1975, **35**, 237 (*Chem. Abs.*, 1976, **84**, 102 282).
- <sup>11</sup> J. A. Lambertson, M. F. Mackay, M. J. McColl, B. J. Poppleton, and H. Suares, *Tetrahedron Letters*, 1975, 3875.
- <sup>12</sup> G. C. Gerrans, A. S. Howard, and M. J. Nattrass, *Phytochemistry*, 1976, **15**, 816.
- <sup>13</sup> E. G. Tkeshelashvili and K. S. Mudzhiri, *Khim. prirod. Soedinenii*, 1975, 807 (*Chem. Abs.*, 1976, **84**, 102 357).
- <sup>14</sup> I. Murakoshi, K. Sugimoto, J. Haginiwa, S. Ohmiya, and H. Otomasu, *Phytochemistry*, 1975, **14**, 2714.
- <sup>15</sup> N. Yu. Novgorodova, S. Kh. Maeckh, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, 435 (*Chem. Abs.*, 1976, **84**, 59 823).
- <sup>16</sup> N. Yu. Novgorodova, S. Kh. Maeckh, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, 529 (*Chem. Abs.*, 1976, **84**, 44 497).
- <sup>17</sup> G. Faugeras, R. R. Paris, J. Bourgeois, M. N. Alexis, and J. F. Dobremez, *Plant. Med. Phytother.*, 1975, **9**, 273.
- <sup>18</sup> G. C. Gerrans and A. S. Howard, *Phytochemistry*, 1976, **15**, 1098.
- <sup>19</sup> O. N. Tolkachev, T. E. Monaklova, V. I. Scheichenki, V. S. Kabanov, O. G. Fesenko, and N. F. Proskurnina, *Khim. prirod. Soedinenii*, 1975, 30 (*Chem. Abs.*, 1975, **83**, 97 667).
- <sup>20</sup> A. Ueno, K. Morinaga, S. Fukushima, Y. Titaka, Y. Koiso, and S. Okuda, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 2560.
- <sup>21</sup> S. A. Karakozova, B. A. Abdusalamov, and R. L. Khaganovich, *Khim. prirod. Soedinenii*, 1975, 664 (*Chem. Abs.*, 1976, **84**, 102 280).
- <sup>22</sup> W. J. Keller, *Phytochemistry*, 1975, **14**, 2305.
- <sup>23</sup> L. H. Briggs, R. C. Cambie, and P. K. Montgomery, *N.Z.J. Sci.*, 1975, **18**, 555.

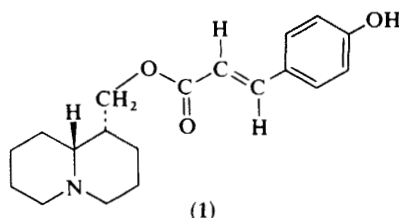
**Table** Isolation of alkaloids

Species	Alkaloid (Structure)	Ref.
<i>Ammothamnus lehmanni</i>	*Lehmannine (23)	4
<i>Cadia purpurea</i>	*13-Ethoxylupanine (7)	5
	12-Hydroxylupanine ester	6
	Lupanine,	
	Sparteine	
<i>Camoensia maxima</i>	*Camoensidine (10)	7
	*Camoensine (8)	
	Leontidine (9)	
<i>Cytisus osmariensis</i>	Anagyrene	8
	Cytisine,	
	Lupanine	
<i>Genista carinalis</i>	Anagyrene,	9
	Cytisine	
	<i>N</i> -methylcytisine,	
	Rhombifoline	
	Anagyrene,	
	Cineverine	
<i>G. lucida</i>	Cytisine,	10
<i>G. ramossissima</i>	13-Hydroxylupanine	
<i>G. spartioides</i>	Lupanine,	
<i>G. valentina</i>	<i>N</i> -methylcystisine	
	Retamine,	
	Sparteine	11
<i>Hovea linearis</i>	*(±)-16-Epiormosanine	
	(±)-Piptanthine	11
<i>Lebeckia plukenetiana</i>	Lupanine	12
	Nuttalline,	
	Sparteine	
<i>Leontice smirnowii</i>	Lupanine	13
	<i>N</i> -methylcytisine,	
	Leontidine	
<i>Lupinus luteus</i>	*Lupinine <i>trans</i> -4-hydroxycinnamate	14
<i>Nitraria schoberi</i>	*Nitramine (14)	15
	* <i>N</i> -Hydroxynitramine (15)	16
<i>Piptanthus nepalensis</i>	Anagyrene,	17
	Cytisine	
	Lupanine,	
	<i>N</i> -methylcytisine	
	Sparteine	18
<i>Podalyria cuneifolia</i>	Lupanine,	
	Sparteine	18
<i>P. glauca</i>	Aphylline,	18
	Lupanine	
	Sparteine	19
<i>Sophora alopecuroides</i>	*Allylaloperine (13)	
	Aloperine (12)	19
<i>S. chrysophylla</i>	Cytisine,	3
	*Mamanine (3)	
	Matrine,	
	*Pohakuline (5)	20
<i>S. flavescens</i>	*Isomatrine (22)	
<i>S. graffithii</i>	Sophocarpine	21
<i>S. secundiflora</i>	Cytisine,	22
	<i>N</i> -methylcytisine	
	Sparteine	23
<i>S. tetraptera</i>	Cytisine,	
	Matrine	

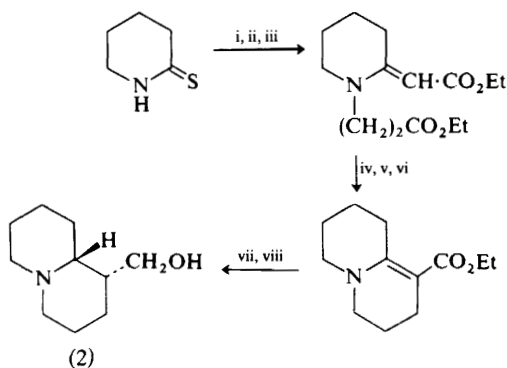
\*New Alkaloids

cytisine, lupanine and sparteine, 12 new alkaloids have been discovered. The melting point of nuttalline (4-hydroxylupanine) from *Lebecka plukenetiana*<sup>12</sup> differs significantly from that recorded for the alkaloid first isolated from *L. nuttallei*.

**Lupinine Group.**—A new lupinine ester (1) obtained from seedlings of *Lupinus luteus* contained traces of the *cis*-isomer, which could be obtained from the *trans*-derivative by irradiation. The structure of the alkaloid was established by hydrolysis and by synthesis from (–)-lupanine and *trans*-4-acetoxycinnamyl chloride.<sup>14</sup>



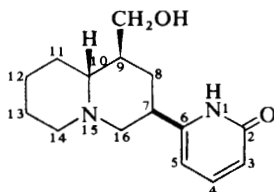
A new synthesis of lupinine (2) starts with 2-thiopiperidine (Scheme 1).<sup>24</sup>



Reagents i,  $\text{CH}_2=\text{CHCO}_2\text{Et}, \text{NaH}$ ; ii,  $\text{BrCH}_2\text{CO}_2\text{Et}$ ; iii,  $\text{Et}_3\text{N}-\text{Ph}_3\text{P}$ ; iv,  $\text{LiAlH}_3\text{OEt}$ ; v,  $\text{NaH}-\text{TsCl}$ ; vi, warm  $\text{MeCN}$ ; vii,  $\text{NaBH}_4$ ; viii,  $\text{LiAlH}_4$ .

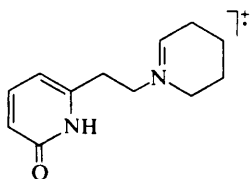
**Scheme 1**

Scheuer and co-workers<sup>3</sup> showed that during the flowering period the bark of *Sophora chrysophylla* contains the alkaloids maminine (3) and its

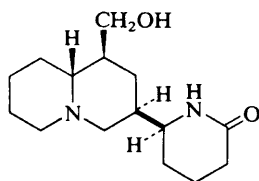


<sup>24</sup> G. C. Gerrans, A. S. Howard, and B. S. Orlek, *Tetrahedron Letters*, 1975, 4171.

tetrahydro-derivative, pohakuline (5). The n.m.r. spectra of maminine and its diacetate suggested that the alkaloid was a pyridone lupinine, and the recognition of the fragment ion (4) in the mass spectrum indicated that the pyridone group was



(4)

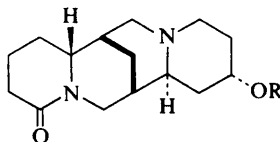


Pohakuline (5)

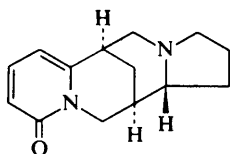
substituted at C-7 rather than at C-11; the structures of maminine and pohakuline finally were established by X-ray analysis. The authors proposed that the biosynthesis of these unbridged tricyclic alkaloids occurs by ring scission of a tetracyclic quinolizidine or through addition of piperidine to a lupinine unit.

**Lupanine-Sparteine Group.**—Further investigation of the alkaloids of *Cadia purpurea* (cf. Vol. 3) resulted in the isolation of 13-hydroxylupanine (6) and two of its derivatives. One is probably its tiglate ester<sup>6</sup> and the other 13-ethoxylupanine (7); a 13-ethoxylupanine prepared by reaction of 13-hydroxylupanine tosylate with ethanol is believed to be the  $\beta$ -ethoxy-derivative.<sup>5</sup> Cadiamine,  $C_{15}H_{26}N_2O_3$ , an alkaloid of unknown structure containing two hydroxy-groups, was also obtained.<sup>6</sup>

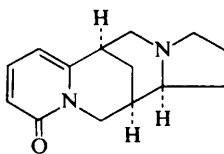
A study of the alkaloids of *Camoensia maxima* resulted in the isolation of leontidine (9) (cf. Vol. 3) and two new alkaloids, camoensine and camoensidine.<sup>7</sup> Camoensine was shown to have structure (8) by conversion with mercury(II) acetate into an immonium salt which furnished leontidine (9) on reduction with borohydride. Catalytic reduction of camoensine gave camoensidine; hence the latter is the quinolizidone (10) with *cis*-stereochemistry at C-6, C-7. A synthesis of ( $\pm$ )-



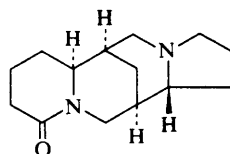
(+)-13-Hydroxylupanine (6) R = H  
13-Ethoxylupanine (7) R = Et



Camoensine (8)



Leontidine (9)

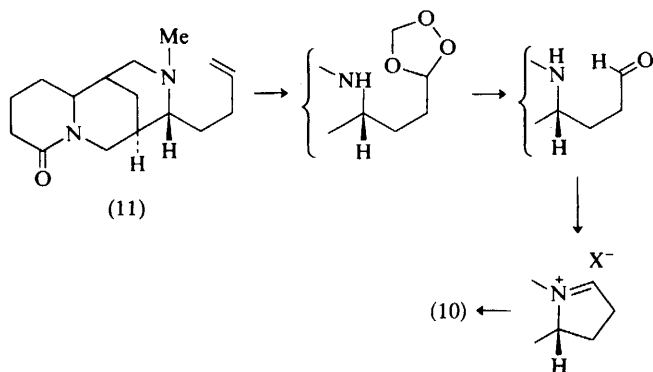


Camoensidine (10)

camoensidine from ( $\pm$ )-lupanine was accomplished by Hofmann degradation and reaction of one of the products (11) with ozone followed by treatment with zinc and

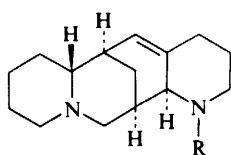


acetic acid. The authors favour a mechanism (Scheme 2) whereby ozone effects demethylation of the *N*-methylamino group.

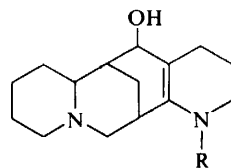


**Scheme 2**

The conversion of lupanine into camoensidine may represent a biosynthetic pathway, and cleavage of the C-16:C-17 bond of a tetracyclic quinolizidine [*cf.* maminine (3)] followed by carbon-carbon cyclization could lead to tetracyclic derivatives containing terminal piperidine rings. New alkaloids of this type have been obtained recently. Aloperine was first isolated from *Sophora alopecuroides* over forty years ago, and structure (12) has now been assigned to the alkaloid on the basis of spectral studies.<sup>19</sup> Allylaloferine (13) is a constituent of the same species.<sup>19</sup> Nitraramine (14)<sup>15</sup> and *N*-hydroxynitraramine (15)<sup>16</sup> from *Nitraria schoberi* are

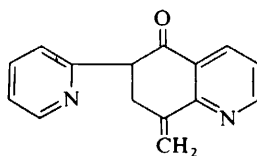


Aloperine (12) R = H  
Allylaloferine (13) R = CH<sub>2</sub>=CHMe



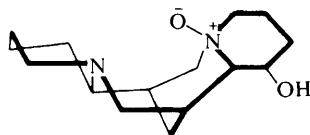
Nitraramine (14) R = H  
*N*-Hydroxynitraramine (15) R = OH

believed to be hydroxy-derivatives of aloperine; dehydrogenation of nitraramine was reported to give the pyridine derivative (16) and reduction of *N*-hydroxynitraramine with hydride furnished nitraramine.



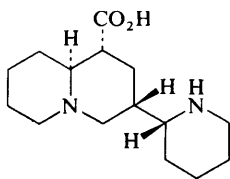
(16)

Ribas and co-workers<sup>25</sup> have continued their investigations of retamine *N*-oxides and confirmed structures (17) and (18) for the *N*-1-oxide and for the *N*-16-oxide, respectively, by i.r. and n.m.r. studies. Reaction of the *N*-1-oxide (17) with methyl iodide in acetone at 70° C resulted in loss of the oxygen function and formation of retamine and formaldehyde. The *N*-oxide group in isomer (18) apparently is too

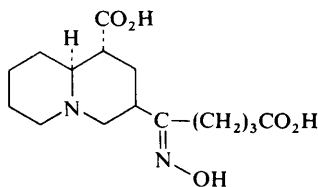
Retamine *N*-1-oxide (17)Retamine *N*-16-oxide (18)

hindered to undergo this reaction and the *N*-oxide hydriodide was formed instead; sparteine *N*-16-oxide behaved in the same way. The structure of sparteine *N*-16-oxide sesquiperchlorate containing one lithium cation (*cf.* Vol. 4) was further investigated by spectral studies and by X-ray analysis.<sup>26</sup>

Aslanov *et al.*<sup>27</sup> have extended their work on aphyllic acid (19). Oxidation of aphyllic acid with hydrogen peroxide gives the diacid (20), which can be converted into a 2,10-dioxosparteine.



(19)



(20)

**Matrine Group.**—Further information is now available on the structure of neosophoramine (*cf.* Vol. 6).<sup>28</sup> Comparison of the mass spectra of sophoramine and neosophoramine shows that the two alkaloids are stereoisomers. The presence of an axial proton at C-5 in neosophoramine was apparent from the n.m.r. spectrum, and the absence of Bohlmann bands in the i.r. spectrum indicated a *cis* A/B ring junction. Since sophoramine has  $\beta$ -hydrogen at C-5, C-6, and C-7 and in isosophoramine all three ring junctions are *trans*, neophoramine was assigned structure (21).

The roots of *Sophora flavescens* contains isomatrine (22), a stereoisomer of matrine that was epimerized into a mixture of matrine and allomatrine. X-ray analysis established the structure and absolute configuration of the new alkaloid.<sup>20</sup> Structure (23) has been proposed for lehmannine from *Ammothamnus lehmanni* as a result of spectral information and catalytic reduction of the alkaloid to matrine.<sup>4</sup>

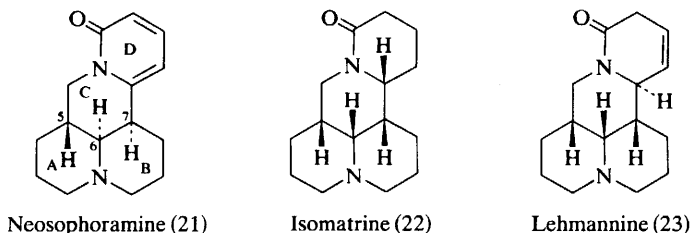
**Ormosia Group.**—Alkaloids of this type have been isolated for the first time from *Hovea* species.<sup>11</sup> *H. linearis* contains ( $\pm$ )-piptanthine and ( $\pm$ )-16-epiormosanine,

<sup>25</sup> I. Ribas, L. Castedo, and R. Mosquera, *Anales de Quim.*, 1974, **70**, 1049.

<sup>26</sup> J. Skolik, K. Langowska, and M. Wiewiorowski, *Bull. Acad. polon. Sci., Sér. Sci. Chim.*, 1975, **23**, 215.

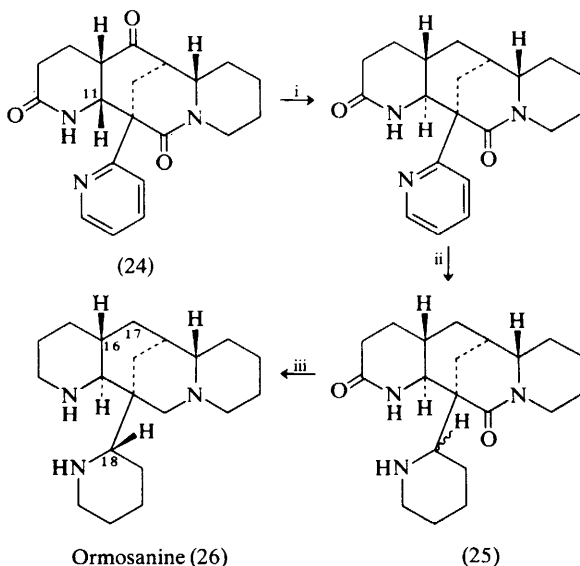
<sup>27</sup> A. N. Nizamkhodzhaeva, A. I. Ishbaev, and Kh. A. Aslanov, *Doklady Akad. Nauk Uzbek S.S.R.*, 1974, **31**, 24 (*Chem. Abs.*, 1976, **84**, 150 817).

<sup>28</sup> T. E. Monakhova, O. N. Tolachev, V. S. Kabanov, M. E. Perelson, and N. F. Proskurnina, *Khim. prirod. Soedinenii*, 1974, 472.



*cf.* (26); the latter has been obtained previously only as the reduction product of the 16,17-ene, podopetaline.

Valenta's efficient and stereoselective synthesis of ormosanine (26) and related alkaloids has been published in full.<sup>29</sup> The paper includes an account of the stereochemical features of the reactions involved and assigns a revised structure to the key dilactam (24). Conversion of the latter compound into ormosanine (Scheme 3) apparently involves epimerization at C-11 in the course of Wolff-Kishner reduction. A minor product of the reaction of intermediate (25) and diborane is 18-epiormosanine, which is a constituent of *O. semicastrata* (*cf.* Vol. 2).



Reagents: i,  $\text{NH}_2\text{NH}_2\text{-KOH}$ - triethylene glycol, 190 °C; ii, Pt,  $\text{H}_2$ , AcOH; iii,  $\text{B}_2\text{H}_6$ , THF.

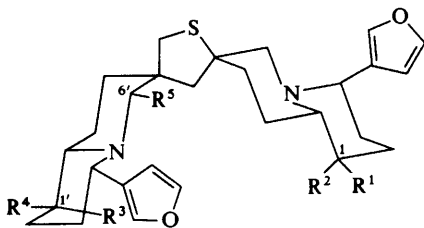
**Scheme 3**

## 2 Sesquiterpenoid Alkaloids from *Nuphar* Species

More new alkaloids of the thiobinupharidine group have been obtained from *Nuphar luteum*. In thiobinupharidine (27) there are equatorial methyl groups at C-1 and at

<sup>29</sup> H.-J. Liu, Y. Sato, Z. Valenta, J. S. Wilson, and T. T. J. Yu, *Canad. J. Chem.*, 1976, **54**, 97.

C-1', and La Londe and Wong<sup>30</sup> have now separated 1-epi-1'-epi-thiobinupharidine (28) containing two axial methyl groups and a mixture of isomers (29) and (30) with axial methyl substituents at C-1 and at C-1', respectively. Configurations at C-1 were apparent from the <sup>1</sup>H and <sup>13</sup>C n.m.r. spectra, the axial methyl groups in (28), for example, resulting in a downfield shift of the methyl signals in the proton n.m.r. spectrum relative to (27).



Thiobinupharidine (27)  $R^1 = R^4 = \text{Me}$ ;  $R^2 = R^3 = R^5 = \text{H}$

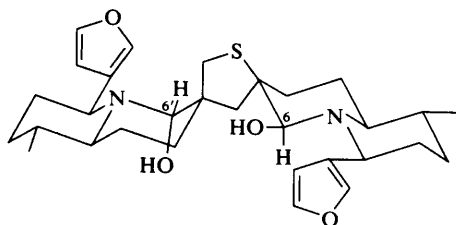
1-Epi-1'-epithiobinupharidine (28)  $R^2 = R^3 = \text{Me}$ ;  $R^1 = R^4 = R^5 = \text{H}$

1-Epithiobinupharidine (29)  $R^2 = R^4 = \text{Me}$ ;  $R^1 = R^3 = R^5 = \text{H}$

1'-Epithiobinupharidine (30)  $R^1 = R^3 = \text{Me}$ ;  $R^2 = R^4 = R^5 = \text{H}$

6'-Epi-monohydroxythiobinupharidine (31)  $R^1 + R^2 = \text{Me} + \text{H}$ ;  $R^3 + R^4 = \text{Me} + \text{H}$ ;  $R^5 = \text{OH}$

The unresolved mixture of 6-hydroxy- and 6'-hydroxy-neothiobinupharidine [cf. (32) and Vol. 6] has since been separated. The structures of the isomers were elucidated in the usual way by a study of the n.m.r. and mass spectra of the alkaloids and their monodeuterio-derivatives. Distinction between an  $\alpha$ - (i.e., C-6) and a  $\beta$ - (i.e., C-6') thiohemiaminal can also be made on the basis of the u.v. spectrum in acid solution and from c.d. data.<sup>31</sup>



6,6'-Dihydroxynethiobinupharidine (32)

Isolation of the first 6,6'-dihydroxynethiobinupharidine (32) has been reported by Wróbel and his co-workers.<sup>32</sup> The structure of the alkaloid was established by spectroscopic methods and by its conversion with borohydride into neothiobinupharidine. Although the n.m.r. spectrum of the alkaloid indicated the presence of an equatorial proton at C-6' and an axial proton at C-6, dideuteriobinupharidine, obtained with sodium borodeuteride, appeared to have equatorial protons at both positions; this result was attributed to preferred attack of deuteride in the direction opposite to that of the axial sulphur group.

<sup>30</sup> R. T. La Londe and C. Wong, *Canad. J. Chem.*, 1975, **53**, 3545.

<sup>31</sup> R. T. La Londe and C. Wong, *J. Org. Chem.*, 1976, **41**, 291.

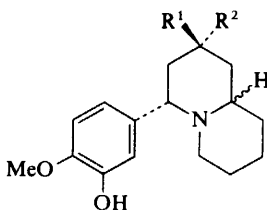
<sup>32</sup> J. T. Wróbel, A. Iwanov, and K. Wojtasiewicz, *Bull. Acad. polon. Sci., Sér. Sci. Chim.*, 1975, **23**, 735.

A  $C_{30}$  hemiaminal from *N. luteum* was shown from its mass spectrum and by its conversion into deuteriothiobinupharidine to contain a single equatorial hydroxy-group at the 6'-position. The new base, for which structure (31) is proposed, apparently is not identical with 6'-hydroxythiobinupharidine isolated by La Londe *et al.* (cf. Vol. 6) and has been named 6'-epi-monohydroxythiobinupharidine.<sup>32</sup>

Another paper has appeared on the mass spectra of *Nuphar* bases,<sup>33</sup> and a study of the  $^{13}C$  n.m.r. spectra of this group of alkaloids and analogous compounds has been published.<sup>34</sup>

### 3 *Lythraceae* Alkaloids

Two new biphenyl alkaloids isolated from *Heima salicifolia* are believed to be stereoisomers of lythrine.<sup>35</sup> Another study of *H. salicifolia*, involving identification of alkaloids at various stages of growth, was designed to probe the biosynthetic sequence.<sup>36</sup> Further arylquinolizidines (33), apparently related to the macrocyclic alkaloids (cf. Vol. 6), were obtained from seedlings of *H. salicifolia* as a mixture of isomers differing in configuration at the bridgehead carbon; the corresponding ketone (34) was isolated by radioactive dilution.<sup>37</sup>



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

(34)  $R^1 + R^2 = O$

There is still considerable activity in the synthesis of *Lythraceae* alkaloids, although no new methods have emerged this year. Details have appeared of two independent syntheses of the biphenyl ether alkaloid decaline.<sup>38,39</sup> Arata's approach to the synthesis of decaline (35)<sup>38</sup> (cf. Vol. 5) has been applied to lagarine (36), using a benzyl group to protect the phenolic hydroxyl substituent.<sup>40</sup> 4-Arylquinolizidin-2-ones, cf. (34), are important synthetic intermediates, and their synthesis from isopelletierine and a variety of 2-bromobenzaldehyde derivatives has been studied.<sup>41</sup>

The biphenyl alkaloid decanine (37) was synthesized by a route similar to that employed for methyldecinine (cf. Vol. 6). The hydroxy-group was protected as its methyl sulphonate ester and calcium hydroxide was used in the reaction of the

<sup>33</sup> R. T. La Londe and C. Wong, *Org. Mass Spectrometry*, 1976, **11**, 183.

<sup>34</sup> R. T. La Londe, T. N. Donvito, and A. I. M. Tsai, *Canad. J. Chem.*, 1975, **53**, 1714.

<sup>35</sup> X. A. Domínguez, J. Marroquin, B. S. Quintero, and S. B. Vargas, *Phytochemistry*, 1975, **14**, 1883.

<sup>36</sup> R. H. Dobberstein, J. M. Edwards, and A. E. Schwarting, *Phytochemistry*, 1975, **14**, 1769.

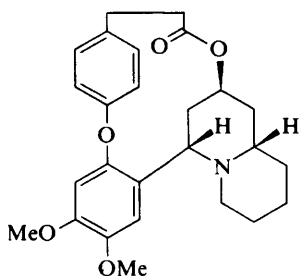
<sup>37</sup> A. Rother and A. E. Schwarting, *Lloydia*, 1975, **38**, 477.

<sup>38</sup> M. Hanaoka, N. Ogawa, and Y. Arata, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 2140.

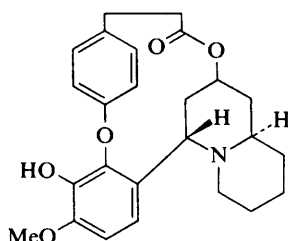
<sup>39</sup> J. T. Wrobel and N. M. Golebiewski, *Bull. Acad. polon. Sci., Sér. Sci. Chim.*, 1975, **23**, 601.

<sup>40</sup> M. Hanaoka, M. Kamei, and Y. Arata, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 2191.

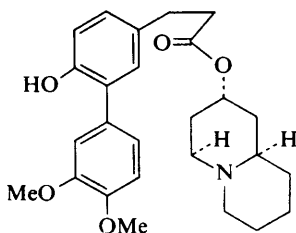
<sup>41</sup> J. T. Wrobel and W. M. Golebiewski, *Bull. Acad. polon. Sci., Sér. Sci. Chim.*, 1975, **23**, 593.



Decaline (35)



Lagarine (36)

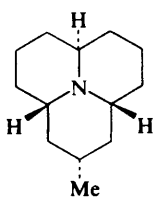


Decinine (37)

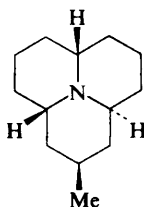
requisite biphenyl aldehyde with isopelletierine.<sup>42</sup> The Japanese synthesis of methyldecinine has been published in full.<sup>43</sup>

#### 4 9*b*-Azaphenalene Alkaloids

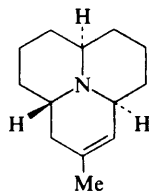
The defensive substances present in two species of ladybird beetles from Western Canada have been studied.<sup>44</sup> The known 2 $\alpha$ -methylperhydro-9*b*-azaphenalenes precoccinelline (38) and its *N*-oxide, coccinelline were identified in *Coccinella transversoguttata* and hippodamine (39) and its *N*-oxide convergine in *Hippodamia caseyi*. The latter species was also shown to contain two new pentahydro-azaphenalenes, hippocasine (40) and hippocasine *N*-oxide. The structure of the oxide was indicated by n.m.r. resonances at 4.58 (1H,  $-\text{CH}=\text{C}-$ ), 5.73–5.93



Precoccinelline (38)



Hippodamine (39)



Hippocasine (40)

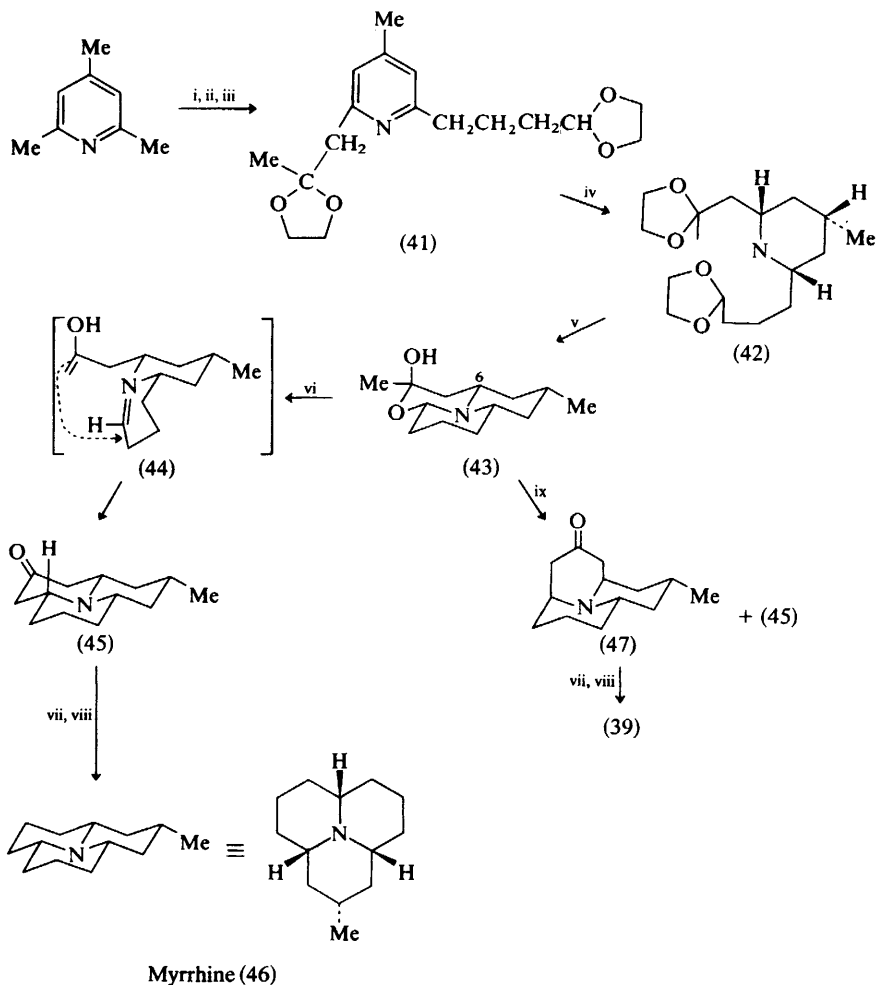
<sup>42</sup> I. Lantos and B. Loev, *Tetrahedron Letters*, 1975, 2011.

<sup>43</sup> M. Hanaoka, H. Sassa, C. Shimezawa, and Y. Arata, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 2478.

<sup>44</sup> W. A. Ayer, M. J. Bennett, L. M. Browne, and J. T. Purdham, *Canad. J. Chem.*, 1976, **54**, 1807.

(3H,3  $\text{CH}-\text{N}$ ) and 8.22 $\tau$  ( $-\text{CH}=\text{C}-\text{CH}_3$ ) and confirmed by X-ray analysis of the hydrochloride salt. Hippocasine was converted into the *N*-oxide by reaction with hydrogen peroxide.

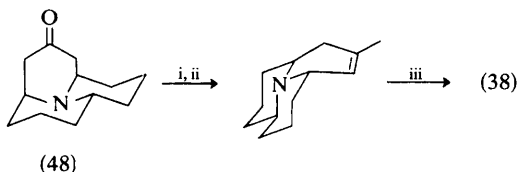
Two stereoisomers of perhydro-9*b*-azaphenalene were synthesized recently (*cf.* Vol. 6), and the total synthesis of three methylperhydro-9*b*-azaphenalenes has now been achieved by Ayer and his co-workers. The route to myrrhine (46) and hippodamine (39) (Scheme 4)<sup>1</sup> is based on an earlier synthesis of the ring system of



Reagents: i,  $\text{BrCH}_2\text{CH}_2\text{CH}(\text{OMe})_2$ ,  $\text{BuLi}$ ; ii,  $\text{PhLi}$ , ether, slow addition of  $\text{MeCN}$ ; iii,  $\text{TsOH}-(\text{CH}_2\text{OH})_2-\text{PhMe}$ ; iv, Na-isoamyl alcohol; v, 5% aq.  $\text{HCl}$ ; vi,  $\text{TsOH}-\text{PhMe}$ , reflux; vii,  $(\text{HSCH}_2)_2-\text{BF}_3$ ; viii, Raney  $\text{Ni}-\text{EtOH}$ , reflux; ix, pyrrolidine- $\text{AcOH}-\text{THF}$ .

Scheme 4

the Lycopodium alkaloid, cerniutine, and involves reduction of the pyridine (41) to the thermodynamically more stable all-*cis* piperidine derivative (42). Treatment of the hemiketal (43) with acid is believed to result in formation of the third ring *via* an immonium salt (44), as indicated. When the cyclization of the hemiketal was carried out with pyrrolidine and acetic acid two products (45) and (47) were obtained and then converted into a mixture of myrrhine and, unexpectedly, hippodamine (39); in the formation of ketone (47) epimerization at C-6 is believed to occur prior to cyclization. The alkaloid precocinelline (38) was also synthesized (Scheme 5).<sup>2</sup> In this case, the ketone (48), prepared essentially as for the methyl analogue, was converted into precocinellin by standard procedures.



Reagents: i, MeLi-ether; ii,  $\text{SOCl}_2\text{-CH}_2\text{Cl}_2$ ; iii,  $\text{Pt-H}_2\text{-MeOH}$ .

**Scheme 5**



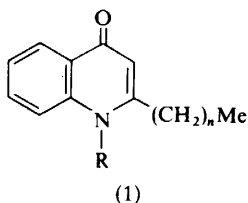
## Quinoline and Acridone Alkaloids

BY M. F. GRUNDON

### 1 Quinoline Alkaloids

*Ptelea trifoliata* has star qualities in its production of quinoline alkaloids and the work of Mitscher<sup>1</sup> and Reisch<sup>2,3</sup> and their respective collaborators published during the year has added eight new alkaloids to the long list of quinolines already identified as constituents of this species. Other notable events include the isolation of araliopsine (48), the first angular hydroxyisopropylidihydrofuroquinoline alkaloid,<sup>4</sup> and the identification of two alkaloids with unique structures, perfamine (11) from a *Haplophyllum* species<sup>5</sup> and melochinone (2) from a member of the Sterculiaceae.<sup>6</sup>

**Non-hemiterpenoid Quinolines.**—Extraction of the leaves and fruit of *Evodia rutaecarpa* resulted in the isolation of three 2-(n-alkyl)-1-methyl-4-quinolones, dihydroevocarpine (1; R = Me, n = 12), the pentadecyl derivative (1; R = Me, n = 14), and the undecylquinolone (1; R = Me, n = 10).<sup>7</sup> The structures of the three



alkaloids were established by n.m.r. and mass spectroscopy and by synthesis. The synthetic procedure, applied previously to the preparation of dihydroevocarpine, involved formation of quinolones (1; R = H) from  $\beta$ -ketoalkanoic acids and aniline and subsequent methylation to a mixture of *N*- and *O*-methyl derivatives. 4-

<sup>1</sup> (a) L. A. Mitscher, M. S. Bathala, G. W. Clark, and J. L. Beal, *Lloydia*, 1975, **38**, 117; (b) *ibid.*, p. 109.

<sup>2</sup> (a) J. Reisch, J. Körösi, K. Szendrei, I. Novák, and E. Minker, *Phytochemistry*, 1975, **14**, 1678; (b) *ibid.*, p. 2722.

<sup>3</sup> J. Körösi, K. Szendrei, I. Novák, J. Reisch, G. Blazso, E. Minker, and M. Koltai, *Herba Hung.*, 1976, **15**, 9 (*Chem. Abs.*, 1976, **85**, 30 608).

<sup>4</sup> J. Vaquette, M. S. Hifnawy, J. L. Pousset, A. Fournet, A. Bouquet, and A. Cavé, *Phytochemistry*, 1976, **15**, 743.

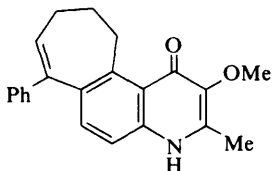
<sup>5</sup> D. M. Razakova, I. A. Bessonova, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, **11**, 812 (*Chem. Abs.*, 1976, **84**, 180 443).

<sup>6</sup> G. J. Kapadia, B. D. Paul, J. V. Silvertown, M. H. Fales, and E. A. Sokoloski, *J. Amer. Chem. Soc.*, 1975, **97**, 6814.

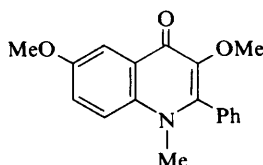
<sup>7</sup> T. Kamikado, C.-F. Chang, S. Murakoshi, and A. Sakurai, *Agric. and Biol. Chem. (Japan)*, 1976, **40**, 605 (*Chem. Abs.*, 1976, **84**, 180 446).

Quinolones (1; R = H,  $n = 10-13$ ), lacking the *N*-methyl group, were detected recently in roots of *Ruta graveolens* (cf. Vol. 6); a new *N*-methyl-4-quinolone (1; R = Me,  $n = 8$ ) has now been isolated from the above-ground parts of this species.<sup>8</sup>

*Melochia tomentosa* (Sterculiaceae) was found to contain the unusual 4-quinolone alkaloid melochinone (2).<sup>6</sup> Although spectroscopic studies revealed many features of the molecule, the presence of a 4-quinolone system was not recognized until the complete structure was elucidated by *X*-ray crystallographic analysis. The quinolone portion of the molecule is analogous to that of japonine (3) from *Orixa japonica*, but the origin of the non-isoprenoid phenylcycloheptane ring is not readily apparent.

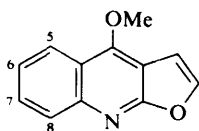


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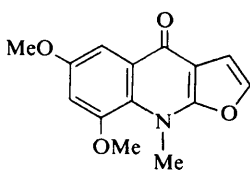


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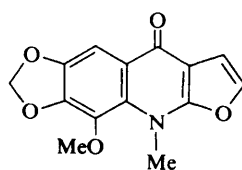
**Furoquinoline Alkaloids.**—Well known furoquinoline alkaloids have been obtained from new sources, dictamnine (4) from *Zanthoxylum belizense*<sup>9</sup> and from *Z. arnotianum*,<sup>10</sup> skimmianine (7,8-dimethoxydictamnine) from *Z. belizense*,<sup>9</sup> *Z. dinklagei*,<sup>11</sup> and *Haplophyllum latifolium*,<sup>12</sup> robustine (8-hydroxydictamnine) and haplopine (7-hydroxy-8-methoxydictamnine) from *Z. arnotianum*,<sup>10</sup> pteleine (6-methoxydictamnine) from *Ptelea trifoliata*,<sup>1a</sup> maculine (6,7-methylenedioxydictamnine) and kokusaginine (8) from *Araliopsis soyauxii*,<sup>4</sup> and flindersiamine (6,7-methylenedioxy-8-methoxydictamnine) from *A. soyauxii* and from *Helietta parvifolia*.<sup>13</sup> Isomaculosidine (5), isolated previously from *Dictamnus albus*,<sup>14</sup> was shown to be a constituent of *P. trifoliata*.<sup>1a</sup> The natural occurrence of isoflindersiamine (6) (in *H. parvifolia*) has been reported for the first time.<sup>13</sup>



Dictamnine (4)



(5)



Isoflindersiamine (6)

**Heliparvifoline.** Extracts of *H. parvifolia* were active against lymphocytic leukaemia and a study of the constituents led to the isolation of a new furoquinoline, heliparvifoline.<sup>13</sup> The alkaloid was shown to be either 7-hydroxy-6-methoxydictamnine (7)

<sup>8</sup> M. F. Grundon and H. M. Okely, unpublished work.

<sup>9</sup> S. Najjar, G. A. Cordell, and N. R. Farnsworth, *Phytochemistry*, 1975, **14**, 2309.

<sup>10</sup> H. Ishii, K. Hosoya, Y. Ishikawa, E. Ueda, and J. Haginiwa, *Yakugaku Zasshi*, 1974, **94**, 322 (*Chem. Abs.*, 1974, **81**, 132 753).

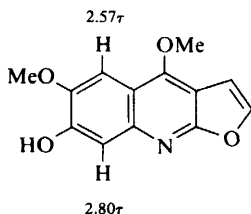
<sup>11</sup> F. Fish, I. A. Meshab, and P. G. Waterman, *Phytochemistry*, 1975, **14**, 2094.

<sup>12</sup> E. F. Nesmelova, I. A. Bessonova, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, 666 (*Chem. Abs.*, 1976, **84**, 105 863).

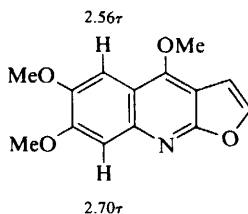
<sup>13</sup> P. T. O. Chang, G. H. Aynilian, G. A. Cordell, M. Tin-Wa, H. H. S. Fong, R. E. Perdue, and N. Farnsworth, *J. Pharm. Sci.*, 1976, **65**, 561.

<sup>14</sup> R. Storer and D. W. Young, *Tetrahedron*, 1973, **29**, 1217.

or the 6-hydroxy-7-methoxy-isomer on the basis of spectral studies and of its conversion with diazomethane into kokusaginine (8). The chemical shifts of aromatic protons of heliparvifoline in [ $^2\text{H}_6$ ]DMSO (2.57 and 2.80 $\tau$ ) and in the presence of  $\text{D}_2\text{O}$ -NaOD (2.63 and 2.97 $\tau$ ), compared with the data for 6,7-dimethoxydictamnine (8), indicated that the higher-field resonance was due to a C-8 proton adjacent to a phenolic group as in structure (7).

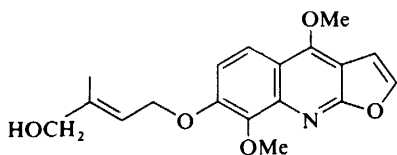


Heliparvifoline (7)

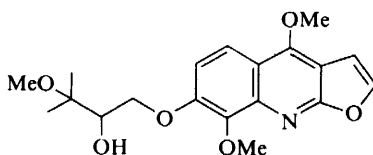


(8)

**Haplatine, Methylevoxine, and Perfamine.** *Haplophyllum* species have continued to yield new furoquinoline alkaloids. 7-Isopentenyl-8-methoxydictamnine is a constituent of *H. perforatum* (cf. Vol. 6) and its oxidation product, haplatine (9), has now been isolated from *H. latifolium*;<sup>12</sup> acid hydrolysis furnishes haplopine (7-hydroxy-8-methoxydictamnine). Methylevoxine (10) was obtained from *H. perforatum*,<sup>15</sup> but



Haplatine (9)

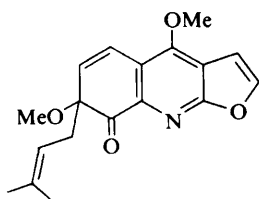


Methylevoxine (10)

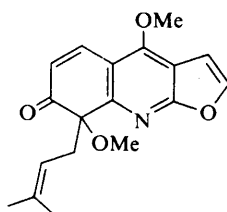
another new furoquinoline, perfamine, from this species is of greater interest.<sup>5</sup> The n.m.r. spectrum shows that the alkaloid is a 4-methoxyfuroquinoline incorporating as additional substituents a methoxy-group, a C-prenyl group, and an oxygen function. The presence of a conjugated ketonic carbonyl group is apparent from the i.r. absorption at 1670  $\text{cm}^{-1}$  and the u.v. spectrum. Resonances in the n.m.r. spectrum at 6.96 $\tau$  (OMe at saturated carbon) and at 2.10 and 3.88 $\tau$  ( $-\text{CH}=\text{CH}-$ ) and the optical activity of the alkaloid are in accord with the proposed structure (11), although (12) does not appear to be excluded. Treatment of perfamine with concentrated sulphuric acid and reaction of the product with diazomethane afforded 7,8-dimethoxydictamnine. A reasonable biosynthetic pathway to perfamine involves C-prenylation of 8-hydroxy-7-methoxydictamnine (or the 7-hydroxy-8-methoxy-isomer). Perfamine thus represents an interesting link with the more reduced alkaloids of *H. perforatum*, perforine and haplophyllidine, which have been assigned structures (13) and (14), respectively.<sup>16</sup>

<sup>15</sup> V. I. Akhmedzhanova, I. A. Bessonova, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, 272 (*Chem. Abs.*, 1975, **83**, 97 662).

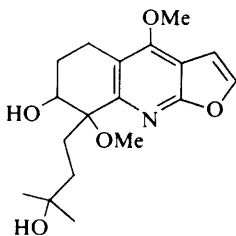
<sup>16</sup> Z. Sh. Faizutdinov, I. A. Bessonova, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1967, 356 (*Chem. Abs.*, 1968, **68**, 69 160); K. L. Seitanidi, M. R. Yagudaev, and S. Yu. Yunusov, *ibid.*, 1973, 507 (*Chem. Abs.*, 1974, **80**, 60 054).



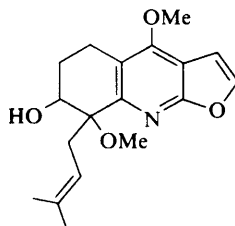
Perfamine (11)



(12)



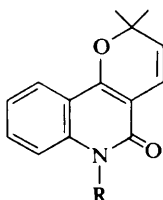
Perforine (13)



Haplophyllidine (14)

**3-Prenylquinoline Alkaloids.**—A large number of alkaloids have already been separated from *Ptelea trifoliata*, including the hemiterpenoids with terminal double bonds that are characteristic of this species (*cf.* Vols. 1—3, 5, and 6). Two groups have now continued the investigation of the tertiary bases and quaternary salts of *P. trifoliata*.

Extraction of the root bark yielded *N*-methylflindersine (16), not found previously in this species, and the new 3-prenyl-2-quinolone (23),<sup>2a</sup> which has been syn-

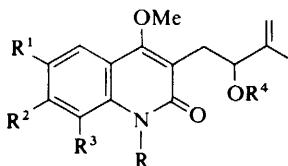


Flindersine (15) R = H

*N*-Methylflindersine (16) R = Me

thesized<sup>17</sup> (Scheme 1). Most of the tertiary bases found in the stems and branches contain a 7,8-methylenedioxy-group; in addition to the known leaf constituent ptelefoline methyl ether (18), the ketone lunidonine (20), obtained previously from *Lunasia amara*, was isolated.<sup>1a</sup> The structure of the new alkaloid hydroxylunidonine (25) from the stems<sup>1a</sup> and from the flowers<sup>2b</sup> was established by spectroscopy and by conversion with zinc and acetic acid into lunidonine (20), presumably by a process of reduction-elimination. The related stem alkaloids 6-methoxylunidine (26), 6-methoxyhydroxylunidine (27), and 6-methoxylunidonine (21) were obtained

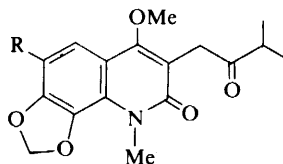
<sup>17</sup> J. L. Gaston and M. F. Grundon, unpublished work.



Ptelefoline (17)  $R^1 = R^3 = \text{OMe}$ ,  $R^2 = R^4 = \text{H}$

Ptelefoline methyl ether (18)  $R^1 = R^3 = \text{OMe}$ ,  $R^2 = \text{H}$ ,  $R^4 = \text{Me}$

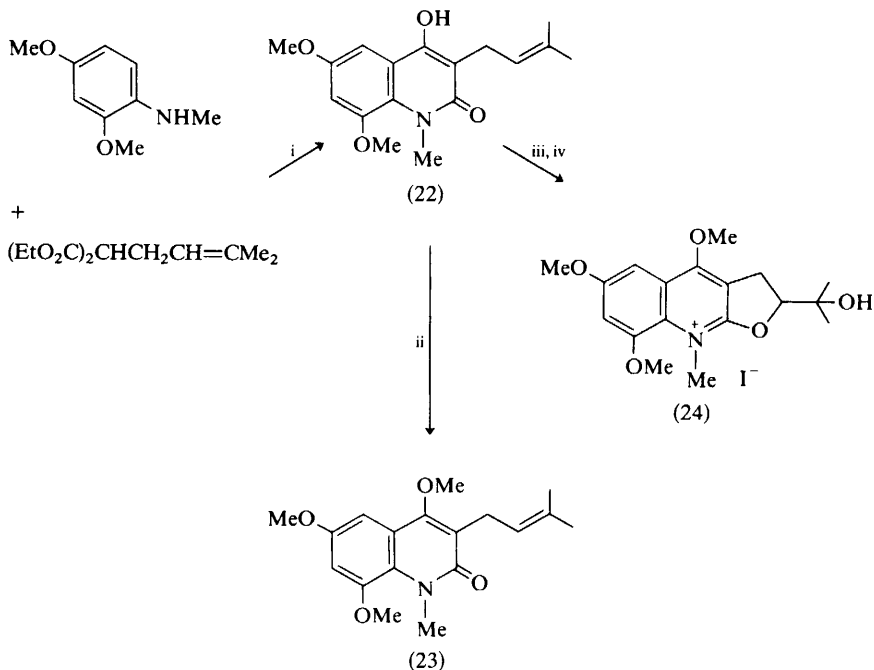
Ptelefolidine (19)  $R^1 = R^4 = \text{H}$ ,  $R^2 + R^3 = \text{OCH}_2\text{O}$



Lunidonine (20)  $R = \text{H}$

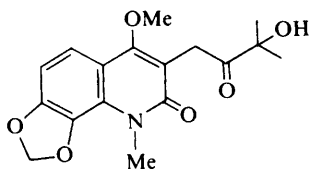
6-Methoxylunidonine (21)  $R = \text{Me}$

for the first time;<sup>1a</sup> their structures were determined by interconversions. Thus, the ketone (21) was formed from the alcohol (26) by oxidation and the reverse process

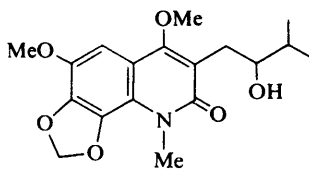


Reagents: i,  $\text{Ph}_2\text{O}$ , reflux; ii,  $\text{CH}_2\text{N}_2$ ; iii,  $m\text{-ClC}_6\text{H}_4\text{CO}_3\text{H}$ ; iv,  $\text{MeI-MeOH}$ ,  $20^\circ\text{C}$ .

Scheme 1

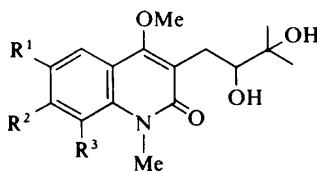


Hydroxylunidonine (25)



6-Methoxylunidine (26)

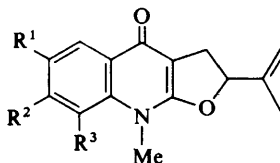
was effected by hydride reduction; dehydration of the diol (27) with toluene-*p*-sulphonic acid furnished the ketone (21). The isopropenyldihydrofuroquinolone ptelefolone (30) was shown previously to be a constituent of *P. trifoliata* and now a second terminal olefin of this type, ptelefolidine (31), has been isolated from the same source.<sup>2b</sup>



6-Methoxyhydroxylunidine (27)  $R^1 = \text{OMe}$ ,  $R^2 + R^3 = \text{OCH}_2\text{O}$

Hydroxylunidine (28)  $R^1 = \text{H}$ ,  $R^2 + R^3 = \text{OCH}_2\text{O}$

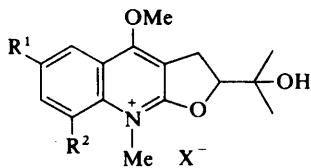
6,8-Dimethoxyedulinine (29)  $R^1 = R^3 = \text{OMe}$ ,  $R^2 = \text{H}$



Ptelefolone (30)  $R^1 = R^3 = \text{OMe}$ ,  $R^2 = \text{H}$

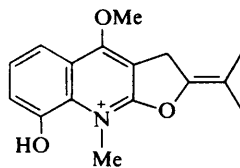
Ptelefolidone (31)  $R^1 = \text{H}$ ,  $R^2 + R^3 = \text{OCH}_2\text{O}$

A full report has appeared of the isolation and characterization of the antimicrobial quaternary derivative pteleatinium salt (32).<sup>1b</sup> Dehydration of the chloride with concentrated sulphuric acid and recovery of the product from a basic solution gave a yellow compound,  $\text{C}_{16}\text{H}_{18}\text{NO}_3$ , formulated as the 8-hydroxy-derivative (34), but by analogy with the compound obtained from ribalinium salt (33)<sup>18</sup> the dehydration product of pteleatinium salt is more likely to be the zwitterion



Pteleatinium salt (32)  $R^1 = \text{H}$ ,  $R^2 = \text{OH}$

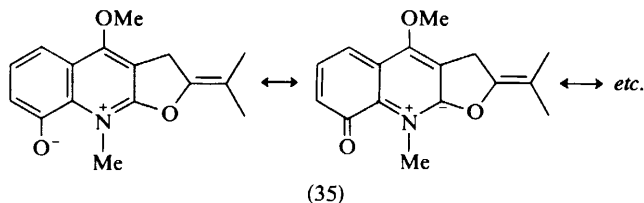
Ribalinium salt (33)  $R^1 = \text{OH}$ ,  $R^2 = \text{H}$



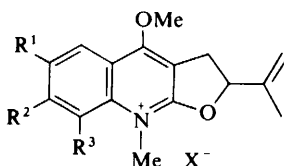
(34)

<sup>18</sup> R. A. Corral and O. O. Orazi, *Tetrahedron*, 1966, **22**, 1153.

(35),  $C_{16}H_{17}NO_3$ ; the u.v. spectrum and analytical data are consistent with this structure. The presence of a tetrasubstituted double bond in compound (35) is of some interest, since dehydration of hydroxyisopropylidihydrofuroquinolines usually furnishes isopropylfuroquinolines. Pteleatinium salt is the principal alkaloid of the



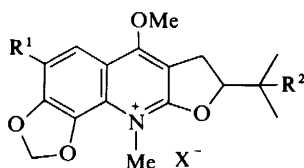
stem and branches of *P. trifoliata* but *O*-methylptelefolonium salt (36), shown previously to be the major quaternary component of the leaves, and the new alkaloid



*O*-Methylptelefolonium salt (36)  $R^1 = R^3 = OMe$ ,  $R^2 = H$

(37)  $R^1 = H$ ,  $R^2 + R^3 = OCH_2O$

(-)-*O*-methylhydroxyluninium salt (38) were also identified.<sup>1b</sup> The structure of the quaternary salt (38) was established by conversion with pyridine into the known

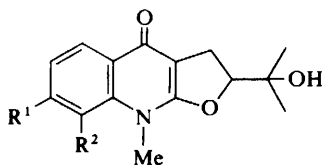


*O*-Methylhydroxyluninium salt (38)  $R^1 = H$ ,  $R^2 = OH$

*O*-Methyl-luninium salt (39)  $R^1 = R^2 = H$

(40)  $R^1 = OMe$ ,  $R^2 = OH$

tertiary base hydroxylunine (41); although an optical rotation is not recorded, the product is likely to be the (+)-derivative, because this enantiomer was obtained



Hydroxylunine (41)  $R^1 + R^2 = OCH_2O$

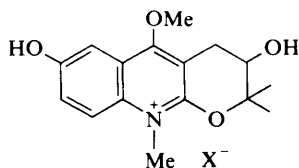
Balfouridine (42)  $R^1 = H$ ,  $R^2 = OMe$

Isoplatydesmine (43)  $R^1 = R^2 = H$

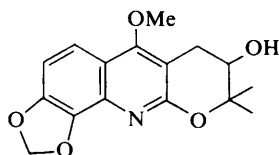
from the leaves of *P. trifoliata*.<sup>19</sup> (–)-*O*-Methylhydroxyluninium salt (38) apparently has the (*S*)-configuration, since the c.d. spectrum is opposite in sign to that of (*R*)-pteleatinium salt (32).<sup>1b</sup> Thus the two quaternary salts of *P. trifoliata* would appear to be derived biosynthetically from epoxides of configuration (*R*) and (*S*), respectively, contrary to the stereochemical correlations usually observed.<sup>20</sup>

*P. trifoliata* contains a number of quaternary alkaloids in addition to the salts *O*-methylptelefolonium (36), pteleatinium (32), *O*-methyluninium (39), and *O*-methylhydroxyluninium (38) that have been identified positively. Thus, treatment of the mixed quaternary fraction with sodium hydroxide is reported to give five hydroxy-derivatives, ptelefolin (17), hydroxylunidine (28), 6,8-dimethoxyedulinine (29), ptelefolidine (19), and 6-methoxyhydroxylunidine (27).<sup>3</sup> The reaction with base clearly results in ring cleavage, suggesting that the new dihydrofuroquinolinium salts (24), (37), and (40) are present in the quaternary fraction as well as *O*-methylptelefolonium salt (36) and *O*-methylhydroxyluninium salt (38). One of these new compounds, 6,8-dimethoxy-*N*-methylplatydesminium iodide (24), has been synthesized recently from the 3-prenyl-2-quinolone (22)<sup>17</sup> (Scheme 1). Cleavage of dihydrofuroquinolinium salts, which occurs very readily with base and some diols, has been shown to be an artefact of the isolation procedures (*cf.* Vol. 6); alkaloids of *P. trifoliata* containing 2-hydroxy-3-methylbutyl groups, *cf.* (27), and 2-hydroxy-3-methylbut-3-enyl substituents, *cf.* (17), also may originate in this way. An alternative interpretation of the base-catalysed reaction of the mixed quaternary alkaloid fraction of *P. trifoliata* is that the hydroxy-derivatives result from ring scission of hydroxydihydropyranoquinolinium salts. One such compound, rutalinium salt (44), was identified earlier as a constituent of rutaceous species (*cf.* Vol. 5) and *P. trifoliata* has now yielded tertiary bases of the hydroxydihydropyranoquinoline series, pteleflorin (45) from the flowers<sup>2b</sup> and the isomeric neohydroxylunine (46) from the stems.<sup>1a</sup> Neohydroxylunine is a known rearrangement product of hydroxylunine (41) (also a constituent of *P. trifoliata*) but hitherto has not been obtained from natural sources.

The hydroxydihydropyranoquinolone (–)-ribalinine (47) is a constituent of the trunk and root bark of *Araliopsis soyauxii*;<sup>4</sup> the (+)-enantiomer (folifine) was obtained earlier from *Haplophyllum* species<sup>21</sup> and the racemate, which has been synthesized<sup>22,23</sup> was isolated from *B. riedelianum*.<sup>23</sup> (+)-Isoplatydesmine (43) has also been isolated from *A. soyauxii* and can be regarded as a new alkaloid since isoplatydesmine obtained recently from *Pelea barbigera* (*cf.* Vol. 6) probably is the



Rutalinium salt (44)



Pteleflorin (45)

<sup>19</sup> J. Reisch, L. Szendrei, I. Novák, E. Minker, and V. Pápay, *Tetrahedron Letters*, 1969, 3803.

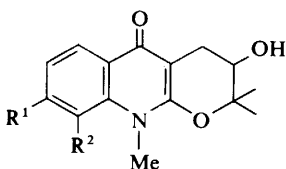
<sup>20</sup> M. F. Grundon and I. S. McColl, *Phytochemistry*, 1975, **14**, 143.

<sup>21</sup> Z. Sh. Faizutdinova, I. A. Bessonova, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1967, 257.

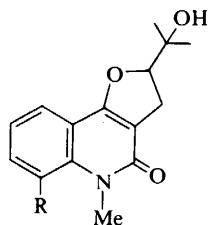
<sup>22</sup> R. M. Bowman and M. F. Grundon, *J. Chem. Soc. (C)*, 1966, 1504.

<sup>23</sup> R. A. Corral and O. O. Orazi, *Tetrahedron Letters*, 1967, 583.





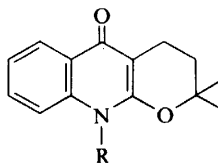
Neohydroxylunine (46)  $R^1 + R^2 = \text{OCH}_2\text{O}$   
 Ribalinine (47)  $R^1 = R^2 = \text{H}$



Araliopsine (48)  $R = \text{H}$   
 $\psi$ -Balfourdine (49)  $R = \text{OMe}$

(-)-enantiomer or the racemate. The most interesting alkaloid of *A. soyauxii* is the dihydrofuroquinolone (+)-araliopsine (48). Although the analogous 8-methoxy-2-quinolone (49) is a well-known rearrangement product of balfourdine (42),<sup>24</sup> angular furoquinolones of this type have not been recognized previously as natural constituents.

A new alkaloid, haplobucharine from *H. bucharicum*, was shown by spectral studies to be the *N*-prenyl derivative (51) of another *Haplophyllum* alkaloid, khaplofoline (50).<sup>25</sup>

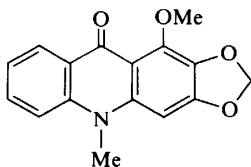


Khaplofoline (50)  $R = \text{H}$   
 Haplobucharine (51)  $R = \text{CH}_2\text{CH} = \text{CMe}_2$

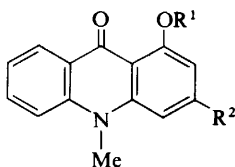
A high-yield synthesis of flindersine (15), involving base-catalysed reaction of 4-hydroxy-2-quinolone with 3-methylbut-2-enal, has been reported.<sup>26</sup>

## 2 Acridone Alkaloids

Evoxanthine (52) has been isolated from *Oricia gabonensis*<sup>27</sup> and the roots of *Boenninghausenia albiflora* are shown to contain the acridone (53) and two unidentified acridone alkaloids.<sup>28</sup>



(52)



(53)  $R^1 = R^2 = \text{H}$   
 (54)  $R^1 = \text{Me}, R^2 = \text{OMe}$

<sup>24</sup> H. Rapoport and K. E. Holden, *J. Amer. Chem. Soc.*, 1960, **82**, 4395; M. F. Grundon and K. J. James, *Chem. Comm.*, 1970, 337.

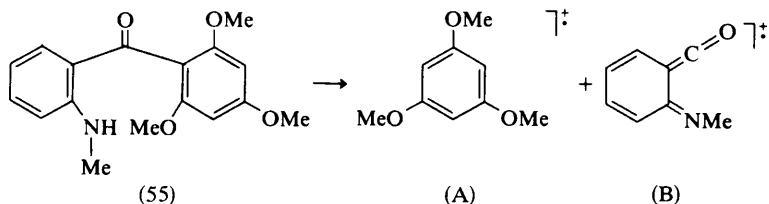
<sup>25</sup> E. F. Nesmelova, I. A. Bessonova, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, 815 (*Chem. Abs.*, 1976, **84**, 150 808).

<sup>26</sup> Ae. De Groot and B. J. M. Jansen, *Tetrahedron Letters*, 1975, 3407.

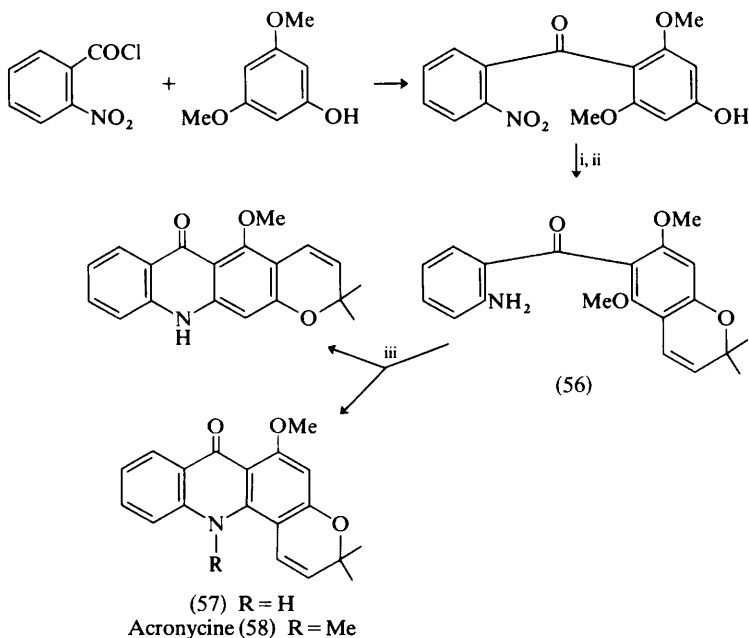
<sup>27</sup> P. G. Waterman, *Phytochemistry*, 1975, **14**, 2092.

<sup>28</sup> J. Vaquette, A. Cavé, A. Fournet, and A. Bouquet, *Plant. Med. Phytother.*, 1975, **9**, 304.

Tecleanone (55), the first *o*-aminobenzophenone to be isolated from a natural source, is a constituent of *Diphasia klaineana*,<sup>29</sup> *Teclea verdoorniana*,<sup>29</sup> and *T. grandifolia*.<sup>30</sup> The structure assigned to tecleanone was based on the spectral data, fragmentation in the mass spectrometer into the ions (A) and (B) being particularly



informative. Lewis and co-workers<sup>31</sup> showed that reaction of tecleanone with sodium hydride in DMSO furnishes the acridone (54), an alkaloid found in two rutaceous plants, and suggested that this represents the biosynthetic route. On this basis, a new biomimetic synthesis of the antitumour alkaloid acronycine (58) was accomplished (Scheme 2).<sup>32</sup> Cyclization of the *o*-aminobenzophenone (56) resulted



Reagents: i,  $\text{HC}\equiv\text{C}-\text{C}(\text{Cl})\text{Me}_2$ ; ii,  $\text{Zn}-\text{EtOH}$ ; iii,  $\text{NaH}-\text{DMSO}$ .

**Scheme 2**

<sup>29</sup> Zs. Rozsa, K. Szendrei, I. Novák, J. Reisch, and E. Minker, *Pharmazie*, 1975, **30**, 753.

<sup>30</sup> A. C. Casey and A. Malhotra, *Tetrahedron Letters*, 1975, 401.

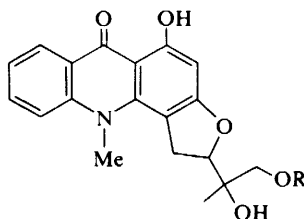
<sup>31</sup> M. S. Khan, J. R. Lewis, and R. A. Watt, *Chem. and Ind.*, 1975, 744.

<sup>32</sup> J. Adams, P. Gupta, and J. R. Lewis, *Chem. and Ind.*, 1976, 109.

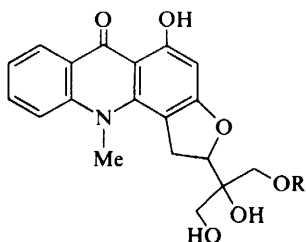
in displacement of a methoxy-group to give a mixture of acridones with linear and angular annelation; the latter (57) was converted into acronycine by methylation.

Dihydrofuroacridones, including gravacridone diol (59), were obtained from *Ruta graveolens* some time ago (cf. Vol. 4). A further investigation has now resulted in the isolation of a new alkaloid, gravacridone triol (61), and an inseparable mixture of glycosides (60) and (62), which were hydrolysed to the corresponding aglycones.<sup>33</sup> The glucose residues are attached to secondary hydroxy-groups, since acetylation of the glycoside mixture with acetic anhydride and pyridine gives acetates containing tertiary hydroxyl functions.

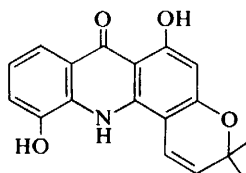
Atalaphyllidine obtained from *Atlanta monophylla* was shown to have structure (63).<sup>34</sup>



(59) R = H  
(60) R = glucosyl



Gravacridone triol (61) R = H  
(62) R = glucosyl



Atalaphyllidine (63)

<sup>33</sup> J. Reisch, Zs. Rozsa, K. Szendrei, I. Novák, and E. Minker, *Phytochemistry*, 1976, **15**, 240.

<sup>34</sup> S. C. Basa, *Experientia*, 1975, **31**, 1387.

**1 General**

A list of new heterocyclic natural products and of new syntheses of heterocyclic natural products is now issued as a periodical feature. The literature coverage extends from 1975 and the natural products are classified as steroids, alkaloids, antibiotics, *etc.*<sup>1</sup> New alkaloids appearing in the literature during 1974 and 1975 also appear in two further volumes of a more general compendium.<sup>2</sup> Data on more than 3000 alkaloids and their derivatives have been collected in a two-volume work.<sup>3</sup> A new series reviewing progress in alkaloid chemistry has been launched, Boit's classical text being regarded as Volume 1.<sup>4</sup>

Reviews have appeared on the distribution and systematic significance of alkaloids of the Rutaceae<sup>5</sup> and of the Papaveraceae<sup>6</sup> and on the taxonomic significance of benzyltetrahydroisoquinoline-derived alkaloids in particular.<sup>7</sup> The isolation of alkaloids from plants in the Soviet Union has been discussed.<sup>8</sup> In addition to continued alkaloid screening studies,<sup>9</sup> surveys encompassing detection of alkaloids have been carried out on plants from Argentina,<sup>10</sup> India,<sup>11</sup> and Morelos State, Mexico.<sup>12</sup>

In another study, plants were examined both for their effect on larvae and for the presence of alkaloids although no correlation was obtained.<sup>13</sup> The occurrence and chemistry of alkaloids of Central Asian plants have been surveyed.<sup>14</sup> Sections on the chemistry of isoquinoline alkaloids are included in two books on natural product

<sup>1</sup> T. Kametani, K. Fukumoto, and the editorial staff, *Heterocycles*, 1975, **3**, 732 and features in subsequent issues.

<sup>2</sup> 'Dictionary of Organic Compounds', 11th and 12th Supplements, ed. J. B. Thomson, Eyre and Spottiswoode, London, 1975 and 1976.

<sup>3</sup> J. S. Glasby, 'Encyclopedia of the Alkaloids, Vols. 1 and 2', Plenum, New York, 1975.

<sup>4</sup> W. Dopke, 'Ergebnisse der Alkaloid Chemie', 1960—1968, Vol. 2 and 1969—1970, Vol. 3, Akademie Verlag, Berlin, 1976.

<sup>5</sup> P. G. Waterman, *Biochem. Syst. Ecol.*, 1975, **3**, 149.

<sup>6</sup> J. A. Duke, *C.R.C. Crit. Rev. Toxicol.*, 1974, **3**, 1.

<sup>7</sup> C. M. Andrade da Mata Rezende, O. R. Gottlieb, and M. C. Marx, *Biochem. Syst. Ecol.*, 1975, **3**, 63.

<sup>8</sup> S. Yu. Yunusov, in 'Some Recent Developments in the Chemistry of Natural Products', ed. S. Rangaswami and N. V. Subba Rao, Prentice-Hall, New Delhi, 1972, p. 380.

<sup>9</sup> S. J. Smolenski, H. Silinis, and N. R. Farnsworth, *Lloydia*, 1975, **38**, 225, 411, 497.

<sup>10</sup> O. Hnatyszyn, R. V. D. Rondina, and J. D. Coussio, *Planta Med.*, 1976, **29**, 234.

<sup>11</sup> L. D. Kapoor, A. Singh, S. L. Kapoor, and S. N. Srivastava, *Lloydia*, 1975, **38**, 221; H. O. Saxena, *ibid.*, p. 346.

<sup>12</sup> J. Vazquez Sanchez, *Ciencia (Mexico City)*, 1974, **29**, 139.

<sup>13</sup> B. D. Patterson, S. K. W. Khalil, L. J. Schermeister, and M. S. Quraishi, *Lloydia*, 1975, **38**, 391.

<sup>14</sup> A. S. Sadykov, *Nauka Uzb.*, 1974, **1**, 205 (*Chem. Abs.*, 1976, **84**, 102 264).

chemistry.<sup>15,16</sup> The chemistry<sup>17</sup> and pharmacology<sup>17,18</sup> of alkaloids of the genus *Berberis* have been reviewed. Another review deals with convulsant alkaloids.<sup>19</sup> The latest volume of Manske and Holmes includes a review of the pharmacology and toxicology of the Papaveraceae alkaloids.<sup>20</sup>

Application of bis-(2-ethylhexyl) orthophosphate as a liquid ion exchanger in the complete or selective extraction of alkaloids from a buffered aqueous phase has been described.<sup>21</sup> The behaviour of the salts of various alkaloids upon titration with base has been compared.<sup>22</sup> Correlations have been made between the  $R_f$  of a number of alkaloids and the pH of an aqueous buffer solution which extracts half of the alkaloid from an aqueous solution.<sup>23</sup> The stabilization of alkaloid solutions has been discussed.<sup>24</sup> Chromatographic separations of alkaloids by ion-exchange,<sup>25</sup> adsorption,<sup>26</sup> thin-layer,<sup>27</sup> paper,<sup>27</sup> and liquid chromatography<sup>28</sup> have been reviewed. Reference lists have been compiled for methods and applications published in 1970–73 of chromatography<sup>29</sup> and of electrophoresis<sup>30</sup> of alkaloids on paper and thin layers. The optimum composition of Dragendorff's reagent for efficient alkaloid precipitation has been examined.<sup>31</sup>

Chiral lanthanide n.m.r. shift reagents have been used to determine the enantiomeric composition of samples of salsolidine, tetrahydropalmatine, *N*-methylpavine, and laudanosine.<sup>32</sup> The study of various types of isoquinoline alkaloid is included in a review of applications of chiroptical techniques.<sup>33</sup>

## 2 $\beta$ -Phenethylamine Alkaloids

Alkaloid isolations and structural elucidations are summarized in Table 1. The cactus *Ariocarpus scapharostrus*, which has not previously been investigated, afforded four phenethylamines including hordenine and *NN*-dimethyl-3,4-dimethoxyphenethylamine. This is the first recorded occurrence of the latter in a

<sup>15</sup> S. Ho, in 'Natural Products Chemistry', Vol. 2, ed. K. Nakanishi, T. Goto, S. Ho, S. Natori, and S. Nozoe, Kodansha, Tokyo and Academic Press, New York, 1975.

<sup>16</sup> T. R. Govindachari and N. Viswanathan, ref. 8, p. 119.

<sup>17</sup> M. Ikram, *Planta Med.*, 1975, **28**, 353.

<sup>18</sup> K. Drost, M. Szafer, and Z. Kowalewski, *Herba Pol.*, 1974, **20**, 301 (*Chem. Abs.*, 1975, **83**, 101).

<sup>19</sup> D. R. Curtis and G. A. R. Johnston, 'Poisons of Plant Origin, Vol. 2. Neuropoisons: Their Pathophysiological Actions', ed. L. L. Simpson and D. R. Curtis, Plenum, New York, 1974, p. 207.

<sup>20</sup> V. Preininger, in 'The Alkaloids', Vol. 15, ed. R. H. F. Manske, Academic Press, New York, 1975, p. 207.

<sup>21</sup> L. Jusiak, *Acta Pol. Pharm.*, 1974, **31**, 635 (*Chem. Abs.*, 1975, **83**, 15 537).

<sup>22</sup> I. V. A. El-Rabbat and A. A. Abou-Ouf, *Egypt. J. Pharm. Sci.*, 1974, **15**, 277 (*Chem. Abs.*, 1975, **83**, 125 857).

<sup>23</sup> T. Artykova, Kh. N. Aripov, and T. T. Shakirov, *Khim. prirod. Soedinenii*, 1975, **11**, 28 (*Chem. Abs.*, 1975, **83**, 79 420).

<sup>24</sup> J. Lutomski, *Herba Pol.*, 1974, **20**, 386 (*Chem. Abs.*, 1975, **83**, 84 734).

<sup>25</sup> Z. Deyl, *J. Chromatogr. Libr.*, 1975, **3** (Liquid Column Chromatography), 637.

<sup>26</sup> K. Macek, ref. 25, p. 887.

<sup>27</sup> K. Macek, 'Pharmaceutical Applications of Thin Layer and Paper Chromatography', ed. K. Macek, Elsevier, Amsterdam, 1972, p. 431.

<sup>28</sup> R. Verpoorte and A. B. Svendsen, *Pharm. Weekblad*, 1975, **110**, 1021.

<sup>29</sup> K. Macek, I. M. Hais, J. Kopecky, V. Schwarz, J. Gasparic, and J. Churacek, *J. Chromatog., Suppl. Vol. 5*, 1976, 278.

<sup>30</sup> Z. Deyl, J. Kopecky, J. Davidek, M. Juricova, and R. Helm, *J. Chromatog., Suppl. Vol. 4*, 1975, 558.

<sup>31</sup> T. Mitsui and Y. Fujimura, *Eisei Kagaku*, 1975, **21**, 183 (*Chem. Abs.*, 1976, **84**, 159 352).

<sup>32</sup> N. A. Shaath and J. O. Soine, *J. Org. Chem.*, 1975, **40**, 1987.

<sup>33</sup> P. M. Scopes in 'Progress in the Chemistry of Organic Natural Products', ed. W. Herz, H. Grisebach, and G. W. Kirby, Springer, New York, 1975, **32**, 204.

**Table 1** Isolation of  $\beta$ -phenethylamine alkaloids

Species	Alkaloid	Ref.
<i>Acacia spirorbis</i>	Hordeanine	39
<i>Ariocarpus scapharostus</i>	Hordeanine	34
	NN-Dimethyl-3,4-dimethoxyphenethylamine	
	N-Methyl-3,4-dimethoxyphenethylamine	
	N-Methyltyramine	
<i>Aspergillus glaucus</i>	Asperglaucide <sup>a</sup>	50
<i>Azureocereus ayacuchensis</i>	Tyramine	35
<i>Boletus zelleri</i>	N-Methyltyramine <sup>b,c,d</sup>	42
	Hordeanine <sup>b,e</sup>	
	Tyramine <sup>b,c,f</sup>	
	Unidentified alkaloids <sup>c,g</sup>	
<i>Cannabis sativa</i> <sup>h</sup>	Hordeanine	40
<i>Cereus jacamaru</i>	Tyramine	36
<i>Combretum zeyheri</i>	L-3-(3-Aminomethylphenyl)alanine	43
	3-(3-Carboxyphenyl)alanine	44
	3-(3-Hydroxymethylphenyl)alanine	
	N-Methyl-L-tyrosine	46
<i>Corphantha bumamma</i>	Hordeanine	37
	N-Methyl-3,4-dimethoxyphenethylamine <sup>i</sup>	
	N-Methyl-4-methoxyphenethylamine <sup>i</sup>	
<i>C. calipensis</i> <sup>i</sup>	Hordeanine <sup>i</sup>	37
	N-Methyltyramine <sup>i</sup>	
<i>C. grenwoodii</i>	NN-Dimethyl-3,4-dimethoxy- $\beta$ -methoxy-phenethylamine	37
	NN-Dimethyl-3,4-dimethoxyphenethylamine <sup>i</sup>	
	Hordeanine <sup>i</sup>	
	$\beta$ -O-Methylnormacromerine	
	$\beta$ -O-Methylsynephrine <sup>i</sup>	37, 38
	N-Methyl-3,4-dimethoxyphenethylamine	
	Normacromerine	38
	Synephrine	
<i>C. radians</i>	Hordeanine	37
	N-Methyltyramine	
<i>C. vivipara</i>	Hordeanine	37
<i>Dolicothele longimamma</i>	Longimammine <sup>k</sup>	47, 48
	(-)-Normacromerine	
	( $\pm$ )-Synephrine	
<i>Euphorbia fischeriana</i>	Asperglaucide <sup>a</sup>	49
<i>Fagara rubescens</i>	Rubesamide (1)	51
<i>Pachycereus pectenaboriginum</i>	3,4-Dimethoxyphenethylamine	36

<sup>a</sup> I.e. O-Acetyl-N-(N'-benzoyl-L-phenylalanyl)-L-phenylalaninol; <sup>b</sup> Also detected in *Polyporus berkleyi* and *P. sulphureus*; <sup>c</sup> Also detected in *P. giganteus* (ref. 37); <sup>d</sup> Also detected in *Fomes pini* and *P. guttulatus* (ref. 37); <sup>e</sup> Also detected in *P. cristatus*; <sup>f</sup> Also detected in *P. tomentosus*; <sup>g</sup> Also detected in *Fomes conchatus*, *F. fraxineus*, *Polyporus abietinus*, *P. borealis*, *P. cinnabarinus*, *P. giganteus*, *P. guttulatus*, *P. lapponicus*, *P. rhodes*, and *P. spumeus*; <sup>h</sup> Cannabamines A, B, C, and D also isolated (cf. Vol. 4); <sup>i</sup> In traces; <sup>j</sup> cf. Vol. 5; <sup>k</sup> i.e. N-Methyl-4-methoxy- $\beta$ -hydroxy- $\beta$ -phenethylamine.

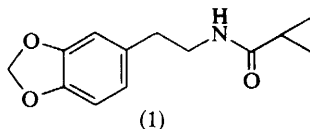
species of *Ariocarpus*.<sup>34</sup> Tyramine was the single major alkaloid of the cacti *Azureocereus azucuchensis*<sup>35</sup> and *Cereus jamacaru*.<sup>36</sup> Five cactus species of the genus *Coryphantha* were shown to contain nine different known  $\beta$ -phenethylamines

<sup>34</sup> J. G. Bruhn, *Phytochemistry*, 1975, **14**, 2509.

<sup>35</sup> T. M. Lee, J. L. McLaughlin, and W. H. Earle, *Lloydia*, 1975, **38**, 363.

<sup>36</sup> J. G. Bruhn and J.-E. Lindgren, *Lloydia*, 1976, **39**, 175.

using t.l.c., g.l.c., g.c.-m.s.<sup>37</sup> In the case of *C. greenwoodii*, three of the alkaloids were isolated and fully characterized in an independent study.<sup>38</sup> Hordenine, which was detected in all five species,<sup>37</sup> has also been isolated from the trunk bark of *Acacia spirorbis*<sup>39</sup> and the leaves of *Cannabis sativa*.<sup>40,41</sup> The isolation of this alkaloid from collections of *Polyporus berkleyi* (cf. Vol. 6, p. 113) has prompted examination of other higher fungi, e.g. *Boletus zelleri*.<sup>42</sup> Although hordenine, tyramine, and/or *N*-methyltyramine were detected in twelve of the fifty-three specimens examined, little chemotaxonomic significance could be gleaned from the results.<sup>42</sup> Three *meta*-substituted derivatives of phenylalanine have been isolated from the seeds of *Combretum zeyheri*.<sup>43,44</sup> Of these, the carboxy and hydroxymethyl derivatives<sup>44</sup> were previously isolated from the legume *Caesalpinia tinctoria*.<sup>45</sup> The most recent addition to the group was shown to be the aminomethyl derivative.<sup>43</sup> The seeds also afforded *N*-methyl-L-tyrosine,<sup>46</sup> this enantiomer not having been obtained previously from natural sources. The Mexican 'peyote' cactus *Dolichothele longimamma* afforded the new alkaloid longimammine (*N*-methyl-4-methoxy- $\beta$ -hydroxy- $\beta$ -phenethylamine) together with (-)-normacromerine and ( $\pm$ )-synephrine.<sup>47,48</sup> A new phenylalaninol derivative, *O*-acetyl-*N*-(*N'*-benzoyl-L-phenylalanyl)-L-phenylalaninol, has been isolated from *Euphorbia fischeriana* and its structure confirmed by synthesis.<sup>49</sup> The same compound was also isolated from *Aspergillus glaucus* and named asperglaucide.<sup>50</sup> The novel alkaloid rubesamide (1) isolated from the root bark of *Fagara rubescens* contains a cyclopropane carboxamide grouping.<sup>51</sup> Early peyote research has been reviewed.<sup>52</sup>



Reviews of the different assay methods for catecholamines<sup>53,54</sup> and biogenic amines<sup>55</sup> are not readily available. Gas-chromatographic and spectrofluorometric methods of analyzing catecholamines have been compared.<sup>56</sup> In another comparative study it has been concluded that replacement of personnel employed in t.l.c.

<sup>37</sup> J. G. Bruhn, S. Agurell, and J.-E. Lindgren, *Acta Pharm. Suecica*, 1975, **12**, 199.

<sup>38</sup> R. L. Ranieri and J. L. McLaughlin, *Lloydia*, 1976, **39**, 172.

<sup>39</sup> C. Poupat and T. Sevenet, *Phytochemistry*, 1975, **14**, 1881.

<sup>40</sup> F. S. El-Ferali and C. E. Turner, *Phytochemistry*, 1975, **14**, 2304.

<sup>41</sup> F. S. El-Ferali and C. E. Turner, *Lloydia*, 1975, **38**, 538.

<sup>42</sup> T. M. Lee, L. G. West, J. L. McLaughlin, L. R. Brady, J. L. Lowe, and A. H. Smith, *Lloydia*, 1975, **38**, 450.

<sup>43</sup> K. Mivauluka, B. V. Charlwood, J. M. Briggs, and E. A. Bell, *Biochem. Physiol. Pflanz.*, 1975, **168**, 15.

<sup>44</sup> E. A. Bell, K. Mivauluka, and B. V. Charlwood, *Phytochemistry*, 1975, **14**, 858.

<sup>45</sup> R. Watson and J. L. Fowden, *Phytochemistry*, 1973, **12**, 617.

<sup>46</sup> K. Mivauluka, E. A. Bell, B. V. Charlwood, and J. M. Briggs, *Phytochemistry*, 1975, **14**, 1657.

<sup>47</sup> R. L. Ranieri and J. L. McLaughlin, *Lloydia*, 1975, **38**, 537.

<sup>48</sup> R. L. Ranieri and J. L. McLaughlin, *J. Org. Chem.*, 1976, **41**, 319.

<sup>49</sup> D. Uemura, K. Sugiura, and Y. Hirata, *Chem. Letters*, 1975, 537.

<sup>50</sup> R. E. Cox, K. K. Chexal, and J. S. E. Holker, *J.C.S. Perkin I*, 1976, 578.

<sup>51</sup> B. A. Dadson and A. Minta, *J.C.S. Perkin I*, 1976, 146.

<sup>52</sup> J. G. Bruhn and B. Holmstedt, *Econ. Bot.*, 1974, **28**, 353.

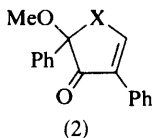
<sup>53</sup> K. Imai and Z. Tamura, *Rinsho Kagaku*, 1975, **4**, 12 (*Chem. Abs.*, 1976, **84**, 147 014).

<sup>54</sup> W. C. Lee, *Taehan Yakrihak Chapehi*, 1972, **8**, 1 (*Chem. Abs.*, 1975, **83**, 39 557).

<sup>55</sup> T. Nagatsu, *Rinsho Kagaku*, 1975, **4**, 1 (*Chem. Abs.*, 1976, **84**, 147 016).

<sup>56</sup> B. I. Keda and K. B. Vinnitskaya, *Lab. Delo*, 1975, 515 (*Chem. Abs.*, 1975, **83**, 189 921).

assay of amphetamines and other drugs of abuse by automated immunoassay systems cannot be justified in view of the exorbitant costs of running the latter.<sup>57</sup> Reviews<sup>58-67</sup> and applications of individual methods of analysis to various types of phenethylamine are summarized in Table 2. A number of the methods of analysis involve formation of fluorescent derivatives with dansyl chloride<sup>68,69</sup> or with fluorescamine.<sup>70</sup> 2-Acyloxy- and 2-alkoxy-3(2*H*)-furanones, e.g. (2; X = O) react with primary amines, RNH<sub>2</sub>, in a similar way to the latter reagent to give fluorescent derivatives (2; X = NR).<sup>71</sup>



Two further analytical methods are based on the formation of metal complexes. Reaction of dopamine with K<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub> gives a Cr complex which can be assayed by atomic absorption spectroscopy, carbon rod absorption spectroscopy or, if K<sub>2</sub><sup>51</sup>Cr<sub>2</sub>O<sub>7</sub> has been used, by liquid scintillation spectroscopy. Since the complex still gives a reaction with fluorescamine, the side-chain is thought not to be involved in the formation of the complex.<sup>72</sup> Methamphetamine hydrochloride can be precipitated as a Bi complex. Determination of the amount of Bi remaining in solution by atomic absorption spectroscopy provides an indirect method of assay for the amphetamine.<sup>73</sup>

It has been shown that reaction of dopa with diazomethane gives a variety of *O*- and *N*-methylated derivatives, e.g. (3; R = Me), together with methyl 3,4-dimethoxycinnamate. The n.m.r. spectrum of the intermediate (3; R = CHO) used in the synthesis of (3; R = Me) showed an interesting doubling of the methoxy and

<sup>57</sup> K. K. Kaistha and R. Tadrus, *J. Chromatog.*, 1975, **109**, 149.

<sup>58</sup> F. W. D. Rost and A. G. E. Pearse, 'Fluorescence Techniques in Cell Biology, Proceedings of the Conference on Quantitative Fluorescence Techniques as Applied to Cell Biology 1972', ed. A. A. Thayer and M. Sernetz, Springer, New York, 1973, p. 199.

<sup>59</sup> A. Bjorklund and B. Falck, ref. 58, p. 171; A. Bjorklund, B. Falck, and Ch. Owman, *Methods Invest. Diagn. Endocrinol. (Thyroid Biog. Amines)*, 1972, **1**, 318.

<sup>60</sup> G. Jonsson, ref. 58, p. 191.

<sup>61</sup> K. Morita and M. Oka, *Rinsho Kagaku*, 1975, **4**, 17 (*Chem. Abs.*, 1976, **84**, 132 235); T. Nagatsu, *ibid.*, 1975, **3**, 364 (*Chem. Abs.*, 1976, **84**, 161 265); A. A. Anton and D. F. Sayre, *Methods Invest. Diagn. Endocrinol. (Thyroid Biog. Amines)*, 1972, **1**, 398.

<sup>62</sup> A. Mori, *Rinsho Kagaku*, 1975, **4**, 34 (*Chem. Abs.*, 1976, **84**, 132 132); S. Wilk, S. E. Gitlow, and L. M. Bertani, *Methods Invest. Diagn. Endocrinol. (Thyroid Biog. Amines)*, 1972, **1**, 452.

<sup>63</sup> B. Hartman and S. Spector, *Methods Invest. Diagn. Endocrinol. (Thyroid Biog. Amines)*, 1972, **1**, 497.

<sup>64</sup> T. Nagatsu, *Rinsho Kagaku*, 1975, **4**, 5 (*Chem. Abs.*, 1976, **84**, 147 015).

<sup>65</sup> K. Engelman, *Methods Invest. Diagn. Endocrinol. (Thyroid Biog. Amines)*, 1972, **1**, 437; I. J. Kopin, *ibid.*, p. 489.

<sup>66</sup> L. Bertilsson and M. Asberg, Proceedings of the 6th International Congress on Pharmacology, 1975, ed. M. Airaksinen, Pergamon, Oxford, 1976, Vol. 3, p. 269; H. Miyazaki and Y. Hashimoto, *Rinsho Kagaku*, 1975, **4**, 53 (*Chem. Abs.*, 1976, **84**, 161 255).

<sup>67</sup> J. J. Pisano, *Methods Invest. Diagn. Endocrinol. (Thyroid Biog. Amines)*, 1972, **1**, 474.

<sup>68</sup> H. Yoshida and T. Nakajima, *Rinsho Kagaku*, 1975, **3**, 417 (*Chem. Abs.*, 1976, **84**, 161 267).

<sup>69</sup> Cf. Table 2, refs. p, pp, and kkk.

<sup>70</sup> Cf. Table 2, refs. i, u, nn, and jji.

<sup>71</sup> M. Weigle, J. P. Teng, S. De Bernardo, R. Czajkowski, and W. Leimgruber, *J. Org. Chem.*, 1976, **41**, 388.

<sup>72</sup> N. E. Naftchi, M. A. Becker, and A. S. Akerkar, *Analyt. Biochem.*, 1975, **66**, 423.

<sup>73</sup> T. Mitsui, Y. Fujimura, and T. Suzuki, *Bunseki Kagaku*, 1975, **24**, 244 (*Chem. Abs.*, 1976, **84**, 35 390).



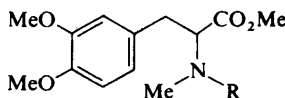
**Table 2** Analysis of *β*-phenethylamines

Method	Substances analysed
Chemical ionization m.s.	A <sup>a</sup>
Colorimetry	A, <sup>b</sup> C, <sup>c,d</sup> dopa, <sup>d,e</sup> D, <sup>f</sup> PA, <sup>f</sup> tyrosine <sup>d-f</sup>
Cytofluorometry and microspectrophotometry	Arylethylamines, <sup>58</sup> B, <sup>59</sup> C, <sup>g</sup> D, <sup>g</sup> dopa <sup>g</sup>
Enzymic double-isotope method	C <sup>h</sup>
Fluorometry	A, <sup>i</sup> B, <sup>60</sup> C, <sup>60,61,j-k</sup> dopa, <sup>k,r</sup> D, <sup>k,l,n,o,q,s,t</sup> MT, <sup>k,m,n</sup> 3-methoxytyrosine, <sup>u</sup> MD, <sup>v</sup> tyrosine, <sup>q</sup> A, <sup>w</sup> B, <sup>x</sup> dopamine 3- and 4- <i>O</i> -sulphates, <sup>y</sup> T <sup>x</sup> A, <sup>w,z,aa-cc</sup> C <sup>62,cc-rr</sup> , NN-dimethylphenethylamine, <sup>cc</sup> D, <sup>ff</sup> MT, <sup>88</sup> N-methylphenethylamine, <sup>cc</sup> β-phenethyl- amine, <sup>cc</sup> PA, <sup>hh</sup> T <sup>ff</sup>
Immunoassay	C <sup>63</sup>
Ion-exchange paper chromatography	A <sup>ii</sup>
Isotopic methods	B, <sup>64</sup> C <sup>65</sup>
Liquid chromatography	A, <sup>jj</sup> 3,4-dimethoxyphenethylamine, <sup>kk</sup> dopa, <sup>ll,mm</sup> D, <sup>ll-nnn</sup> dopamine sulphate, <sup>y</sup> α-methyl dopa, <sup>ll</sup> C <sup>ll-pp</sup>
Mass fragmentography	A, <sup>qq</sup> C, <sup>rr,ss</sup> MT, <sup>ss</sup> B <sup>66</sup>
α <sub>D</sub> of 2,4-dinitrophenyl derivative	A <sup>tt</sup>
Oxidation to aryl aldehyde	C <sup>67,uu</sup>
Polarography	C, <sup>vv</sup> dopa, <sup>vv</sup> D, <sup>vv</sup> α-methyl dopa <sup>vv</sup>
Radioimmunoassay	A, <sup>ww</sup> C, <sup>xx</sup> dopa, <sup>xx</sup> D, <sup>xx</sup> 3,4-dimethoxyphenethylamine <sup>kk,yy</sup>
Resonance Raman spectroscopy	C <sup>zz</sup>
Spin immunoassay	A <sup>aaa,bbb</sup>
Titration	C <sup>ccc,ddd</sup>
T.l.c.	A, <sup>bb,eee-hhh</sup> B, <sup>iii</sup> cactus alkaloid, <sup>jjj</sup> C, <sup>fff,ggg,kkk,lll</sup> dopa, <sup>iii</sup> D, <sup>iii,kkk</sup> mescaline, <sup>fff,ggg</sup> N-methylphenethylamine, <sup>fff</sup> β-phenethylamine, <sup>fff,ggg</sup> β-phenethylamines, <sup>iii</sup> T <sup>mmm</sup>
Tyrosinase-catalysed O <sub>2</sub> consumption	L-Tyrosine <sup>nnn</sup>
Ultrahistochemistry	B, <sup>ooo</sup> C <sup>ooo,ppp</sup>

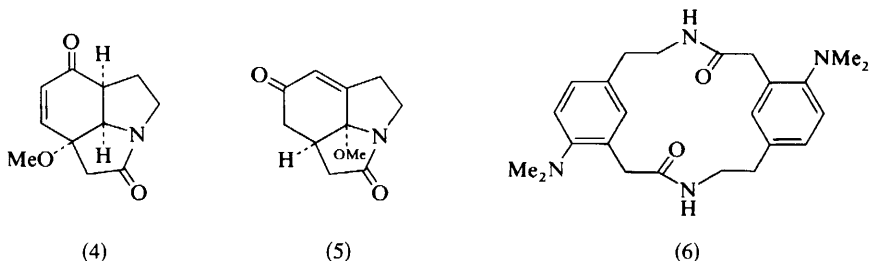
A = amphetamines, B = biogenic amines, C = catecholamines, D = dopamine, MD = 3-methoxydopamine, MT = 3-methoxytyramine, PA = phenylalanine, T = tyramine.

<sup>a</sup> R. J. Weinkan, J. Gal, P. Callery, and N. Castagnoli, jun., *Analyt. Chem.*, 1976, **48**, 203; <sup>b</sup> I. M. Johnson, *Canad. J. Med. Technol.*, 1974, **36**, 469, 474, 480, 487; <sup>c</sup> J. Doullakas, *Pharm. Acta Helv.*, 1975, **50**, 66; V. B. Korchagin, D. E. Satarova, E. V. Kochetkova, and S. M. Mikhailova, *Antibiotiki (Moscow)*, 1975, **20**, 991 (*Chem. Abs.*, 1976, **84**, 119 893); N. Taneva, *Trudy Nauchnoizsled. Khim.-Farm. Inst.*, 1974, **9**, 481 (*Chem. Abs.*, 1975, **83**, 65 530); A. Zobin and M. Gracza-Lukacs, *Acta Pharm. Hung.*, 1975, **45**, 101 (*Chem. Abs.*, 1975, **83**, 152 429); A. Zobin and M. Gracza-Lukacs, *Gyogyszereszet*, 1975, **19**, 455 (*Chem. Abs.*, 1976, **84**, 126 802); <sup>d</sup> V. E. Gan, H. F. Haberman, and I. A. Menon, *J. Invest. Dermatol.*, 1975, **64**, 139 (*Chem. Abs.*, 1975, **83**, 4149); <sup>e</sup> J. Chrastil, *Analyt. Chem.*, 1975, **47**, 2293; <sup>f</sup> R. S. Ersser, *Med. Lab. Sci.*, 1976, **33**, 57; <sup>g</sup> O. Lindvall, A. Bjorklund, B. Falck, and L. A. Svensson, *J. Histochem. Cytochem.*, 1975, **23**, 703; <sup>h</sup> W. Maeurer, W. Kuebler, Y. Yoshida, H. Kuhn, and G. Briethardt, *Verh. Deutsch. Ges. Inn. Med.*, 1974, **80**, 240 (*Chem. Abs.*, 1975, **83**, 4229); <sup>i</sup> H. G. Nowicki, *J. Forensic Sci.*, 1976, **21**, 154; <sup>j</sup> J. Diamant and S. O. Byers, *J. Lab. Clin. Med.*, 1975, **85**, 678; A. Dolphin, P. Jenner, and C. D. Marsden, *J. Neurochem.*, 1975, **25**, 897; J. Halmekoski and A. Kaukinen, *Farm. Aikak.*, 1974, **83**, 179 (*Chem. Abs.*, 1975, **83**, 33 106); M. Hashimoto, K. Miyoshi, N. Kudo, Y. Takeda, K. Hashimoto, and K. Tsunashima, *Rinsho Kensa*, 1976, **20**, 297 (*Chem. Abs.*, 1976, **84**, 176 128); K. Hashimoto, K. Tsunashima, S. Yozai, N. Kudo, and M. Hashimoto, *Rinsho Kensa*, 1975, **19**, 192 (*Chem. Abs.*, 1975, **83**, 39 659); T. Kaito, K. Kasuya, K. Sagara, and T. Yoshida, *Yakagaku Zasshi*, 1975, **95**, 985 (*Chem. Abs.*, 1976, **84**, 35 396); F. N. Minard, J. C. Cain, and D. S. Grant, *J. Pharm. Pharmacol.*, 1975, **27**, 288; G. Schwedt, *Analyt. Chim. Acta*, 1976, **81**, 361; G. Schwedt and I. Hildebrand, *Z. analyt. Chem.*, 1975, **275**, 23; W. Von Studnitz, 'Methoden Hormon Bestimmung', ed. H. Breuer, D. Hamel, and H. L. Krueskemper, Thieme, Stuttgart, 1975, p. 150; L. A. Svensson, A. Bjorklund, and O. Lindvall, *Acta Chem. Scand.*, 1975, **B29**, 341; U. Werner, *Z. klin. Chem. klin. Biochem.*, 1975, **13**, 341 (*Chem. Abs.*, 1975, **83**, 110 759); W. G. Wood and R. W. Mainwaring-Burton, *Clin. Chim. Acta*, 1975,

- 61, 297; \* J. De Bellerocche, C. R. Dykes, and A. J. Thomas, *Analyt. Biochem.*, 1976, **71**, 193; † R. F. Butterworth, F. Landreville, M. Guitard, and A. Barbeau, *Clin. Biochem.*, 1975, **8**, 298; ‡ T. Karasawa, *Rinsho Kagaku*, 1975, **4**, 24 (*Chem. Abs.*, 1976, **84**, 161 354); § T. Karasawa, K. Furukawa, K. Yoshida, and M. Shimizu, *Jap. J. Pharmacol.*, 1975, **25**, 727 (*Chem. Abs.*, 1976, **84**, 117 951); ¶ B. N. Manukhin, L. V. Berdysheva, and E. V. Volina, *Voprosy Med. Khim.*, 1975, **21**, 317 (*Chem. Abs.*, 1975, **83**, 110 723); †† F. Nachtmann, H. Spitz, and R. W. Frei, *Analyt. Chim. Acta*, 1975, **76**, 57; ††† W. H. Riffée and M. C. Gerald, *Arch. Int. Pharmacodyn. Ther.*, 1976, **219**, 70 (*Chem. Abs.*, 1976, **84**, 132 214); †††† G. Schwedt and H. H. Bussemas, *J. analyt. Chem.*, 1975, **276**, 55; ††††† T. Seki and H. Wada, *J. Chromatog.*, 1975, **114**, 227; †††††† A. L. N. Prasad, S. Fahn, and W. P. Isgreen, *Biochem. Med.*, 1975, **14**, 24; ††††††† L. K. Cheng, M. Levitt, and Ho-Leung Fung, *J. Pharm. Sci.*, 1965, **64**, 839; †††††††† Y. Dalmaz and L. Peyrin, *J. Chromatog.*, 1976, **116**, 379; ††††††††† K. K. Midha, I. J. McGilveray, S. P. Bhatnagar, and J. K. Cooper, *J. Pharm. Sci.*, 1976, **65**, 188; †††††††††† F. Addeo, A. Malorni, and M. Ameno, *Ann. Fac. Sci. Agrar. Univ. Studi Napoli, Portici*, 1973, **7**, 283 (*Chem. Abs.*, 1976, **84**, 27 573); ††††††††††† R. L. Bronaugh, S. E. Hattox, M. M. Hoehn, R. C. Murphy, and C. O. Rutledge, *J. Pharmacol. Exp. Ther.*, 1975, **195**, 441; †††††††††††† R. J. Shippe and J. Savory, *Ann. Clin. Lab. Sci.*, 1975, **5**, 57 (*Chem. Abs.*, 1975, **83**, 37 410); ††††††††††††† C. C. Clark, *J. Assoc. Offic. Analyt. Chemists*, 1975, **58**, 1174; N. C. Jain, R. D. Budd, and T. C. Sneath, *Clin. Toxicol.*, 1975, **8**, 211; S. Reite and B. Salvessen, *Medd. Nor. Farm. Selsk.*, 1974, **36**, 15 (*Chem. Abs.*, 1976, **84**, 144 455); †††††††††††††† J. W. Schweitzer and A. J. Friedhoff, 'Biological Diagnosis of Brain Disorders', Proceedings of the 5th International Conference, 1972, ed. S. Bogoch, Spectrum Publications, Flushing, New York, 1973, p. 382; R. W. Souter, *J. Chromatog.*, 1975, **108**, 265; ††††††††††††††† R. B. Szelwar, *European J. Toxicol. Environ. Hyg.*, 1975, **8**, 5 (*Chem. Abs.*, 1975, **83**, 71 365); †††††††††††††††† M. Donike and D. Stratmann, *Z. analyt. Chem.*, 1976, **279**, 129; ††††††††††††††††† M. G. Bigdell and M. A. Collins, *Biochem. Med.*, 1975, **12**, 55; †††††††††††††††††† J. C. Deavin, J. S. Foster, M. Mitchard, D. H. Mitchell, R. Sinar, R. N. Thornhill, D. A. Wheeler, E. Fuller, and P. W. Shallis, *Analyst*, 1975, **100**, 136; G. Schwedt, A. Bloedorn, and H. H. Bussemas, *Clin. Chim. Acta*, 1975, **65**, 309; ††††††††††††††††††† L. J. Haefliger, J. S. Magen, and O. D. Kowlessar, *J. Chromatog.*, 1976, **118**, 425; †††††††††††††††††††† G. Schwedt and H. H. Bussemas, *J. Chromatog.*, 1975, **106**, 440; ††††††††††††††††††††† S. Brown, *Clin. Chem.*, 1975, **21**, 735; †††††††††††††††††††††† G. J. Alexander, *Clin. Chem.*, 1975, **21**, 1803; ††††††††††††††††††††††† I. Jane, *J. Chromatog.*, 1975, **111**, 227; †††††††††††††††††††††††† L. J. Riceberg and H. Van Vunakin, *Biochem. Pharmacol.*, 1975, **24**, 259; ††††††††††††††††††††††††† P. T. Kissinger, R. M. Riggan, R. L. Alcorn, and L.-D. Rau, *Biochem. Med.*, 1975, **13**, 299; A. Kojima-Sudd, *Ind. Health*, 1975, **13**, 69; †††††††††††††††††††††††††† R. M. Riggan, M. J. McCarthy, and P. T. Kissinger, *J. Agric. Food Chem.*, 1976, **24**, 189; ††††††††††††††††††††††††††† G. Schwedt, *J. Chromatog.*, 1976, **118**, 429; K. Mori, *Sangyo Igaku*, 1975, **17**, 116 (*Chem. Abs.*, 1976, **84**, 27 602); †††††††††††††††††††††††††††† K. Mori, *Sangyo Igaku*, 1974, **16**, 490, 494 (*Chem. Abs.*, 1975, **83**, 24 569, 24 570); ††††††††††††††††††††††††††††† H. H. Bussemas, *Chromatographia*, 1976, **9**, 17 (*Chem. Abs.*, 1976, **84**, 86 305); R. W. Frei, W. Santi, and M. Thomas, *J. Chromatog.*, 1976, **116**, 365; ††††††††††††††††††††††††††††† F. Cattabeni, G. Racagni, and R. Paoletti, *J. Psychiatric Res.*, 1974, **11**, 45; †††††††††††††††††††††††††††††† M.-T. Wang, K. Imai, M. Yoshioka, and Z. Tamura, *Clin. Chim. Acta*, 1975, **63**, 13; ††††††††††††††††††††††††††††††† M.-T. Wang, M. Yoshioka, K. Imai, and Z. Tamura, *Clin. Chim. Acta*, 1975, **63**, 21; ††††††††††††††††††††††††††††††† J. D. Weber, *J. Pharm. Sci.*, 1976, **65**, 105; †††††††††††††††††††††††††††††††† T. W. Fendley and C. S. Frings, *Clin. Biochem. (Ottawa)*, 1976, **9**, 106; †††††††††††††††††††††††††††††††† D. Cantin, J. Alary, and A. Coeur, *Analyst*, 1975, **3**, 241 (*Chem. Abs.*, 1975, **83**, 136 987); ††††††††††††††††††††††††††††††††† T. S. Sulkowski, G. Lathrop, J. H. Merritt, J. H. Landez, and E. R. Noe, *J. Forensic Sci.*, 1975, **20**, 524; ††††††††††††††††††††††††††††††††† H. Sato and T. Yamada, *Igaku No Ayumi*, 1975, **95**, 149 (*Chem. Abs.*, 1976, **84**, 27 711); †††††††††††††††††††††††††††††††††† E. Knoll and H. Wisser, *Z. analyt. Chem.*, 1976, **279**, 119; †††††††††††††††††††††††††††††††††† M. S. Rahaman and M. D. Morris, *Talanta*, 1976, **23**, 65; ††††††††††††††††††††††††††††††††††† M. R. Moeller and R. E. Grillmaier, *Beitr. Gerichtl. Med.*, 1975, **33**, 197 (*Chem. Abs.*, 1976, **84**, 39 406); †††††††††††††††††††††††††††††††††††† J. A. Pedersen, L. T. Muus, O. V. Olesen, and A. Amdisen, *Ugeskr. Laeger*, 1975, **137**, 1148 (*Chem. Abs.*, 1975, **83**, 125 978); ††††††††††††††††††††††††††††††††††††† Z. Zakrzewski, B. Chalasinka, and I. Ozieblo, *Farm. Pol.*, 1975, **31**, 307 (*Chem. Abs.*, 1975, **83**, 168 535); †††††††††††††††††††††††††††††††††††††† A. Charteris and R. John, *Analyt. Biochem.*, 1975, **66**, 365; †††††††††††††††††††††††††††††††††††††† D. Eskes, *J. Chromatog.*, 1976, **117**, 442; ††††††††††††††††††††††††††††††††††††††† J. C. Hudson and W. P. Rice, *J. Chromatog.*, 1976, **117**, 449; †† K. K. Kaistha, R. Tadrus, and R. Janda, *J. Chromatog.*, 1975, **107**, 359; ††† K. Szymkowska, Z. Legowska, and M. Piekarewicz, *Farm. Pol.*, 1975, **31**, 211 (*Chem. Abs.*, 1975, **83**, 72 833); †† O. M. Zryakov, *Ukrain. biokhim. Zhur.*, 1976, **48**, 234 (*Chem. Abs.*, 1976, **84**, 176 081); ††† R. L. Ranieri and J. L. McLaughlin, *J. Chromatog.*, 1975, **111**, 234; †† E. Bancher, J. Washuettl, P. Riederer, and H. Stachelberger, *Wien. tierarztl. Monatsschr.*, 1975, **62**, 232 (*Chem. Abs.*, 1975, **83**, 191 454); †† L. N. Mikhailova, M. N. Preobrazhenskaya, G. M. Kadatskii, and S. D. Sokolov, *Khim.-Farm. Zhur.*, 1975, **9**, 49 (*Chem. Abs.*, 1976, **84**, 95 657); ††† K. Fuecker, R. A. Meyer, and H. P. Pietsch, *Nahrung*, 1976, **20**, 81 (*Chem. Abs.*, 1976, **84**, 161 320); †† A. Kumar and G. D. Christian, *Clin. Chem.*, 1975, **21**, 325; †† R. Krause, H. Hahn, V. Dorsch, P. Fehrmann, and R. Sulzmann, *Acta Histochem.*, 1975, **54**, 153; ††† J. G. Wood and D. Harling, *Proc. Annual Meetings, Electron Microsc. Soc. Amer.*, 1975, **33**, 448.



aldehyde signals in particular, due to the presence of equal populations of rotamers.<sup>74</sup> Photocyclization of *N*-chloroacetyl derivatives of 3-dimethylaminophenethylamine<sup>75</sup> and 2,5-dimethoxyphenethylamine<sup>76</sup> gave benzazepinones (cf. Vol. 4, p. 132). Reaction of the dimethoxy-derivative, however, also afforded two pyrroloindoles (4) and (5).<sup>76</sup> Similar irradiation of the *N*-chloroacetyl derivative of 4-dimethylaminophenethylamine gave the novel diazametacyclophane (6) together with the cage compound previously obtained by irradiation of *N*-chloroacetyltyramine (cf. Vol. 4).<sup>75</sup>



Autoxidation of *N*-hydroxyamphetamine gives the nitroso-derivative which isomerizes to the corresponding oxime.<sup>77</sup> A variety of *N*-oxygenated products which might arise by oxidation, *in vitro* or *in vivo*, of 3,4-dimethoxyamphetamine and its *N*-alkyl derivatives have been prepared.<sup>78</sup> A similar study has been carried out on the metabolic oxidation products of norephedrine.<sup>79</sup>

Useful 'Gabriel'-type syntheses of amines have been developed. Dialkylation of trifluoromethylsulphonamide ('triflamide') or monoalkylation of an *N*-alkyltriflamide followed by reductive cleavage of the triflyl group with  $\text{LiAlH}_4$  affords secondary amines. In addition, the *N*-triflyl derivative of phenylglycine methyl ester and the corresponding derivative (7) of 9-fluorenamine are effective reagents for converting primary alkyl halides into primary amines in one step, since alkylation and elimination of trifluoromethylsulphinic acid occur under the same basic conditions (e.g. Scheme 1).<sup>80</sup> Reductive cleavage of the cyano-group in (8;  $\text{R}^1 = \text{R}^2 = \text{Me}$ ) or (8;  $\text{R}^1 = \text{H}$ ,  $\text{R}^2 = \text{Ac}$ ) can be effected almost quantitatively by treatment with sodium in liquid ammonia.<sup>81</sup> Procedures have been published for the preparation of  $^2\text{H}$ - and  $^3\text{H}$ -labelled phenethylamines,<sup>82</sup> phenethanolamines,<sup>82,83</sup> and 6-hydroxydopamine,<sup>82</sup> and of dopamine stereospecifically labelled in the 2-position.<sup>84</sup> Commercial DL-[ $G$ - $^3\text{H}$ ]phenylalanine was shown by degradation and  $^3\text{H}$  n.m.r. to have the label distributed more in the aromatic nucleus (73%) than in the

<sup>74</sup> J. F. Siuda, *J. Org. Chem.*, 1975, **40**, 3611.

<sup>75</sup> N. Numao and O. Yonemitsu, *Heterocycles*, 1976, **4**, 1096.

<sup>76</sup> Y. Okuno, M. Kawamori, K.-I. Hirao, and O. Yonemitsu, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 2584.

<sup>77</sup> B. Lindeke, E. Anderson, G. Lundkvist, U. Jonsson, and S. O. Eriksson, *Acta Pharm. Suecica*, 1975, **12**, 183.

<sup>78</sup> P. H. Morgan and A. H. Beckett, *Tetrahedron*, 1975, **31**, 2595.

<sup>79</sup> A. H. Beckett, G. R. Jones, and S. Al-Sarraj, *J. Pharm. Pharmacol.*, 1974, **26**, 945.

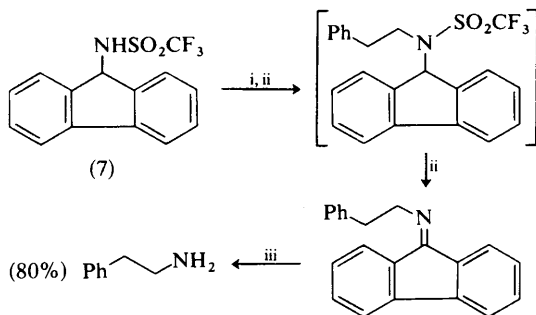
<sup>80</sup> J. B. Hendrickson, R. Bergeron, and D. D. Sternbach, *Tetrahedron*, 1975, **31**, 2517.

<sup>81</sup> S. Yamada, K. Tomioka, and K. Koga, *Tetrahedron Letters*, 1976, 61.

<sup>82</sup> A. Rotman, J. W. Daly, and C. R. Creveling, *J. Labelled Compounds*, 1975, **11**, 445.

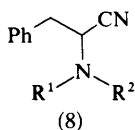
<sup>83</sup> R. C. Murphy, *J. Labelled Compounds*, 1975, **11**, 341.

<sup>84</sup> A. R. Battersby, P. W. Sheldrake, J. Staunton, and D. C. Williams, *J.C.S. Perkin I*, 1976, 1056.



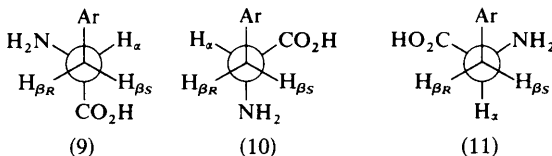
Reagents: i,  $\text{PhCH}_2\text{CH}_2\text{Cl}$ ; ii,  $\text{K}_2\text{CO}_3\text{-MeCN}$ ; iii, 10% aq.  $\text{HCl}$ .

**Scheme 1**



side-chain (27%).<sup>85</sup> The (+)-enantiomer of the drug 'prenylamine' has been prepared in four steps from (–)-norephedrine.<sup>86</sup> A facile preparation of L-dopa and its monomethyl ethers involves enzyme-catalysed asymmetric synthesis of L-N-benzoyl-3,4-dimethoxyphenylalanine anilide from DL-N-benzoyl-3,4-dimethoxyphenylalanine and aniline.<sup>87</sup> A remarkable optical resolution of N-acetyl-3,4-dimethoxyphenylalanine and its  $\alpha$ -methyl analogue, without the aid of an optically active resolving agent, has been achieved by simple crystallization of the corresponding di-n-butylamine salt. Hydrolysis–demethylation with phenol–aqueous  $\text{HCl}$  then gave optically pure dopa and  $\alpha$ -methyl dopa enantiomers.<sup>88</sup>

Proton n.m.r. spectra of catecholamines have been determined and analysed by computer simulations.<sup>89</sup> The effect of shift reagent on the n.m.r. spectra of amphetamines have also been measured.<sup>90</sup> An n.m.r. study of the conformations of amino-acids including phenylalanine and tyrosine has been facilitated by use of  $\alpha$ -deuterio-derivatives. The population of conformation (9) was found to be about double the population of each of the other two staggered conformations (10) and (11).<sup>91</sup> The conformational properties of biological phenethylamines have been



<sup>85</sup> M. C. Clifford, E. A. Evans, A. E. Kilner, and D. W. Warrell, *J. Labelled Compounds*, 1975, **11**, 435.

<sup>86</sup> M. Tomie, H. Sugimoto, and N. Yoneda, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 1033.

<sup>87</sup> E.-O. Renth, *Angew. Chem. Internat. Edn.*, 1975, **14**, 361.

<sup>88</sup> S. Yamada, M. Yamamoto, and I. Chibata, *J. Org. Chem.*, 1975, **40**, 3360.

<sup>89</sup> F. Lambert, M. Ellenberger, L. Merlin, and Y. Cohen, *Org. Magn. Resonance*, 1975, **7**, 266.

<sup>90</sup> R. V. Smith, P. W. Erhardt, D. B. Rusterholz, and C. F. Barfknecht, *J. Pharm. Sci.*, 1976, **65**, 412.

<sup>91</sup> M. Kainosho and K. Ajisaka, *J. Amer. Chem. Soc.*, 1975, **97**, 5630.

explored by MO techniques.<sup>92</sup> The validity of the *N*-salicylidene sector rule for determining the absolute configuration of optically active amines related to amphetamine and ephedrine has been demonstrated.<sup>93</sup> The crystallization behaviour of various mixtures of the optical antipodes of ephedrine hydrochloride and pseudoephedrine hydrochloride has been interpreted on the basis of thermal analyses.<sup>94</sup>

An active area of phenethylamine research continues to be the synthesis and pharmacological evaluation of analogues. The compounds studied include homologues of dopa,  $\alpha$ -methyldopa, and dopamine,<sup>95</sup>  $\alpha$ -hydroxymethyl derivatives of dopa and tyrosine,<sup>96</sup> halogenated derivatives of dopamine<sup>97</sup> and phenylalanine,<sup>98,99</sup> and analogues of dopamine<sup>100,101</sup> and tyramine<sup>102</sup> as well as new catecholamines<sup>103–105</sup> and amphetamines.<sup>106,107</sup>

Reviews on the pharmacology,<sup>108</sup> extraction and identification,<sup>109</sup> and abuse<sup>110</sup> of amphetamines have appeared. Other studies deal with the pharmacology of various phenethanolamines<sup>111–114</sup> and of *N*-acetoacetyldopa.<sup>115</sup> It is considered likely that the hypotensive and lethal action of the venoms of the bald-faced hornet *Vespula maculata* and the yellow jacket *V. maculifrons* is due to the combined action of many constituents. Of these histamine, dopamine, and norepinephrine have now been identified.<sup>116</sup>

<sup>92</sup> B. Pullman, H. Berthod, and Ph. Courriere, *Internat. J. Quantum Chem., Quantum Biol. Symp.*, 1975, **1**, 93 (*Chem. Abs.*, 1975, **83**, 59 119).

<sup>93</sup> C. D. Mount, H. E. Smith, and R. I. Mani, *J. Tennessee Acad. Sci.*, 1974, **49**, 134 (*Chem. Abs.*, 1975, **83**, 192 388).

<sup>94</sup> M. Kuhnert-Brandstaetter and R. Linder, *Mikrochim. Acta*, 1975, **2**, 593.

<sup>95</sup> M. Winn, R. Rasmussen, F. Minard, J. Kyncl, and N. Plotnikoff, *J. Medicin. Chem.*, 1975, **18**, 434.

<sup>96</sup> R. A. Schnettler, J. T. Suh, and R. C. Dage, *J. Medicin. Chem.*, 1976, **19**, 191.

<sup>97</sup> J. S. Fowler, R. R. MacGregor, A. P. Wolf, A. N. Ansari, and H. L. Atkins, *J. Medicin. Chem.*, 1976, **19**, 356.

<sup>98</sup> R. W. Goulding and S. W. Gunasekera, *Internat. J. Appl. Radiat. Isotopes*, 1975, **26**, 561 (*Chem. Abs.*, 1976, **84**, 44 622).

<sup>99</sup> R. A. Houghton and H. Rapoport, *J. Medicin. Chem.*, 1974, **17**, 556.

<sup>100</sup> J. G. Cannon, J. P. O'Donnell, T. Lee, C. R. Hoppin, J. P. Long, M. Ilhan, B. Costall, and R. J. Naylor, *J. Medicin. Chem.*, 1975, **18**, 1212.

<sup>101</sup> D. E. Nerland and E. E. Smissman, *J. Medicin. Chem.*, 1976, **19**, 163.

<sup>102</sup> Yu. A. Davidovitch, D. N. Maslin, V. I. Butaeva, V. G. Yashunskii, and S. V. Rogozhin, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1975, 1416 (*Chem. Abs.*, 1975, **83**, 193 664).

<sup>103</sup> R. M. Bartholow and E. J. Walaszek, *J. Medicin. Chem.*, 1976, **19**, 189.

<sup>104</sup> C. Kaiser, M. S. Schwartz, D. F. Colella, and J. R. Wardell, jun., *J. Medicin. Chem.*, 1975, **18**, 674.

<sup>105</sup> L. I. Petlichnaya, O. G. Demchuk, and E. I. Besyadetskaya, *Farm. Zhur. (Kiev)*, 1976, **31**, 32 (*Chem. Abs.*, 1976, **84**, 165 079).

<sup>106</sup> J. C. Guillard, J. Klepping, A. Escousse, J. P. Didier, G. Rucart, and J. Mounie, *Therapie*, 1975, **30**, 117 (*Chem. Abs.*, 1975, **83**, 53 508).

<sup>107</sup> A. T. Shulgin and D. C. Dyer, *J. Medicin. Chem.*, 1975, **18**, 1201.

<sup>108</sup> L. L. Simpson, 'Drug Treatment of Mental Disorders', ed. L. L. Simpson, Raven, New York, 1976, pp. 109, 161.

<sup>109</sup> E. Marozzi and V. Gambaro, *Zacchia*, 1975, **11**, 153.

<sup>110</sup> F. M. Yatsu, D. R. Wesson, and D. E. Smith, 'Medical Aspects of Drug Abuse', ed. R. W. Richter, Harper and Row Med. Dept., Hagerstown, Maryland, 1975, p. 50.

<sup>111</sup> A. E. Ciarlone, *J. Amer. Dent. Assoc.*, 1976, **92**, 748.

<sup>112</sup> M. Hava, J. Bernstein, E. E. Smissman, and S. El-Antably, *J. Medicin. Chem.*, 1976, **19**, 52.

<sup>113</sup> C. K. Maitai, *East African Med. J.*, 1975, **52**, 330 (*Chem. Abs.*, 1975, **83**, 201 768).

<sup>114</sup> G. G. Ferguson and W. J. Keiller, *J. Pharm. Sci.*, 1975, **64**, 1431.

<sup>115</sup> H. Ozawa, K. Sugawara, M. Kooi, and T. Kato, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 2075.

<sup>116</sup> R. G. Geller, H. Yoshida, M. A. Beaven, Z. Horakova, F. L. Atkins, Y. Yamabe, and J. J. Pisano, *Toxicol.*, 1976, **14**, 27 (*Chem. Abs.*, 1976, **84**, 160 358).

### 3 Simple Isoquinoline Alkaloids

Alkaloid isolations and structural elucidations are summarized in Table 3. Reduction of a new quaternary alkaloid isolated from *Berberis oblonga* gave 6-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline and the alkaloid was deduced to

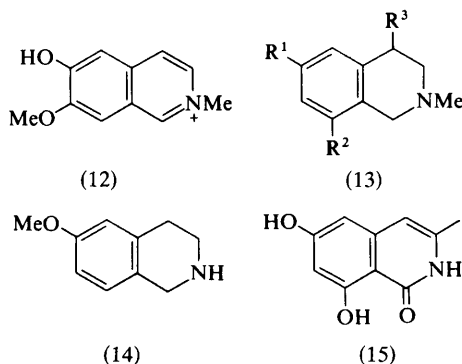
**Table 3** Isolation of simple isoquinoline alkaloids

Source	Alkaloid	Ref.
<i>Berberis oblonga</i>	Isoquinolinium salt [(12) or its 3,4-dihydro-derivative]	117
<i>Cassia siamea</i>	Siamine (15)	119
<i>Corydalis speciosa</i>	Corypalline	a
<i>Dolicothele longimamma</i>	Longimammadine (13; $R^1 = R^3 = H$ ; $R^2 = OH$ )	47, 48
	Longimammamine (13; $R^1 = H$ , $R^2 = R^3 = OH$ )	
	Longimammatine (14)	
	Longimammosine (13; $R^1 = OH$ , $R^2 = R^3 = H$ )	
<i>Lophophora diffusa</i>	O-Methylpellotine	118
<i>Pachycereus pectenaboriginum</i>	Salsolidine	36

a C. Tani, N. Nagakura, and N. Sugiyama, *Yakugaku Zasshi*, 1975, **95**, 838 (*Chem. Abs.*, 1975, **83**, 93 897).

be either (12) or its 3,4-dihydroderivative.<sup>117</sup> O-Methylpellotine has been isolated for the first time from a natural source, namely the cactus *Lophophora diffusa*.<sup>118</sup>

Another cactus, *Dolicothele longimamma*, has yielded four new tetrahydroisoquinoline alkaloids, namely longimammadine (13;  $R^1 = R^3 = H$ ,  $R^2 = OH$ ), longimammamine (13;  $R^1 = H$ ,  $R^2 = R^3 = OH$ ), longimammatine (14), and logimammosine (13;  $R^1 = OH$ ,  $R^2 = R^3 = H$ ).<sup>47,48</sup> A new isoquinolone alkaloid siamine (15) has been isolated from *Cassia siamea*, its structure being established by spectroscopy, including <sup>13</sup>C n.m.r., and by synthesis.<sup>119</sup> The synthesis of amphibine-I (*cf.* Vol. 6, p. 120) has been reported.<sup>120</sup>



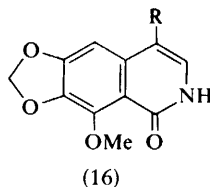
Narciclasine aldehyde (16;  $R = CHO$ ), a key degradation product in the structural elucidation of the alkaloid narciclasine, has been synthesized *via* the isoquinolone

<sup>117</sup> A. Karimov, M. V. Telezhenetskaya, K. L. Lutfullin, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, **11**, 530 (*Chem. Abs.*, 1976, **84**, 44 479).

<sup>118</sup> J. G. Bruhn and S. Agurell, *Phytochemistry*, 1975, **14**, 1442.

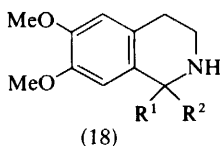
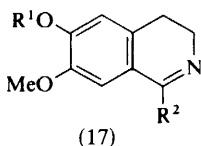
<sup>119</sup> B. Z. Ahn and F. Zymalkowski, *Tetrahedron Letters*, 1976, 821.

<sup>120</sup> R. Tschesche, J. Moch, and C. Spilles, *Chem. Ber.*, 1975, **108**, 2247.



(16; R = H). Bromination gave the 4-bromo-derivative which afforded (16; R = CN) and (16; R = CHO) by successive cyanization and Raney nickel reduction.<sup>121</sup> The reported synthesis of the isoquinolone alkaloid thalactamine from 2,3,4-trimethoxyphenethylamine is unexceptional but an alternative synthesis involving bromination of 6,7-dimethoxy-2-methyl-1(2*H*)-isoquinolone followed by methanolysis in methanolic sodium methoxide is somewhat surprising.<sup>122</sup> A number of new methods for preparing *N*-substituted 1(2*H*)-isoquinolones include reaction of homophthalic acids with Vilsmeier reagent<sup>123</sup> and borohydride reduction of homophthalimides.<sup>124</sup> The effect of various substituents on the fluorescence of such isoquinolones has been studied.<sup>125</sup>

Oxidation of the aroyl imines (17; R<sup>1</sup> = Me, R<sup>2</sup> = C(=O)Ph) and (17; R<sup>1</sup> = Me, R<sup>2</sup> = veratroyl) with periodic acid gave corydaline together with benzoic or veratric acid.<sup>126</sup> Demethylation occurred, however, during similar oxidation of the tetrahydroisoquinolines (18; R<sup>1</sup> = H, R<sup>2</sup> = CH<sub>2</sub>OH) and [18; R<sup>1</sup> = Ph, R<sup>2</sup> = CHOH(Ph)] with formation of the phenolic imines (17; R<sup>1</sup> = H, R<sup>2</sup> = H) and (17; R<sup>1</sup> = H, R<sup>2</sup> = Ph) respectively. These two products were also obtained from the acids (18; R<sup>1</sup> = H, R<sup>2</sup> = CO<sub>2</sub>H) and (18; R<sup>1</sup> = Ph, R<sup>2</sup> = CO<sub>2</sub>H) under the same conditions.<sup>126</sup> The ease



of oxidative decarboxylation of 1-carboxy-1,2,3,4-tetrahydroisoquinolines has been correlated with electron density of the aryl ring and a concerted two-electron mechanism has been proposed for the process.<sup>127</sup> Nucleophilic displacement of alkoxy-groups in protoberberinium salts by amino-functions is described in Section 11. The reaction appears to be general and the *O*-methyltarconine chloride (19; R<sup>1</sup>R<sup>2</sup> = OCH<sub>2</sub>O) reacts with *n*-propylamine to give the aminophenol (19; R<sup>1</sup> = NHPr, R<sup>2</sup> = OH) (see ref. 366). Reaction of (17; R<sup>1</sup> = R<sup>2</sup> = Me) with phenethyl bromide using sodium hydride and DMSO gave the C-4 alkylated product (20; R = CH<sub>2</sub>CH<sub>2</sub>Ph). Under the same conditions, reaction of (17; R<sup>1</sup> = Me, R<sup>2</sup> = H) with 3,4-methylenedioxyphenethyl bromide unexpectedly gave only the C-1 methylated

<sup>121</sup> S. Passannanti, M. P. Paternostro, F. Piozzi, and G. Savona, *Chem. and Ind.*, 1975, 791.

<sup>122</sup> Kh. Duchevska and N. Mollov, *Izvest. Khim. (Sofia)*, 1975, **8**, 134 (*Chem. Abs.*, 1976, **84**, 150 809).

<sup>123</sup> V. H. Belgaonkar and R. N. Usgaonkar, *Tetrahedron Letters*, 1975, 3849.

<sup>124</sup> H. Iida, K. Kawano, T. Kikuchi, and F. Yoshimizu, *Yakugaku Zasshi*, 1976, **96**, 176 (*Chem. Abs.*, 1976, **84**, 135 898).

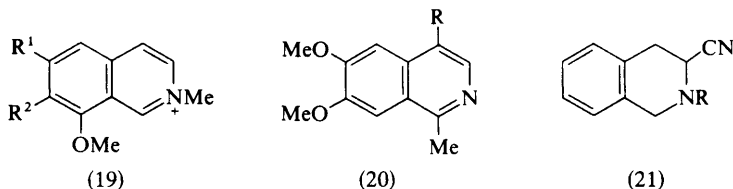
<sup>125</sup> R. A. Henry, C. A. Heller, and D. W. Moore, *J. Org. Chem.*, 1975, **40**, 1760.

<sup>126</sup> G. Mahuzier, M. Hamon, M. Chaigneau, J. Gardent, and P. Maitte, *Analisis 1973—1974*, 1974, **2**, 647 (*Chem. Abs.*, 1975, **83**, 206 075).

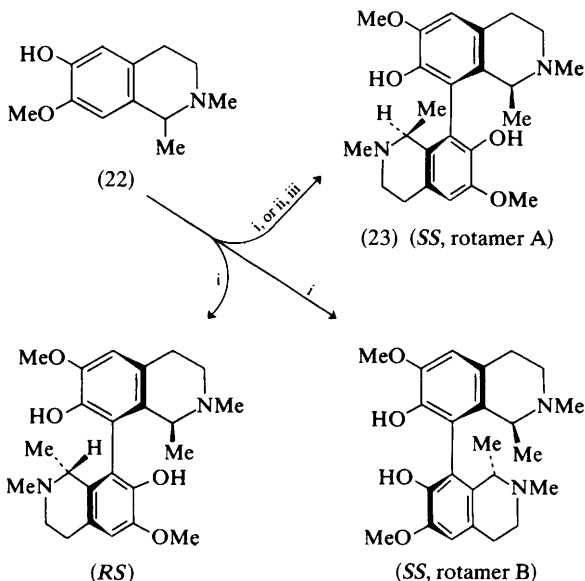
<sup>127</sup> J. M. Bobbitt and T. Y. Cheng, *J. Org. Chem.*, 1976, **41**, 443.

product (20; R = H) and 3-(3,4-methylenedioxyphenyl)propyl methyl sulfoxide.<sup>128</sup>

Reductive removal of the nitrile function in (21; R = Ac) and (21; R = Me) was achieved in excellent yield using sodium in liquid ammonia, giving 1,2,3,4-tetrahydroisoquinoline and its *N*-methyl derivative respectively.<sup>81</sup>



Electrochemical oxidation of racemic 1,2-dimethyl-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (22) gives a number of dimers (*cf.* Vols. 2 and 4) but of the three possible racemic C-8—C-8' dimers (*cf.* Scheme 2) only one, the racemate corresponding to (23), was obtained.<sup>129</sup> Evidently only molecules of (22)



Reagents: i,  $K_3Fe(CN)_6$ ; ii, 0.1M-NaOMe in MeOH; iii, Electrolysis at 0.16 V in wet MeCN at a graphite felt anode with  $Et_4N^+ClO_4^-$  as an electrolyte.

**Scheme 2**

having the same configuration at C-1 couple with one another to form product (*R* with *R* and *S* with *S*) and only one (rotamer A) of two possible rotational isomers is formed. All the C—C dimers are obtained by chemical oxidation and the stereoselectivity of the electrochemical reaction is attributed to a surface phenome-

<sup>128</sup> T. Kametani, H. Nemoto, M. Takeuchi, M. Takeshita, and K. Fukumoto, *Heterocycles*, 1976, **4**, 921

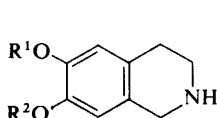
<sup>129</sup> J. M. Bobbitt, I. Noguchi, H. Yagi, and K. H. Weisgraber, *J. Org. Chem.*, 1976, **41**, 845.



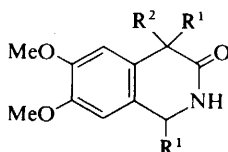
non.<sup>129</sup> The optically active dimer obtained in the same way from *S*-(–)-(22) was shown to have the (1*S*, 1'*S*, biphenyl *S*) configuration (23) from chiroptical studies.<sup>130</sup> The oxidation of various 7- or 6-hydroxytetrahydroisoquinolines with lead tetraacetate has been reviewed.<sup>131</sup>

The transformation of isoquinolinium salts into naphthalene derivatives described in connection with berberine (*cf.* Section 11) may have general applicability since similar reaction of isoquinoline methiodide gave  $\beta$ -naphthyl acetate, albeit in small yield (*see ref.* 362).

Amongst the isoquinoline analogues of potential biological interest which have been prepared are glucosyloxy analogues (24;  $R^1$  = glucosyl,  $R^2$  = Me and *vice-versa*),<sup>132</sup> 3-oxotetrahydroisoquinoline analogues, *e.g.* (25;  $R^1$  and  $R^2$  = H or alkyl),<sup>133</sup> bis-[2-(*N*-salsolidinyl)ethyl]amine<sup>105</sup> and derivatives, or (24;  $R^1$  =  $R^2$  = H) substituted at C-1<sup>134</sup> or at C-2 and C-4.<sup>135</sup>



(24)



(25)

Analysis of salsoline and/or salsolidine has been studied by t.l.c. and fluorometry,<sup>136</sup> spectrophotometry,<sup>137,138</sup> and photometric titration.<sup>139</sup> A new ion-exchange method has been developed for isolating these alkaloids from *Salsola richleri*.<sup>140</sup> Salsolinol has been identified as a major dopamine metabolite in ripening bananas, using cyclic voltammetry, t.l.c., and g.c.-m.s.<sup>141</sup> Pharmacological properties of *S*- and *R*-salsolinol have been compared.<sup>142</sup> Polarography<sup>143</sup> and photocolourimetry and liquid chromatography have been used for analysis of cotarnine.<sup>144</sup>

<sup>130</sup> G. G. Lyle, *J. Org. Chem.*, 1976, **41**, 850.

<sup>131</sup> B. Umezawa and O. Hoshino, *Heterocycles*, 1975, **3**, 961.

<sup>132</sup> M. Barczai-Beke and C. Szantay, *Acta Chim. Acad. Sci. Hung.*, 1974, **80**, 111 (*Chem. Abs.*, 1976, **84**, 90 500).

<sup>133</sup> G. Deak, K. Gall-Istok, and L. Sterk, *Acta Chim. Acad. Sci. Hung.*, 1976, **88**, 87 (*Chem. Abs.*, 1976, **84**, 179 999).

<sup>134</sup> S. Morita, T. Ito, and T. Tono, *Agric. and Biol. Chem. (Japan)*, 1975, **39**, 547.

<sup>135</sup> E. E. Smismán, J. R. Reid, D. A. Walsh, and R. T. Borchardt, *J. Medicin. Chem.*, 1976, **19**, 127.

<sup>136</sup> J. G. Allen and J. L. Haigh, *J. Chromatog.*, 1975, **104**, 217.

<sup>137</sup> M. S. Karawya and A. M. Bian, *J. Assoc. Offic. Analyt. Chemists*, 1975, **58**, 1169.

<sup>138</sup> S. Kh. Mushinskaya, A. T. Shein, and L. I. Lelyuk, *Farm. Zhur. (Kiev)*, 1975, **30**, 65 (*Chem. Abs.*, 1975, **83**, 103 314); E. N. Vegeichik, E. N. Ermonenok, and V. G. Belikov, *Farmatsiya (Moscow)*, 1976, **25**, 76 (*Chem. Abs.*, 1976, **84**, 140 787).

<sup>139</sup> E. M. Rakhman'ko, G. L. Starobinets, *Vesti Akad. Navuk. B.S.S.R., Ser. khim. Navuk.*, 1975, **38** (*Chem. Abs.*, 1976, **84**, 35 377).

<sup>140</sup> S. Kh. Mushinskaya, Yu. V. Shostenko, A. T. Shein, Yu. P. Temirov, and V. P. Frolova, *Khim.-Farm. Zhur.*, 1975, **9**, 25 (*Chem. Abs.*, 1976, **84**, 71 439).

<sup>141</sup> *Cf.* Table 2, *ref. mm.*

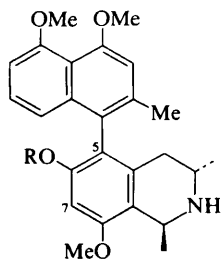
<sup>142</sup> D. R. Feller, R. Venkatraman, and D. D. Miller, *Biochem. Pharmacol.*, 1975, **24**, 1357.

<sup>143</sup> Yu. V. Tsukanov, L. I. Brutko, and M. K. Polievktov, *Farmatsiya (Moscow)*, 1975, **24**, 77 (*Chem. Abs.*, 1976, **84**, 126 807).

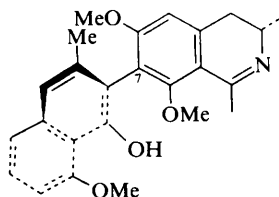
<sup>144</sup> B. I. Shvydkii and Z. A. Kytsya, *Farmatsiya (Moscow)*, 1975, **24**, 80 (*Chem. Abs.*, 1975, **83**, 84 911).

#### 4 Naphthalenoisoquinoline Alkaloids

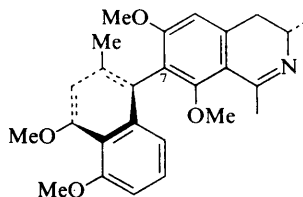
The six known 1'-oxynaphthalenoisoquinoline alkaloids (*cf.* Vols. 2—6) belong to three skeletal classes, according to whether the isoquinoline to 1'-oxynaphthalene link is [5—4'] as in ancistrocladine (26; R = H, 5*R*) ancistrocladinine, ancistrocladonine, and ancistroealensine, [7—2'] as in ancistrocladidine (27), or [7—4'] as in ancistrocladisine (28). The past year has seen the isolation of six new alkaloids of the



(26)



(27)



(28)

first type and four of the last as summarized in Table 4. Hamatine (26; R = H, 5*S*), which was isolated from *Ancistrocladus hamatus*, is a stereoisomer of (–)-ancistrocladine, having the same absolute configuration at C-1 and C-3 but the

**Table 4** Isolation of naphthalenoisoquinoline alkaloids

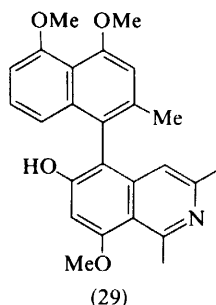
Source	Alkaloid	Ref.
<i>Ancistrocladus congolensis</i>	(–)-Ancistrocladine (26; R = H; 5 <i>R</i> )	148
	'(+)-Ancistrocladine'	
	Ancistrocongine (30; R <sup>1</sup> = R <sup>2</sup> = H)	
	Ancistrocongolensine (30; R <sup>1</sup> = OMe, R <sup>2</sup> = Me)	
<i>A. ealaensis</i>	<i>O</i> -Methylancistrocladine (26; R = Me)	147
	Ancistine (31; R <sup>1</sup> = OMe, R <sup>2</sup> = H)	
	Ancistrine (31; R <sup>1</sup> = OH, R <sup>2</sup> = Me)	
	Ancistrocladeine (29)	
<i>A. hamatus</i>	Hamatine (26; R = H; 5 <i>S</i> )	145
<i>A. tectorius</i>	Ancistrocladine	146
	Ancistrocladeine (29)	
<i>Triphyophyllum peltatum</i>	Triphyopeltine (32)	149
	Triphyophylline (31; R <sup>1</sup> = R <sup>2</sup> = H)	

opposite biaryl chirality.<sup>145</sup> The last feature follows from the enantiomeric nature of the isoquinolines obtained by dehydrogenation of the respective *O*-methyl ethers (*cf.* Vol. 6, p. 119). Ancistrocladeine, (29) a new alkaloid isolated from *A. tectorius*<sup>146</sup> and *A. ealaensis*,<sup>147</sup> should be related to one of these enantiomers. From *A. congolensis* have been obtained (–)-ancistrocladine and four new alkaloids including *O*-methylancistrocladine (26; R = Me) and another stereoisomer of (26; R = H) which was designated as (+)-ancistrocladine, implying a (1*R*,3*R*,5*S*) configuration. However, the alkaloid was chromatographically distinct from (–)-ancistrocladine

<sup>145</sup> T. R. Govindachari, P. C. Parthasarathy, T. G. Rajagopalan, H. K. Desai, K. S. Ramachandran, and E. Lee, *Indian J. Chem.*, 1975, **13**, 641.

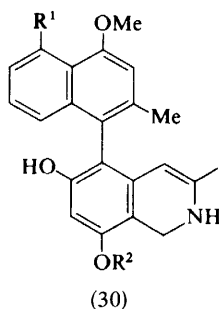
<sup>146</sup> J. P. Foucher, J. L. Pousset, A. Cavé, and R. R. Paris, *Plantes Medicin. Phytother.*, 1975, **9**, 26.

<sup>147</sup> J. P. Foucher, J. L. Pousset, and A. Cavé, *Phytochemistry*, 1975, **14**, 2699.

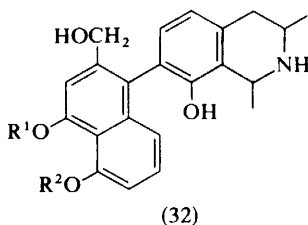
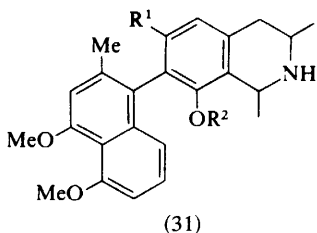


and the c.d. curves of the two alkaloids were not mirror images. Comparison of this alkaloid with hamatine might be of interest.

The two remaining alkaloids isolated from this species, namely ancistrocongine (30;  $R^1 = R^2 = H$ ) and the ancistrocongolsine (30;  $R^1 = OMe$ ,  $R^2 = Me$ ) have an



ancistrocladine-type skeleton lacking a methyl substituent at C-1 and the latter has only one oxygen function in the naphthalene moiety.<sup>148</sup> In common with ancistrocladine mentioned above, these alkaloids are probably chiral biaryls although giving a zero value for  $\alpha_{578}^{20}$ . Two of the new ancistrocladisine-type alkaloids, namely triphyphylline (31;  $R^1 = R^2 = H$ ) and triphyopeltine (32;  $R^1 = H$ ,  $R^2 = Me$  or  $R^1 =$



$Me$ ,  $R^2 = H$ ) were isolated from *Triphyophyllum peltatum* and are the first 1'-oxynaphthalenoisoquinolines to be isolated from a family (Dionchophyllaceae) other than the Ancistrocladaceae.<sup>149</sup> The absolute configurations (3*S*,7*R* in each case) of ancistrocladisine (28) and of the [7—2']-linked 1'-oxynaphthalenoiso-

<sup>148</sup> J. P. Foucher, J. L. Pouset, A. Cavé, A. Bouquet, and R. Paris, *Plantes Medicin. Phytother.*, 1975, **9**, 87.

<sup>149</sup> J. Bruneton, A. Bouquet, A. Fournet, and A. Cavé, *Phytochemistry*, 1976, **15**, 217.

quinoline ancistrocladidine (27) have been established using the exciton chirality method (*cf.* Vol. 6, p. 119) and chemical degradation.<sup>150</sup> Recent work in this area has been summarized.<sup>151</sup>

### 5. Benzyloquinoline Alkaloids

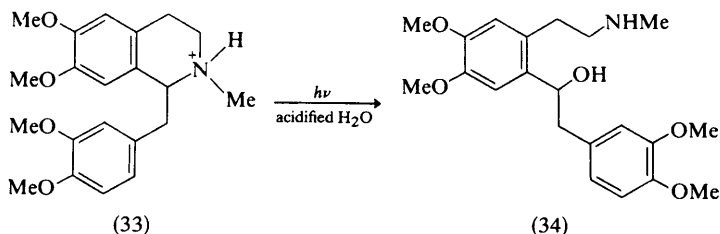
Alkaloid isolations are summarized in Table 5.<sup>152–158</sup> Photolysis of laudanidine hydrochloride (33) or laudanidine metho-salts in hydroxylic media yields cleavage

**Table 5** Isolation of benzyloquinoline alkaloids

Source	Alkaloid	Ref.
<i>Anona glabra</i> <sup>a</sup>	Reticuline	152
<i>Cocculus hirsutus</i>	Cocclaurine	153
<i>Cryptocarya alba</i>	(+)-Reticuline	154
<i>Liriodendron tulipifera</i>	<i>b</i>	155
<i>Ocotea</i> sp. (Brazil) <sup>c</sup>	1- <i>p</i> -Methoxybenzyl-6,7-dimethoxyisoquinoline	156
	1- <i>p</i> -Methoxybenzyl-6,7-methylenedioxyisoquinoline	156
<i>Zanthoxylum dipetetalum</i>	Tembetarine	157
<i>Z. myriacanthum</i>	Tembetarine	158

<sup>a</sup> Five aporphines and an unknown base (HBr, m.p. 215–218 °C) also isolated; <sup>b</sup> Main alkaloids were aporphines, but two minor phenolic alkaloids thought to be 1-benzyltetrahydroisoquinolines were also isolated; <sup>c</sup> Four aporphine alkaloids also isolated.

products (34) or its *O,N*-dimethyl derivative respectively (Scheme 3).<sup>159</sup> Compound (34) was also obtained from laudanidine using the modified von Braun degradation which was previously applied to protoberberines (*cf.* Vol. 4).<sup>159</sup> Details have



**Scheme 3**

<sup>150</sup> T. R. Govindachari, P. C. Parthasarathy, T. G. Rajagopalan, H. K. Desai, K. S. Ramachandran, and E. Lee, *J.C.S. Perkin I*, 1975, 2134.

<sup>151</sup> T. R. Govindachari, *Proc. Nat. Acad. Sci., India, Part A*, 1975, **41**, 1.

<sup>152</sup> T.-H. Yang and C.-M. Chen, *T'ai-wan Yao Hsueh Tsa Chih*, 1973, **25**, 1 (*Chem. Abs.*, 1976, **84**, 102 339).

<sup>153</sup> V. J. Tripathi, A. B. Ray, and B. Dasgupta, *Indian J. Chem. (B)*, 1976, **14**, 62 (*Chem. Abs.*, 1976, **84**, 147 736).

<sup>154</sup> A. Urzva, R. Torres, and B. Cassels, *Rev. Latinoamer. Quím.*, 1975, **6**, 102 (*Chem. Abs.*, 1975, **83**, 111 149).

<sup>155</sup> C.-L. Chen, H.-M. Chang, and E. B. Cowling, *Phytochemistry*, 1976, **15**, 547.

<sup>156</sup> N. C. Franca, A. M. Giesbrecht, O. R. Gottlieb, A. F. Magalhaes, E. G. Magalhaes, and J. G. S. Maia, *Phytochemistry*, 1975, **14**, 1671.

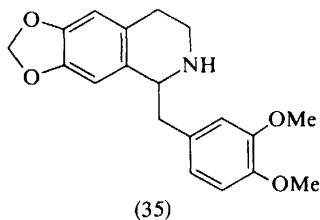
<sup>157</sup> F. Fish, A. I. Gray, and P. G. Waterman, *Phytochemistry*, 1975, **14**, 2073.

<sup>158</sup> P. G. Waterman, *Phytochemistry*, 1975, **14**, 2530.

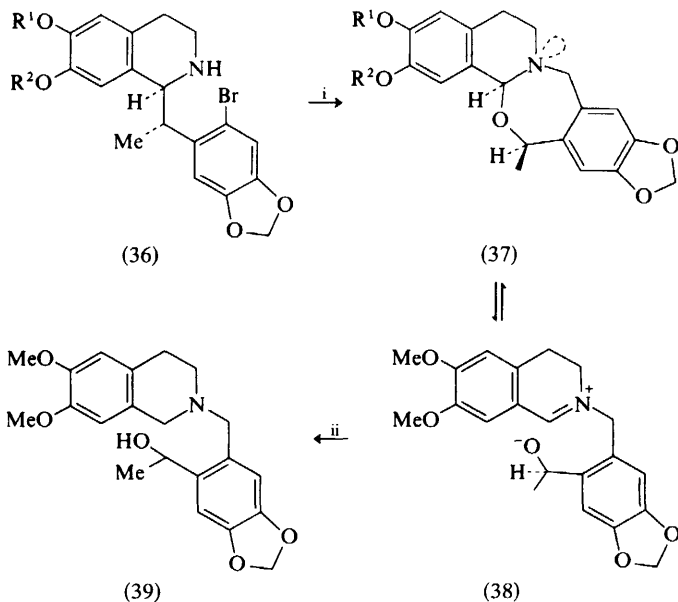
<sup>159</sup> J. B. Bremner and Le Van Thuc, *Chem. and Ind.*, 1976, 453.

appeared of the biogenetic-type synthesis of (*S*)-laudanosine from L-dopa (*cf.* Vol. 4).<sup>160</sup> (*S*)-Reticuline has been prepared in similar fashion.<sup>161</sup>

Treatment of the base (35) with boron trichloride followed by hydrogenolysis of the corresponding bis-tetrazolyl ether resulted in total and selective removal of the



methylenedioxy function.<sup>162</sup> Application of the usual procedure for inserting the 'berberine bridge' to the bromobenzylisoquinoline (36;  $R^1 = R^2 = \text{Me}$ ) unexpectedly gave the benzoxazepin (37;  $R^1 = R^2 = \text{Me}$ ) in 75% yield (Scheme 4).<sup>163</sup> The u.v.



Reagents: i, Excess 30% aq.  $\text{CH}_2\text{O}$ , aq.  $\text{HCl}$ , 100 °C, 3 h; ii,  $\text{NaBH}_4$ -MeOH.

**Scheme 4**

spectrum of (37;  $R^1 = R^2 = \text{Me}$ ) in ethanol showed that this compound exists in equilibrium with (38) (or its protonated form), with the latter in preponderance. The

<sup>160</sup> M. Konda, T. Shioiri, and M. Fujino, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 1025.

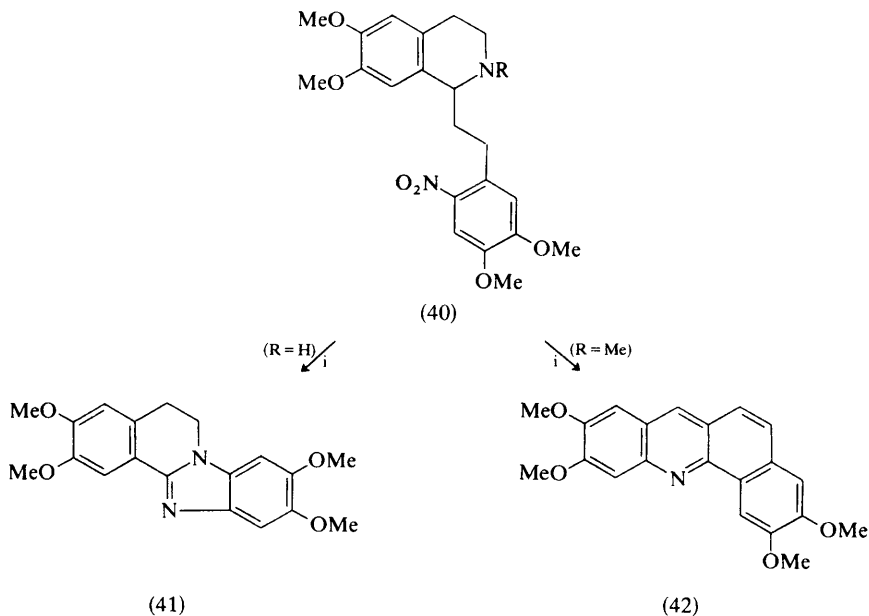
<sup>161</sup> M. Konda, T. Shioiri, and S.-I. Yamada, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 1063.

<sup>162</sup> S. Teitel and J. P. O'Brien, *J. Org. Chem.*, 1976, **41**, 1657.

<sup>163</sup> S. Natarajan, B. R. Pai, R. Rajaraman, C. S. Swaminathan, K. Nagarajan, V. Sudarsanam, D. Rogers, and A. Quick, *Tetrahedron Letters*, 1975, 3573.

benzoxazepin form (37;  $R^1 = R^2 = \text{Me}$ ) predominates, however, in alkaline ethanol or in aprotic solvents like chloroform. This equilibrium explains the formation of (39) upon reduction with methanolic sodium borohydride. The relative stereochemistry of the bismethylenedioxy analogue (37;  $R^1 R^2 = \text{CH}_2$ ) was established by *X*-ray crystallography.<sup>163</sup>

Reductive cyclization of the nitroarylethylisoquinolines (40;  $R = \text{H}$ ) and (40;  $R = \text{Me}$ ) with triethylphosphite gave the benzimidazoisoquinoline (41)<sup>164,165</sup> and the benzacridine (42)<sup>165,166</sup> respectively (Scheme 5). These products were each synthesized by independent routes. The formation of (42) is analogous to the formation of a benzocarbazole from 6-nitroaudanosine (*cf.* Vol. 1). The reactions of various bromaralkylisoquinolines with methylsulphonyl carbanion are described in Section 7.



Reagent: i,  $(\text{EtO})_3\text{P}$ .

**Scheme 5**

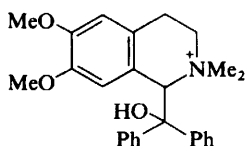
Under the conditions for Hofmann degradation, the quaternary salt (43) undergoes loss of the C-1 substituent as benzophenone, followed by further degradation to the *o*-vinylbenzylamine (44). The Bischler-Napieralski reaction used in the synthesis of (43) afforded the chlorinated by-product (45;  $R = \text{Cl}$ ) which reacted rapidly with methanol to give (45;  $R = \text{OMe}$ ).<sup>167</sup> The 1-(2'-picolyl)- and 1-(6'-methyl-2'-picolyl)-isoquinolines (46;  $R = \text{H}$ ) and (46;  $R = \text{Me}$ ), like their 3,4-

<sup>164</sup> T. Kametani, Y. Fujimoto, and M. Mizushima, *J. Heterocyclic Chem.*, 1975, **12**, 1271.

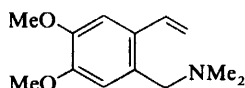
<sup>165</sup> T. Kametani, Y. Fujimoto, and M. Mizushima, *Heterocycles*, 1975, **3**, 619.

<sup>166</sup> T. Kametani, Y. Fujimoto, and M. Mizushima, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 2025.

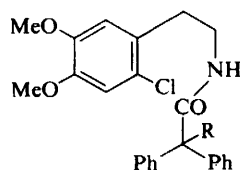
<sup>167</sup> W. Wiegerebe, B. Rohrbach-Munz, W. Awe, and D. Kirk, *Helv. Chim. Acta*, 1975, **58**, 1825.



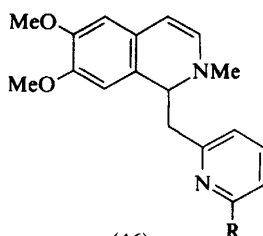
(43)



(44)



(45)



(46)

dimethoxybenzyl analogue (*cf.* Vol. 2, p. 112), undergo acid-catalysed cleavage to an *N*-methyl-6,7-dimethoxyisoquinolinium salt.<sup>168,169</sup> Ethaverine is reported to undergo autoxidation more readily than eupaverine or papaverine.<sup>170</sup> The preparation of papaverine tannate and the physical effects produced by triturating it with potato starch have been described.<sup>171</sup>

Ionization constants for papaverine have been determined in a number of non-aqueous solvents.<sup>172</sup> An *X*-ray study of 1-benzyl-3,4-dihydroisoquinoline hydrochloride has demonstrated the existence in the crystal of a C-1 to N double bond and that the dihydroisoquinoline moiety is significantly non-planar.<sup>173</sup> In crystals of papaverine hydrochloride, the hydrogen atom protonating the nitrogen atoms forms a strong hydrogen bond with the chloride ion, the N—Cl distance being 3.01 Å. The dihedral angle between the plane of the benzene ring and the best plane through the isoquinoline group is 109°.<sup>174</sup>

The enantiomers of trimetoquinol have been synthesized<sup>175</sup> and their activities in  $\beta$ -adrenoceptor systems compared.<sup>142</sup> A number of new 1- and 3-benzylisoquinoline analogues of papaverine were found to have up to a third of the muscle-relaxing activity of papaverine.<sup>176</sup> Also compared with papaverine, *N*-butylpapaverinium bromide had the same spasmolytic effect<sup>177</sup> and an *N*-benzylpapaverinium salt had a more prolonged antiarrhythmic effect.<sup>178</sup> Other new

<sup>168</sup> J. Knabe and G. Link, *Arch. Pharm. (Weinheim)*, 1976, **309**, 72.

<sup>169</sup> J. Knabe and G. Link, *Arch. Pharm. (Weinheim)*, 1975, **308**, 519.

<sup>170</sup> E. Pawelezyk and T. Hermann, *Ann. Pharm. (Poznan)*, 1975, **11**, 91 (*Chem. Abs.*, 1975, **83**, 48 141).

<sup>171</sup> T. Kobayashi, K. Sato, and K. Suzuki, *Yakuzaigaku*, 1974, **34**, 85 (*Chem. Abs.*, 1975, **83**, 136 847).

<sup>172</sup> T. V. Maksimova and V. A. Drozdov, *Khim.-Farm. Zhur.*, 1975, **9**, 52 (*Chem. Abs.*, 1976, **84**, 150 802).

<sup>173</sup> K. Simon, Z. Meszaros, and A. Kalman, *Cryst. Structure Comm.*, 1975, **4**, 135 (*Chem. Abs.*, 1975, **83**, 19 578).

<sup>174</sup> C. D. Reynolds, R. A. Palmer, and B. Gorinsky, *J. Cryst. Mol. Structure*, 1974, **4**, 213 (*Chem. Abs.*, 1976, **84**, 82 954).

<sup>175</sup> D. D. Miller, P. Osei-Gyimah, J. Bardin, and D. R. Feller, *J. Medicin. Chem.*, 1975, **18**, 454.

<sup>176</sup> E. Prudhommeaux, G. Ernouf, O. Foussard-Blanpin, and C. Viel, *European J. Med. Chem.-Chim. Ther.*, 1975, **10**, 19 (*Chem. Abs.*, 1976, **84**, 17 102).

<sup>177</sup> P. Babin and J. F. Pinon, *Bull. Soc. Pharm. Bordeaux*, 1974, **113**, 101 (*Chem. Abs.*, 1975, **83**, 131 799).

<sup>178</sup> K. Kh. Khaidarov and A. L. Vovsi-Kol'shtein, *Khimiya v Tadzshikistane*, 1973, 53 (*Chem. Abs.*, 1976, **84**, 84 182).

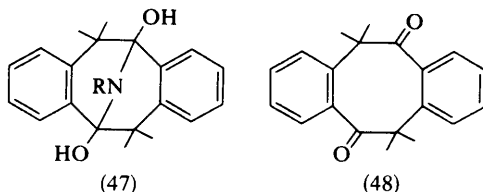
analogues prepared include *N*-aroyl-1-benzyltetrahydroisoquinolines,<sup>179</sup> halogen-substituted benzyl-3,4-dihydroisoquinolines,<sup>180</sup> and 4-spiro-cyclohexanyl-1-benzyl-3,4-dihydroisoquinolines.<sup>181</sup>

Methods applied to analysis of papaverine in mixtures include iodometry,<sup>182</sup> ligand-exchange chromatography,<sup>183</sup> liquid chromatography,<sup>184</sup> spectrofluorometry,<sup>185</sup> spectrophotometry,<sup>186,187</sup> t.l.c.,<sup>188—193</sup> and titration.<sup>194</sup>

## 6 Pavine Alkaloids

Among the quaternary alkaloids found in the roots of *Argemone platyceras* were platycerine methohydroxide and traces of an alkaloid thought to be argemonine methohydroxide.<sup>195</sup> Argemonine itself has been isolated from *Leontice smirnowii*<sup>196</sup> and *Thalictrum strictum*.<sup>197</sup> Amurensine and *O*-methylthalisopavine have been isolated from *Papaver radiculatum*. The last alkaloid was prepared by methylation of thalisopavine but has not previously been found in nature.<sup>198</sup>

Reviews on the isopavine alkaloids have appeared dealing with various synthetic approaches<sup>199</sup> and with that using lead tetra-acetate oxidation in particular.<sup>131</sup> The preparation of a number of argemonine analogues (47) by transannular addition of various biogenic amines, *e.g.* 5-methoxytryptamine to the dione (48), has been reported.<sup>200</sup>



<sup>179</sup> S. Vomero and F. Chimenti, *Farmaco, Ed. sci.*, 1976, **31**, 98 (*Chem. Abs.*, 1976, **84**, 164 586).

<sup>180</sup> D. B. Godbole and J. R. Merchant, *Current Sci.*, 1975, **44**, 429.

<sup>181</sup> E. A. Markaryan, Zh. S. Arustamyan, S. S. Vasilyan, and K. Zh. Markaryan, *Armenian. khim. Zhur.*, 1975, **28**, 829 (*Chem. Abs.*, 1976, **84**, 164 575).

<sup>182</sup> P. P. Suprun, *Farmatsiya (Moscow)*, 1975, **24**, 67 (*Chem. Abs.*, 1975, **83**, 168 522).

<sup>183</sup> E. Murgia and H. F. Walton, *J. Chromatog.*, 1975, **104**, 417.

<sup>184</sup> H. W. Ziegler, T. H. Beasley, and D. W. Smith, *J. Assoc. Offic. Analyt. Chemists*, 1975, **58**, 888.

<sup>185</sup> R. A. Chalmers and A. F. J. Jackson, *Mikrochim. Acta*, 1975, **2**, 273 (*Chem. Abs.*, 1975, **83**, 209 445).

<sup>186</sup> V. E. Chichiro and A. V. Suranova, *Farmatsiya (Moscow)*, 1975, **24**, 61 (*Chem. Abs.*, 1975, **83**, 48 272).

<sup>187</sup> V. V. Mikhno and G. K. Levitskaya, *Farmatsiya (Moscow)*, 1975, **24**, 76 (*Chem. Abs.*, 1975, **83**, 90 564).

<sup>188</sup> G. E. Baiulescu and T. Constantinescu, *Analyt. Chem.*, 1975, **47**, 2156.

<sup>189</sup> A. Brantner, J. Vamos, E. Jeney, and G. Szasz, *Gyogyszereszet*, 1975, **19**, 10 (*Chem. Abs.*, 1975, **83**, 33 099).

<sup>190</sup> A. Gyeresi and G. Racz, *Rev. Med. (Tirgu-Mures, Romania)*, 1975, **21**, 35 (*Chem. Abs.*, 1976, **84**, 49 866).

<sup>191</sup> H. Thielemann and F. Groh, *Pharmazie*, 1975, **30**, 255 (*Chem. Abs.*, 1975, **83**, 120 932).

<sup>192</sup> M. Lastovkova, *Cesk. Farm.*, 1975, **24**, 212 (*Chem. Abs.*, 1976, **84**, 22 131).

<sup>193</sup> Cf. Table 2, ref. ggg.

<sup>194</sup> B. Lipinski, Z. Herman, and H. Ludwicki, *Farm. Pol.*, 1975, **31**, 745 (*Chem. Abs.*, 1976, **84**, 95 654).

<sup>195</sup> J. Slavik and L. Slavikova, *Coll. Czech. Chem. Comm.*, 1976, **41**, 285.

<sup>196</sup> E. G. Tkeshelashvili and K. S. Mudzhiri, *Khim. prirod. Soedinenii*, 1975, **11**, 807 (*Chem. Abs.*, 1976, **84**, 102 357).

<sup>197</sup> P. G. Gorovoi, A. A. Abragimov, S. Kh. Maekh, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, **11**, 533 (*Chem. Abs.*, 1975, **83**, 190 361).

<sup>198</sup> H. Böhm, L. Dolejs, V. Preininger, F. Santavy, and V. Simanek, *Planta Med.*, 1975, **28**, 210.

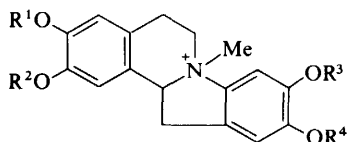
<sup>199</sup> T. Kametani and K. Fukumoto, *Heterocycles*, 1975, **3**, 931.

<sup>200</sup> R. M. Lagidze, N. K. Iremadze, L. P. Chigogidze, D. R. Lagidze, and R. R. Devdariani, *Soobshch. Akad. Nauk Gruz. S.S.R.*, 1975, **80**, 601 (*Chem. Abs.*, 1976, **84**, 150 803).

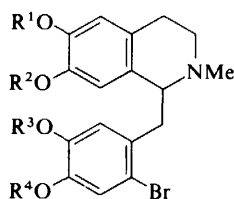


**7 Dibenzopyrrocoline Alkaloids**

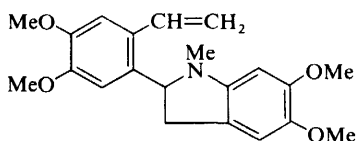
Cryptausoline (49;  $R^1 = R^3 = R^4 = \text{Me}$ ,  $R^2 = \text{H}$ ) and cryptowoline (49;  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ,  $R^3R^4 = \text{CH}_2$ ) have been synthesized by cyclization of bromobenzyltetrahydroisoquinolines (50).<sup>201</sup> In this type of reaction the product is stable only if a free phenolic group is present at C-7.<sup>202,203</sup> Otherwise Hofmann degradation occurs with formation of indole derivatives, e.g. (51) and (52;  $R = \text{Et}$ )<sup>203</sup> or (52;  $R = \text{vinyl}$ ).<sup>202</sup> Products (51) and (52;  $R = \text{Et}$ ) were also obtainable from the dibenzopyrrocolinium



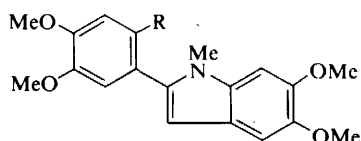
(49)



(50)

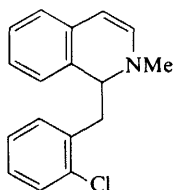


(51)

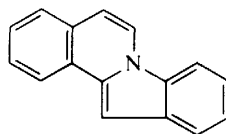


(52)

salt (49;  $R^1 = R^2 = R^3 = R^4 = \text{Me}$ ) prepared indirectly from 2'-bromotetrahydropapaverine by reaction with  $\text{KNH}_2\text{-NH}_3$  followed by quaternization.<sup>203</sup> Reaction of the 1,2-dihydroisoquinoline (53) with  $\text{KNH}_3\text{-NH}_3$  gives the



(53)



(54)

dibenzopyrrocoline (54).<sup>202</sup> When the reaction of the bromo-compounds (50) was carried out in the presence of potassium, good yields of dibenzazonines (55) were obtained.<sup>202</sup> The structures of the dibenzazonines obtained from bromo-compounds of the type (50) with methyl sulphinyl carbanion (*cf.* Vol. 6, p. 130) have been revised to (56).<sup>204,205</sup> Dibenzopyrrocolinium salts behave as intermediates; e.g. (49;  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ,  $R^3R^4 = \text{CH}_2$ ) reacts with methyl sulphinyl carbanion to give (56;

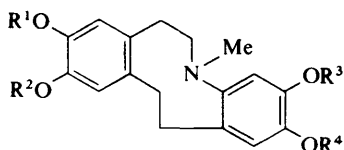
<sup>201</sup> S. V. Kessar, S. Batra, U. K. Nadir, and S. S. Gandhi, *Indian J. Chem.*, 1975, **13**, 1109.

<sup>202</sup> S. V. Kessar, Pawanjit, P. Singh, and S. S. Gandhi, *Indian J. Chem.*, 1975, **13**, 1116.

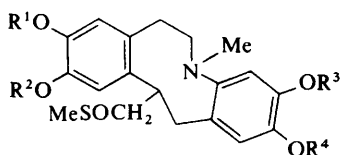
<sup>203</sup> I. Ahmad and M. S. Gibson, *Canad. J. Chem.*, 1975, **53**, 3660.

<sup>204</sup> S. Kano, E. Komiya, T. Ogawa, Y. Takahagi, T. Yokomatsu, and S. Shibuya, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 2058.

<sup>205</sup> S. Kano, E. Komiya, Y. Takahagi, and S. Shibuya, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 648.

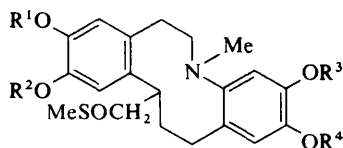


(55)



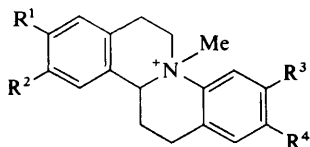
(56)

$R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ,  $R^3 R^4 = \text{CH}_2$ ).<sup>204,206</sup> Similarly, the benzazecines formed from 2'-bromophenethyltetrahydroisoquinolines are now represented as (57).<sup>204,205</sup> The

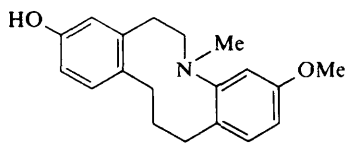


(57)

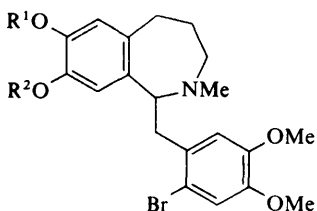
reactivity of the central C—N bond in the presumed dibenzoquinolizinium intermediates (58) is indicated by the ready hydrogenolysis of the model compound (58;  $R^1 = \text{OH}$ ,  $R^2 = R^4 = \text{H}$ ,  $R^3 = \text{OMe}$ ) to (59).<sup>205</sup> The bromobenzylbenzazepines (60) undergo reaction with methyl sulphanyl carbanion to give not only methylsulphanyl-methyldibenzazecines, *e.g.* (61), but also *cis*- and/or *trans*-olefinic dibenzazecines, *e.g.* (62) and (63).<sup>207</sup>



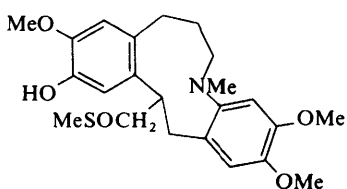
(58)



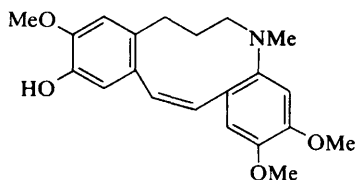
(59)



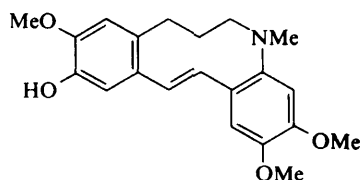
(60)



(61)



(62)



(63)

<sup>206</sup> S. Kano, E. Komiyama, K. Nawa, and S. Shibuya, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 310.

<sup>207</sup> S. Kano, T. Yokomatsu, and S. Shibuya, *Heterocycles*, 1976, **4**, 933.

## 8. Morphine Alkaloids

Alkaloid isolation and structural elucidation is summarized in Table 6. In addition to known constituents, codeine and neopine have been isolated from *Papaver bracteatum*.<sup>208</sup> Although callus cells from this plant contain thebaine at early stages of subculturing, only traces are found later.<sup>209,210</sup> Thebaine was identified among seventeen isoquinoline alkaloids detected in, or isolated from *P. syriacum*.<sup>211</sup>

**Table 6** Isolation of morphine alkaloids

Source	Alkaloid	Ref.
<i>Colchicum luteum</i>	Collutine (68)	216
<i>C. szovitsii</i>	Szovitsidine (67)	215
<i>Ocotea brachybotra</i>	14-Episinomenine (66)	214
	Ocobotrine (65)	
	Pallidine	
	Sinacutine	
<i>Papaver bracteatum</i> <sup>a</sup>	Codeine	208
	Neopine	
<i>P. bracteatum</i> (callus)	Thebaine	209, 210
<i>P. orientale</i>	Oripavine	
	Thebaine	211
<i>P. pseudo-orientale</i> <sup>b</sup>	Salutaridine	
<i>P. radiculatum</i>	Amurine	198
<i>P. syriacum</i>	Thebaine	212
<i>Stephania abyssinica</i>	6-Dihydroepistephamiarsine 6-acetate (73)	219
<i>S. delovayi</i>	Isostephodeline (64)	213
<i>S. japonica</i>	Epistephamiarsine (69; R <sup>1</sup> = OMe, R <sup>2</sup> = H)	217
	16-Oxohasubanonine	218
	16-Oxoprotometaphanine (72)	
	Oxostephamiarsine (70)	217
	Stephamiarsine (69; R <sup>1</sup> = H, R <sup>2</sup> = OMe)	
	Stephasunoline (71)	

<sup>a</sup> The presence of five unknown alkaloids is also reported; <sup>b</sup> The novel alkaloid aryapavine and alkaloids Or<sub>1</sub> and Or<sub>2</sub> were also isolated.

Isostephodeline, isolated from the roots of *Stephania delovayi*, has been assigned structure (64), stephodeline being its C-4a and C-9 epimer.<sup>212</sup> Two new *trans*-morphinan alkaloids, ocobotrine (65) and 14-episinomenine (66), have been isolated from *Ocotea brachybotra* along with sinacutine and pallidine.<sup>213</sup> Szovitsidine (67) and collutine (68) are new homomorphine alkaloids isolated from *Colchicum szovitsii*<sup>214</sup> and *C. luteum*<sup>215</sup> respectively. The absolute stereochemistry of the latter alkaloid was established by its conversion into *O*-methylandrocymbine using

<sup>208</sup> F. J. E. M. Kuppers, C. A. Saleminck, M. Bastart, and M. Paris, *Phytochemistry*, 1976, **15**, 444.

<sup>209</sup> S. Kamimura and M. Nishikawa, *Agric. and Biol. Chem. (Japan)*, 1976, **40**, 907.

<sup>210</sup> S. Kamimura, M. Akutsu, and M. Nishikawa, *Agric. and Biol. Chem. (Japan)*, 1976, **40**, 913.

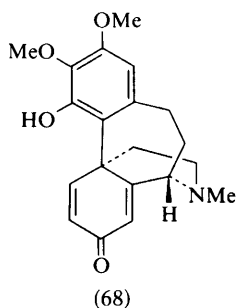
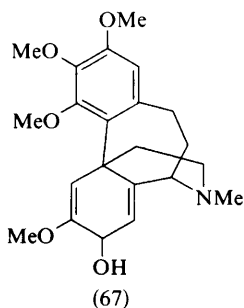
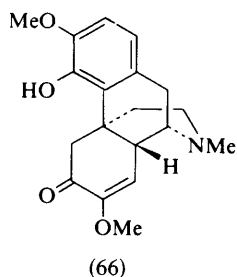
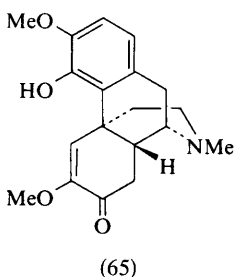
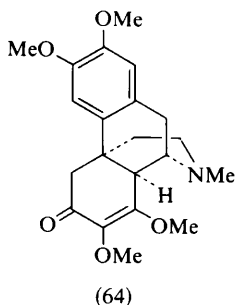
<sup>211</sup> J. Slavik and L. Slavikova, *Coll. Czech. Chem. Comm.*, 1976, **41**, 290.

<sup>212</sup> M. E. Perel'son, I. I. Fadeeva, and T. N. Il'inskaya, *Khim. prirod. Soedinenii*, 1975, **11**, 188 (*Chem. Abs.*, 1975, **83**, 79 434).

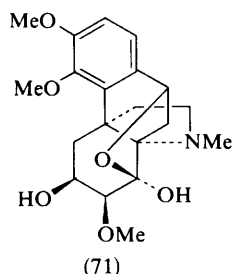
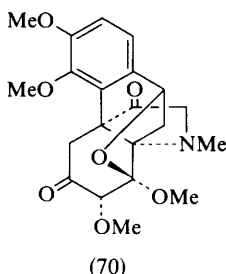
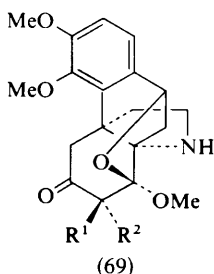
<sup>213</sup> V. Vecchiotti, C. Casagrande, and G. Ferrari, *Tetrahedron Letters*, 1976, 1631.

<sup>214</sup> M. K. Yusupov, Kh. A. Aslanov, and Dinh Thi Ngo, *Khim. prirod. Soedinenii*, 1975, **11**, 271 (*Chem. Abs.*, 1976, **84**, 44 473).

<sup>215</sup> N. L. Mukhamed'yarova, M. K. Yusupov, Kh. A. Aslanov, and A. S. Sadykov, *Khim. prirod. Soedinenii*, 1975, **11**, 758 (*Chem. Abs.*, 1976, **84**, 150 804).



diazomethane.<sup>215</sup> Six new hasubanan alkaloids have been isolated and chemically interrelated, namely stephamiersine (69;  $R^1 = H$ ,  $R^2 = OMe$ ),<sup>216</sup> epistephamiersine (69;  $R^1 = OMe$ ,  $R^2 = H$ ),<sup>216</sup> oxostephamiersine (70),<sup>216</sup> stephasunoline (71),<sup>216</sup> and



16-oxoprometaphanine (72),<sup>217</sup> all from *Stephania japonica*, and 6-dihydroepistephamiersine 6-acetate (73) from *S. abyssinica*.<sup>218</sup> Also isolated from *S. japonica* was 16-oxohasubananine, known previously only as a synthetic intermediate (cf. Vol. 6, p. 134).<sup>217</sup>

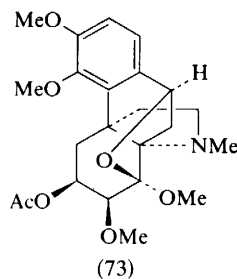
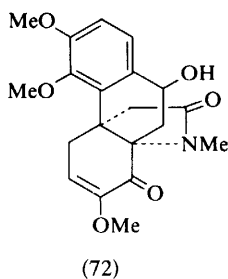
The role of alkaloids as taxonomic markers, particularly in the case of thebaine-containing species of *Papaver bracteatum*, has been critically reviewed.<sup>219</sup> Another survey deals with new plant sources of opiates and the morphological and chemical

<sup>216</sup> M. Matsui, Y. Watanabe, T. Ibuka, and K. Tanaka, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 1323.

<sup>217</sup> Y. Watanabe, M. Matsui, and M. Uchida, *Phytochemistry*, 1975, **14**, 2695.

<sup>218</sup> A. J. Van Wyk, *J. S. African Chem. Inst.*, 1975, **28**, 284 (*Chem. Abs.*, 1975, **83**, 203 766).

<sup>219</sup> D. Gröger, *Planta Med.*, 1975, **28**, 269.



differences between *P. bracteatum*, *P. orientale*, and *P. pseudo-orientale*.<sup>220</sup> A rapid spot test method of differentiating these species<sup>221</sup> and a g.l.c. method for determining thebaine and other alkaloids in *P. orientale*<sup>222</sup> have been described. In view of contradictory results which have been reported for the alkaloid content of these three species, specimens which had been classified according to haploid chromosome number (7, 14, and 21 for *P. bracteatum*, *P. orientale*, and *P. pseudo-orientale* respectively) were examined. *P. orientale* afforded oripavine and thebaine. These were not present in *P. pseudo-orientale* which contained aporphine and protoberberine alkaloids, together with minor amounts of salutaridine.<sup>223</sup> Several publications deal with particular varieties of *P. somniferum* and their alkaloid content<sup>224–227</sup> and the effect of stem length on the latter has been discussed.<sup>228</sup> Methods of isolating the morphine and codeine from poppies have been described.<sup>229–231</sup>

The reactions of nucleophiles with codeine tosylate (74; R = OMe)<sup>232</sup> and pseudocodeine tosylate (76; R = OTs)<sup>233</sup> have been elucidated using kinetic measurements. Thus codeine tosylate, when treated with LiCl in DMF at 40 °C, undergoes an  $S_N2$  reaction to give  $\alpha$ -chlorocodeine (75; R<sup>1</sup> = Cl, R<sup>2</sup> = H), which rearranges by an  $S_N1'$  mechanism to  $\beta$ -chlorocodeine (76; R = Cl) when heated at 120 °C in DMF.<sup>232</sup> Pseudocodeine tosylate (76; R = OTs) reacts with weak nucleophiles by an  $S_N1'$  mechanism, e.g. chloride ion gives (75; R<sup>1</sup> = Cl, R<sup>2</sup> = H), and with more

<sup>220</sup> J. W. Fairbairn, *Planta Med.*, 1976, **29**, 26.

<sup>221</sup> P. G. Vincent, C. E. Bare, and W. A. Gentner, *Lloydia*, 1976, **39**, 76.

<sup>222</sup> K. M. Nyomarkay, S. Nyiredy, jun., and J. Takacs, *Herba Hung.*, 1974, **13**, 115 (*Chem. Abs.*, 1975, **83**, 40 172).

<sup>223</sup> A. Shafiee, I. Lalezari, P. Nasser-Nouri, and R. Asgharian, *J. Pharm. Sci.*, 1975, **64**, 1570.

<sup>224</sup> H. Kaneshima, M. Mori, T. Yamagishi, H. Ogawa, A. Kanetoshi, and Y. Kinoshita, *Hokkaido-ritsu Eisei Kenkyushoho*, 1975, **25**, 152 (*Chem. Abs.*, 1976, **84**, 86 795).

<sup>225</sup> K. R. Khanna and U. P. Singh, *Planta Med.*, 1975, **28**, 92.

<sup>226</sup> P. Popov, I. Dimitrov, and T. Deneva, *Rastenievud. Nauki*, 1975, **12**, 34 (*Chem. Abs.*, 1976, **84**, 2250); P. Popov, I. Dimitrov, S. Georgiev, T. Deneva, and L. Iliev, *Farmatsiya (Sofia)*, 1975, **25**, 33 (*Chem. Abs.*, 1976, **84**, 79 629).

<sup>227</sup> M. Tin-Wa, F. A. Crane, R. Baines, and N. R. Farnsworth, *J. Pharm. Sci.*, 1975, **64**, 2024.

<sup>228</sup> T. Deneva, *Rastenievud. Nauki*, 1975, **12**, 49 (*Chem. Abs.*, 1976, **84**, 28 012).

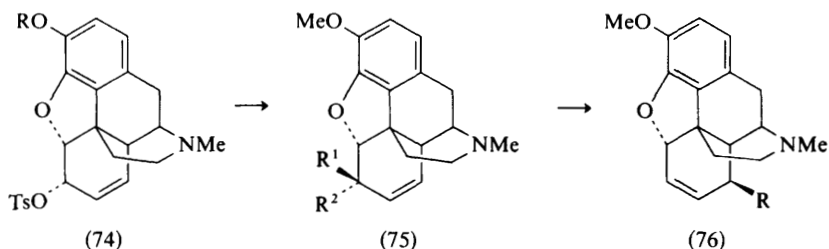
<sup>229</sup> B. Dimov and I. Tonev, *Trudy Nauchnoizsled. Khim.-Farm. Inst.*, 1974, **9**, 517 (*Chem. Abs.*, 1975, **83**, 103 195).

<sup>230</sup> H. Mitsuhashi, T. Yamagishi, K. Inoue, and N. Homma, *Shoyakugaku Zasshi*, 1975, **29**, 45 (*Chem. Abs.*, 1976, **84**, 65 203).

<sup>231</sup> Yu. V. Shostenko, E. S. Vysotskaya, S. Kh. Mushinskaya, N. G. Bozhko, and S. G. Sedova, *Farm. Zhur. (Kiev)*, 1975, **30**, 58 (*Chem. Abs.*, 1976, **84**, 155 559).

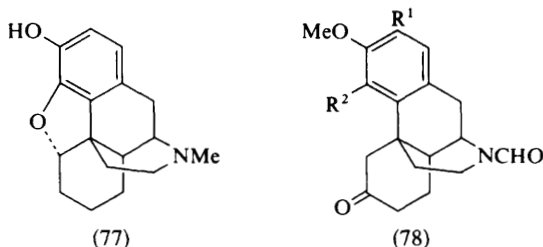
<sup>232</sup> S. Makleit, T. Mile, and R. Bogнар, *Magyar Kém. Folyóirat*, 1975, **81**, 564 (*Chem. Abs.*, 1976, **84**, 90 360).

<sup>233</sup> S. Makleit, G. Somogyi, and R. Bogнар, *Magyar Kém. Folyóirat*, 1975, **81**, 517 (*Chem. Abs.*, 1976, **84**, 90 359).



powerful nucleophiles by an  $S_N1$  mechanism accompanied by retention of configuration, e.g. azide ion gives (76;  $R = N_3$ ).<sup>233</sup> The preparation of azidomorphines in this way has been described<sup>234</sup> and reviews of these compounds have appeared.<sup>235,236</sup>

Reductive detosylation is the key step in the preparation from morphine tosylate (74;  $R = H$ ) of deoxycodine E (75;  $R^1 = R^2 = H$ ) and the morphinan (77).<sup>237</sup> Selective removal of the phenolic hydroxy-group at C-2 in the synthetic morphinans (78;  $R^1 = OH$ ,  $R^2 = H$ )<sup>238</sup> and (78;  $R^1 = R^2 = OH$ )<sup>239</sup> has been accomplished by



reduction of the 1-phenyltetrazol-5-yl ethers (cf. Vol. 6, p. 136). The latter transformation realizes a convenient total synthesis of codeine and morphine by the Grewe method. The *N*-methylmorphinan (79;  $R = \beta\text{-H}$ ,  $X = H_2$ ) was found to undergo an abnormal reaction with osmium tetroxide, giving the corresponding *N*-formyl analogue (3%) and the keto-lactam (79;  $R = \beta\text{-H}$ ,  $X = O$ ) (10%). The isomorphinan (79;  $R = \alpha\text{-H}$ ,  $X = H_2$ ) behaved in similar fashion but the 14-hydroxymorphinan (79;  $R = \beta\text{-OH}$ ,  $X = H_2$ ) appeared to be resistant to oxidation under these conditions.<sup>240</sup> Intramolecular coupling of *N*-alkoxycarbonyl-*N*-norreticulines by electrochemical oxidation (cf. Vols. 4–6) affords *N*-alkoxycarbonyl-*N*-norpallidines in ca. 18% yield.<sup>241</sup> A review on applications of lead tetra-acetate oxidation includes a section on the synthesis of ( $\pm$ )-8-

<sup>234</sup> R. Bogner, S. Makleit, J. Knoll, S. Berenyi, and G. Horvath, *Izvest. Khim.*, 1975, **8**, 203 (*Chem. Abs.*, 1976, **84**, 135 895).

<sup>235</sup> R. Bogner, S. Makleit, J. Knoll, S. Berenyi, and G. Horvath, *Kém. Kozl.*, 1975, **44**, 1 (*Chem. Abs.*, 1976, **84**, 135 889).

<sup>236</sup> J. Knoll, Proceedings of the 6th International Congress of Pharmacology, 1975, ed. H. Vapaatalo, Pergamon, Oxford, 1976, Vol. 4, p. 31.

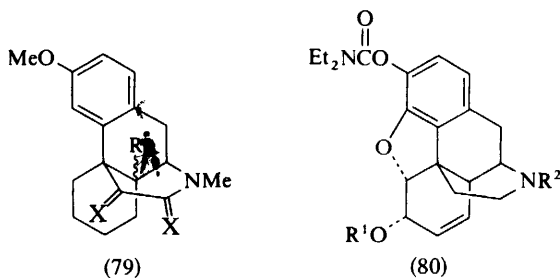
<sup>237</sup> S. Makleit, S. Berenyi, and R. Bogner, *Magyar Kém. Folyóirat*, 1975, **81**, 449 (*Chem. Abs.*, 1976, **84**, 122 089).

<sup>238</sup> H. C. Beyerman, E. Buurman, T. S. Lie, and L. Maat, *Rec. Trav. chim.*, 1976, **95**, 43 (*Chem. Abs.*, 1976, **84**, 105 868).

<sup>239</sup> H. C. Beyerman, T. S. Lie, L. Maat, H. H. Bosman, E. Buurman, E. J. M. Bijsterveld, and H. J. M. Sinnige, *Rec. Trav. chim.*, 1976, **95**, 24 (*Chem. Abs.*, 1976, **84**, 90 365).

<sup>240</sup> Y. K. Sawa, S. Maeda, and M. Adachi, *Tetrahedron*, 1975, **31**, 953.

<sup>241</sup> J. M. Bobbitt, I. Noguchi, R. S. Ware, K. Ng Chiong, and S. J. Huang, *J. Org. Chem.*, 1975, **40**, 2924.



chloromorphinandienones and ( $\pm$ )-8-chlorohomomorphinandienones *via p*-quinol acetates.<sup>131</sup> Successive reaction with phenyl chloroformate and 84.5% hydrazine has been recommended for *N*-demethylation of 6,7-benzomorphans.<sup>242</sup> Acetate groups would not be expected to survive such treatment with hydrazine or the hydrolysis step in the classical cyanogen bromide demethylation procedure. The diethylcarbamoyl grouping, however, is retained in the conversion of (80;  $R^1 = \text{Ac}$ ,  $R^2 = \text{Me}$ ) into (80;  $R^1 = R^2 = \text{H}$ ) using the latter procedure.<sup>243</sup> In an alternative approach to *O*-substituted *N*-normorphines, reaction of morphine with 2,2,2-trichloroethyl chloroformate<sup>243</sup> or *t*-butyl azidoformate<sup>244</sup> gave *O*-3,*N*-bisalkoxycarbonyl compounds. After base hydrolysis and acetylation, the urethane function was selectively cleaved to give 3,6-diacetyl-*N*-normorphine. This and 6-acetyl-*N*-normorphine, which was also prepared, were found to have *ca.* 5% of the analgesic activity of heroin.<sup>244</sup> A variety of 6-hydroxy-6-substituted morphine derivatives [*e.g.* (75;  $R^1 = \text{C}\equiv\text{CH}$ ,  $R^2 = \text{OH}$ )] have been prepared from appropriate 6-oxomorphines.<sup>245–247</sup> Reports have also appeared on the preparation of thebaine and oripavine from codeine and morphine,<sup>248</sup> and of morphine 3-glucuronide.<sup>249</sup> Kinetic studies have been carried out on the deacetylation of heroin<sup>250</sup> and on the autoxidation of codeine and its phosphate in solution.<sup>251</sup>

An unusual synthesis of 3-methoxyhasubanan (81) involves an intramolecular amination. This is believed to arise by transfer of hydride ion from the benzylic-allylic position of (82) as shown in Scheme 6.<sup>252</sup> The sulphate ester (84), obtained by the action of methyl sulphate on the 9-hydroxyhasuban-6-one (83), reacted with base to give the 7,14-cyclodihydrocodeine derivative (85) (Scheme 7).<sup>253</sup> Further publications have appeared on the synthesis and pharmacological properties of

<sup>242</sup> K. C. Rice, *J. Org. Chem.*, 1975, **40**, 1850.

<sup>243</sup> I. J. Borowitz and V. Diakiw, *J. Heterocyclic Chem.*, 1975, **12**, 1123.

<sup>244</sup> K. C. Rice and A. E. Jacobson, *J. Medicin. Chem.*, 1975, **18**, 1033.

<sup>245</sup> P. Kerekes, R. Bognar, G. Gaal, and G. Horvath, *Acta Chim. Acad. Sci. Hung.*, 1974, **82**, 211 (*Chem. Abs.*, 1974, **81**, 136 337).

<sup>246</sup> R. Bognar, G. Gaal, G. Horvath, and P. Kerekes, *Kém. Kozl.*, 1975, **44**, 11 (*Chem. Abs.*, 1976, **84**, 135 893).

<sup>247</sup> R. Bognar, G. Gaal, G. Horvath, and P. Kerekes, *Izvest. Khim.*, 1975, **8**, 194 (*Chem. Abs.*, 1976, **84**, 135 894).

<sup>248</sup> R. B. Barber and H. Rapoport, *J. Medicin. Chem.*, 1975, **18**, 1074.

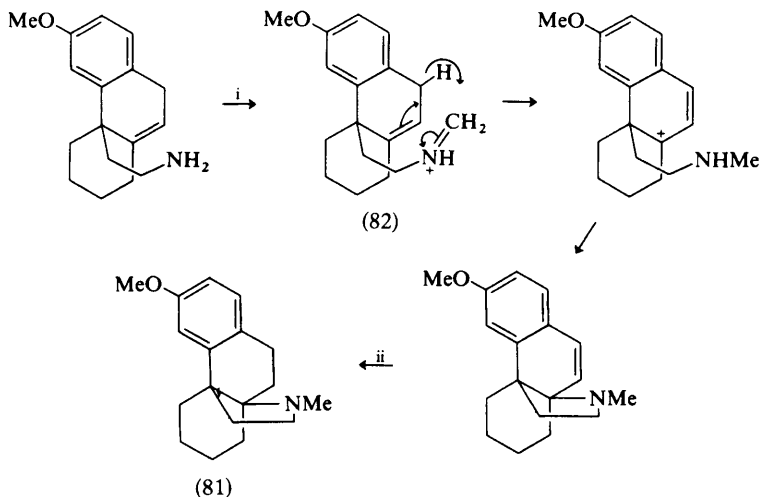
<sup>249</sup> B. Berrang, C. E. Twine, G. L. Hennessee, and F. I. Carroll, *Synth. Comm.*, 1975, **5**, 231.

<sup>250</sup> G. R. Nakamura, J. I. Thornton, and T. T. Noguchi, *J. Chromatog.*, 1975, **110**, 81.

<sup>251</sup> E. Pawelczyk and R. Wachowiak, *Herba Pol.*, 1974, **20**, 253 (*Chem. Abs.*, 1975, **83**, 32 971).

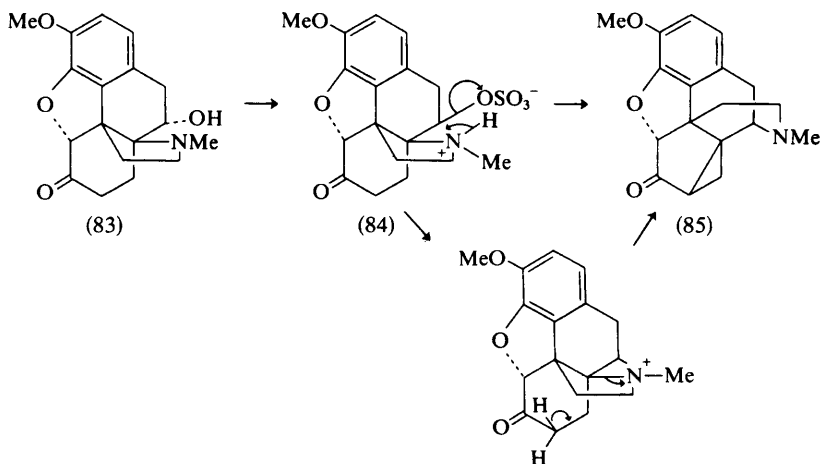
<sup>252</sup> S. Shiotani and T. Kometani, *Tetrahedron Letters*, 1976, 769.

<sup>253</sup> W. Fleishhacker and A. Klement, *Monatsh.*, 1975, **106**, 1513 (*Chem. Abs.*, 1976, **84**, 121 681).



Reagents: i,  $\text{CH}_2\text{O}-\text{HCO}_2\text{H}$ ; ii,  $\text{H}_2-\text{Pd/C}$ .

**Scheme 6**



**Scheme 7**

oxygenated isomorphinans, hasubanans, and morphinans (*cf.* Vol. 6, p. 134).<sup>254-257</sup> Also prepared for pharmacological study have been ring-D enlarged morphinans and isomorphinans,<sup>258</sup> D-normorphinans,<sup>259</sup> pentacyclic morphinans, *e.g.* (86),<sup>260</sup>

<sup>254</sup> I. Monkovic, H. Wong, B. Belleau, I. J. Pachter, and Y. G. Perron, *Canad. J. Chem.*, 1975, **53**, 2515.

<sup>255</sup> I. Monkovic and H. Wong, *Canad. J. Chem.*, 1976, **54**, 883.

<sup>256</sup> I. Monkovic, H. Wong, A. W. Pircio, Y. G. Perron, I. J. Pachter, and B. Belleau, *Canad. J. Chem.*, 1975, **53**, 3094.

<sup>257</sup> M. Menard, P. Rivest, B. Belleau, J.-P. Daris, and Y. G. Perron, *Canad. J. Chem.*, 1976, **54**, 429.

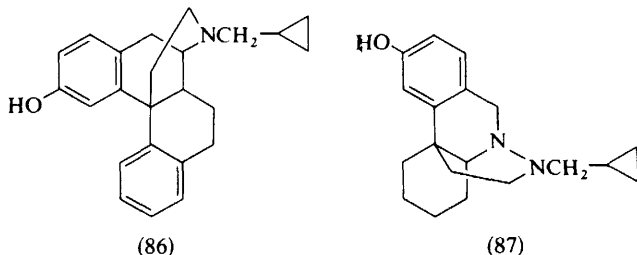
<sup>258</sup> S. Shiotani, *J. Org. Chem.*, 1975, **40**, 2033.

<sup>259</sup> T. T. Conway, T. W. Doyle, Y. G. Perron, J. Chapuis, and B. Belleau, *Canad. J. Chem.*, 1975, **53**, 245.

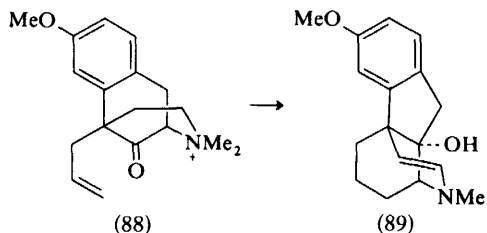
<sup>260</sup> J. L. Douglas and J. Meunier, *Canad. J. Chem.*, 1975, **53**, 3681.



and various olefins formed by the action of Wittig reagents or sulphur ylides upon naloxone and naltrexone.<sup>261</sup> The (–)-form of the azamorphinan (87) ('a fantastic analgesic') was found to be five times as active as pentazocine.<sup>262</sup>



The structure (89) of the product obtained by pyrolysis of the 5-allyl-9-oxobenzomorphan metho-salt (88) has been established by X-rays. A radical



mechanism is suggested for this unusual molecular rearrangement.<sup>263</sup> The 7,8-benzomorphan (91) has been obtained by Stevens rearrangement of the tetrahydropyridinium salt (90).<sup>264</sup> A number of reports deal with the synthesis and pharmacological properties of various 6,7-benzomorphans<sup>265–275</sup> and benzazocines,<sup>273,276</sup> and an alternative synthesis of pentazocine has been described.<sup>277</sup> The (+)-enantiomers of both C-9 epimers of (92) were found to be virtually inactive

<sup>261</sup> E. F. Hahn, J. Fishman, and R. D. Heilman, *J. Medicin. Chem.*, 1975, **18**, 259.

<sup>262</sup> T. Kametani, K. Kigasawa, M. Hiiragi, N. Wagatsuma, O. Kusama, and T. Uryu, *Heterocycles*, 1976, **4**, 41.

<sup>263</sup> F. R. Ahmed, M. Saucier, and I. Monokovic, *Canad. J. Chem.*, 1975, **53**, 3276.

<sup>264</sup> J. Bosch, J. Canals, and R. Granados, *J. Heterocyclic Chem.*, 1975, **12**, 1117.

<sup>265</sup> J. Bosch, J. Canals, and R. Granados, *Anales de Quim.*, 1975, **71**, 253 (*Chem. Abs.*, 1975, **83**, 206 071).

<sup>266</sup> N. F. Albertson, *J. Medicin. Chem.*, 1975, **18**, 619.

<sup>267</sup> H. Inoue and E. L. May, *J. Medicin. Chem.*, 1976, **19**, 259.

<sup>268</sup> H. Inoue, T. Ohishi, and E. L. May, *J. Medicin. Chem.*, 1975, **18**, 787.

<sup>269</sup> H. Merz, K. Stockhaus, and H. Wick, *J. Medicin. Chem.*, 1975, **18**, 996.

<sup>270</sup> W. F. Michne, *J. Org. Chem.*, 1976, **41**, 894.

<sup>271</sup> K. C. Rice and A. E. Jacobson, *J. Medicin. Chem.*, 1976, **19**, 430.

<sup>272</sup> K. C. Rice, A. E. Jacobson, and E. L. May, *J. Medicin. Chem.*, 1975, **18**, 854.

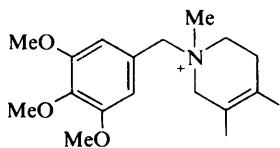
<sup>273</sup> M. E. Rogers, H. H. Ong, E. L. May, and W. A. Klee, *J. Medicin. Chem.*, 1975, **18**, 1036.

<sup>274</sup> K. Tamaki, N. Naito, and K. Fujii, *Yuki Gosei Kagaku Kyokai Shi*, 1976, **34**, 95 (*Chem. Abs.*, 1976, **84**, 150 464).

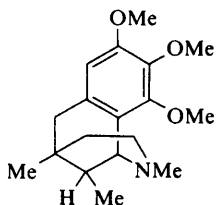
<sup>275</sup> H. Yamamoto, C. Saito, S. Inaba, T. Inukai, K. Kobayashi, T. Fukumaru, Y. Koga, T. Homma, and Y. Asami, *Arzneim.-Forsch.*, 1975, **25**, 795 (*Chem. Abs.*, 1975, **83**, 126 249).

<sup>276</sup> Y. Sawa, Y. Kawakami, T. Hattori, T. Masuda, M. Hori, and H. Fujimara, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 2211.

<sup>277</sup> T. Kametani, T. Honda, S.-P. Huang, and K. Fukumoto, *Canad. J. Chem.*, 1975, **53**, 3820.

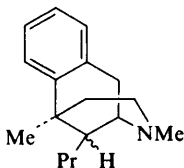


(90)

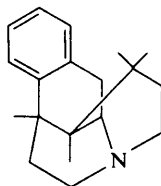


(91)

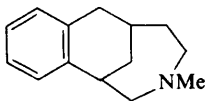
whereas the (–)-enantiomers were as potent as, or more potent than morphine as an analgesic.<sup>271</sup> Other potential analgesics prepared include novel tetracyclic bridged benzazocines, *e.g.* (93),<sup>278</sup> homobenzomorphans, *e.g.* (94),<sup>279</sup> 1,5-methanobenzazocines, *e.g.* (95),<sup>280</sup> azabenzomorphans, *e.g.* (96),<sup>281</sup> various 1,3-bridged 2-aminotetralins,<sup>282–284</sup> dibenzomorphans,<sup>285</sup> thienomorphans,<sup>286</sup> benzazepines,<sup>287</sup> and 2,5-dimethyl-6,7-naphthomorphan.<sup>288</sup>



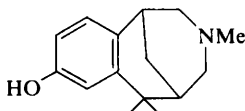
(92)



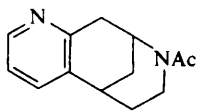
(93)



(94)



(95)



(96)

A comprehensive two-volume work dealing with structure–activity relationships in various aromatic compounds, and in particular those incorporating a catechol monoether structural unit, provides a full survey of chemical physical and phar-

<sup>278</sup> M. Kimura, T. Nakajima, T. Asumi, Y. Koga, and H. Yamamoto, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 3208; M. Kimura, T. Nakajima, S. Inaba, and H. Yamamoto, *Bull. Chem. Soc. Japan*, 1974, **47**, 1404.

<sup>279</sup> T. Kometani, S. Shiotani, and K. Mitsuhashi, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 541.

<sup>280</sup> Y. Sawa, T. Kato, T. Matsuda, M. Hori, and H. Fujimura, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 1932.

<sup>281</sup> J. Adachi, K. Nomura, and K. Mitsuhashi, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 85.

<sup>282</sup> M. E. Freed, J. R. Potoski, G. L. Conklin, and S. C. Bell, *J. Medicin. Chem.*, 1976, **19**, 560.

<sup>283</sup> M. E. Freed, J. R. Potoski, E. H. Freed, G. L. Conklin, and S. C. Bell, *J. Medicin. Chem.*, 1976, **19**, 476.

<sup>284</sup> J. L. Malis, M. E. Rosenthale, and M. I. Gluckman, *J. Pharmacol. Exp. Ther.*, 1975, **194**, 488 (*Chem. Abs.*, 1976, **84**, 229).

<sup>285</sup> R. K. Pandey, P. Pandey, and B. C. Joshi, *Bull. Acad. polon. Sci., Sér. Sci. chim.*, 1975, **23**, 469 (*Chem. Abs.*, 1975, **83**, 193 053).

<sup>286</sup> J. Bosch, R. Granados, and F. Lopez, *J. Heterocyclic Chem.*, 1975, **12**, 651.

<sup>287</sup> Y. Sawa, T. Kato, T. Matsuda, M. Hori, and H. Fujimura, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 1917.

<sup>288</sup> R. K. Pandey and B. C. Joshi, *Bull. Acad. polon. Sci., Sér. Sci. chim.*, 1975, **23**, 385 (*Chem. Abs.*, 1975, **83**, 114 691).

macological properties of morphine alkaloids.<sup>289</sup> The u.v. and i.r. spectra of enones and dienones related to promorphine and homopromorphine<sup>290</sup> and the chiroptical properties of various codeine derivatives<sup>291</sup> have been discussed. The C-13 n.m.r. spectra have been analysed of morphine alkaloids<sup>292</sup> and of oxymorphone and oxycodone.<sup>293</sup> Weak phosphorescence emission from the triplet state of heroin in ethanol at 77 K has been found to have a maximum at 445 nm, which differs significantly from that of morphine ( $\lambda_{\text{max}} = 522$  nm, 10 times more intense). The fluorescence emissions of heroin and morphine at 25 °C showed maxima at 312 and 340 nm respectively.<sup>294</sup> The formation with magnesium ion is attended by a shift in the fluorescence to higher wavelength.<sup>295</sup> Acid dissociation constants for morphine have been determined in aqueous methanol.<sup>296</sup> For morphine, nalorphine, and *N*-phenethylmorphine, the relationship between conformation and the binding and interaction with active site has been discussed in the light of quantum chemical studies.<sup>297</sup> X-Ray photoelectron measurement of nitrogen electron densities for various congener agonist-antagonist pairs, *e.g.* morphine and nalorphine, confirm quantum chemical calculations that, contrary to customary pharmacological assumptions, the electron densities are the same in such pairs.<sup>298</sup> The results also indicate that  $\text{p}K_{\text{a}}$  values measured in solution cannot be directly correlated with nitrogen electron densities.<sup>298</sup>

The pharmacology and metabolism of naltrexone have been reviewed.<sup>299</sup> Details of the isolation and identification of  $6\beta$ -naltrexol, the major human metabolite of naltrexone, have appeared.<sup>300</sup> A new metabolite has been identified as 2-hydroxy-3-*O*-methyl- $6\beta$ -naltrexol.<sup>301</sup> This appears to be able to penetrate membranes and may contribute to the length of action of the drug. Increased duration of action is observed when cyclazocine and naloxone are used in the form of water-insoluble salts, *e.g.* zinc tannate complexes.<sup>302</sup> The physiological effects of etorphine on cows, sheep, and goats<sup>303</sup> and on free-ranging moose<sup>304</sup> have been reported. Simple models [*e.g.* (97)] for the *endo*-6,14-ethenotetrahydrothebaine type of compound

<sup>289</sup> H. L. Holmes, 'Structure Activity Relations for some Conjugated Heteroenoic Compounds, Catechol Monoethers and Morphine Alkaloids', Vols. 1 and 2, ed. H. L. Holmes, Defence Research Establishment, Suffield, Ralston, Alberta, 1975.

<sup>290</sup> S. Dvorackova, L. Hruban, V. Preininger, and F. Santavy, *Heterocycles*, 1975, **3**, 575.

<sup>291</sup> R. Bognar, G. Gaal, P. Kerekes, A. Levai, and S. Makleit, *Coll. Czech. Chem. Comm.*, 1975, **40**, 670.

<sup>292</sup> F. I. Carroll, C. G. Moreland, G. A. Brine, and J. A. Kepler, *J. Org. Chem.*, 1976, **41**, 996; Y. Terui, K. Tori, S. Maeda, and K. Sawa, *Tetrahedron Letters*, 1975, 2853.

<sup>293</sup> C. J. Kelley, R. C. Harruff, and M. Carmack, *J. Org. Chem.*, 1976, **41**, 449.

<sup>294</sup> A. Bowd and J. H. Turnbull, *J.C.S. Chem. Comm.*, 1975, 651.

<sup>295</sup> S. C. Lin, V. C. Sutherland, and E. L. Way, *Proc. West. Pharmacol. Soc.*, 1975, **18**, 181 (*Chem. Abs.*, 1975, **83**, 197 733).

<sup>296</sup> E. S. Vysotskaya, S. Kh. Mushinskaya, and Yu. V. Shostenko, *Zhur. fiz. Khim.*, 1975, **49**, 1859 (*Chem. Abs.*, 1975, **83**, 206 460).

<sup>297</sup> G. H. Loew and D. S. Berkowitz, *J. Medicin. Chem.*, 1975, **18**, 656.

<sup>298</sup> L. J. Saethre, Y. A. Carlson, J. J. Kaufman, and W. S. Koski, *Mol. Pharmacol.*, 1975, **11**, 492 (*Chem. Abs.*, 1975, **83**, 179 339).

<sup>299</sup> K. Verebely and S. J. Mule, *Amer. J. Drug Alcohol Abuse*, 1975, **2**, 357 (*Chem. Abs.*, 1976, **84**, 25 635).

<sup>300</sup> E. J. Cone, C. W. Gorodetzky, and S. Y. Yeh, *J. Pharm. Sci.*, 1975, **64**, 618.

<sup>301</sup> K. Verebely, M. A. Chedekel, S. J. Mule, and D. Rosenthal, *Res. Comm. Chem. Pathol. Pharmacol.*, 1975, **12**, 67 (*Chem. Abs.*, 1976, **84**, 92).

<sup>302</sup> A. P. Gray and D. S. Robinson, *Adv. Biochem. Psychopharmacol.*, 1973, **8**, 555 (*Chem. Abs.*, 1975, **83**, 53 179).

<sup>303</sup> B. F. Kania, *Med. Weterynar. (Poland)*, 1975, **31**, 158 (*Chem. Abs.*, 1975, **83**, 71 783).

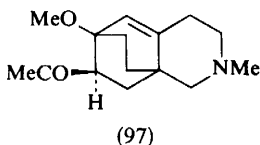
<sup>304</sup> Y. E. Roussel and R. Patenaude, *J. Wildlife Management*, 1975, **39**, 634 (*Chem. Abs.*, 1975, **83**, 157 915).

**Table 7** Analysis of morphine alkaloids

Substance analysed	Methods
A	Colorimetry, <sup>a,b</sup> fluorometry, <sup>c-g,p*,185</sup> immunoassay, <sup>g</sup> g.l.c., <sup>c,d,h-l,z*</sup> i.r., <sup>m</sup> liquid chromatography, <sup>n,o,pp*,ij*,183</sup> paper and column chromatography with titanium arsenate, <sup>p</sup> countercurrent distribution and spectrophotometry, <sup>186</sup> polarography, <sup>q</sup> radioimmunoassay, <sup>g,r,-i,uu*</sup> spin immunoassay, <sup>c,u,v,aaa*</sup> t.l.c., <sup>d,j,s,w,b*,p*,ggg*,189</sup> t.l.c. and microreactions, <sup>188</sup> titration <sup>ccc*,194</sup>
B	Colorimetry, <sup>a,x</sup> fluorometry, <sup>f</sup> g.l.c., <sup>k,l,y,z,aa</sup> i.r., <sup>m</sup> liquid chromatography, <sup>o,ij*</sup> ionization m.s., <sup>bb</sup> polarography, <sup>q</sup> spin immunoassay, <sup>v</sup> t.l.c., <sup>z,ggg*,hhh*,188,189</sup> titration <sup>cc,ccc*</sup>
C	g.l.c., <sup>i,z,aa</sup> t.l.c. <sup>z</sup>
D	Countercurrent distribution and spectrophotometry, <sup>186</sup> fluorometry, <sup>dd,185</sup> g.l.c., <sup>ee,231</sup> g.c.-m.s., <sup>ff</sup> liquid chromatography, <sup>ij*,184</sup> polarography, <sup>gg</sup> t.l.c., <sup>hh,190,191</sup>
E	g.l.c., <sup>ii</sup> ion-exchange chromatography and spectrophotometry, <sup>jj</sup> paper chromatography, t.l.c., g.l.c., and spectrophotometry, <sup>kk</sup> radioimmunoassay, <sup>ll</sup> t.l.c.-spectrophotometry <sup>mm</sup>

\* For asterisk references see Table 2.

A, Codeine and/or morphine; B, Morphine derivatives, e.g. heroin; C, Metabolites of morphine, codeine, or heroin; D, Opium alkaloids, thebaine; E, Synthetic. <sup>a</sup> T. P. Benzar, *Farm. Zhur. (Kiev)*, 1975, **30**, 59 (*Chem. Abs.*, 1975, **83**, 65 505); <sup>b</sup> M. A. Camacho and E. Selles-Flores, *Clenc. Ind. Farm.*, 1974, **6**, 403 (*Chem. Abs.*, 1975, **83**, 15 707); <sup>c</sup> J. Cate, M. Clarkson, J. Strickland, and N. A. D'Amato, *Clin. Toxicol.*, 1976, **9**, 235; <sup>d</sup> V. F. Cordova and T. A. Banford, *J. Forensic Sci.*, 1975, **20**, 58; <sup>e</sup> V. Gillis and T. A. Kubic, *I.S.A. Trans.*, 1975, **14**, 261 (*Chem. Abs.*, 1976, **84**, 100 323); <sup>f</sup> V. Gillis and T. A. Kubic, *Adv. Instrum.*, 1974, **29**, Pt. 3, 750 (*Chem. Abs.*, 1975, **83**, 54 050); <sup>g</sup> V. R. Spiehler, D. Reed, R. H. Cravey, W. P. Wilcox, R. F. Shaw, and S. Holland, *J. Forensic Sci.*, 1975, **20**, 647; <sup>h</sup> B. Dahlstrom and L. Paalzow, *J. Pharm. Pharmacol.*, 1975, **27**, 172; M. R. Stevens, *J. Pharm. Sci.*, 1975, **64**, 1686; R. A. Zweidinger, F. M. Weinberg, and R. W. Handy, *J. Pharm. Sci.*, 1976, **65**, 427; <sup>i</sup> M. K. Brunson and J. F. Nash, *Clin. Chem.*, 1975, **21**, 1956; <sup>j</sup> N. C. Jain, T. C. Sneath, R. D. Budd, and W. J. Leung, *Clin. Chem.*, 1975, **21**, 1486; <sup>k</sup> F. Medzhradsky and P. J. Dahlstrom, *Pharmacol. Res. Comm.*, 1975, **7**, 55; <sup>l</sup> S. P. Sobol and A. R. Sperling, *A.C.S. Symposium Ser.*, 1975, **13** (*Forensic Sci., Symp.*, 1974), 170; <sup>m</sup> A. Puech, G. Kister, and M. Ribes, *Trav. Soc. Pharm. Montpellier*, 1975, **35**, 167 (*Chem. Abs.*, 1975, **83**, 136 976); <sup>n</sup> I. Jane and J. F. Taylor, *J. Chromatog.*, 1975, **109**, 37; V. Quercia, B. Tucci Bucci, and A. R. La Tegola, *Fitoterapia*, 1975, **46**, 3 (*Chem. Abs.*, 1975, **83**, 125 983); <sup>o</sup> W. A. Trinler and D. J. Reuland, *J. Forensic Sci. Soc.*, 1975, **15**, 153; <sup>p</sup> M. Qureshi, S. A. Nabi, and N. Zehra, *Talanta*, 1976, **23**, 31; <sup>q</sup> G. E. Baiulescu and S. Popescu, *Rev. Chim. (Roumania)*, 1975, **26**, 253 (*Chem. Abs.*, 1975, **83**, 136 984); <sup>r</sup> M. Usategui-Gomez, J. E. Heveran, R. Cleeland, B. McGhee, Z. Telischak, T. Awdziej, and E. Grunberg, *Clin. Chem.*, 1975, **21**, 1378; <sup>s</sup> R. J. Kokoski and M. Jais, *Clin. Chem.*, 1975, **21**, 417; <sup>t</sup> R. Davis, J. Feldhaus, J. Heveran, R. Wicks, and M. Peckham, *Clin. Chem.*, 1975, **21**, 1498; <sup>u</sup> M. R. Montgomery, R. L. Holtzman, and R. K. Leute, *Clin. Chem.*, 1975, **21**, 1323; <sup>v</sup> J. A. Pedersen, L. T. Muus, O. V. Olesen, and A. Amidsen, *Ugeskr. Laeger*, 1975, **137**, 1142 (*Chem. Abs.*, 1975, **83**, 125 977); <sup>w</sup> F. Goc-Pietras, *Farm. Pol.*, 1975, **31**, 311 (*Chem. Abs.*, 1975, **83**, 168 536); <sup>x</sup> P. Lo Greco, A. Cruciat, and T. Pagani, *Friuli Med.*, 1973, **28**, 475 (*Chem. Abs.*, 1975, **83**, 53 110); <sup>y</sup> J. A. McIntyre and A. E. Armandi, *Clin. Chem.*, 1976, **22**, 396; M. Petkovic, *Arh. Farm.*, 1973, **23**, 309 (*Chem. Abs.*, 1975, **83**, 84 904); <sup>z</sup> P. A. F. Pranitis and A. Stolman, *J. Chromatog.*, 1975, **106**, 485; <sup>aa</sup> J. S. Shohet, *J. Pharm. Sci.*, 1975, **64**, 1011; <sup>ab</sup> E. P. J. Van der Slooten and H. J. Van der Helm, *Forensic Sci.*, 1975, **6**, 83; <sup>ac</sup> P. Liras, *J. Chromatog.*, 1975, **106**, 238; <sup>ad</sup> S. Y. Yeh and R. L. McQuinn, *J. Pharm. Sci.*, 1975, **64**, 1237; <sup>ae</sup> F. W. Karasek, H. H. Hill, jun., and S. H. Kim, *J. Chromatog.*, 1976, **117**, 327; <sup>af</sup> I. Jardine and C. Fenselau, *J. Forensic Sci.*, 1975, **20**, 373; <sup>ag</sup> H. Piasecka, *Farm. Pol.*, 1975, **31**, 123 (*Chem. Abs.*, 1975, **83**, 103 315); <sup>ah</sup> R. A. Chalmers and A. F. T. Jackson, *Mikrochim. Acta*, 1975, **2**, 273 (*Chem. Abs.*, 1976, **84**, 209 445); <sup>ai</sup> J. W. Fairbairn and K. Helliwell, *J. Pharm. Pharmacol.*, 1975, **27**, 217; H. Kaneshima, Y. Kinoshita, M. Mori, T. Yamagishi, Shioichi Honma, Shojiro Honma, and H. Mitsuhashi, *Shoyakugaku Zasshi*, 1974, **28**, 127 (*Chem. Abs.*, 1975, **83**, 152 416); <sup>aj</sup> J. M. Weber and T. S. Ma, *Mikrochim. Acta*, 1975, **2**, 401 (*Chem. Abs.*, 1976, **84**, 22 134); <sup>ak</sup> G. E. Baiulescu and S. Popescu, *Rev. Chim. (Roumania)*, 1975, **26**, 603 (*Chem. Abs.*, 1976, **84**, 126 804); <sup>al</sup> N. V. R. Rao and H. R. K. Murty, *J. Indian Acad. Forensic Sci.*, 1974, **13**, 18; <sup>am</sup> J. L. Fabregas and A. Margalet, *J. Pharm. Sci.*, 1975, **64**, 1005; K. Verebey, M. J. Kogan, A. De Pace, and S. J. Mule, *J. Chromatog.*, 1976, **118**, 331; K. Verebey, S. J. Mule, and D. Jukofsky, *J. Chromatog.*, 1975, **111**, 141; <sup>an</sup> G. B. Strada, *Rev. Fac. Farm., Univ. Cent. Venez.*, 1975, **30**, 34 (*Chem. Abs.*, 1975, **83**, 168 554); <sup>ao</sup> K. H. Beyer, 'Pentazocin-Neuer Weg, Berichte, Pentazocin Symposium, 1974', ed. G. A. Neuhaus and St. K. Kubicki, Thieme, Stuttgart, 1975, p. 7; <sup>ap</sup> B. A. Berkowitz, S. H. Ngai, J. Hempstead, and S. Spector, *J. Pharmacol. Exp. Ther.*, 1975, **195**, 499; <sup>aq</sup> M. R. Pluchino, *Rev. Fac. Farm., Univ. Cent. Venez.*, 1974, **29**, 31 (*Chem. Abs.*, 1975, **83**, 136 973).



have been prepared from hexahydromethoxyisoquinolines.<sup>305</sup> Reviews on opiates<sup>306</sup> and on the mechanism of morphine action<sup>307</sup> are also available.

The prolific literature on the analysis of morphine and related compounds is summarized in Table 7. The value of a number of different methods has been assessed.<sup>308</sup> Detection of drugs of abuse by toxicological and immunotoxicological<sup>309</sup> and by radioimmunoassay procedures<sup>310</sup> have been reviewed. The cost of immunoassay procedure for this purpose has, however, been compared unfavourably with that of chromatographic methods.<sup>57</sup> After a single euphorogenic dose of etorphine, opiates could not be detected in human urine, using homogeneous enzyme immunoassay, t.l.c., or g.l.c.<sup>311</sup> A sensitive radioimmunoassay for etorphine has, however, been developed.<sup>312</sup>

## 9 Colchicine Alkaloids

Alkaloid isolation and identification work is summarized in Table 8.<sup>313–315</sup> The coroms of *Gloriosa superba* are a fruitful source of colchicine alkaloids.<sup>314</sup> Of eight colchicine alkaloids isolated from this source for the first time, six were detected by t.l.c. or obtained in amorphous form while 2-demethylcolchicine and 3-methyl-N-formyl-N-decacyl- $\beta$ -lumicolchicine were obtained in crystalline form. Variations of alkaloid content in this and related species collected at different periods and in various localities were also examined.<sup>314</sup> The isolation, structures, and properties of colchicine alkaloids obtained from *Colchicum* varieties and other plants of the Wurmbeoideae in the U.S.S.R. have been reviewed.<sup>316</sup>

Colorimetric and volumetric assays<sup>317</sup> and radioimmunoassay<sup>318</sup> of colchicine have been described. Various thiocolchicines have been prepared and tested for antileukaemic activity.<sup>319</sup> Haematological effects have been noted for N-

<sup>305</sup> T. A. Crabb and J. R. Wilkinson, *J.C.S. Perkin I*, 1976, 644.

<sup>306</sup> J. Fishman and E. F. Hahn, ref. 110, p. 37.

<sup>307</sup> F. Bergmann, *Pahlavi Med. J.*, 1975, **6**, 473 (*Chem. Abs.*, 1975, **83**, 188 055).

<sup>308</sup> J. C. F. Kok, *Pharm. Weekblad*, 1976, **111**, 139.

<sup>309</sup> M. M. Baden, N. N. Valanju, S. K. Verma, and S. N. Valanju, ref. 110, p. 72.

<sup>310</sup> H. Matsushita, *Kagaku To Seibutsu*, 1975, **13**, 88 (*Chem. Abs.*, 1975, **83**, 53 018).

<sup>311</sup> C. W. Gorodetzky and M. P. Kullberg, *Clin. Pharmacol. Ther.*, 1975, **17**, 273.

<sup>312</sup> J. D. Robinson, B. A. Morris, and V. Marks, *Res. Comm. Chem. Pathol. Pharmacol.*, 1975, **10**, 1.

<sup>313</sup> M. I. K. Yusupov, Dinh Thi Bik Ngo, and Kh. A. Aslanov, *Khim. prirod. Soedinenii*, 1975, **11**, 526 (*Chem. Abs.*, 1976, **84**, 44 476).

<sup>314</sup> R. S. Thakur, H. Potesilova, and F. Santavy, *Planta Med.*, 1975, **28**, 201.

<sup>315</sup> T. K. Razdan, G. L. Koul, and B. L. Sapru, *J. Indian Chem. Soc.*, 1974, **51**, 910.

<sup>316</sup> A. S. Sadykov and M. K. Yusupov, *Acta Univ. Palacki Olomuc., Fac. Med.*, 1975, **73**, 13 (*Chem. Abs.*, 1976, **84**, 176 646).

<sup>317</sup> M. S. Karawya and A. M. Diab, *J. Assoc. Offic. Analyt. Chemists*, 1975, **58**, 1171.

<sup>318</sup> C. Boudene, F. Duprey, and C. Bohuon, *Biochem. J.*, 1975, **151**, 413.

<sup>319</sup> K. K. De, G. T. Shiau, and R. E. Harmon, *J. Carbohydrates, Nucleosides, Nucleotides*, 1975, **2**, 171 (*Chem. Abs.*, 1976, **84**, 12 336); *ibid.*, p. 259 (*Chem. Abs.*, 1976, **84**, 31 339); G. T. Shiau, K. K. De, and R. E. Harmon, *J. Pharm. Sci.*, 1975, **64**, 646.

**Table 8** Isolation of colchicine alkaloids

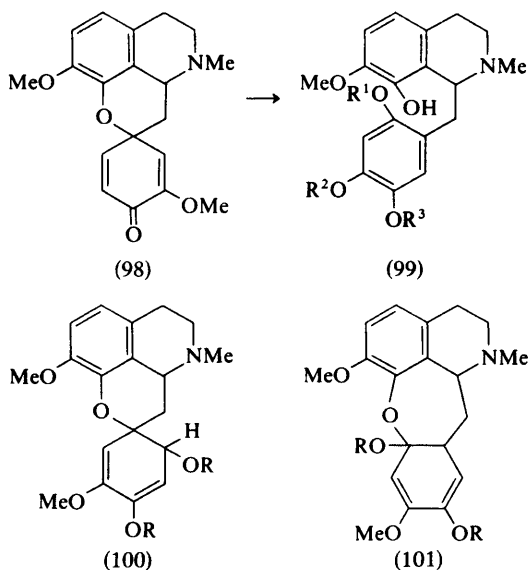
Source	Alkaloid	Ref.
<i>Colchicum szovitsii</i>	Colchicine	313
	2-Demethylcolchicine	
	3-Demethyl- $\beta$ -lumicolchicine	
<i>Gloriosa superba</i> <sup>a</sup>	2-Demethylcolchicine	314
	3-Demethylcolchicine	
	2-Demethylcolchicine	
	2,3-Demethylcolchicine	
	2,3-Demethyl- <i>N</i> -desacetylcolchicine	
	3-Demethyl- <i>N</i> -formyl- <i>N</i> -desacetylcolchicine	
	3-Demethyl- <i>N</i> -formyl- <i>N</i> -desacetyl- $\beta$ -lumicolchicine	
<i>Saussurea sacra</i>	3-Demethyl- $\gamma$ -lumicolchicine	315
	Colchicine	

<sup>a</sup> Fourteen alkaloids previously obtained from this plant were also identified.

desacetylthiocolchicine in the dog.<sup>320</sup> The pharmacology of colchicine itself has been reviewed.<sup>321</sup>

### 10 Cularine Alkaloids

Details of the preparation and novel ring-opening reaction of the spirodienone (98) to (99; R = Me) with methanolic HCl have been published (*cf.* Vol. 3).<sup>322</sup> Compound (100; R = Me) rather than (101; R = Me) appears to be an intermediate since the product formed with ethanolic HCl was (99; R<sup>1</sup> = R<sup>2</sup> = Et, R<sup>3</sup> = Me) rather than (99; R<sup>1</sup> = R<sup>3</sup> = Et, R<sup>2</sup> = Me).



<sup>320</sup> B. Ruckstuhl, *Schweiz. Arch. Tierheilkd.*, 1975, **117**, 45 (*Chem. Abs.*, 1975, **83**, 149 436).

<sup>321</sup> W. A. Creasey, *Handb. Exp. Pharmacol.*, 1975, **38** (Antineoplast. Immunosuppr. Agents, Pt. 2), 670 (*Chem. Abs.*, 1975, **83**, 188 096).

<sup>322</sup> A. J. Birch, A. H. Jackson, P. V. R. Shannon, and G. W. Stewart, *J.C.S. Perkin I*, 1975, 2492.

## 11 Protoberberine Alkaloids

Alkaloid isolation and structural elucidation are summarized in Table 9.<sup>323-343</sup> The structures of corynoxidine and epicorynoxidine, two new alkaloids from *Corydalis*

**Table 9** Isolation of protoberberine alkaloids

Source	Alkaloid	Ref
<i>Aquilegia olympica</i>	Berberine	323
<i>Argemone platyceras</i> <sup>a</sup>	(-)- $\alpha$ -Canadine methohydroxide	195
	Cyclanoline [(-)- $\alpha$ -scoulerine methosalt]	195
<i>A. polyanthemos</i> ,	Berberine	324
<i>A. subfusiformis</i>		
<i>subfusiformis</i> ,		
<i>A. subfusiformis</i>		
<i>subinermis</i>		
<i>Berberis julianae</i> <sup>b</sup>	Berberine	325
	Jatrorrhizine	
	Palmatine	
<i>B. oblonga</i> <sup>c</sup>	Berberine	326
	Columbamine	
	Jatrorrhizine	
	Palmatine	
<i>Bocconia frutescens</i> <sup>d,e</sup>	Columbamine	327
	(-)-Isocorypalmine	
<i>Coptis japonica</i> <sup>d,f</sup>	Berberine	328
<i>C. japonica</i> (callus	Berberine	329
cultures)	Jatrorrhizine	
<i>Corydalis cava</i>	Coptisine	330
	Corysamine	
	8-Oxocoptisine	
	(+)-Stylopine	

<sup>323</sup> F. V. Efimova and D. A. Murav'eva, *Aktual. Voprosy Farm.*, 1974, **2**, 34 (*Chem. Abs.*, 1976, **84**, 147 617).

<sup>324</sup> A. L. Bandoni, F. R. Stermitz, R. V. D. Rondina, and J. D. Coussio, *Phytochemistry*, 1975, **14**, 1785.

<sup>325</sup> B. Brazdovicova, D. Kostalova, J. Slavik, and J. Tomko, *Chem. Zvesti*, 1975, **29**, 265 (*Chem. Abs.*, 1975, **83**, 40 223).

<sup>326</sup> A. Karimov, M. V. Telezhenetskaya, K. L. Lutfullin, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, **11**, 433 (*Chem. Abs.*, 1976, **84**, 14 662).

<sup>327</sup> J. Slavik and L. Slavikova, *Coll. Czech. Chem. Comm.*, 1975, **40**, 3206.

<sup>328</sup> H. Fujiwara, G. Nonaka, A. Yagi, and I. Nishioka, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 407.

<sup>329</sup> A. Ikuta, K. Syono, and T. Furuya, *Phytochemistry*, 1975, **14**, 1209.

<sup>330</sup> V. Preininger, R. S. T. Thakur, and F. Santavy, *J. Pharm. Sci.*, 1976, **65**, 294.

<sup>331</sup> C. Tani, N. Nagakura, S. Hattori, and N. Masaki, *Chem. Letters*, 1975, 1081.

<sup>332</sup> V. A. Chelombit'ko, *Aktual. Voprosy Farm.*, 1974, **2**, 29 (*Chem. Abs.*, 1976, **84**, 147 616).

<sup>333</sup> S.-T. Lu, T.-L. Su, T. Kametani, A. Ujiie, M. Ihara, and K. Fukumoto, *J.C.S. Perkin I*, 1976, 63.

<sup>334</sup> T. Kametani, M. Takemura, M. Ihara, and K. Fukumoto, *Heterocycles*, 1976, **4**, 723.

<sup>335</sup> C. Tani, N. Nagakura, and S. Hattori, *Yakugaku Zasshi*, 1975, **95**, 1103 (*Chem. Abs.*, 1976, **84**, 2251).

<sup>336</sup> Cf. Table 3, ref. a.

<sup>337</sup> M. Hamonnière, M. Leboeuf, A. Cavé, and R. R. Paris, *Plantes Medicin. Phytother.*, 1975, **9**, 296 (*Chem. Abs.*, 1976, **84**, 147 628).

<sup>338</sup> V. B. Pandey, A. B. Ray, and B. Dasgupta, *Phytochemistry*, 1976, **15**, 545.

<sup>339</sup> E. Brochmann-Hanssen and W. J. Richter, *J. Pharm. Sci.*, 1975, **64**, 1040.

<sup>340</sup> O. Gasic, V. Preininger, H. Potesilova, B. Belia, and F. Santavy, *Glasnik Hem. Drustva, Beograd*, 1974, **39**, 499 (*Chem. Abs.*, 1976, **84**, 102 292).

<sup>341</sup> A. Ikuta and H. Itokawa, *Phytochemistry*, 1976, **15**, 577.

<sup>342</sup> T. Baytop and M. Berghmans, *Istanbul Univ. Eczacilik Fak. Mecm.*, 1975, **11**, 58 (*Chem. Abs.*, 1976, **84**, 40 710).

<sup>343</sup> Wu-Nan Wu, J. L. Beal, G. W. Clark, and L. A. Mitscher, *Lloydia*, 1976, **39**, 65.

**Table 9** Isolation of protoberberine alkaloids—continued

Source	Alkaloid	Ref.
<i>C. koidzumiana</i>	Corynoxidine (102; B/C <i>trans</i> )	331
	Epicorynoxidine (102; B/C <i>cis</i> )	
<i>C. marschalliana</i> <sup>c</sup>	Corydaline	332
<i>C. ochotensis</i>	Corytenchine (103)	333
	Corytenchirine (104; R <sup>1</sup> = R <sup>3</sup> = H, R <sup>2</sup> = Me)	
	Didehydrocheilanthifoline	
<i>C. ochotensis</i> , var. <i>raddeana</i>	Aobamine (105)	334
<i>C. pallida</i> var. <i>tenuis</i>	Dehydrocapaurimine chloride	335
	Dehydrocapaurine chloride	
	Dehydrocorydalmine chloride	
	Palmatine chloride	
<i>C. speciosa</i>	Capaurimine	336
	Capaurine	
	(±)-Tetrahydropalmatine	
<i>Enantia chlorantha</i> <sup>g</sup>	Columbamine	337
	Jatrorrhizine	
	Palmatine	
<i>Fumaria indica</i>	Coptisine chloride	338
	Dehydrocheilanthifoline <sup>h</sup>	
Opium <sup>i</sup>	Stepholidine	339
<i>Papaver bracteatum</i> (callus cultures)	L-stylopin <sup>j</sup>	209
<i>P. pseudo-orientale</i> <sup>k</sup>	Alborine	223
	Aryapavine (106)	
	Orientalidine	
<i>P. radicatum</i>	Berberine	198
<i>P. rhoeas</i>	(-)- <i>N</i> -Methylstylopinium chloride	340
<i>P. syriacum</i> <sup>l</sup>	Coptisine	212
	(-)-Stylopin	
	(-)-β-Stylopin methohydroxide	
	(±)-Mecambridine <sup>m</sup>	
<i>Pteridophyllum racemosum</i> <sup>b</sup>	Corydalispirone	341
<i>Thalictrum lucidum</i> <sup>c,n</sup>	Berberine	342
	Jatrorrhizine	
<i>T. rugosum</i> <sup>o</sup>	Columbamine	343
	Deoxythalidastine	
	Thalifendine	

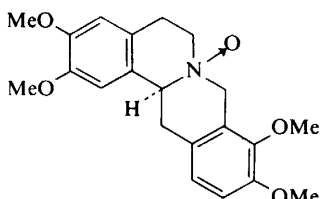
<sup>a</sup> This is the richest source found so far of (-)-α-stylopin methiodide (cf. Vol. 6, p. 142); <sup>b</sup> Aerial parts;

<sup>c</sup> Roots; <sup>d</sup> Leaves; <sup>e</sup> Traces of berberine, coptisine, and corysamine also obtained; <sup>f</sup> Coptisides I and II (cf. Vol. 3) also obtained; <sup>g</sup> Blossoms; <sup>h</sup> Of Indian origin; <sup>i</sup> First reported isolation from a *Fumaria* sp.; <sup>j</sup> Not present in the parent plant; <sup>k</sup> Alkaloids Or<sub>1</sub>, Or<sub>2</sub>, and PO-4 also obtained; <sup>l</sup> Traces of berberine and corysamine also obtained; <sup>m</sup> First reported occurrence of the racemic form in nature; <sup>n</sup> Traces of palmatine thought to be present; <sup>o</sup> Three very minor unknown bases also isolated.

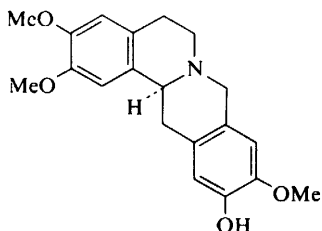
*koidzumiana*, were shown to be isomeric *N*-oxides of (-)-tetrahydropalmatine, namely (102; B/C *trans*) and (102; B/C *cis*), from X-ray crystallography and chemical studies. <sup>13</sup>C N.m.r. evidence allowed assignment of the relative stereochemistry.<sup>331</sup> Two phenolic alkaloids, corytenchine, and corytenchirine, isolated from *C. ochotensis*, have been assigned structures (103)<sup>333</sup> and (104; R<sup>1</sup> = R<sup>3</sup> = H, R<sup>2</sup> = Me).<sup>333, 344</sup> Samples of *O*-methylcorytenchirine (104; R<sup>1</sup> = H, R<sup>2</sup> = R<sup>3</sup> =

<sup>344</sup> T. Kametani, K. Fukumoto, M. Ihara, A. Ujiie, and M. Takemura, *Hukusokan Kagaki Toronkai Koen Yoshishu* 8th, 1975, 129 (*Chem. Abs.*, 1976, **84**, 150 813).

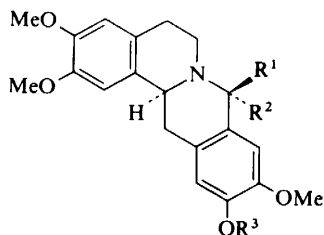




(102)

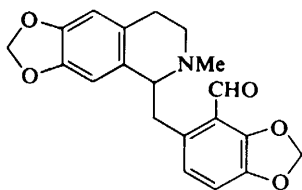


(103)

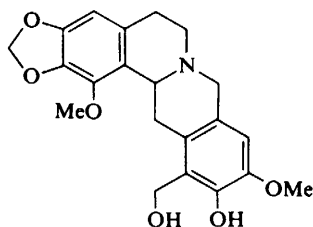


(104)

Me) prepared from corytenchirine<sup>333</sup> or by total synthesis<sup>345</sup> were compared with the synthetic compound coralydine (104;  $R^1 = R^3 = \text{Me}$ ,  $R^2 = \text{H}$ ), leading to assignment of the relative stereochemistry of these compounds at C-8 and C-13a. The 13a-*S* configuration of both new alkaloids were deduced from their negative rotations.<sup>333</sup> Corytenchirine is the first 8-substituted berbine alkaloid to be found in nature. Aobamine (105), a new alkaloid isolated from *C. ochotensis* var. *raddeana* as an unstable oil, is closely related to the recently isolated canadiline (cf. Vol. 6, p. 143).<sup>334</sup> Aryapavine, a new alkaloid isolated from *P. pseudo-orientale* was shown to be 11-demethylmecambridine (106),<sup>223</sup> previously known as an intermediate in the



(105)



(106)

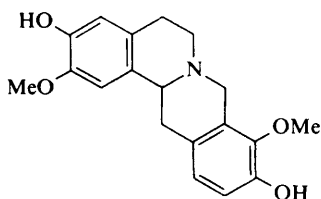
synthesis of orientalidine.<sup>346</sup> Stepholidine has been isolated from opium.<sup>339</sup> Mass-spectral evidence suggests that discretamine is its isomer with ring A substituents switched, i.e. (107).<sup>347</sup>

Groenlandicine (109;  $R = \text{H}$ ) has been synthesized as in Scheme 8 *via* the bromobenzyltetrahydroisoquinoline (108), a major by-product being the 10,11-

<sup>345</sup> H. Bruderer, J. Metzger, and A. Brossi, *Helv. Chim. Acta*, 1975, **58**, 1719.

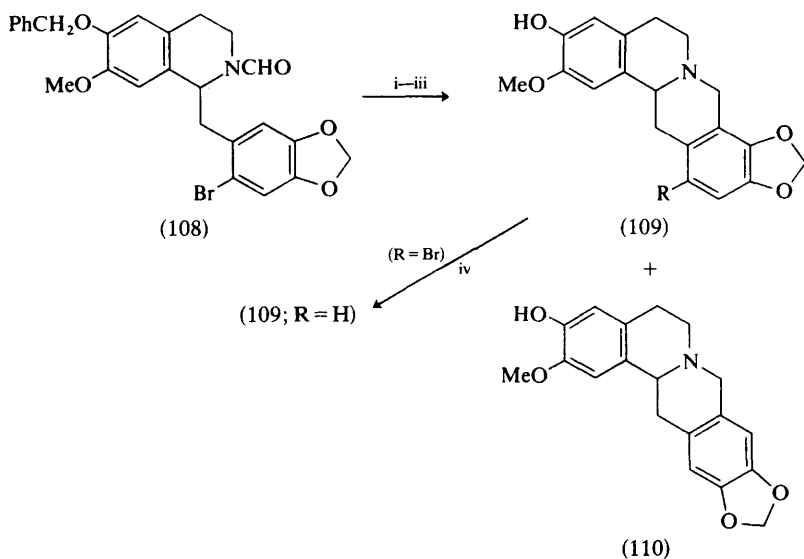
<sup>346</sup> T. Kametani, A. Ujiie, M. Ihara, and K. Fukumoto, *J.C.S., Perkin I*, 1975, 1822; Cf. Vol. 6, p. 144; Cf. also ref. 344.

<sup>347</sup> W. J. Richter and E. Brochmann-Hanssen, *Helv. Chim. Acta*, 1975, **58**, 209.



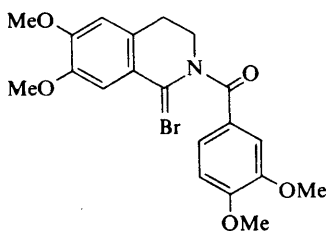
(107)

substituted protoberberine (110).<sup>348</sup> The bromoenamide (111) undergoes cyclic dehydrohalogenation either by photolysis or by treatment with sodium and liquid ammonia.<sup>349</sup> It has been found that small amounts of protoberberines are produced



Reagents: i,  $\text{POCl}_3$ -benzene; ii,  $\text{NaBH}_4$ ; iii,  $\text{HCl}$ -EtOH; iv,  $\text{H}_2$ -Pd/C.

Scheme 8

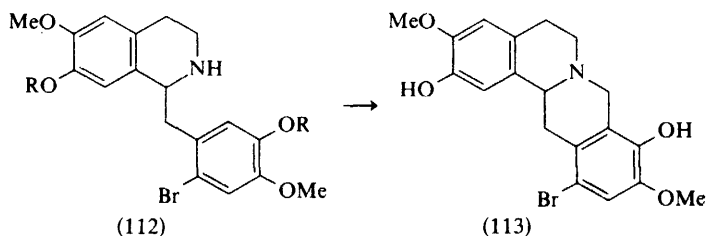


(111)

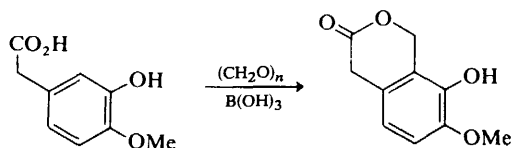
<sup>348</sup> H. Suguna and B. R. Pai, *Coll. Czech. Chem. Comm.*, 1976, **41**, 1219.

<sup>349</sup> T. Kametani, T. Honda, T. Sugai, and K. Fukumoto, *Heterocycles*, 1976, **4**, 927.

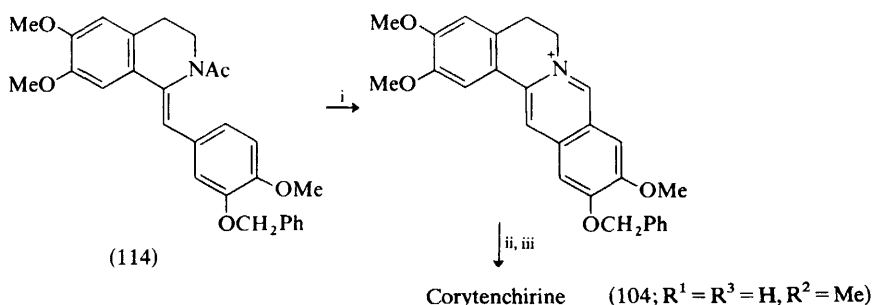
when phenolic benzyltetrahydroisoquinolines are refluxed with concentrated HCl in purified ethanol; e.g. (112; R = CH<sub>2</sub>Ph) gives ca. 1% of 12-bromoscoulerine (113). A formaldehyde equivalent is thought to arise by decomposition of some of the starting material. 12-Bromoscoulerine is also formed upon irradiation of the hydrochloride of (112; R = H).<sup>350</sup> A specific *ortho* hydroxymethylation reaction



using boric acid (Scheme 9) opens a new and efficient route to 9,10-disubstituted protoberberines.<sup>351</sup> (±)-Corytenchirine (*cf.* above) has been synthesized by Mannich reaction of MeCHO with the appropriate phenolic benzyltetrahydroiso-

**Scheme 9**

quinoline and also by photocyclization of the arylidene-tetrahydroisoquinoline (114) (Scheme 10).<sup>352</sup> The latter type of synthesis was also used to prepare the 10-hydroxy-2,3,11-trimethoxy-isomer of corytenchirine. Further reports have



Reagents: i, *hv* in MeOH–dioxan in presence of HI; ii, NaBH<sub>4</sub>–MeOH; iii, conc. aq. HCl, EtOH.

**Scheme 10**

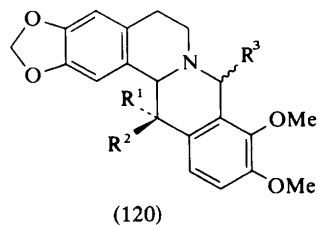
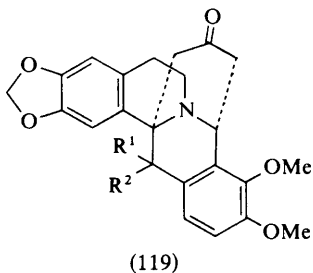
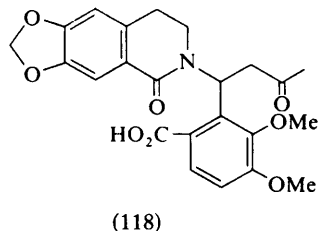
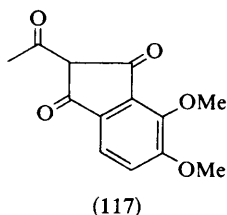
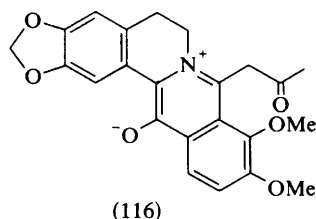
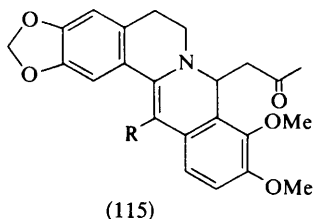
<sup>350</sup> T. Kametani, K. Fukumoto, M. Ihara, M. Takemura, H. Matsumoto, B. R. Pai, K. Nagarajan, M. S. Premila, and H. Suguna, *Heterocycles*, 1975, 3, 811.

<sup>351</sup> W. Nagata, H. Hazaki, K. Okada, T. Wakabayashi, K. Shibata, and N. Tokutake, *Chem. and Pharm. Bull. (Japan)*, 1975, 23, 2867.

<sup>352</sup> T. Kametani, A. Ujije, M. Ihara, K. Fukumoto, and S.-T. Lu, *J.C.S. Perkin I*, 1976, 1218.

appeared of photocyclizations of 2-aryl-1-methylenetetrahydroisoquinolines to give cavidine,<sup>353</sup> thalictrifoline,<sup>353</sup> xylopinine,<sup>353,354</sup> tetrahydropalamatine,<sup>354</sup> and sinacutine.<sup>354</sup> Cyclizations of 2-aryl-1-ethylidene- or -benzylidene-tetrahydroisoquinolines are thought to involve electrocyclic closure of the *Z*-isomer followed by suprafacial 1,5 hydrogen transfer, since only the isomer with the 13-substituent axial and a *cis* arrangement of the C-13 and C-13a hydrogens is formed.<sup>355</sup>

Permanganate oxidation of acetone-berberine (115; R = H) gives interesting products, namely (116)—(118)<sup>356</sup> and the 8,13a-propanoberberine (119; R<sup>1</sup> = OH, R<sup>2</sup> = H).<sup>356,357</sup> Borohydride reduction of (116) gives [120; R<sup>1</sup> = OH, R<sup>2</sup> = H, R<sup>3</sup> = CH<sub>2</sub>CH(OH)Me] while upon reduction of (116) with zinc and acetic acid concomitant elimination of the acetonyl group occurs with the formation of (120; R<sup>1</sup> = R<sup>3</sup> = H,



R<sup>2</sup> = OH).<sup>356</sup> Although similar oxidation of acetone-palmatine gives an 8,13a-propanoberberine analogous to (119; R<sup>1</sup> = OH, R<sup>2</sup> = H), 13-methyl-acetone-berberine (115; R = Me) gives mainly the lactam (121) together with small amounts

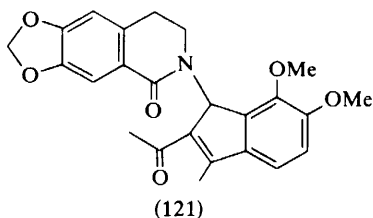
<sup>353</sup> I. Ninomiya, T. Naito, and H. Takasugi, *J.C.S. Perkin I*, 1975, 1791.

<sup>354</sup> I. Ninomiya, T. Naito, and H. Takasugi, *J.C.S. Perkin I*, 1975, 1720.

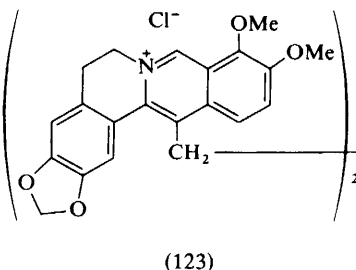
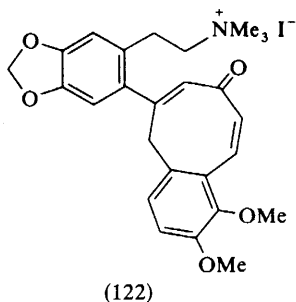
<sup>355</sup> G. R. Lenz, *J. Org. Chem.*, 1976, **41**, 2201.

<sup>356</sup> Y. Kondo and T. Takemoto, *Yakugaku Zasshi*, 1975, **95**, 1161 (*Chem. Abs.*, 1976, **84**, 17 585).

<sup>357</sup> S. Naruto, H. Nishimura, and H. Kaneko, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 1276.



of the 13-methyl-13-hydroxypropanoberberine (119;  $R^1 = \text{OH}$ ,  $R^2 = \text{Me}$ ) and the related hemiacetal.<sup>357</sup> Methylation of acetone-berberine with methyl iodide is known to give 13-methylberberinium and berberinium iodides, but minor products now identified are the 8,13a-propanoberberines (119;  $R^1 = R^2 = \text{Me}$ ) and (119;  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ).<sup>358</sup> It has also been found that the crude acetone adducts of quaternary protoberberinium salts, e.g. 13-methylberberinium chloride and berberinium chloride, are contaminated with a few per cent of 8,13a-propanoberberine derivatives, e.g. (119;  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ) and (119;  $R^1 = R^2 = \text{H}$ ) respectively.<sup>359</sup> The presence of the latter in crude acetone-berberine was deduced from the isolation of the cyclo-octatrienone (122) as a minor product upon treatment of the crude acetone-berberine with methyl iodide. Compound (119;  $R^1 = R^2 = \text{H}$ ) is evidently susceptible to facile Hoffmann degradation. The structure of (122) was supported by spectroscopy and a study of its reduction products.<sup>359</sup> 5,6-Dihydroberberine reacts with formaldehyde to give 13-methylberberine and the dimeric compound (123). 5,6-Dihydropalmatine reacts similarly.<sup>360</sup>



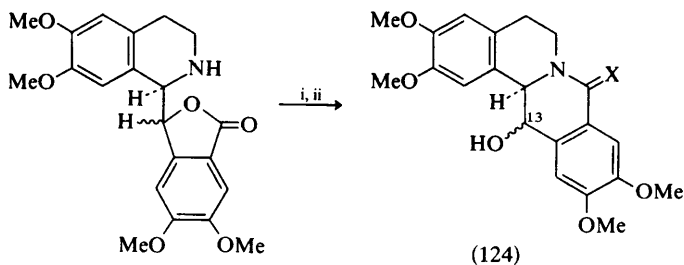
13-Hydroxylated protoberberines (124;  $X = \text{H}_2$ ) are conveniently prepared from *erythro*- and *threo*-norphthalaldehydeisoquinolines (*cf.* Vol. 6, p. 156) as indicated in Scheme 11. The 13 $\beta$ -hydroxy-epimer of the intermediate lactam (124;  $X = \text{O}$ ) tends to lose water with formation of (125;  $R^1 = R^2 = \text{Me}$ ,  $R^3 = \text{H}$ ,  $R^4 = \text{OMe}$ ) but was readily reduced by  $\text{LiAlH}_4$  to the 13 $\beta$ -hydroxyprotoberberine.<sup>361</sup> A new and unusual ring-opening reaction of berberine (126) affords a mixture of the naphthalene derivatives (127;  $R = \text{OH}$ ) and [127;  $R = \text{CH}=\text{C}(\text{OAc})_2$ ] (Scheme

<sup>358</sup> S. Naruto, H. Nishimura, and H. Kaneko, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 1271.

<sup>359</sup> S. Naruto, H. Nishimura, and H. Kaneko, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 1565.

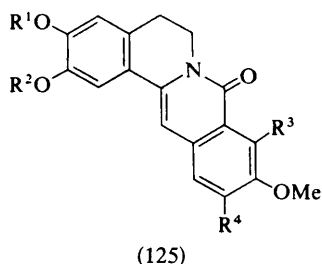
<sup>360</sup> S. Naruto, H. Mizuta, A. Kagemoto, and H. Nishimura, *Yakugaku Zasshi*, 1975, **95**, 1400 (*Chem. Abs.*, 1976, **84**, 74 476).

<sup>361</sup> M. Shamma and V. St. Georgiev, *Tetrahedron*, 1976, **32**, 211.

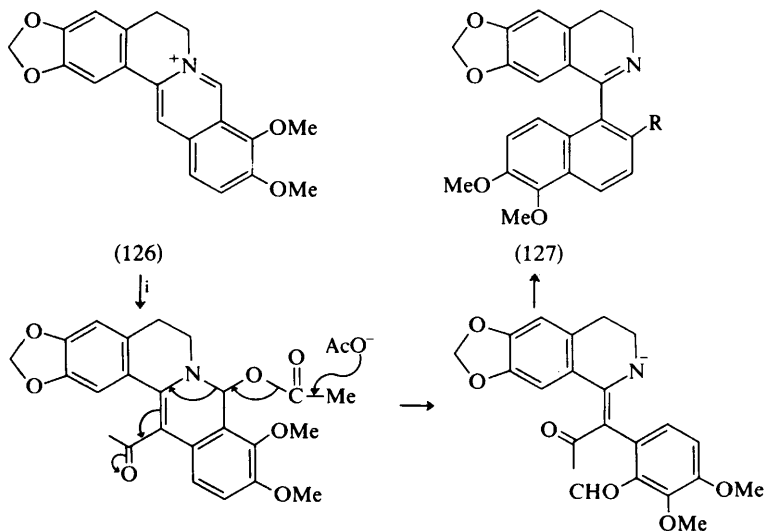


Reagents: i, aq. NaOH; ii,  $\text{LiAlH}_4$ .

**Scheme 11**



12).<sup>362</sup> Compound (127;  $\text{R} = \text{OH}$ ) exists in solution as a mixture with its red enamino-ketone tautomer and gives [127;  $\text{R} = \text{CH}=\text{C}(\text{OAc})_2$ ] by further reaction

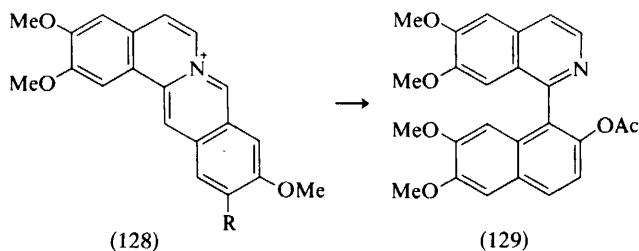


Reagent: i,  $\text{NaOAc}-\text{Ac}_2\text{O}$ , heat 24 h.

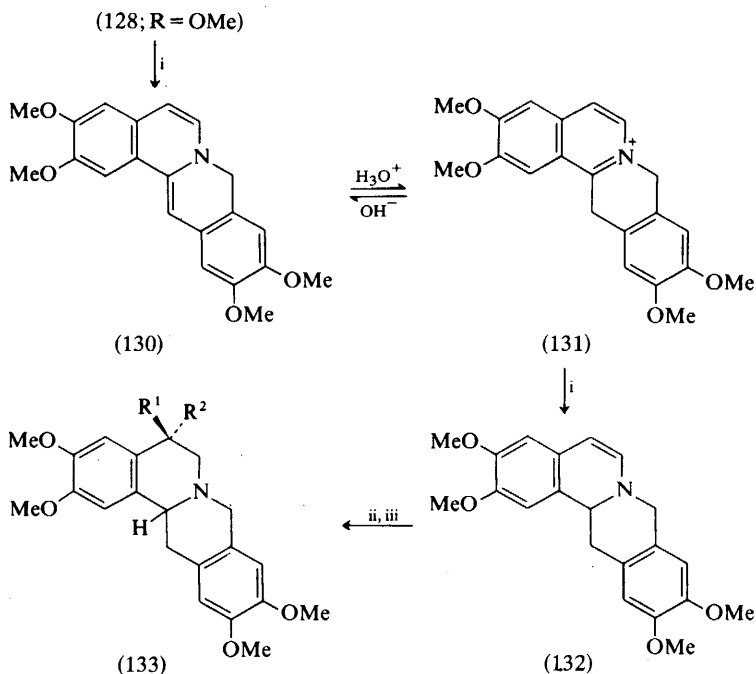
**Scheme 12**

<sup>362</sup> M. Shamma, L. A. Smeltz, J. L. Moniot, and L. Toke, *Tetrahedron Letters*, 1975, 3803.

with  $\text{Ac}_2\text{O}$ . Under the same conditions the dibenzoquinolizinium salt (128;  $\text{R} = \text{OMe}$ ) gave (129) in 70% yield, the presence of the additional double bond in ring B inducing immediate aromatization of the product.<sup>362</sup> Other transformations of the



salt (128;  $\text{R} = \text{OMe}$ ) are indicated in Schemes 13 and 14. The enamine (130), obtained by borohydride reduction, is converted by acid into a new type of protoberberine salt (131) having rings A, B, and D aromatic and ring C partially reduced. This salt was used to obtain tetrahydropprotoberberines functionalized at C-5, namely (133;  $\text{R}^1 = \text{OH}$ ,  $\text{R}^2 = \text{H}$ ) and (133;  $\text{R}^1 = \text{H}$ ,  $\text{R}^2 = \text{OH}$ ) *via* the unstable enamine (132).<sup>363</sup> The N-7 to C-8 bond of (128;  $\text{R} = \text{OMe}$ ) is susceptible to cleavage

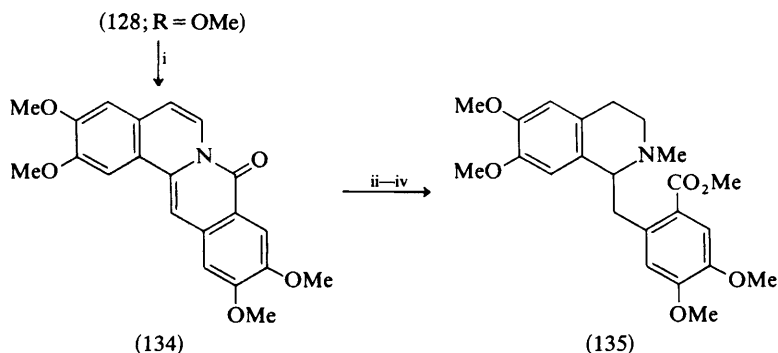


Reagents: i,  $\text{NaBH}_4$ -pyridine; ii, hydroboration; iii, 30%  $\text{H}_2\text{O}_2$ , 20% aq.  $\text{NaOH}$ .

**Scheme 13**

<sup>363</sup> M. Shamma and L. A. Smeltz, *Tetrahedron Letters*, 1976, 1415.

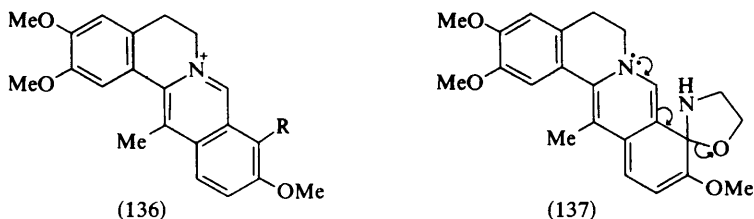
with alkali *via* the pyridone (134) and a stable seco-derivative (135) was obtained as shown in Scheme 14. Significantly, oxyberberine (125;  $R^1R^2 = CH_2$ ,  $R^3 = OMe$ ,



Reagents: i, 20% aq. KOH; ii, KOH-MeOH; iii, MeI-MeCN; iv,  $NaBH_4$ -MeOH.

**Scheme 14**

$R^4 = H$ ), which lacks the 5,6 double bond, is virtually unaffected by methanolic base.<sup>363</sup> Kinetic studies of the interconversion of coralynium ion [8-methyl derivative of (128; R = OMe)] and 6'-acetylpapaverine have been made.<sup>364</sup> Hydrazinolysis of the protoberberine salt (136; R =  $OCH_2CH_2N$ -phthaloyl) with hydrazine hydrate and hydrobromic acid gave, almost quantitatively, the unexpected product (136; R =  $NHCH_2CH_2OH$ ). This is thought to arise by Smiles rearrangement [*cf.* (137)].<sup>365</sup> Following this observation it was found that a variety of 6- of 8-



alkoxyisoquinolinium salts afford 6- or 8-amino-substituted isoquinolinium derivatives upon treatment with primary amines.<sup>366</sup> Protoberberine salts prepared in this way include (128; R =  $NHCH_2Ph$ ) and (136; R =  $NHPr$ ). Treatment of (136; R = OMe) with pyrrolidine, however, gave (136; R = OH) in 90% yield.<sup>366</sup> Selective removal of the methylenedioxy function in tetrahydropprotoberberine gives (138).<sup>162</sup>

Pseudobase formation by the addition of methoxide ion to protoberberinium and pseudoprotoberberinium cations has been studied by u.v. and  $^1H$  n.m.r. spectroscopy.<sup>367</sup> The  $\alpha$ - and  $\beta$ -forms of quaternary protoberberinium alkaloids can easily be

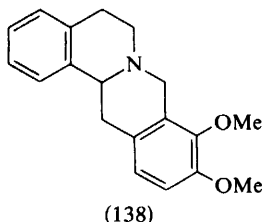
<sup>364</sup> M. J. Cho, A. J. Repta, C. C. Cheng, K. Y. Zee-Cheng, T. Higuchi, and I. H. Pitman, *J. Pharm. Sci.*, 1975, **64**, 1825.

<sup>365</sup> S. Naruto, H. Mizuta, J. Nakano, and H. Nishimura, *Tetrahedron Letters*, 1976, 1595.

<sup>366</sup> S. Naruto, H. Mizuta, and H. Nishimura, *Tetrahedron Letters*, 1976, 1597.

<sup>367</sup> V. Simanek, V. Preininger, and J. Lasovsky, *Coll. Czech. Chem. Comm.*, 1976, **41**, 1050.

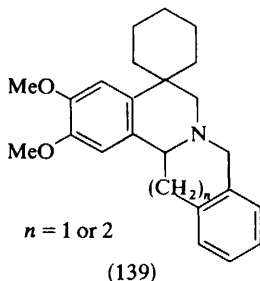




distinguished by  $^{13}\text{C}$  n.m.r. spectroscopy. The *N*-methyl and  $^{13}\text{C}$  signals in  $\alpha$ -canadine methochloride, for instance, appear at lower fields by 11.8 and 5.3 p.p.m. than those in the  $\beta$ -form and the C-6 signal in the  $\alpha$ -form appears at 9.7 p.p.m. higher field than that of the  $\beta$ -form.<sup>368</sup> The conformation of tetrahydropyprotoberberines has been studied by i.r. (both in solution and in the solid state,<sup>369</sup> by  $^1\text{H}$  n.m.r. (in deuteriotoluene),<sup>369</sup> and by  $^{13}\text{C}$  n.m.r. spectroscopy.<sup>344,369</sup> 9-Methoxy-substituents in tetrahydropyprotoberberines can be detected by the presence of abundant  $(M-\text{OMe})^+$  ions in the mass spectrum.<sup>370</sup>

The current state of knowledge of the chemistry<sup>17,371,372</sup> and pharmacology<sup>17,18,371,373,374</sup> of berberine alkaloids has been amply reviewed. A tetrahydropyprotoberberine has been identified for the first time in the urine of Parkinsonian patients receiving L-dopa, and evidently results from an *in vivo* reaction of tetrahydropapaveroline.<sup>375</sup>

Dehydrocorydaline chloride is a promising anti-peptic ulcer agent.<sup>376</sup> Synthetic pyprotoberberine analogues which have been prepared include compounds (139),<sup>181</sup> (140),<sup>377</sup> and amino-acid derivatives typified by (141).<sup>378</sup> The determination of



<sup>368</sup> K. Yoshikawa, I. Morishima, J. Kunimoto, M. Ju-Ichi, and Y. Yoshida, *Chem. Letters*, 1975, 961.

<sup>369</sup> T. Kametani, M. Ihara, A. Ujiie, and H. Koizumi, *J. Org. Chem.*, 1975, **40**, 3280.

<sup>370</sup> W. J. Richter and E. Brochmann-Hanssen, *Helv. Chim. Acta*, 1975, **58**, 203.

<sup>371</sup> Y. Kondo, *Heterocycles*, 1976, **4**, 197.

<sup>372</sup> T. Kametani, M. Ihara, and T. Honda, *Heterocycles*, 1976, **4**, 483.

<sup>373</sup> F. E. Hahn and J. Ciak, in 'Antibiotics', ed. D. Gottlieb, P. D. Shaw, and J. W. Corcoran, Springer, New York, 1975, Vol. 3, p. 577.

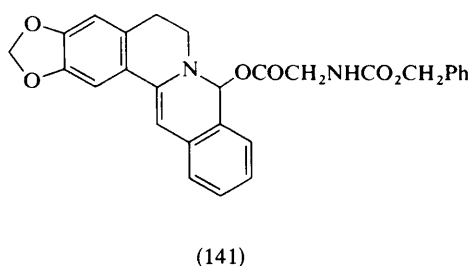
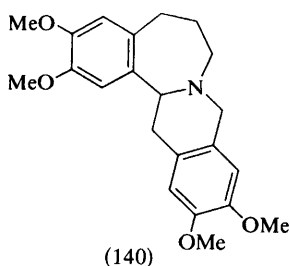
<sup>374</sup> I. F. Shvarev and A. L. Tsetlin, *Mater. Vses. Konf. Issled. lek. Rast. Perspekt. Ikh Ispol'z. Proizvod Lek.*, ed. A. D. Turova, Vses. Nauchno-Issled. Inst. Lek. Rast., Bittsa, U.S.S.R., 1972, p. 245 (*Chem. Abs.*, 1975, **83**, 674).

<sup>375</sup> V. E. Davis, J. L. Cashaw, and K. D. McMurtrey, *Adv. Exp. Med. Biol. (Alcohol Intox. and Withdrawal)*, 1975, **59**, 65 (*Chem. Abs.*, 1976, **84**, 159 458).

<sup>376</sup> Y. Sohji, K. Kawashima, and M. Shimizu, *Nippon Yagurigaku Zasshi*, 1974, **70**, 425 (*Chem. Abs.*, 1975, **83**, 53 402).

<sup>377</sup> D. Berney and T. Jauner, *Helv. Chim. Acta*, 1976, **59**, 623.

<sup>378</sup> Yu. D. Sadykok and V. K. Burichenko, *Doklady Akad. Nauk Tadzh. S.S.R.*, 1975, **18**, 30 (*Chem. Abs.*, 1976, **84**, 44 618).



berberine using gravimetric<sup>379</sup> or spectrophotometric<sup>380—382</sup> methods has been described. The toxicity of berberine sulphate has also been studied.<sup>383</sup>

## 12 Protopine Alkaloids

Alkaloid isolation work is summarized in Table 10.<sup>384—390</sup> Samples of *Argemone mexicana* from Vietnam and Sudan were respectively richer and poorer in alkaloids than samples from the Northern Caucasus.<sup>384</sup> Tissue culture of *Macleaya microcarpa* was still capable of synthesizing alkaloids three years after initiation. The

**Table 10** Isolation of protopine alkaloids

Alkaloid(s) <sup>a</sup>	Species
A, P	<i>Argemone mexicana</i> , <sup>384</sup> <i>A. polyanthemus</i> , <sup>324</sup> <i>A. subfusiformis subfusiformis</i> , <sup>324</sup> <i>A. subfusiformis subinermis</i> , <sup>324</sup> <i>Bocconia frutescens</i> , <sup>327</sup> <i>Corydalis caucasia</i> , <sup>385</sup> <i>C. intermedia</i> , <sup>386</sup> <i>C. marschalliana</i> , <sup>332</sup> <i>C. severtzovii</i> , <sup>386</sup> <i>C. speciosa</i> , <sup>336</sup> <i>Glaucium corniculatum</i> , <sup>387</sup> <i>Macleaya microcarpa</i> (tissue culture), <sup>388</sup> <i>Pteridophyllum racemosum</i> <sup>341</sup>
C, P	<i>Corydalis gortschakovii</i> <sup>386</sup>
C, Ff, P	<i>Fumaria officinalis</i> <sup>389</sup>
A, C, P	<i>Papaver radicatum</i> <sup>198</sup>
P	<i>Corydalis cava</i> , <sup>330</sup> <i>C. ochotensis</i> , <sup>333</sup> <i>C. ochotensis</i> var. <i>raddeana</i> , <sup>334</sup> <i>Fumaria officinalis</i> , <sup>390</sup> <i>Papaver bracteatum</i> (tissue culture), <sup>209</sup> <i>P. syriacum</i> <sup>211</sup>
Pt	<i>Thalictrum rugosum</i> <sup>343</sup>

<sup>a</sup> A = allocryptopine; C = cryptopine; Ff = fumoficinaline (a phenolic alkaloid of unspecified structure possibly containing —OCH<sub>2</sub>O—, OMe, and two OH groups); P = protopine; Pt = protothalipine (142; R = H).

<sup>379</sup> M. Pitea, *Planta Med.*, 1975, **27**, 213 (*Chem. Abs.*, 1975, **83**, 111 102).

<sup>380</sup> B. Cubukcu, *Istanbul Univ. Eczacilik Fak. Mecm.*, 1975, **11**, 82 (*Chem. Abs.*, 1975, **83**, 189 980).

<sup>381</sup> T. Sakai, *Bunseki Kagaku*, 1975, **24**, 135 (*Chem. Abs.*, 1975, **83**, 33 102).

<sup>382</sup> T. Sawda, J. Yamahara, and Y. Shintaini, *Shoyakugaku Zasshi*, 1974, **28**, 150 (*Chem. Abs.*, 1975, **83**, 152 417).

<sup>383</sup> Z. Kowalewski, A. Mroziakiewicz, T. Bobkiewicz, K. Drost, and B. Hladon, *Acta Pol. Pharm.*, 1975, **32**, 13 (*Chem. Abs.*, 1975, **83**, 91 108).

<sup>384</sup> D. A. Murav'eva and Bui Thi Tu, *Aktual. Voprosy Farm.*, 1974, **2**, 24 (*Chem. Abs.*, 1976, **84**, 147 614).

<sup>385</sup> V. A. Chelombit'ko, *Aktual. Voprosy Farm.*, 1974, **2**, 17 (*Chem. Abs.*, 1976, **84**, 118 429).

<sup>386</sup> I. A. Israelov, M. U. Ibragimova, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, **612** (*Chem. Abs.*, 1976, **84**, 86 727).

<sup>387</sup> V. A. Chelombit'ko and D. A. Murav'eva, *Aktual. Voprosy Farm.*, 1974, **2**, 27 (*Chem. Abs.*, 1976, **84**, 147 615).

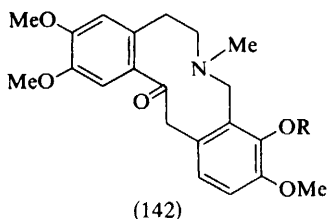
<sup>388</sup> H. Koblitz, U. Schumann, H. Boehm, and J. Franke, *Experientia*, 1975, **31**, 768.

<sup>389</sup> L. G. Molokhova and B. A. Figurkin, *Trudy Permsk. Gos. Med. Inst.*, 1973, **118**, 33 (*Chem. Abs.*, 1975, **83**, 128 664).

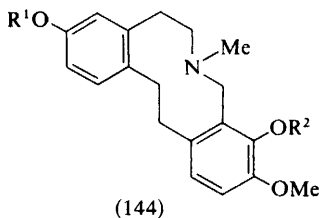
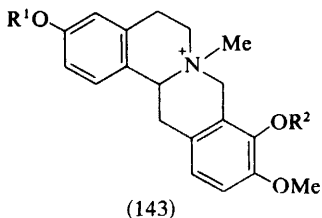
<sup>390</sup> B. A. Figurkin and D. A. Murav'eva, *Aktual. Voprosy Farm.*, 1974, **2**, 20 (*Chem. Abs.*, 1976, **84**, 118 430).

alkaloids accumulate in yellow coloured cells scattered throughout the tissue.<sup>388</sup> The alkaloid content of *Fumaria officinalis* at different stages of growth has been studied.<sup>390</sup> The principal alkaloids of this plant are reported to be protopine and fumoficinaline with minor amounts of cryptopine.<sup>389</sup>

A new alkaloid, protothalipine (142; R = H), isolated from *Thalictrum rugosum*, gives muramine (142; R = Me) upon *O*-methylation.<sup>343</sup> The location of the phenolic hydroxy-group was deduced with the aid of ASIS studies.



Trioxxygenated protopines, *e.g.* (144; R<sup>1</sup> = MeOCH<sub>2</sub>O, R<sup>2</sup> = H) have been prepared *via* Emde reduction of appropriate tetrahydropyroberberine methiodides.<sup>391</sup> If, however, the ring A function in the latter was a free phenolic hydroxy-group or, like a benzyloxy-group, was cleaved under the reaction conditions (sodium and liquid ammonia), N-7 to C-8 cleavage occurred giving a methylbenzyltetrahydroisoquinoline. With a suitable phenolic protecting group, N-7 to C-13a cleavage predominated. For example the salt (143; R<sup>1</sup> = cyclopropylmethyl, R<sup>2</sup> = CH<sub>2</sub>Ph) gave (144; R<sup>1</sup> = cyclopropylmethyl, R<sup>2</sup> = H) and this was readily converted into (144; R<sup>1</sup> = H, R<sup>2</sup> = Me).<sup>391</sup>



### 13 Benzophenanthridine Alkaloids

Work on alkaloid isolation is summarized in Table 11.<sup>392–396</sup> Arnottianamide (145; R<sup>1</sup> = H, R<sup>2</sup> = Me) and isoarnottianamide (145; R<sup>1</sup> = Me, R<sup>2</sup> = H) have been isolated as minor constituents of *Zanthoxylum cuspidatum*. These amides can be obtained chemically by Baeyer–Villiger-type oxidation of the immonium group in chelerythrine and nitidine respectively and a similar biogenesis is suggested.<sup>394</sup> Three *Argemone subfusiformis* taxa and *A. polyanthemus* contained mainly the same

<sup>391</sup> W. Nagata, K. Okada, H. Itazaki, and S. Uyeo, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 2878.

<sup>392</sup> B. A. Figurkin and V. A. Chelombit'ko, *Aktual. Voprosy Farm.*, 1974, **2**, 15 (*Chem. Abs.*, 1976, **84**, 118 428).

<sup>393</sup> S. R. Hemingway and J. D. Phillipson, *J. Pharm. Pharmacol.*, 1975, **27**, Suppl., 84P.

<sup>394</sup> H. Ishi, T. Ishikawa, S.-T. Lu, and I.-S. Chen, *Tetrahedron Letters*, 1976, 1203.

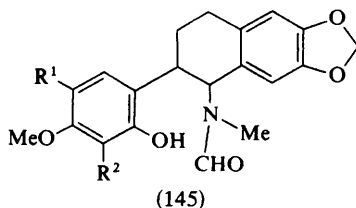
<sup>395</sup> F. Fish, I. A. Meshal, and P. G. Waterman, *Phytochemistry*, 1975, **14**, 2094.

<sup>396</sup> P. G. Waterman, *Phytochemistry*, 1976, **15**, 578.

**Table 11** Isolation of benzophenanthridine alkaloids

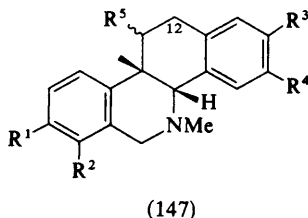
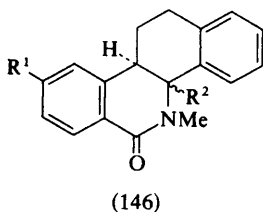
Source	Alkaloid <sup>a</sup>	Ref.
<i>Argemone polyanthemum</i> <sup>b,c</sup>	Norchelerythrine	324
<i>Corydalis severtzovii</i> <sup>b,c</sup>	Dihydrosanguinarine	386
<i>Fagara rubescens</i>	Dihydrochelerythrine	51
	9-Ethoxydihydrochelerythrine <sup>d</sup>	
<i>Pteridophyllum racemosum</i> <sup>b,c</sup>	Dihydrosanguinarine	341
	Norsanguinarine	
	Oxysanguinarine	
<i>Zanthoxylum cuspidatum</i>	Arnottianamide (145; R <sup>1</sup> = H, R <sup>2</sup> = Me)	394
	Isoarnottianamide (145; R <sup>1</sup> = Me, R <sup>2</sup> = H)	
<i>Z. dinklagei</i>	Nitidine	395
<i>Z. dipetetalum</i> <sup>c</sup>	Nitidine	157
<i>Z. flavum</i> <sup>c</sup>	Nitidine	396
<i>Z. myriacanthum</i>	Dihydnitidine	158
	Nitidine	

<sup>a</sup> Also sanguinarine was found in *Argemone mexicana*,<sup>384</sup> *Fumaria officinalis*,<sup>392</sup> *Macleaya microcarpa* (tissue culture),<sup>388</sup> *Meconopsis cambrica*,<sup>393</sup> and *Papaver radiculatum*,<sup>198</sup> while sanguinarine and chelerythrine were found in *A. subfusiformis subfusiformis* (two strains),<sup>324</sup> *A. subfusiformis subinermis*,<sup>324</sup> *Bocconia frutescens*,<sup>327</sup> and *Corydalis caucasica*;<sup>385</sup> <sup>b</sup> Sanguinarine also present; <sup>c</sup> Chelerythrine also present; <sup>d</sup> Known artefact from chelerythrine.



protoberberine, protopine, and benzophenanthridine alkaloids. *A. polyanthemum* differed from the other taxa in the relative amounts and distribution of individual alkaloids and in containing *N*-norchelerythrine.<sup>324</sup>

Some lactams, e.g. (146; R<sup>1</sup> = CO<sub>2</sub>Me, R<sup>2</sup> =  $\beta$ -H), obtained by enamide photocyclization (cf. Vol. 6, p. 150), gave the B/C *cis*-isomer upon further irradiation.<sup>397</sup> Simple analogues of corynoline (147; R<sup>1</sup>R<sup>2</sup> = R<sup>3</sup>R<sup>4</sup> = OCH<sub>2</sub>O, R<sup>5</sup> =  $\alpha$ -OH), e.g.

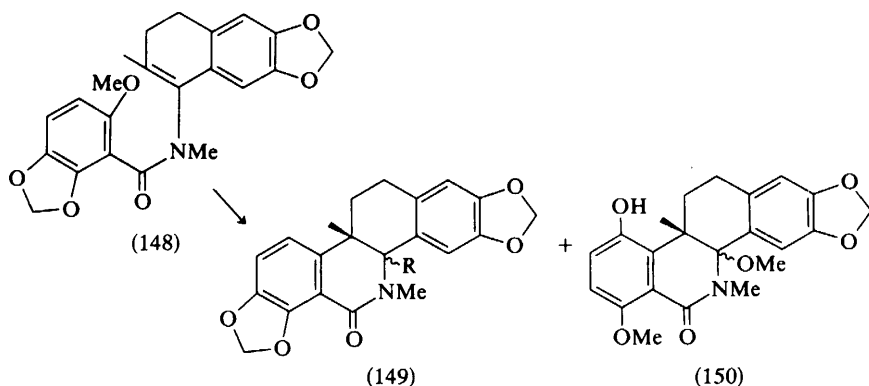


(147; R<sup>1</sup> = R<sup>2</sup> = R<sup>3</sup> = R<sup>4</sup> = H, R<sup>5</sup> =  $\alpha$ -OH), have been synthesized *via* enamide photocyclization<sup>398</sup> and this approach has been extended to provide the first total syntheses of corynoline and 12-hydroxycorynoline. The key photocyclization reac-

<sup>397</sup> I. Ninomiya, T. Kiguchi, O. Yamamoto, and T. Naito, *Heterocycles*, 1976, 4, 467.

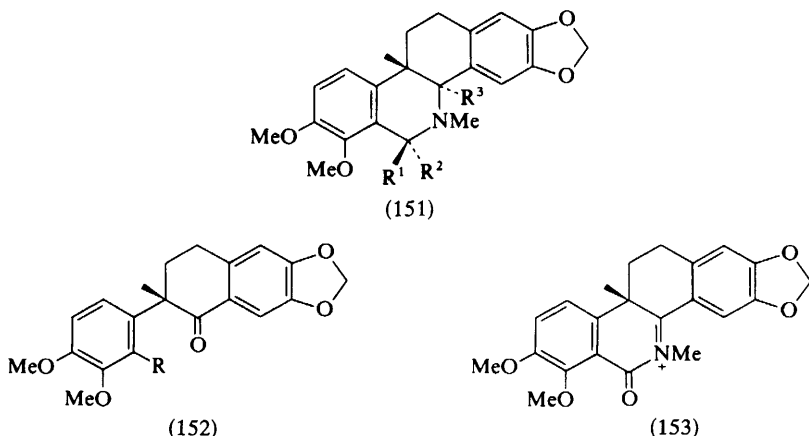
<sup>398</sup> I. Ninomiya, O. Yamamoto, and T. Naito, *Heterocycles*, 1976, 4, 743.

tion (Scheme 15) gave both (149) and (150) as a result of cyclization at the *o*-methoxy- and methylenedioxy-groups respectively.<sup>399</sup> Oxygenation of the ben-



**Scheme 15**

zophenanthridine derivative (151;  $R^1 = \text{OH}$ ,  $R^2 = R^3 = \text{H}$ ) gave the epidioxide (151;  $R^1 = \text{H}$ ,  $R^1R^3 = \text{O}-\text{O}$ ). Treatment of the latter with DDO gave a mixture of the amide (152;  $R = \text{CONH}_2$ ) and the aldehyde (152;  $R = \text{CHO}$ ), together with (151;  $R^1R^2 = \text{O}$ ,  $R^3 = \text{CN}$ ) and its  $\beta$ -cyano-epimer. These nitriles are thought to arise *via* (151;  $R^1R^2 = \text{O}$ ,  $R^3 = \text{OH}$ ) and the immonium salt (153).<sup>400</sup> The formation of the ethanol adducts of sanguinarine and chelerythrine has been studied.<sup>401</sup>



A review of selected potential anticancer principles includes chelidimerine, sanguidimerine, and fagaronine.<sup>402</sup> Extracts of the roots of *Fagara xanthoxyloides*

<sup>399</sup> I. Ninomiya, O. Yamamoto, and T. Naito, *J.C.S. Chem. Comm.*, 1976, 437.

<sup>400</sup> M. Onda, M. Gotoh, and J. Okada, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 1561.

<sup>401</sup> O. N. Tolkachev, O. E. Lasskaya, and G. A. Maslova, *Khim. prirod. Soedinenii*, 1975, 615 (*Chem. Abs.*, 1976, **84**, 105 861).

<sup>402</sup> G. A. Cordell and N. R. Farnsworth, *Heterocycles*, 1976, **4**, 393.

(reputed to contain fagaronine) have been examined for antisickling activity.<sup>403</sup> The effects on photosynthesis of various alkaloids including sanguinarine, chelerythrine, and their dihydro-derivatives have been studied.<sup>404</sup>

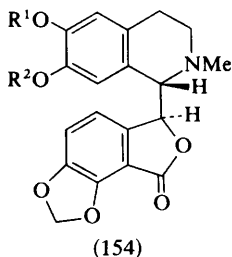
#### 14 Phthalideisoquinoline Alkaloids

Work on alkaloid isolation is summarized in Table 12.<sup>405–409</sup> Corledine (154;  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ) and severzine (154;  $R^1 = \text{H}$ ,  $R^2 = \text{Me}$ ) are new alkaloids isolated

**Table 12** Isolation of phthalideisoquinoline alkaloids

Source	Alkaloid	Ref.
<i>Corydalis cava</i>	Adlumidiceine	} 330
	(-)-Capnoidine	
<i>C. gortschakovii</i>	(-)-Adlumine	386
<i>C. ledebouriana</i>	Corledine (154; $R^1 = \text{Me}$ , $R^2 = \text{H}$ )	405
<i>C. lutea</i>	Hydrastine metho-salt	406
<i>Fumaria parviflora</i>	N-Methylhydrastine	} 406
<i>F. vaillantii</i>	N-Methylhydrastine	
<i>F. schleicheri</i>		
<i>C. ochotensis</i>	Adlumidine	333
<i>C. ochotensis</i> var	Adlumidine	} 334
<i>raddeana</i>	Aobamidine Z-(155; $R = \text{Me}$ )	
<i>C. ochroleuca</i>	Bicuculline (156; $R^1 R^2 = \text{CH}_2$ )	} 407
	Fumarine	
<i>C. severtzovii</i>	Corlumine	386
	Severzine (154; $R^1 = \text{H}$ , $R^2 = \text{Me}$ )	408
<i>Papaver rhoeas</i>	Adlumidiceine	340
Poppy straw	Narcotine	} 409
	Narcotoline	

from *Corydalis ledebouriana*<sup>405</sup> and *C. severtzovii*<sup>408</sup> respectively. In each case *O*-methylation gave (-)-adlumine and the position of the free phenolic hydroxy-group was assigned on spectroscopic grounds. The new alkaloid aobamidine,



<sup>403</sup> G. R. Honig, N. R. Farnsworth, C. Ferenc, and L. N. VIDA, *Lloydia*, 1975, **38**, 387.

<sup>404</sup> C. S. Andreo and R. H. Vallejos, *Cienc. Invest.*, 1974, **30**, 81 (*Chem. Abs.*, 1975, **83**, 128 860).

<sup>405</sup> I. A. Israilov, M. S. Yunusov, N. D. Abdullaev, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, **11**, 536 (*Chem. Abs.*, 1976, **84**, 44 481).

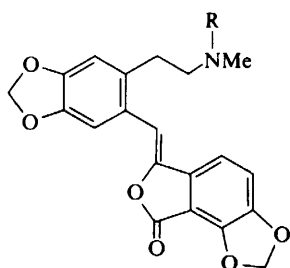
<sup>406</sup> P. Forgacs, J. Provost, J. F. Desconclois, A. Jehanno, and M. Pesson, *Compt. rend.*, 1974, **279**, D, 855 (*Chem. Abs.*, 1975, **83**, 40 150).

<sup>407</sup> R. G. A. Rodrigo, R. H. F. Manske, H. L. Holland, and D. B. Maclean, *Canad. J. Chem.*, 1976, **54**, 471.

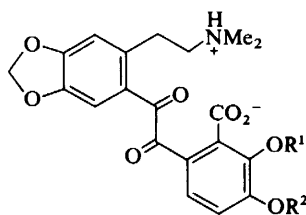
<sup>408</sup> I. A. Israilov, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, **11**, 811 (*Chem. Abs.*, 1976, **84**, 180 442).

<sup>409</sup> P. Gorecki and M. Drozdzyńska, *Herba Pol.*, 1975, **21**, 263 (*Chem. Abs.*, 1976, **84**, 132 637).

*Z*-(155; R = Me), obtained from *C. ochotensis* var. *raddeana*, had similar u.v. absorption to the urethan *Z*-(155; R = CO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>Br-*p*) of established structure.<sup>334</sup> The alkaloid was prepared from adlumidine methiodide by the action of dilute aqueous NaOH to give *E*-(155; R = Me) followed by photochemical isomerization.<sup>334</sup> The structure of bicucullinine (156; R<sup>1</sup>R<sup>2</sup> = CH<sub>2</sub>), a new alkaloid isolated from *C. ochroleuca*, was elucidated with the help of spectral data available for the analogous benzil, oxo-*N*-methylhydrastine (156; R<sup>1</sup> = R<sup>2</sup> = Me) (*cf.* Vol. 4).<sup>407</sup>

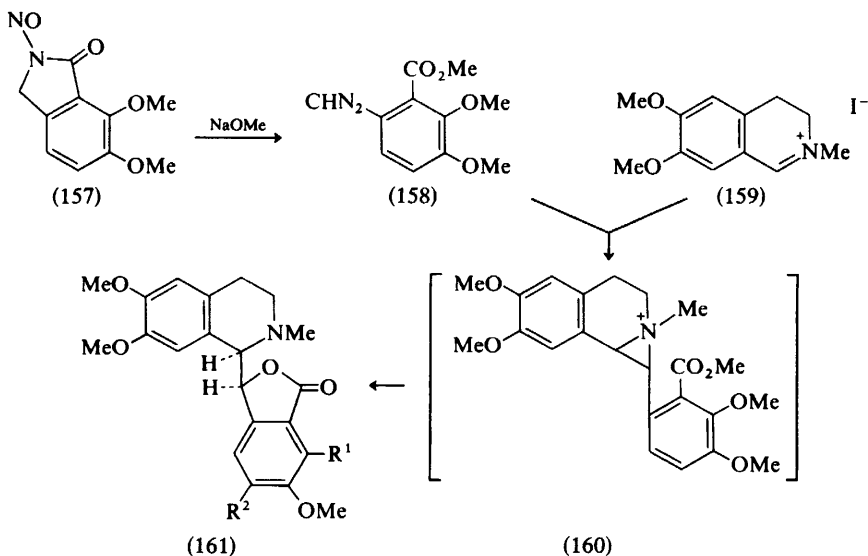


(155)



(156)

A new synthetic route to phthalideisoquinolines is illustrated by the synthesis of cordrastine (161; R<sup>1</sup> = OMe, R<sup>2</sup> = H) as in Scheme 16.<sup>410</sup> The key reaction of the diazotoluene (158) with the 3,4-dihydroisoquinolinium iodide (159) is thought to proceed *via* the aziridinium salt (160). Hydrastine and the isomer (161; R<sup>1</sup> = H, R<sup>2</sup> = OMe) of cordrastine were prepared in similar fashion.<sup>410</sup>



Scheme 16

<sup>410</sup> T. Kametani, T. Honda, H. Inoue, and K. Fukumoto, *Heterocycles*, 1975, **3**, 1091; *J.C.S. Perkin I*, 1976, 1221.

The kinetics and mechanism of hydrolysis of narcotine and of lactonization of narcotic acid have been studied.<sup>411</sup> Another report deals with the instability of bicuculline under physiological conditions.<sup>412</sup> 8-Ethyl narcotoline hydrochloride had antitussive properties similar to codeine phosphate but the hydrochlorides of narcotoline and 8-benzyl narcotoline were weaker.<sup>413</sup>

### 15 Rhoeadine and Papaverrubine Alkaloids

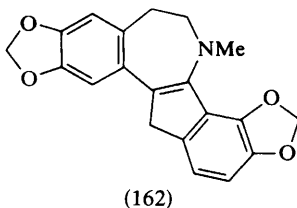
Work on alkaloid isolation is summarized in Table 13. Rhoeadine, previously considered a specific biochemical characteristic of the *Papaver* genus, has been found in *Bocconia frutescens*.<sup>327</sup> This alkaloid was also found in *Papaver syriacum* together with isorhoeadine, rhoeagine, and at least six papaverrubines, indicating a close biochemical relationship of *P. syriacum* with that group of species from the section Orthorhoeades (including, e.g., *P. rhoeas* and *P. strigosum*) which is characterized by the presence of rhoeadine as the main alkaloid with protopine and rhoeagine as minor alkaloids.<sup>211</sup>

**Table 13** Isolation of rhoeadine and papaverrubine alkaloids

Source	Alkaloid	Ref.
<i>Bocconia frutescens</i> <sup>a</sup>	Rhoeadine	327
<i>Papaver bracteatum</i> <sup>b</sup>	Alpinine	208
<i>P. radicatum</i>	Papaverrubine E	198
<i>P. syriacum</i> <sup>c</sup>	Isorhoeadine	} 211
	Rhoeadine	
	Rhoeagine	

<sup>a</sup> A papaverrubine (possibly E) also found in trace amounts; <sup>b</sup> Known constituents, e.g. rhoeadine, and five unknown and unidentified alkaloids were also present; <sup>c</sup> Several papaverrubines were also present.

Synthetic work on rhoeadan and other benzazepine alkaloids has been reviewed.<sup>199</sup> The synthesis of benzindenoazepines from 1-benzoyl-3,4-dihydroisoquinolines (cf. Vol. 6, p. 158) has been applied to the preparation of methylenedioxy analogues, e.g. (162).<sup>414</sup> An alternative to the published procedure



for converting a phthalideisoquinoline into a rhoeadan alkaloid (cf. Vol. 3) is indicated in Scheme 17. A key step is the transformation of the ene-lactone (163)

<sup>411</sup> E. Pawelczyk and M. Zajac, *Pol. J. Pharmacol. Pharm.*, 1975, **37**, 69 (*Chem. Abs.*, 1975, **83**, 103 200).

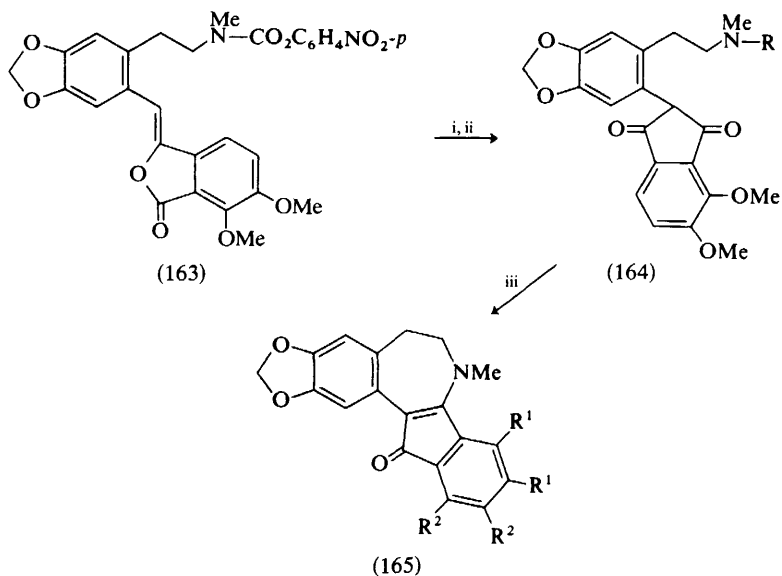
<sup>412</sup> R. W. Olsen, M. Bann, T. Miller, and G. A. R. Johnston, *Brain Res.*, 1975, **98**, 383 (*Chem. Abs.*, 1976, **84**, 25 623).

<sup>413</sup> A. Put, J. Wojcicki, S. Stanosz, and P. Gorecki, *Herba Pol.*, 1974, **20**, 285 (*Chem. Abs.*, 1975, **83**, 22 520).

<sup>414</sup> T. Kametani, M. Premila, S. Hirata, H. Seto, H. Nemoto, and K. Fukumoto, *Canad. J. Chem.*, 1975, **53**, 3824.



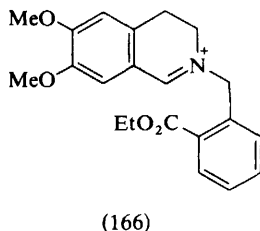
obtained from hydrastine into the indanedione (164;  $R = \text{CO}_2\text{C}_6\text{H}_4\text{NO}_2\text{-}p$ ), a type of reaction previously used in the synthesis of ochroberine (*cf.* Vol. 4). Cyclization of the corresponding free base (164;  $R = \text{H}$ ) then gave a mixture of (165;  $R^1 = \text{H}$ ,



Reagents: i, NaOMe-MeOH; ii, aq. NaOH-DMSO; iii, *p*-TsOH.

**Scheme 17**

$R^2 = \text{OMe}$ ) and (165;  $R^1 = \text{OMe}$ ,  $R^2 = \text{H}$ ).<sup>415</sup> Details of the rhoeadan synthesis from (166) (*cf.* Vol. 5, p. 161) have appeared.<sup>416</sup>



## 16 Spirobenzylisoquinoline Alkaloids

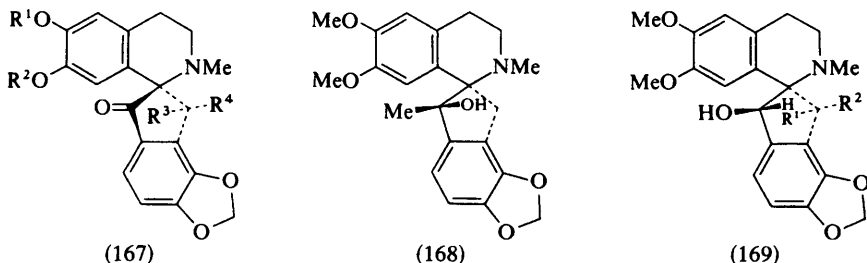
Of five new alkaloids which have been characterized, ledeborine (167;  $R^1 = \text{Me}$ ,  $R^2 = R^3 = \text{H}$ ,  $R^4 = \text{OH}$ ) is a phenolic alkaloid isolated from *Corydalis ledebouriana*.<sup>417</sup> The remaining alkaloids, namely raddeanamine (168), rad-

<sup>415</sup> H. L. Holland, M. Curcumelli-Rodostamo, and D. B. MacLean, *Canad. J. Chem.*, 1976, **54**, 1472.

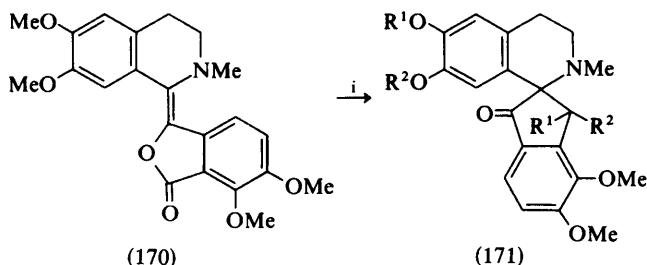
<sup>416</sup> M. Shamma and L. Toke, *Tetrahedron*, 1975, **31**, 1991.

<sup>417</sup> I. A. Israelov, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, **11**, 268 (*Chem. Abs.*, 1975, **83**, 97 661).

deanidine (169;  $R^1 = \text{OAc}$ ,  $R^2 = \text{H}$ ), raddeanine (169;  $R^1 = \text{OH}$ ,  $R^2 = \text{H}$ ), and raddeanone (167;  $R^1 = R^2 = \text{Me}$ ,  $R^3 = \text{OH}$ ,  $R^4 = \text{H}$ ), are non-phenolic and were obtained from *C. ochotensis* var. *raddeana*.<sup>334</sup> The last two alkaloids differ from yenusomine (169;  $R^1 = \text{H}$ ,  $R^2 = \text{OH}$ )<sup>333</sup> and yenusomidine (167;  $R^1 = R^2 = \text{Me}$ ,



$R^3 = \text{H}$ ,  $R^4 = \text{OH}$ )<sup>333</sup> respectively only in configuration at C-8. The structures were assigned mainly on spectral data; e.g. the resonance values for the methine hydrogen at C-8 in raddeanone ( $\delta$  5.56)<sup>334</sup> and yenusomidine ( $\delta$  5.14)<sup>333</sup> were compared with that in sibiricine ( $\delta$  5.57) where this hydrogen atom is *syn* to the nitrogen atom. The tetramethoxy analogues (171;  $R^1 = R^2 = \text{Me}$ ,  $R^3 = \text{H}$ ,  $R^4 = \text{OH}$ ) and (171;  $R^1 = R^2 = \text{Me}$ ,  $R^3 = \text{OH}$ ,  $R^4 = \text{H}$ ) of sibiricine have been obtained in one step from dehydrocordrastine (170) (Scheme 18).<sup>418</sup> The conversion of hydrastine into the amine (164;  $R = \text{H}$ ), described in Section 15, provides another route to spirobenzylisoquinolines since cyclization of (164;  $R = \text{H}$ ) gives the dione (171;  $R^1R^2 = \text{CH}_2$ ,  $R^3R^4 = \text{O}$ ).<sup>415</sup>



Reagent: i, di-isobutylaluminium hydride.

Scheme 18

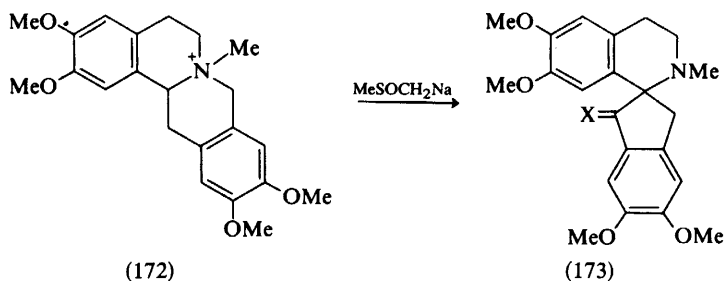
The ochotensine-type base (173;  $X = \text{H}_2$ ) has been obtained by Stevens rearrangement of the non-phenolic *N*-methyltetrahydroprotuberberinium salt (172) with methyl sulphinyl carbanion (Scheme 19).<sup>419</sup> Details have appeared of the benzocyclobutenyl route to (173;  $X = \text{CH}_2$ ) (cf. Vol. 4).<sup>420</sup> The mass-spectral fragmentation pattern of various fumariline type alkaloids has been studied.<sup>421</sup>

<sup>418</sup> H. L. Holland, D. B. MacLean, R. G. A. Rodrigo, and R. H. F. Manske, *Tetrahedron Letters*, 1975, 4323.

<sup>419</sup> S. Kano, T. Yokomatsu, E. Komiya, S. Tokita, Y. Takahagi, and S. Shibuya, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 1171.

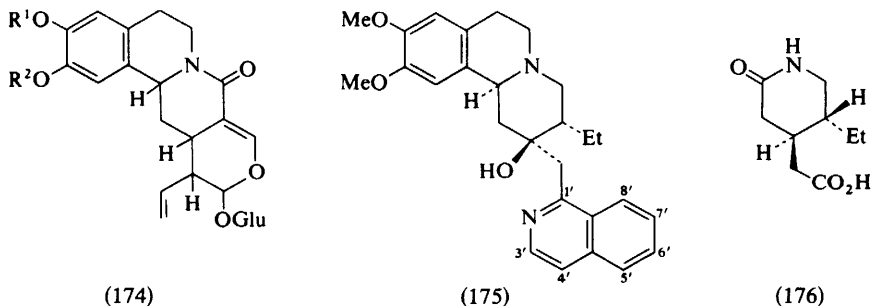
<sup>420</sup> T. Kametani, Y. Hirai, H. Nemoto, and K. Fukumoto, *J. Heterocyclic Chem.*, 1975, **12**, 185.

<sup>421</sup> A. Kato, K. Akagi, H. Irie, and S. Uyeo, *Yakugaku Zasshi*, 1975, **95**, 1058 (*Chem. Abs.*, 1976, **84**, 5210).

**Scheme 19****17 Ipecacuanha Alkaloids**

Details have appeared of the isolation and structural elucidation of alangiside (174;  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ) (cf. Vol. 3).<sup>422</sup> The location of the free phenolic hydroxy-group is based on the non-identity of the alkaloid with a sample of its isomer (174;  $R^1 = \text{H}$ ,  $R^2 = \text{Me}$ ) synthesized from secologanin.<sup>422</sup>

In the course of synthetic work leading to various emetine analogues, an abnormal isoquinoline hydrogenation reaction has been observed. Reduction of the hydroxy-compound (175), for example, gave a 5',6',7',8'-tetrahydro-derivative instead of the expected 1',2',3',4'-tetrahydro-derivative.<sup>423</sup> The hydroxy-group at C-2 apparently plays a part since hydrogenation of emetamine, which lacks this feature, proceeds in a normal manner to give isoemetine. The stereochemistry and *cis-trans* isomerism of the lactam (176), used in the synthesis of ankorine (cf. Vol. 6, p. 163), have been studied.<sup>424</sup> Carbon-13 spectral data for emetine have been published.<sup>425</sup> The total synthesis of emetine has been reviewed from the aspect of chiral economy.<sup>426</sup> A general review of emetine and related alkaloids has also appeared.<sup>427</sup> Iodometric assay of emetine<sup>428</sup> and the use of its dansyl derivative in its analysis<sup>429</sup> have been described.



<sup>422</sup> A. Shueb, K. Raj, R. S. Kapil, and S. P. Popli, *J.C.S. Perkin I*, 1975, 1245.

<sup>423</sup> N. Kumar, P. C. Jain, and N. Anand, *Indian J. Chem.*, 1975, **13**, 285.

<sup>424</sup> T. Fujii, S. Yoshifuji, and M. Taii, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 2094.

<sup>425</sup> M. C. Koch, M. M. Plat, N. Preaux, H. E. Gottlieb, and E. W. Hagaman, *J. Org. Chem.*, 1975, **40**, 2836.

<sup>426</sup> A. Fischli, *Chimia (Switz.)*, 1976, **30**, 4.

<sup>427</sup> P. Grollman and Z. Jarkovsky, in ref. 373, Vol. 3, p. 420.

<sup>428</sup> P. P. Suprun, *Farm. Zhur (Kiev)*, 1975, **30**, 68 (*Chem. Abs.*, 1975, **83**, 168 511).

<sup>429</sup> Cf. Table 2, refs. p and pp.

### 18 Dimeric Benzylisoquinoline Alkaloids

Alkaloid isolation work is summarized in Table 14.<sup>430–441</sup> Thalibrine (179;  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ) and northalibrine (179;  $R^1 = R^2 = \text{H}$ ) are new alkaloids of the dauricine type isolated from *Thalictrum rochebrunnianum*. The spectral data of the *O*-methyl

**Table 14** Isolation of dimeric benzylisoquinoline alkaloids

Source	Alkaloid	Ref.
<i>Abuta panurensis</i>	Norpanurensine (184; $R = \text{H}$ )	430
	Panurensine (184; $R = \text{Me}$ )	
<i>A. splendida</i>	Aromoline	431
	Homomomoline	
	Krukovine <sup>a</sup> (177)	
<i>Berberis oblonga</i>	Berberamine	326
	Oxyacanthine	
<i>Cissampelos pareira</i> <sup>b</sup>	Insularine	432
<i>Cocculus hirsutus</i>	Isotrilobine	153
	Trilobine	
<i>C. pendulus</i> <sup>c</sup>	Pendine <sup>d</sup>	433
	Penduline <sup>e</sup>	
	Pendulinine	
<i>Colubrina faralaotha</i> subsp. <i>trichocarpa</i>	(+)-Limacine	434
<i>Heracleum wallichii</i> <sup>f</sup>	Cycleanine	435
	Isochondrodendrine	
<i>Sciadotenia toxifera</i>	Sciadenine (180)	436
<i>Stephania cepharantha</i> <sup>g</sup>	Aromoline	437
	Berberamine	
<i>Thalictrum rochebrunnianum</i>	Northalibrine (179; $R^1 = R^2 = \text{H}$ )	438
	Thalibrine (179; $R^1 = \text{Me}$ , $R^2 = \text{H}$ )	
<i>T. rugosum</i>	Thalrugosaminine <sup>h</sup> (178)	343
<i>T. thunbergii</i>	Thalictine (183)	439
<i>Triclisia gillettii</i>	Trigilletimine (181)	440
<i>T. patens</i>	Trigilletimine (181)	
	Aromoline	441
<i>T. subcordata</i>	Tetrandrine	441

<sup>a</sup> A new alkaloid of the berberamine type, *OO*-dimethylation of which gives phaeanthine; <sup>b</sup> Cycleanine and isochondrodendrine (known constituents) were also isolated; <sup>c</sup> Cocsoline, coculine, and coculinine were also isolated (*cf.* Vol. 6, p. 166); <sup>d</sup>  $\text{C}_{32}\text{H}_{23}\text{O}_3(\text{NH})(\text{NMe})(\text{OH})(\text{OMe})_2$ ; <sup>e</sup>  $\text{C}_{33}\text{H}_{25}\text{O}_3(\text{NMe})_2(\text{OMe})_3$ ; <sup>f</sup> First reported identification of alkaloids from a *Heracleum* species; <sup>g</sup> Callus tissues; <sup>h</sup> A new alkaloid of the thalispine type (*cf.* Vol. 3).

<sup>430</sup> M. P. Cava, J. M. Saá, M. V. Lakshmikantham, and M. J. Mitchell, *J. Org. Chem.*, 1975, **40**, 2647.

<sup>431</sup> J. M. Saá, M. V. Lakshmikantham, M. J. Mitchell, and M. P. Cava, *J. Org. Chem.*, 1976, **41**, 317.

<sup>432</sup> D. Dwuma-Badu, J. S. K. Ayim, C. A. Mingle, A. N. Tackie, D. J. Slatkin, J. E. Knapp, and P. L. Schiff, jun., *Phytochemistry*, 1975, **14**, 2520.

<sup>433</sup> D. S. Bhakuni and P. P. Joshi, *Tetrahedron*, 1975, **31**, 2575.

<sup>434</sup> H. Guinaudeau, M. Leboeuf, A. Cavé, S. Duret, and R. P. Paris, *Planta Med.*, 1976, **29**, 54.

<sup>435</sup> B. D. Gupta, S. K. Banerjee, and K. L. Handa, *Phytochemistry*, 1976, **15**, 576.

<sup>436</sup> K. Takahashi, M. J. Mitchell, and M. P. Cava, *Heterocycles*, 1976, **4**, 471.

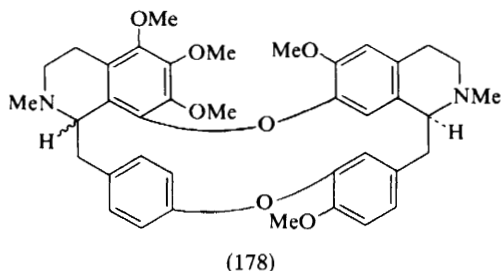
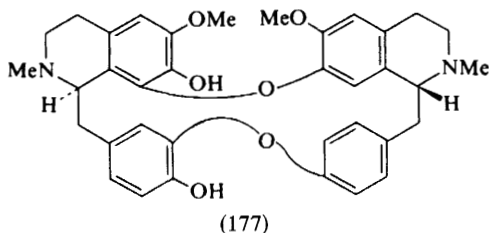
<sup>437</sup> M. Akasu, I. Hideji, and M. Fujita, *Phytochemistry*, 1976, **15**, 471.

<sup>438</sup> J. M. Saá, M. J. Mitchell, M. P. Cava, and J. L. Beal, *Heterocycles*, 1976, **4**, 753.

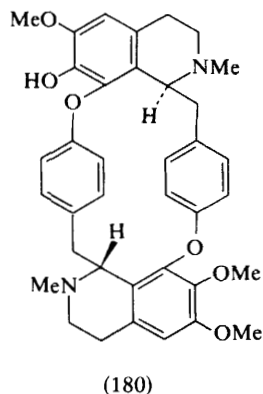
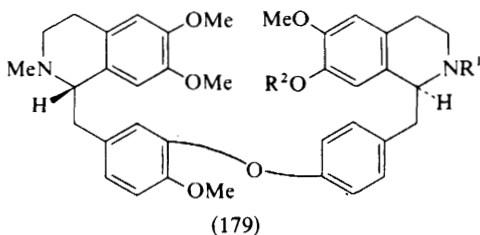
<sup>439</sup> T. Tomimatsu and M. Sasakawa, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 2279.

<sup>440</sup> D. Dwuma-Badu, J. S. K. Ayim, A. N. Tackie, M. A. El Sohly, J. E. Knapp, D. J. Slatkin, and P. L. Schiff, jun., *Experientia*, 1975, **31**, 1251; *Lloydia*, 1975, **38**, 538.

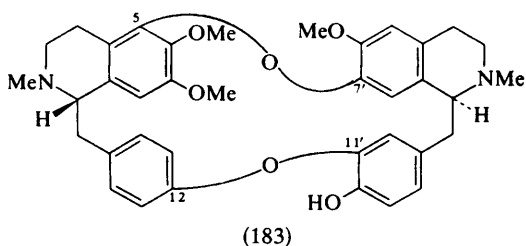
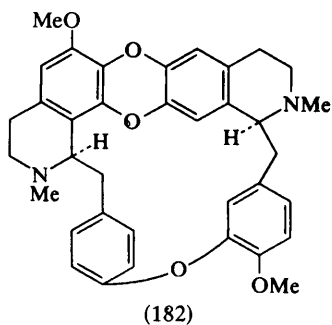
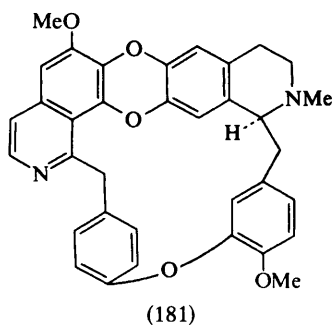
<sup>441</sup> D. Dwuma-Badu, J. S. K. Ayim, A. N. Tackie, J. E. Knapp, D. J. Slatkin, and P. L. Schiff, jun., *Phytochemistry*, 1975, **14**, 2524.



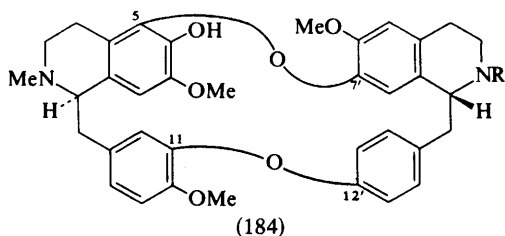
ether of the former were consistent with it being the (*S,S*)-enantiomer of *O*-methylauricine (179;  $R^1 = R^2 = \text{Me}$ ).<sup>438</sup> Sciadenine (180) is a new alkaloid of the



chondrodendrine type isolated from *Sciadenia toxifera*. After *O*-ethylation and Na-NH<sub>3</sub> cleavage, the dimethoxy- and ethoxymethoxy-tetrahydroisoquinoline fragments, although indistinguishable by t.l.c., were separated by 'resolution' using (-)- or (+)-mandelic acid.<sup>436</sup> Three new dibenzodioxin alkaloids, pendulinine, pendine, and penduline, from *Cocculus pendulus* have been characterized. *OO*-Dimethylpendulinine appears from spectral data to be a structural isomer of the *OO*-dimethyl ether of cocculinine (cf. Vol. 6, p. 166), the difference possibly being in the ether link in the benzylic portion.<sup>433</sup> Another new dibenzodioxin alkaloid, trigilletimine (181), isolated from *Triclisia* species, contains an unreduced isoquinoline ring system. Reduction and methylation gave *ON*-dimethylmicranthrane (182). Thalictine (183), a new alkaloid isolated from *Thalictrum thunbergii*, enlarges the small group of bisbenzylisoquinoline alkaloids, typified by thalmine, which are



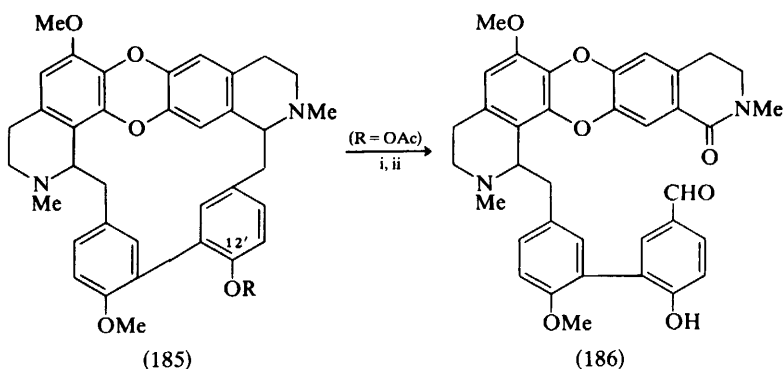
derived by oxidative coupling of a coclaurine and an isococlaurine unit with 5—7' and 12—11' ether links.<sup>439</sup> Panurensine (184; R = Me) and norpanurensine (184;



R = H), new alkaloids isolated from *Abuta panurensis* are the first bisbenzylisoquinoline alkaloids having both a 5—7' and an 11—12' ether bridge.<sup>430</sup> Callus tissues of *Stephania cepharantha* do not synthesize the main alkaloids of the original plant, cepharanthine and isotetrandrine, but afford berbamine and aromoline instead (the latter not being found in the original plant). This is thought to indicate a deficiency in the enzymes controlling specific methylation and methylenedioxy-group formation in the callus.<sup>437</sup>

Work on the alkaloids of *Tiliacora racemosa* has been summarized.<sup>151</sup> The position of the free phenolic hydroxy function in one of these, tiliacorine (185; R = H), has been settled by conversion of *O*-acetyltiliacorine (185; R = Ac) into the *p*-hydroxybenzaldehyde derivative (186) (Scheme 20). It follows that nor-tiliacorinines A and B also have a free phenolic hydroxy-group at the 12'-position.<sup>442</sup>

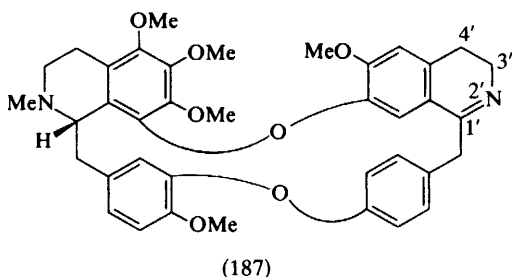
<sup>442</sup> M. Shamma and J. E. Foy, *J. Org. Chem.*, 1976, **41**, 1293.



Reagents: i,  $\text{KMnO}_4$ -acetone; ii, aqueous base.

**Scheme 20**

Polarographic reduction of thalsimine (187) has been studied, the product being the corresponding 1',2'-dihydro-derivative.<sup>443</sup>



A review of the genus *Berberis* lists the alkaloids obtained and includes discussion of the chemistry of some recently isolated alkaloids and the pharmacology of berbamine and the crude extracts of *Berberis* species.<sup>17</sup> The chemistry, biochemistry, and pharmacology of curare have also been reviewed.<sup>444</sup> Other alkaloids whose pharmacology has been discussed are *NN'*-dimethylberbamine and related alkaloids,<sup>445</sup> trilobine and isotrilobine,<sup>446</sup> and isotetrandrine and tetrandrine.<sup>447</sup> The conformation and reactivity of the last alkaloid has been discussed in the light of an *X*-ray study.<sup>448</sup> A method for quantitative extraction of tubocurarine from biological materials has been described.<sup>449</sup>

<sup>443</sup> D. A. Rakhimova, E. K. Dobronravova, and T. T. Shakirov, *Khim. prirod. Soedinenii*, 1975, **11**, 387 (*Chem. Abs.*, 1976, **84**, 59 822).

<sup>444</sup> J. Del Castillo and M. Anderson, ref. 19, p. 99.

<sup>445</sup> I. R. C. Bick and L. J. McLeod, *J. Pharm. Pharmacol.*, 1974, **26**, 988.

<sup>446</sup> J. Yamahara, T. Sawada, and H. Fujimura, *Shoyakugaku Zasshi*, 1974, **28**, 96 (*Chem. Abs.*, 1975, **83**, 53 482).

<sup>447</sup> J. Yamahara, T. Sawada, M. Kozuka, and H. Fujimura, *Shoyakugaku Zasshi*, 1974, **28**, 83 (*Chem. Abs.*, 1975, **83**, 53 481).

<sup>448</sup> C. J. Gilmore, R. F. Bryan, and S. M. Kupchan, *J. Amer. Chem. Soc.*, 1976, **98**, 1947.

<sup>449</sup> D. Wittmer, S. Atwell, and W. G. Haney, jun., *J. Forensic Sci.*, 1975, **20**, 86.

## 1 Introduction

A complete listing of all naturally occurring aporphines, oxoaporphines, and phenanthrenes is now available;<sup>1</sup> and a review on the applications of  $\text{Pb}(\text{OAc})_4$  to the synthesis of several aporphinoids has appeared.<sup>2</sup>

The stereochemical assignments for a number of dihydropyoaporphines have been modified on the basis of new X-ray data.<sup>3</sup> A significant advance in the synthesis of aporphines, as well as in our understanding of possible biogenetic pathways to these alkaloids, has been recorded through a study of the role of morphinandienones as aporphine precursors.<sup>4,5</sup> Pentafluorophenyl copper is an efficient reagent for the formation of the aryl ether linkage present in several dimeric alkaloids.<sup>6</sup> A completely novel aporphinoid alkaloid is eupolauridine, the first known 1,6-diazafluoranthene. Its characterization represents a new dimension in our knowledge concerning the catabolism of aporphines.<sup>7</sup>

## 2 Proaporphines

New proaporphine alkaloids are (+)-isocrotsparinine (1), (+)-*N*-methylisocrotsparinine (2), and ( $\pm$ )-tetrahydroglaziovine (3), all obtained from *Croton sparsiflorus*. The stereochemistry of crotsparinine has been defined as in structure (4). Jacularine and Base-E, two minor alkaloids previously isolated from *C. linearis* have been assigned stereo formulas, with the former being enantiomeric with (1), and the latter being represented by (5).<sup>3</sup>

The compounds ( $\pm$ )- and (-)-glaziovine (6), (-)-pronunciferine (7), and (+)-crotsparinine (8) are present in the leaves of *Ocotea glaziovii*.<sup>8</sup>

(+)-Glaziovine (6), which has interesting psychopharmacological properties,<sup>9</sup> has been prepared in satisfactory yield *via* photolysis of the phenolic diazonium salt (9).

<sup>1</sup> H. Guinaudeau, M. Leboeuf, and A. Cavé, *Lloydia*, 1975, **38**, 275.

<sup>2</sup> B. Umezawa and O. Hoshino, *Heterocycles*, 1975, **3**, 1005.

<sup>3</sup> C. Casagrande, L. Canonica, and G. Severini-Ricca, *J.C.S., Perkin I*, 1975, 1659.

<sup>4</sup> S. M. Kupchan, V. Kameswaran, J. T. Lynn, D. K. Williams, and A. J. Liepa, *J. Amer. Chem. Soc.*, 1975, **97**, 5622.

<sup>5</sup> S. M. Kupchan and C. Kim, *J. Amer. Chem. Soc.*, 1975, **97**, 5623.

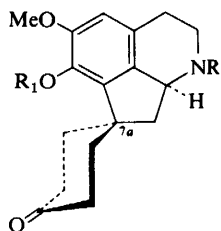
<sup>6</sup> M. P. Cava and A. Afzali, *J. Org. Chem.*, 1975, **40**, 1553.

<sup>7</sup> B. F. Bowden, K. Picker, E. Ritchie, and W. C. Taylor, *Austral. J. Chem.*, 1975, **28**, 2681.

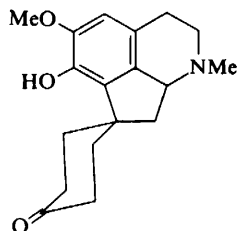
<sup>8</sup> C. Casagrande and G. Ferrari, *Farm. Ed. Sci.*, 1975, **30**, 479 (*Current Abs. Chem.*, 1975, **58**, No. 613, 233479).

<sup>9</sup> B. Buffa, G. Costa and P. Ghirardi, *Current Therap. Res. Clin. Exp.*, 1974, **16**, 621.

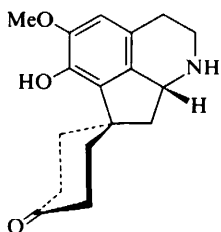




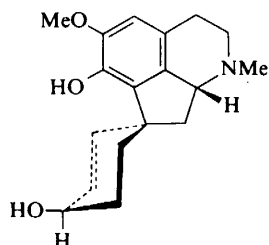
- (1)  $R = H, R_1 = H$   
 (2) a;  $R = Me, R_1 = H$   
 b;  $R = R_1 = Me$



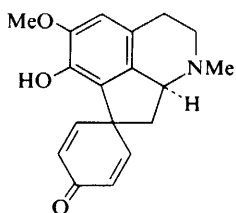
(3)



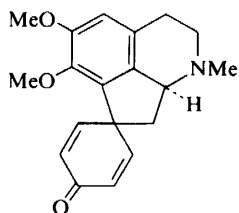
(4)



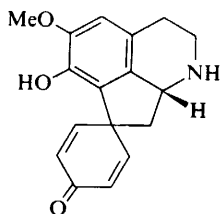
(5)



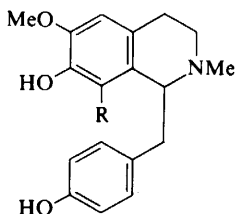
(6)



(7)



(8)



- (9)  $R = N_2^{\oplus}$   
 (10)  $R = Br$

It can be obtained in lesser yield by photolysis of the diphenolic bromo compound (10).<sup>10</sup>

Glaziovine has been synthesized in good yield by a modification of Bernauer's method.<sup>11</sup> *O*-Methylation of the synthetic dihydroproaporphine (2a) produced (+)-amuronine (2b). This new stereochemical assignment for amuronine differs from the

<sup>10</sup> C. Casagrande and L. Canonica, *J.C.S., Perkin I*, 1975, 1647.

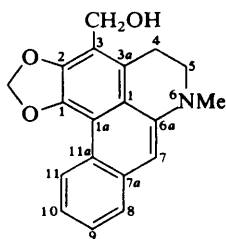
<sup>11</sup> C. Casagrande and L. Canonica, *J.C.S., Perkin I*, 1975, 1652.

old one at C-7a. The configuration of the two asymmetric centres in (2a) was established by *X*-ray diffraction of the HBr salt. A similar revision of stereochemistry at C-7a therefore applies to linearisine (2-*O*-demethylamuronine) and the 1,2-methylenedioxy analogue, roemerone.<sup>11</sup> Catalytic reduction of (–)-glaziovine (6) over Adams catalyst yielded the alkaloid (–)-*N*-methyleoreline which is enantiomeric with the 11, 12-dihydro-derivative of Base-E (5).<sup>11</sup>

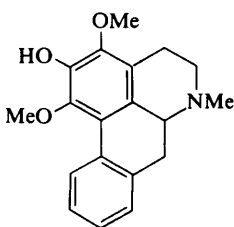
The u.v. and i.r. spectra of alkaloids incorporating a cyclohexadienone or a cyclohexenone ring, including the proaporphines, have been discussed.<sup>12</sup>

### 3 Aporphines

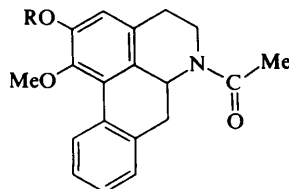
New aporphine alkaloids are cabudine (11), from *Thalictrum isopyroides*,<sup>13</sup> which is also the first aporphinoid to incorporate a hydroxymethyl substituent; and liridinine (12), obtained from *Liriodendron tulipifera*.<sup>14</sup> *L. tulipifera* has also yielded *N*-acetylnornnociferine (13), as well as *N*-acetylasimilobine (14).<sup>15</sup> Interestingly



(11)



(12)



(13) R = Me

(14) R = H

enough, *N*-acetylnornantenine and *N*-acetyl-3-methoxynornantenine had previously been found in *L. tulipifera*.<sup>16a</sup> The botanically related plant *Magnolia obovata* produces *N*-acetylanonaine (1,2-methylenedioxy-6-acetylnoraporphine).<sup>16</sup> Dehydronantenine, which had been detected only by g.c.–m.s. in *Nandina domestica*, has now been isolated from *Ocotea macrophylla*.<sup>17</sup> Episteporphine is a new C-4 hydroxylated aporphine found in a *Colubrina* (Rhamnaceae) species. It is diastereomeric with the known steporphine (1,2-methylenedioxy-4-hydroxyaporphine).<sup>1</sup>

Known aporphines reisolated from natural sources are:

Nantenine

*Ocotea macrophylla*<sup>17</sup>

Corydine

*Corydalis marschalliana*<sup>18</sup>

<sup>12</sup> S. Dvořáčková, L. Hruban, V. Preininger, and F. Šantavý, *Heterocycles*, 1975, **3**, 575.

<sup>13</sup> M. Kurbanov, Kh. Sh. Khusainova, M. Khodzhimatov, A. E. Vezen, K. Kh. Khaidarov and V. K. Burichenko, *Doklady. Akad. Nauk Tadzh. S.S.R.*, 1975, **18**, 20 (*Chem. Abs.*, 1976, **84**, 180440j).

<sup>14</sup> A. Abdusamatov, R. Ziyaev, and S. Y. Yunusov, *Khim. prirod. Soedinenii*, 1975, **11**, 813 (*Chem. Abs.*, 1976, **84**, 150806r).

<sup>15</sup> C.-L. Chen, H. Chang, and E. B. Cowling, *Phytochemistry*, 1976, **15**, 547.

<sup>16</sup> (a) C. D. Hufford and M. J. Funderburk, *J. Pharm. Sci.*, 1974, **63**, 1338; C. D. Hufford, M. J. Funderburk, J. M. Morgan, and L. W. Robertson, *J. Pharm. Sci.*, 1975, **64**, 789; (b) Y. Sashida, R. Sugiyama, S. Iwasaki, H. Shimomura, H. Itokawa, and M. Fujita, *J. Pharm. Soc. Japan*, 1976, **96**, 659.

<sup>17</sup> N. C. Franca, A. M. Giesbrecht, O. R. Gottlieb, A. F. Magalhães, E. G. Magalhães, and J. G. S. Maia, *Phytochemistry*, 1975, **14**, 1671.

<sup>18</sup> Kh. G. Kiryakov, I. A. Israilov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1974, 411; *Chem. Natural Compounds*, 1975, **10**, 418.

Isocorydine	<i>Ocotea macrophylla</i> <sup>17</sup>
	<i>Pteridophyllum racemosum</i> <sup>19</sup>
Glaucine	<i>Alphonsea ventricosa</i> <sup>20</sup>
	<i>Ocotea macrophylla</i> <sup>17</sup>
	<i>Liriodendron tulipifera</i> <sup>15</sup>
Dehydroglaucine	<i>Liriodendron tulipifera</i> <sup>15</sup>
Norglaucine	<i>Alphonsea ventricosa</i> <sup>20</sup>
Isoboldine	<i>Ocotea glaziovii</i> <sup>8</sup>
	<i>Corydalis cava</i> <sup>21</sup>
	<i>C. marschalliana</i> <sup>18</sup>
Dicentrine	<i>Cissampelos pareira</i> <sup>22</sup>
	<i>Glaucium flavum</i> <sup>23</sup>
Dehydrodicentrine	<i>Cissampelos pareira</i> <sup>22</sup>
Bulbocapnine	<i>Corydalis cava</i> <sup>21</sup>
	<i>C. marschalliana</i> <sup>18</sup>
	<i>Glaucium flavum</i> <sup>23</sup>
Domesticine	<i>Corydalis marschalliana</i> <sup>18</sup>
	<i>C. cava</i> <sup>21</sup>
Thalphenine	<i>Thalictrum rugosum</i> <sup>24</sup>
Laurifoline	<i>Zanthoxylum</i> spp <sup>25</sup>
Predicentrine	<i>Corydalis cava</i> <sup>21</sup>
Magnoflorine	<i>Cocculus carolinus</i> <sup>26</sup>
	<i>Zanthoxylum</i> spp <sup>25</sup>
(±)-Apoglaziovine	<i>Ocotea glaziovii</i> <sup>8</sup>
(previously known in the levo form)	
Caaverine	<i>Ocotea glaziovii</i> <sup>8</sup>
Asimilobine	<i>O. glaziovii</i> <sup>8</sup>
	<i>Liriodendron tulipifera</i> <sup>15</sup>
Lirinidine	<i>Ocotea glaziovii</i> <sup>8</sup>
(absolute configuration uncertain)	
Sparsiflorine	<i>Croton sparsiflorus</i> <sup>3</sup>
O-Methylatheroline	<i>Liriodendron tulipifera</i> <sup>15</sup>
Ushinsunine	<i>Cananga odorata</i> <sup>27</sup>
Norushinsunine	<i>Liriodendron tulipifera</i> <sup>15</sup>
(±)-Roemerine	<i>L. tulipifera</i> <sup>28</sup>
(-)-Roemerine	<i>Cananga odorata</i> <sup>27</sup>
(±)-Nornuciferine	<i>Liriodendron tulipifera</i> <sup>28</sup>
(-)-Anonaine	<i>Cananga odorata</i> <sup>27</sup>

<sup>19</sup> A. Ikuta and H. Itokawa, *Phytochemistry*, 1976, **15**, 577.

<sup>20</sup> P. K. Mahanta, R. K. Mathur, and K. W. Gopinath, *Indian J. Chem.*, 1975, **13**, 306.

<sup>21</sup> V. Preininger, R. S. Thakur, and F. Šantavý, *J. Pharm. Sci.*, 1976, **65**, 294.

<sup>22</sup> D. Dwuma-Badu, J. S. K. Ayim, C. A. Mingle, A. N. Tackie, D. J. Slatkin, J. E. Knapp, and P. L. Schiff, jun., *Phytochemistry*, 1975, **14**, 2520.

<sup>23</sup> I. Lalezari, A. Shafiee, and M. Mahjour, *J. Pharm. Sci.*, 1976, **65**, 923.

<sup>24</sup> W. N. Wu, J. L. Beal, G. W. Clark, and L. A. Mitscher, *Lloydia*, 1976, **39**, 65.

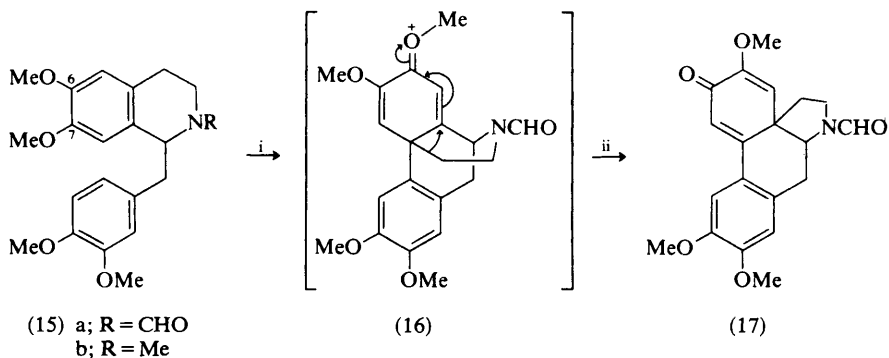
<sup>25</sup> F. Fish, A. I. Gray, P. G. Waterman, and F. Donachie, *Lloydia*, 1975, **38**, 268.

<sup>26</sup> M. A. Elsohly, J. E. Knapp, P. L. Schiff, jun., and D. J. Slatkin, *J. Pharm. Sci.*, 1976, **65**, 132.

<sup>27</sup> M. Leboeuf, J. Streith, and A. Cavé, *Ann. pharm. franç.*, 1975, **33**, 43 (*Current Abs. Chem.*, 1975, **58**, No. 610, 232576).

<sup>28</sup> R. Ziyaev, A. Abdusamatov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1974, 108; *Chem. Natural Compounds*, 1975, **10**, 119.

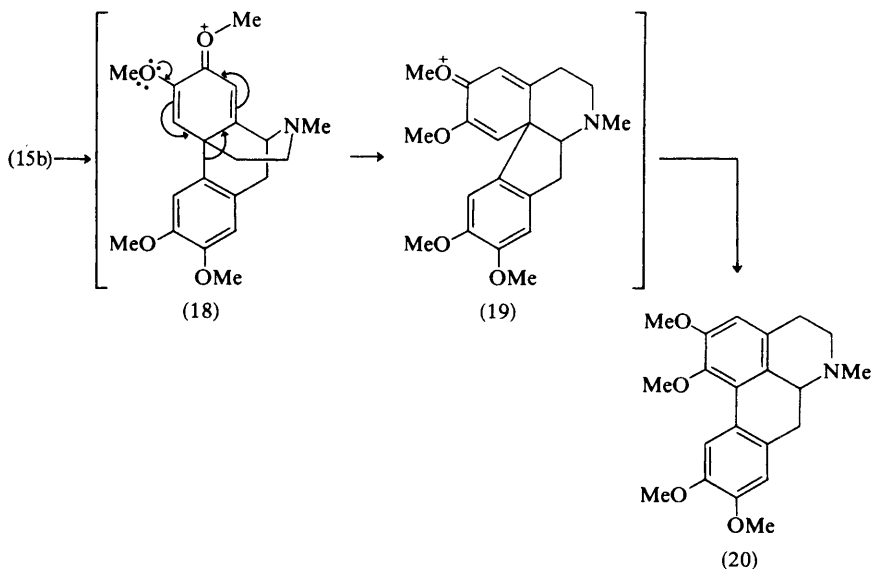
Exciting new developments have occurred related to the synthesis of aporphines. It has been conclusively shown that  $\text{VOF}_3\text{-TFA}$  oxidation of *N*-formylnorlaudanosine (15) provides in high yield the neospirinedienone (17) *via* the morphinandienone intermediate (16) which undergoes loss of the original C-6 methyl substituent (Scheme 1).<sup>4</sup>



Reagents: i,  $\text{VOF}_3\text{-TFA}$ ; ii, alkyl migration.

**Scheme 1**

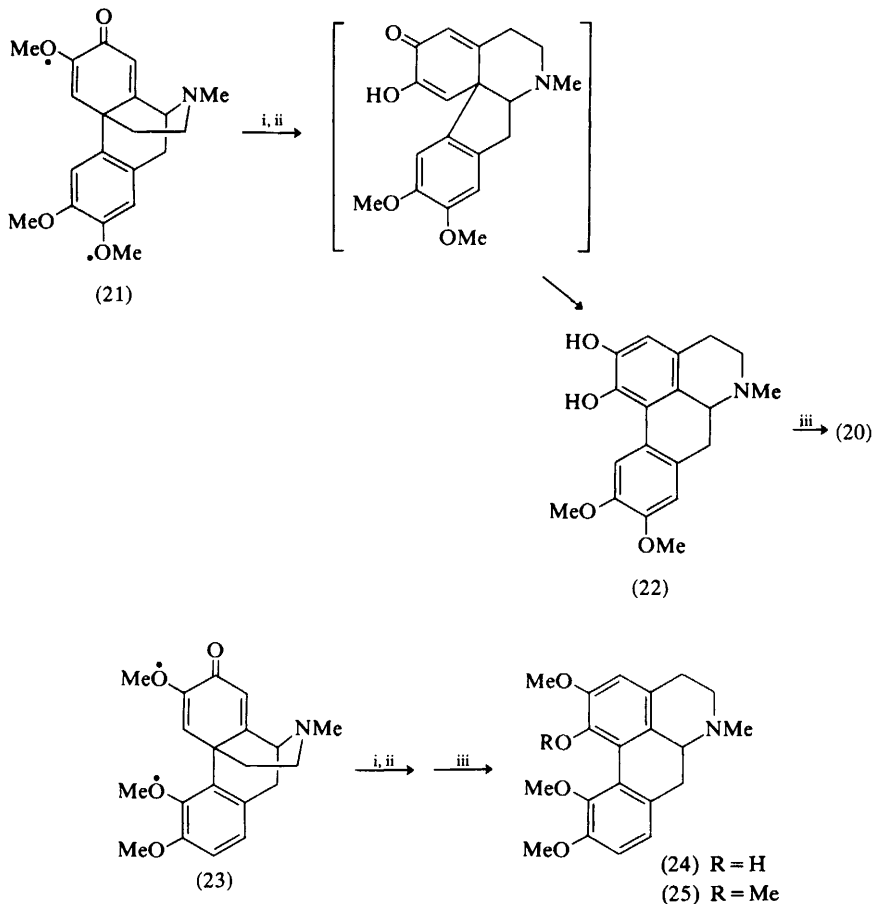
On the other hand, oxidation of laudanosine (15b) itself with  $\text{VOF}_3\text{-TFA}$  gave a 43% yield of glaucine (20). The originally formed morphinandienone intermediate (18) rearranges to the neoproaporphine (19) *via* aryl migration, and (19) in turn undergoes a Wagner–Meerwein shift to supply (20) (Scheme 2).<sup>4</sup>



Reagents: i,  $\text{VOF}_3\text{-TFA}$ ; ii, aryl migration.

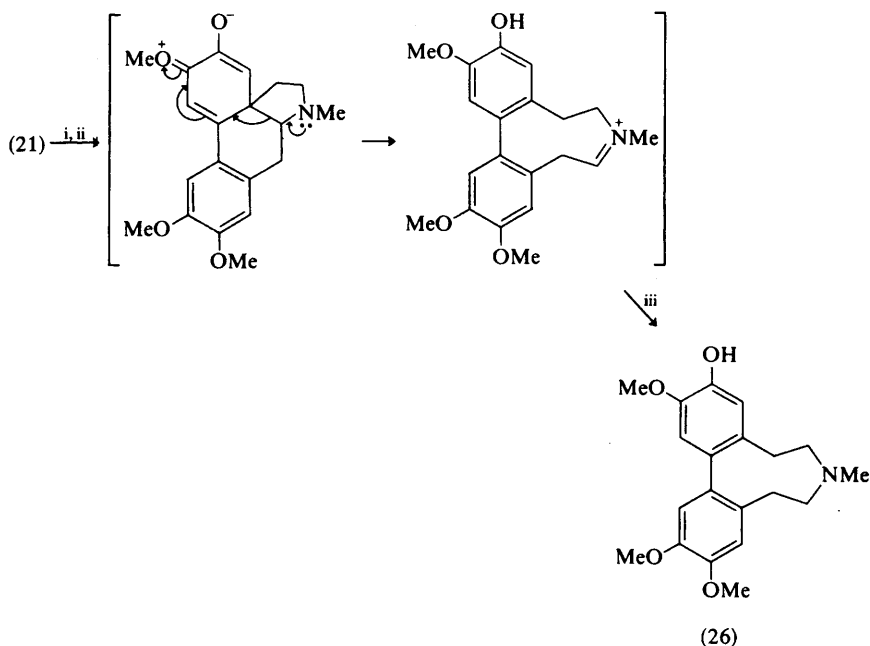
**Scheme 2**

A parallel reaction also leading to aporphines through the sequence morphinandienone  $\rightarrow$  neoproaporphine  $\rightarrow$  aporphine is the conc. HCl catalysed rearrangement of ( $\pm$ )-*O*-methylflavinantine (21) to 1,2-dihydroxy-9,10-dimethoxyaporphine (22) in a remarkable 98% yield. Catechol 22 was then *O*-methylated to glaucine (20). Yet another example is the transformation of ( $\pm$ )-*O*-methylsalutaridine (23) to a mixture of corydine (24) and *O*-methylcorydine (25) (Scheme 3).<sup>4</sup>



Scheme 3

By contrast,  $\text{BF}_3$ -ether catalysed rearrangement of *O*-methylflavinantine (21) leads to alkyl rather than aryl migration. Subsequent reduction with Adams catalyst then generates the dibenzazonine alkaloid erybidine (26) in 85% yield (Scheme 4).<sup>5</sup>



Reagents: i,  $\text{BF}_3$ -ether; ii, alkyl migration, iii,  $\text{H}_2$ , Pt.

Scheme 4

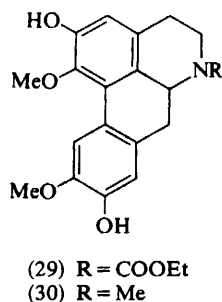
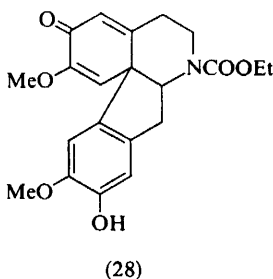
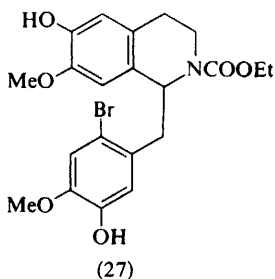
The acid catalysed rearrangement of morphinandienones can thus follow two principal avenues, one leading to aporphines and the other to dibenzazonines.<sup>5</sup> Aporphine formation can occur when the nitrogen of the morphinandienone is in the amine rather than the amide form. Also, such acids as conc. HCl and TFA tend to favour aryl over alkyl migration, thus leading to neoproaporphines which rearrange to aporphines. On the other hand,  $\text{BF}_3$ -ether appears to reinforce the tendency towards alkyl migration resulting in spirines. It can be deduced that, in terms of inductive effect, protonated amides will still allow for alkyl migration, while protonated amines, being poorer in electrons, usually will not. Furthermore, the degree of protonation or complexation at the oxygens indicated (●) in such morphinandienones as (21) and (23) will control the availability of electrons for aryl migration. Lastly, the positions of the equilibria in acid solution between morphinandienones and their sundry rearrangement products may also have to be considered.

Another interesting finding is that electrolytic oxidation of laudanidine (15b) in TFA affords a 17% yield of glaucine (20); the presumed intermediate again being a morphinandienone.<sup>5</sup>

In view of this demonstrated facile *in vitro* conversion of morphinandienones to aporphines,\* there is now a strong possibility that morphinandienones may as well be *in vivo* precursors of aporphine alkaloids.<sup>4,5</sup>

\* For the acid catalysed conversion of the morphinandienone isosalutaridine to a base believed to be 2,10-dimethoxy-3,9-dihydroxyaporphine, see B. Frank, H. I. Lubs, and G. Dunkelmann, *Angew. Chem. Internat. Edn.* 1967, 6, 969.

As a follow up to the above findings, it was observed that photolysis of the bromodiphenol (27) in ethanolic NaOH gave rise to the neoproaporphine (28) in 34% yield, together with *N*-ethoxycarbonylnorboldine (29) in 5% yield. Further photolysis of the neoproaporphine (28) in NaOAc in ethanol produced a 44% yield of the aporphine (29) which could be cleanly reduced with  $\text{LiAlH}_4$  in THF to boldine (30), thus providing the first total synthesis of this alkaloid.<sup>29</sup>



A full paper on the stereospecific synthesis of the C-4 hydroxylated aporphine cataline from thaliporphine (1-hydroxy-2,9,10-trimethoxyaporphine) through lead tetra-acetate oxidation has appeared.<sup>30</sup> This transformation has now been extended to the preparation of ( $\pm$ )-domesticine (1-hydroxy-2-methoxy-9,10-methylenedioxyaporphine) and ( $\pm$ )-nantenine (1,2-dimethoxy-9,10-methylenedioxyaporphine); minor products being C-4 oxygenated aporphines. Homoaporphines may also be obtained using lead tetra-acetate oxidation and starting with properly substituted tetrahydrophenethylisoquinolines.<sup>31</sup>

In a new variation on the above theme, it was determined that treatment of the intermediate quinol acetate with TFA resulted in a substantial increase in the yield of the aporphine, while no C-4 oxygenated aporphine could be detected. Racemic domesticine, thaliporphine and 1-hydroxy-2,9,10,11-tetramethoxyaporphine were thus prepared in 84, 96, and 48% yield, respectively, from the corresponding tetrahydrobenzylisoquinolines.<sup>32</sup> The mechanism of such transformations may be viewed as shown in Scheme 5.

Aporphines synthesized *via* benzyne intermediates obtained from treatment of appropriately substituted 6-methoxy-7-hydroxy-2'-halo-*N*-methyltetrahydrobenzylisoquinolines with  $\text{KNH}_2$  in liquid ammonia include *N*-methylcaaverine (1-hydroxy-2-methoxyaporphine), thaliporphine and domesticine. The upper limit on the yields by this route appears to be 24%, a by-product being the corresponding dibenzopyrrocoline salt resulting from cyclization on nitrogen.<sup>33</sup>

Reaction of the bromophenol (31) with  $\text{KNH}_2$  in liquid ammonia furnished 1-hydroxy-2,10-dimethoxyaporphine in 18% yield. Reactants devoid of the necessary phenolic function in ring A do not afford aporphines on treatment with the strong

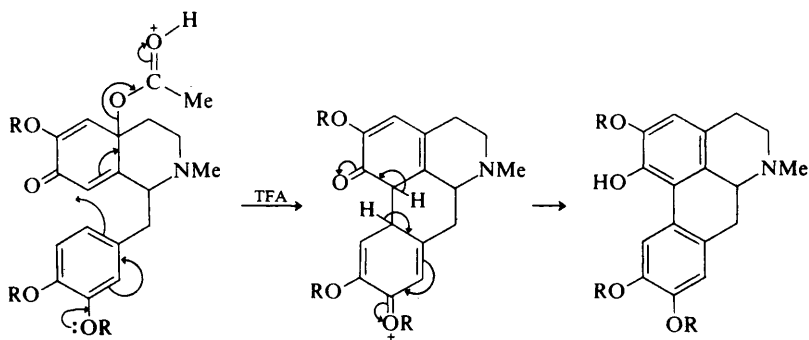
<sup>29</sup> S. M. Kupchan, C. Kim, and K. Miyano, *J.C.S. Chem. Comm.*, 1976, 91.

<sup>30</sup> O. Hoshino, H. Hara, M. Ogawa, and B. Umezawa, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 2578.

<sup>31</sup> O. Hoshino, H. Hara, N. Serizawa, and B. Umezawa, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 2048.

<sup>32</sup> H. Hara, O. Hoshino, and B. Umezawa, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 262.

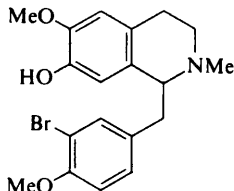
<sup>33</sup> S. V. Kessar, S. Batra, U. K. Nadir, and S. S. Ghandhi, *Indian J. Chem.*, 1975, **13**, 1109.



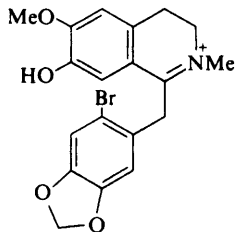
Scheme 5

base.<sup>34</sup> For example, reaction of 2'-bromolaudanosine with the amide anion furnishes 2'-aminolaudanosine.<sup>35</sup>

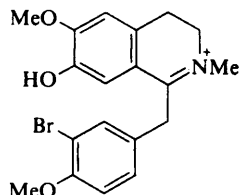
Immonium salts can also be used in the benzyne reaction. Treatment of salt (32) with dimsyl sodium in DMSO gave a 25% yield of dehydromesticine which was reduced to domesticine. Similarly, salt (33) furnished 1-hydroxy-2,10-dimethoxydehydroaporphine which was readily reduced to the corresponding aporphine.<sup>36</sup>



(31)



(32)



(33)

Norpredicentrine,<sup>37</sup> actinodaphnine,<sup>38,39</sup> norisoboldine,<sup>39</sup> and anobine<sup>39</sup> have been obtained, albeit in low yields, from photolysis of the hydrochloride salts of the corresponding 2'-bromotetrahydrobenzylisoquinolines. Predicentrine<sup>40</sup> and 3-methoxy-*N*-acetylnornantenine<sup>41</sup> have also been prepared by the Pschorr cyclization route.

A good method for the conversion of aporphines to dehydroaporphines involves catalytic dehydrogenation using 10% Pd-C in refluxing acetonitrile. Nuciferine,

<sup>34</sup> S. V. Kessar, R. Randhawa, U. K. Nadir, and S. S. Gandhi, *Indian J. Chem.*, 1975, **13**, 1113.

<sup>35</sup> I. Ahmad and M. S. Gibson, *Canad. J. Chem.*, 1975, **53**, 3660.

<sup>36</sup> S. Kano, Y. Takahagi, E. Komiyama, T. Yokomatsu, and S. Shibuya, *Heterocycles*, 1976, **4**, 1013.

<sup>37</sup> M. S. Premila and B. R. Pai, *Indian J. Chem.*, 1975, **13**, 13.

<sup>38</sup> M. S. Premila, B. R. Pai, and P. C. Parthasarathy, *Indian J. Chem.*, 1975, **13**, 945.

<sup>39</sup> T. Kametani, K. Fukumoto, M. Ihara, M. Takemura, H. Matsumoto, B. R. Pai, K. Nagarajan, M. S. Premila, and H. Suguna, *Heterocycles*, 1975, **3**, 811.

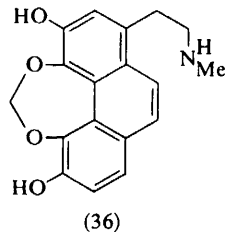
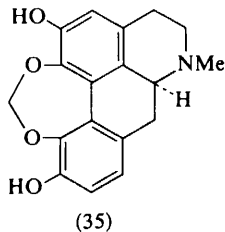
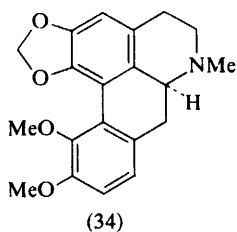
<sup>40</sup> T. Kametani, S. Shibuya, R. Charubala, M. S. Premila, and B. R. Pai, *Heterocycles*, 1975, **3**, 439.

<sup>41</sup> C. D. Hufford and J. M. Morgan, *J. Org. Chem.*, 1976, **41**, 375.



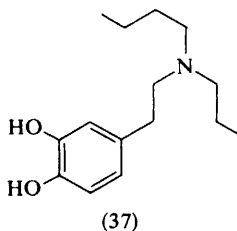
dicentrine, ocopodine and even thalicarpine could thus be dehydrogenated in high yields. The method does not apply to noraporphines or phenolic aporphines.<sup>42</sup>

Treatment of *O*-methylbulbocarpine (34) with at least two moles of  $\text{BBr}_3$  in  $\text{CH}_2\text{Cl}_2$  containing some ethanol provided the dioxepine derivative (35) as the major reaction product. In the absence of ethanol, a mixture of (35) and the phenanthrene (36), isolated as its triacetyl derivative, was obtained. These findings suggest that selective ether cleavage of polyether aporphines with  $\text{BBr}_3$  in  $\text{CH}_2\text{Cl}_2$  can best be carried out on the alkaloidal HBr salts.<sup>43</sup>



The chemistry and pharmacology of apomorphine (10,11-dihydroxyaporphine) and its analogues continue to be of interest. A *Streptomyces* sp converts 10,11-dimethoxyaporphine into an equal mixture of apocodeine (10-methoxy-11-hydroxyaporphine) and isoapocodeine (10-hydroxy-11-methoxyaporphine). However, two cultures of *Cunninghamella* spp yielded isoapocodeine as the predominant metabolite so that selective *O*-demethylation may be achieved with different micro-organisms.<sup>44</sup> Norapomorphine and ten of its *N*-substituted derivatives were tested for emetic activity in dogs. The *N*-ethyl and *N*-propyl compounds were the most potent. The hypotensive effect of apomorphine in the anaesthetized cat was also observed with *N*-*n*-propylnorapomorphine.<sup>45</sup>

The hydrochlorides of a variety of molecular segments of apomorphine were prepared and tested in mice and rats for cholinergic and dopaminergic effects. The catecholic tertiary amine (37) ranked in all tests as the strongest dopamine receptor



agonist, so that it could be of potential use in the study of parkinsonism.<sup>46</sup> ( $\pm$ )-10-Hydroxy-*N*-*n*-propylnoraporphine and ( $\pm$ )-11-hydroxy-*N*-*n*-propylnoraporphine

<sup>42</sup> M. P. Cava, D. L. Edie, and J. M. Saá, *J. Org. Chem.*, 1975, **40**, 3601.

<sup>43</sup> M. Gerecke, R. Borer, and A. Brossi, private communication.

<sup>44</sup> J. P. Rosazza, A. W. Stocklinski, M. A. Gustafson, J. Adrian, and R. V. Smith, *J. Medicin. Chem.*, 1975, **18**, 791; R. V. Smith and J. P. Rosazza, *J. Pharm. Sci.*, 1975, **64**, 1737.

<sup>45</sup> E. R. Atkinson, F. J. Bullock, F. E. Granchelli, S. Archer, F. J. Rosenberg, D. G. Teiger, and F. C. Nachod, *J. Medicin. Chem.*, 1975, **18**, 1000.

<sup>46</sup> J. Z. Ginos, G. C. Cotzias, E. Tolosa, L. C. Tang, and A. LoMonte, *J. Medicin. Chem.*, 1975, **18**, 1194.

are more active than the corresponding parent *N*-methyl analogues as dopamine receptor agonists, thus furnishing direct evidence that a catechol system is not an absolute requirement for dopaminergic activity in the aporphine series.<sup>47</sup> A series of diesters of apomorphine were synthesized and tested for dopaminergic activity in rats. The duration of action generally increased with the size of the ester substituent, indicating that the diesters can serve as prodrugs of apomorphine.<sup>48</sup>

The first studies on the <sup>13</sup>C n.m.r. spectra (in CDCl<sub>3</sub>) of aporphines have been carried out.<sup>49,36,50</sup> Table 1 lists the <sup>13</sup>C chemical shifts for a variety of aporphines. Most of the data is self-explanatory, although it should be pointed out that: (i) the methyl signal of a C-1 methoxyl group appears at lower field than that of other methoxyl groups because of its disposition out of the plane of the benzene ring to which it is attached;<sup>49</sup> (ii) any aromatic carbon appearing downfield from 140 p.p.m. is *ipso* to an oxygenated (OH, OMe, OCH<sub>2</sub>O) function;<sup>50</sup> and (iii) *O*-methylation of a phenolic aporphine will shift the signal for the *ipso* aromatic carbon atom downfield by about 3.5 p.p.m. This last generalization may assist in locating phenolic functions in new aporphines. Not indicated in Table 1 is the fact that *O*-acetylation of a phenolic aporphine results in an even greater ( $\approx 7$  p.p.m.) downfield shift of the *ipso* carbon.<sup>50</sup>

Some generalizations have been drawn concerning the <sup>1</sup>H n.m.r. spectra of aporphines possessing methylenedioxy-groups. The presence of a C-1,2-methylenedioxy in an aporphine or a noraporphine free base is evidenced by an upfield shift of the C-11 proton which appears in the range  $\delta$  7.47–7.86. But if a hydroxyl or a methoxy-group is at C-1, the C-11 proton signal is further downfield, between  $\delta$  7.80 and 8.21. The i.c.s. for the two protons of the methylenedioxy-group is large (4–12 Hz) when the group is located at C-1,2, and small (2–4 Hz) when at C-2,3. No splitting is observed when the group is at C-9,10. In case the methylenedioxy-group is located at C-10,11, the n.m.r. spectrum is characterized by the absence of a C-11 downfield aromatic proton, as well as by a large i.c.s. ( $\approx 8$  Hz) of the two methylene protons.<sup>51</sup> The determination of the enantiomeric purity of isoquinoline alkaloids, particularly glaucine, can be carried out by the use of chiral lanthanide n.m.r. shift reagents such as Eu(facam)<sub>3</sub> in CDCl<sub>3</sub>.<sup>52</sup>

The mass spectra of *N*-acetylnoraporphines exhibit a fragmentation pattern dominated by the *N*-acetyl group.<sup>15</sup>

#### 4 Oxoaporphines

A new oxoaporphine alkaloid is oxostephanine (38) from *Stephania japonica*.<sup>53</sup> Imerubrine, found together with a variety of oxoaporphines and azafluoranthenes in the South American vines *Abuta imene* and *A. rufescens* has been tentatively

<sup>47</sup> J. L. Neumeyer, J. F. Reinhard, W. P. Dafelecker, J. Guarino, and D. S. Kosersky, *J. Medicin. Chem.*, 1976, **19**, 25.

<sup>48</sup> R. J. Borgman, R. J. Baldessarini, and K. G. Walton, *J. Medicin. Chem.*, 1976, **19**, 717.

<sup>49</sup> E. Wenkert, B. L. Buckwalter, I. R. Burfitt, M. J. Gasic, H. E. Gottlieb, E. W. Hagaman, F. M. Schell, and P. M. Wovkulich in 'Topics in C-13 N.M.R. Spectroscopy', ed. G. C. Levey, Wiley-Interscience, New York, 1976, Vol. 2, p. 105.

<sup>50</sup> L. M. Jackman, J. C. Trewella, J. L. Moniot, and M. Shamma, unpublished results.

<sup>51</sup> M. Shamma and J. L. Moniot, *Experientia*, 1976, **32**, 282.

<sup>52</sup> N. A. Shaath and T. O. Soine, *J. Org. Chem.*, 1975, **40**, 1987.

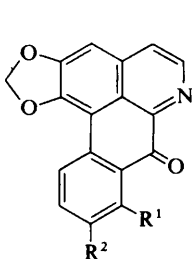
<sup>53</sup> Y. Watanabe, M. Matsui, M. Iibuchi, and S. Hiroe, *Phytochemistry*, 1975, **14**, 2522.

**Table 1**  $^{13}\text{C}$  N.M.R. Spectra of Aporphines in  $\text{CDCl}_3$  (p.p.m.)

Carbon atom	Nuciferine <sup>49</sup>	Glaucine <sup>49</sup>	Nantenine <sup>49</sup>	Isocorydine <sup>49</sup>	Domesticine <sup>36</sup>	Thaliporphine <sup>50</sup>	Predicentrine <sup>50</sup>	Boldine <sup>50</sup>	Dicentrine <sup>50</sup>
1	144.6	143.9	144.0	141.7	140.73	140.7	142.3	142.0	141.7
1a	126.3	126.5	126.4	135.4	119.47 <sup>a</sup>	119.5	126.3	126.8	116.6
1b	128.1	128.6	128.2	128.6	127.22 <sup>a</sup>	127.2	125.9	125.9	126.4
2	151.4	151.5	151.4	150.8	145.83	145.8	148.2	148.1	146.6
3	110.9	110.1	110.3	110.8	109.73	108.7	113.5	113.3	106.1
3a	127.5	127.0	127.0	128.8	123.64	123.9	129.6	129.9	126.6
4	28.9	29.1	29.0	29.1	28.81	29.0	28.7	28.9	29.2
5	52.8	53.1	52.9	52.4	53.31	53.5	53.3	53.4	53.6
6a	61.9	62.3	62.1	62.6	62.45	62.7	62.5	62.6	62.4
7	34.8	34.4	34.9	35.6	34.94	34.5	34.2	34.2	34.3
7a	135.9	129.1	130.4	129.6	140.20 <sup>a</sup>	128.9	129.2	130.2	128.3
8	127.7	110.6	107.8	118.6	108.15 <sup>a</sup>	110.9	110.7	114.2	110.5
9	126.7	147.7	146.0	110.7	145.83	147.6	148.1	145.1	148.2
10	126.4	147.1	145.9	149.0	145.83	147.1	147.6	145.6	147.6
11	127.3	111.4	108.4	143.6	108.74 <sup>a</sup>	112.0	110.0	110.1	111.2
11a	131.6	124.2	125.1	119.8	125.76 <sup>a</sup>	124.8	124.1	123.6	123.4
NMe	43.5	43.4	43.6	43.6	43.91	44.0	43.8	44.0	44.0
C-1 OMe	59.7	59.8	59.8	61.7	—	—	60.3	60.2	—
Other OMe	59.7	55.5	55.4	55.5	56.03	55.9	55.8	56.1	55.9
	55.3	55.5	55.5	55.8	56.0	56.0	56.0	56.1	56.1

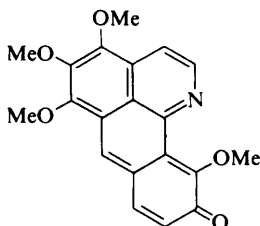
<sup>a</sup> The values for C-1a and C-1b, for C-7a and C-11a, and for C-8 and C-11, have been exchanged, and are therefore different from those given in the original paper.

characterized as (39) or (40).<sup>54</sup> An oxoaporphine extracted from *Magnolia soulangeana* has been stated to be oxolaureline (41).<sup>55</sup>

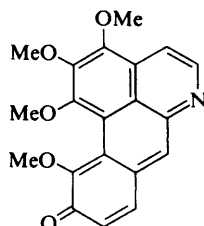


(38)  $R^1 = \text{OMe}$ ,  $R^2 = \text{H}$

(41)  $R^1 = \text{H}$ ,  $R^2 = \text{OMe}$

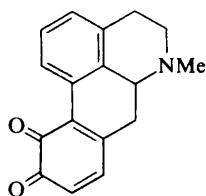


(39)



(40)

Reaction of morphine with conc.  $\text{H}_2\text{SO}_4$  yields the blue ortho quinone (42)<sup>56</sup> whose 1,2-methylenedioxy analogue has been found as a natural product in *Corydalis cava*.<sup>21</sup>



(42)

A full paper on the isolation and characterization of lanuginosine and liriodenine, as well as the noraporphine michelanugine, from *Michelia lanuginosa* has appeared.<sup>57</sup> Known oxoaporphines recently reisolated are:

Lanuginosine

Homomoschatoline

(*O*-methylnmoschatoline)

Liriodenine

*Stephania japonica*<sup>53</sup>

*Liriodendron tulipifera*<sup>58,15</sup>

*Triclisia patens*<sup>59</sup>

*Liriodendron tulipifera*<sup>58,15</sup>

*Eupomatia laurina*<sup>7</sup>

*Cananga odorata*<sup>27</sup>

*Talauma mexicana*<sup>60</sup>

<sup>54</sup> M. P. Cava, K. T. Buck, I. Noguchi, M. Srinivasan, M. G. Rao, and A. I. DaRocha, *Tetrahedron*, 1975, **31**, 1667.

<sup>55</sup> R. Ziyaev, A. Abdusamatov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, **11**, 528 (*Chem. Abst.*, 1976, **84**, 44478a).

<sup>56</sup> G. Ahlers and H. Auterhoff, *Arch. Pharm.*, 1975, **308**, 650; see also M. P. Cava, A. Venkateswarlu, M. Srinivasan, and D. L. Edie, *Tetrahedron*, 1972, **28**, 4299; H. A. Linde and M. S. Ragab, *Helv. Chim. Acta*, 1968, **51**, 683.

<sup>57</sup> S. K. Talapatra, A. Patra, and B. Talapatra, *Tetrahedron*, 1975, **31**, 1105.

<sup>58</sup> A. Abdusamatov, R. Ziyaev and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1974, 112; *Chem. Natural Compounds*, 1975, **10**, 126.

<sup>59</sup> D. Dwuma-Badu, J. S. K. Ayim, A. N. Tackie, J. E. Knapp, D. J. Slatkin, and P. L. Schiff, jun., *Phytochemistry*, 1975, **14**, 2524.

<sup>60</sup> T. Kametani, H. Terasawa, M. Ihara, and J. Iriarte, *Phytochemistry*, 1975, **14**, 1884.

A synthesis of homomoschatoline (1,2,3-trimethoxyoxoaporphine) *via* a Reissert intermediate and Pschorr cyclization has been described,<sup>54</sup> and a photolytic synthesis of atheroline (1,2,10-trimethoxy-9-hydroxyoxoaporphine) is now available.<sup>61</sup> The u.v. spectra of oxoaporphines are strongly dependent on the solvent used.<sup>15</sup>

### 5 Aporphine–Benzylisoquinoline Dimers

A practical route to aporphine–benzylisoquinoline dimers by an improved Ullmann diphenyl ether synthesis has been worked out. The aromatic halide and the phenolic compound are heated with pentafluorophenyl copper in dry pyridine; the average yield of dimer being 50%.<sup>6</sup>

The plasma decay in man of thalicarpine has been studied.<sup>62</sup>

### 6 Phenanthrenes

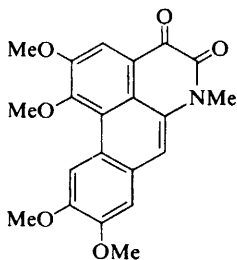
The known phenanthrene alkaloid thaliglucinone has been found in *Thalictrum rugosum*, and it exhibits antimicrobial activity against *Microbacterium smegmatis*.<sup>24</sup> The presence of a methylenedioxy-group at C-3,4 in a phenanthrene alkaloid results in the <sup>1</sup>H n.m.r. spectrum showing an upfield shift of the C-5 proton.<sup>51</sup>

### 7 Dioxoaporphines, Aristolactams, and Aristolochic Acid

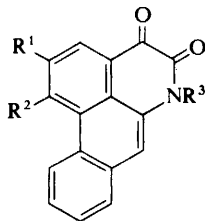
The revised structure (43) has now been given to pontevedrine,<sup>63</sup> so that this alkaloid together with cepharadione-A (44) and -B (45) are dioxoaporphines. As a result of this change, the biogenetic sequence 1,2,4-trioxyaporphine → dioxoaporphine → aristolactam has been postulated,<sup>63</sup> as also independently suggested in a previous Report in this series.<sup>64</sup>

Cepharadione-A and -B have also been found in *Piper auritum*,<sup>65</sup> an example of the rare occurrence of isoquinoline alkaloids in the family Piperaceae. A new dioxoaporphine is norcepharadione-B (46), isolated from the callus tissue of *Stephania cepharantha*.<sup>66</sup>

The first *in vitro* synthesis of cepharadione-B (45) has been reported. Photo-oxidation of dehydronuciferine (1,2-dimethoxydehydroaporphine) in hexane yielded (45) in 7–9% yield, together with a smaller amount of the corresponding



(43)



(44)  $R^1, R^2 = \text{OCH}_2\text{O}, R^3 = \text{Me}$

(45)  $R^1, R^2 = \text{OMe}, R^3 = \text{Me}$

(46)  $R^1 = R^2 = \text{OMe}, R^3 = \text{H}$

<sup>61</sup> T. Kametani, R. Nitadori, H. Teresawa, K. Takahashi, and M. Ihara, *Heterocycles*, 1975, **3**, 821.

<sup>62</sup> P. J. Creaven and L. M. Allen, *Cancer Treatment Reports*, 1976, **60**, 69.

<sup>63</sup> L. Castedo, R. Suau, and A. Mourinho, *Tetrahedron Letters*, 1976, 501.

<sup>64</sup> M. Shamma and J. L. Moniot in 'The Alkaloids', ed. M. F. Grundon, (Specialist Periodical Reports), The Chemical Society, London, 1976, Vol. 6, pp. 179 and 185.

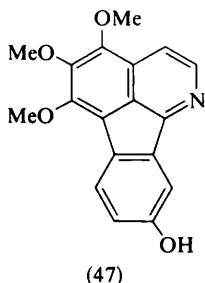
<sup>65</sup> R. Hänsel, A. Leuschke, and A. Gomez-Pompa, *Lloydia*, 1976, **38**, 529.

<sup>66</sup> M. Akasu, H. Itokawa, and M. Fujita, *Phytochemistry*, 1975, **14**, 1673.

oxoaporphine lysicamine (1,2-dimethoxyoxoaporphine).<sup>67</sup> A synthesis of a polysubstituted 10-aminophenanthrene which could be of further use in the preparation of aristolactams and aristolochic acids has appeared.<sup>68</sup>

### 8 Azafluoranthenes

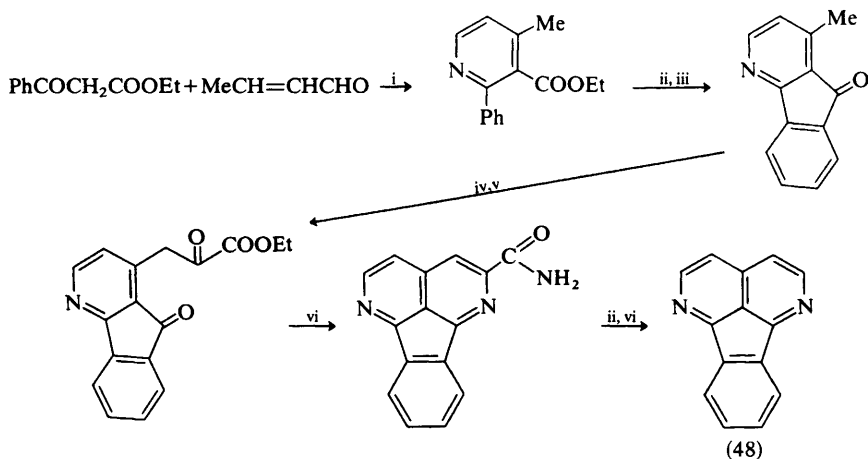
A new azafluoranthene alkaloid, produced by *Abuta imene* and *A. rufescens*, is the phenolic norrufescine (47).<sup>54</sup>



### 9 1,6-Diazafluoranthenes

An investigation of the alkaloidal content of the Australian *Eupomatia laurina* R. Br. (Eupomatiaceae), yielded a number of alkaloids, among which are the oxoaporphine liriodenine and the 7-hydroxynoraporphine norushinsunine. A new minor alkaloid from this source is eupolauridine (48) whose structure was proven conclusively by total synthesis (Scheme 6).<sup>7</sup>

Eupolauridine (48) is most probably an aporphinoid, derived from an aporphine precursor by biological oxidative decarboxylation or decarbonylation.



Reagents: i, Conc.  $\text{NH}_4\text{OH}$ ; ii, hydrolysis; iii, PPA; iv, diethyl oxalate; v, K 3°-butoxide; vi,  $\text{NH}_3\text{-EtOH}$ ; vii,  $\Delta$ ,  $-\text{CO}_2$ .

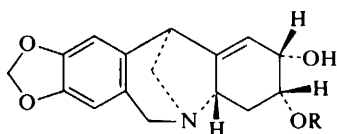
**Scheme 6**

<sup>67</sup> J. M. Saá, M. J. Mitchell, and M. P. Cava, *Tetrahedron Letters*, 1976, 601.

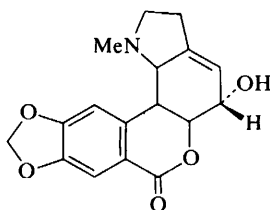
<sup>68</sup> L. R. Hughes and R. A. Raphael, *Tetrahedron Letters*, 1976, 1543.

This group has been recently reviewed.<sup>1</sup>

The structure and absolute stereochemistry of brunsvigine (1; R = H) isolated from *Brusvigia cooperii* have been established on the basis of the X-ray crystallographic analysis of its *OO'*-di-*p*-bromobenzoate.<sup>2</sup> Recent n.m.r., c.d., and mass spectral studies are consistent with this assignment.<sup>3</sup> Furthermore, chemical correlation of *OO'*-*N*-trimethylbrunsvigine picrate with *O*-methyl- $\beta$ -isocrinamine methopicate, prepared from the known  $\beta$ -isocrinamine (1; R = Me), was achieved. Hippeastrine (2) has been isolated from *Clivia miniata*<sup>4</sup> and *Hippeastrum vittatum*.<sup>5</sup>

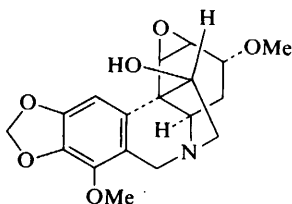


(1)



(2)

The latter also yields the known alkaloids lycorine, tazettine, vittatine, and hippacine in addition to three new bases, hippadine ( $C_{16}H_{10}NO_3$ ), hippagine ( $C_{16}H_{17}NO_4$ ), and hippafine. The structure of carinine (3), a new alkaloid from *H. punecium*, has been



(3)

<sup>1</sup> C. Fuganti, in 'The Alkaloids', Vol. 15, ed. R. H. F. Manske, Academic Press, New York, 1975, p. 83.

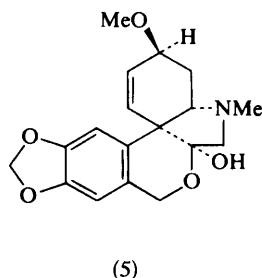
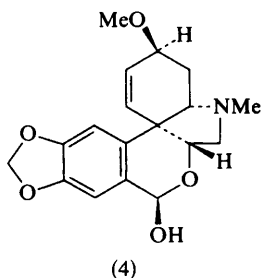
<sup>2</sup> M. Laing and R. C. Clark, *Tetrahedron Letters*, 1974, 583.

<sup>3</sup> R. C. Clark, F. L. Warren, and K. G. R. Pachler, *Tetrahedron*, 1975, **31**, 1855.

<sup>4</sup> A. Abdusamatov, S. A. Khamidkhodzhaev, and S. Yu. Yunnusov, *Khim. prirod. Soedinenii*, 1975, 273.

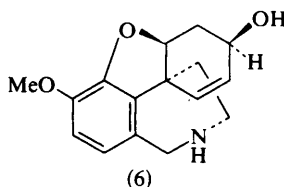
<sup>5</sup> A. M. El Moghazi, A. A. Ali, and M. K. Mesbah, *Planta Med.*, 1975, **28**, 336.

established mainly on the basis of its mass spectral fragmentation which shows equally prominent pathways triggered by the hydroxyl and epoxide functions.<sup>6</sup> Further work concerning the isolation and distribution of lycorine and gelanthamine in *Lencojum aestivum* and *L. vernum* has been reported.<sup>7,8</sup> The isolation of pretazettine (4) has been difficult owing to its facile rearrangement into tazettine (5)



during the extraction procedure.<sup>1</sup> An efficient method for the isolation of pretazettine from *Narcissus tazetta* has now been devised and it has been shown, as in a number of other instances,<sup>1</sup> that tazettine is not the major alkaloidal constituent.<sup>9</sup> The number of alkaloids isolated from *Pancreatium maritimum* has been increased to include lycorine and tazettine.<sup>10</sup> Optimized conditions for the extraction of lycorine from *Ungernia severtzowii* have been reported.<sup>11</sup> A polarographic method for the determination of narwedine in *U. severtzowii* and *U. victoris* has been devised.<sup>12</sup>

A comparative n.m.r. study of dihydrogalanthamine and dihydroepigalanthamine and their acetyl derivatives has been reported.<sup>13</sup> The crystal structure of ( $\pm$ )-norgalanthamine (6), incorrectly named ( $\pm$ )-galanthamine, but corrected in *Chemical Abstracts*, has been determined by direct methods.<sup>14</sup>



A detailed account concerning the isolation and characterization of the pyrido-mesembran alkaloids A<sub>4</sub>(7) and *N*-formyltortuosamine (8) and the mesembran bases (9; R<sup>1</sup> = H, R<sup>2</sup> = OMe), (10), and (9; R<sup>1</sup> = R<sup>2</sup> = H) from *Sceletium namaquense* and *S. strictum* has appeared.<sup>15</sup> Their structures were established by detailed <sup>1</sup>H and

<sup>6</sup> E. H. C. Samuel, *Org. Mass Spectrometry*, 1975, **10**, 427.

<sup>7</sup> I. D. Kalashnikov, *Khim. prirod. Soedinenii*, 1974, 259.

<sup>8</sup> Zh. Stefanov, P. Savchev, and I. Mitkov, *Farmatsiya (Sofia)*, 1974, **24**, 16.

<sup>9</sup> E. Furusawa, S. Furusawa, S. Tani, H. Irie, K. Kitamura, and C. Wildman, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 336.

<sup>10</sup> A. Amico, S. Bruno, and V. Bonvino, *Ann. Fac. Agrar., Univ. Bari*, 1972, **25**, 129.

<sup>11</sup> T. Sadikov, I. N. Zatorskaya, and T. T. Shakirov, *Uzbekh. khim. Zhur.*, 1974, **18**, 74.

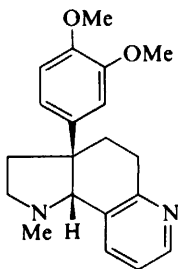
<sup>12</sup> A. D. Volodina, E. K. Dobronravova, and T. T. Shakirov, *Khim. prirod. Soedinenii*, 1975, 610.

<sup>13</sup> M. R. Yagudaev, A. Abdusamatov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1974, 183.

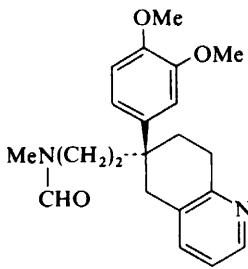
<sup>14</sup> R. Roques and J. Lapasset, *Acta Cryst.*, 1976, **B32**, 579.

<sup>15</sup> W. Jeffs, T. Capps, D. B. Johnson, J. M. Karle, N. H. Martin, and B. Rauckman, *J. Org. Chem.*, 1974, **39**, 2703.

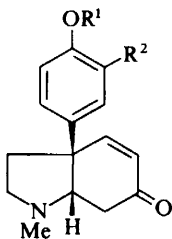




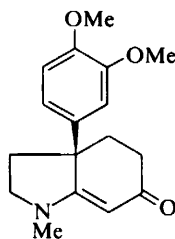
(7)



(8)



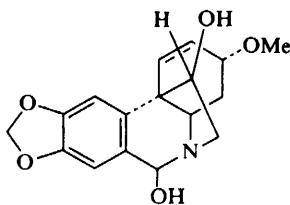
(9)



(10)

$^{13}\text{C}$ n.m.r. analysis and limited chemical evidence. Of considerable interest to biosynthetic and synthetic chemists in this report is the proposal of a unified biogenetic scheme for both classes of alkaloid. Available evidence does not allow the formulation of a single biosynthetic pathway.

Synthetic studies on the *Amaryllidaceae* alkaloids have continued at a high level of activity. Details concerning the stereospecific total synthesis of haemanthidine (11)

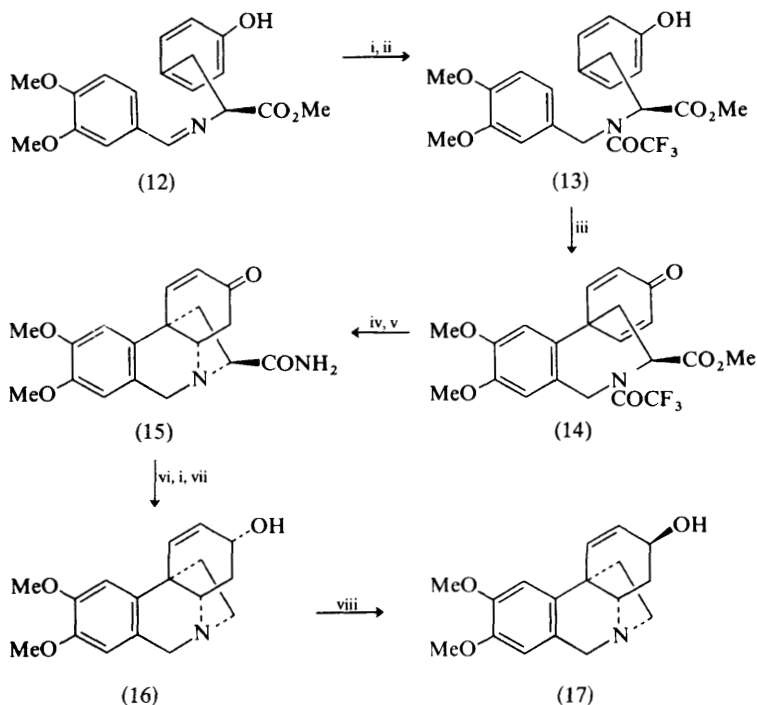


(11)

and tazettine (5) (see Volume 2 of these Reports) have become available.<sup>16</sup> This report also stresses the utility of rational synthetic design principles in formulating the potential approaches to the target molecule. In continuing work on chiral synthesis, Yamada and co-workers have devised a biogenetic-type, asymmetric route to (+)-maritidine (17) (Scheme 1).<sup>17</sup> The Schiff base (12), readily available from L-tyrosine methyl ester and veratraldehyde, was converted into the reduced trifluoroacetyl derivative (13) which, upon phenol oxidative coupling using the promising reagent thallium trifluoroacetate, provided the dienone (14) in 67% yield.

<sup>16</sup> J. B. Hendrickson, T. L. Bogard, M. E. Fisch, S. Grossert, and N. Yoshimura, *J. Amer. Chem. Soc.*, 1974, **96**, 7781.

<sup>17</sup> S. Yamada, K. Tomioka, and K. Koga, *Tetrahedron Letters*, 1976, 57.



Reagents: i, NaBH<sub>4</sub>-MeOH; ii, (CF<sub>3</sub>CO)<sub>2</sub>O-py; iii, Tl(OCOCF<sub>3</sub>)<sub>3</sub>-CF<sub>3</sub>CO<sub>2</sub>H-MeCN; iv, NH<sub>3</sub>-MeOH; v, NaOH-MeOH-H<sub>2</sub>O; vi, POCl<sub>3</sub>-py-CHCl<sub>3</sub>; vii, Na-liq. NH<sub>3</sub>-THF, -78 °C; viii, 10% HCl.

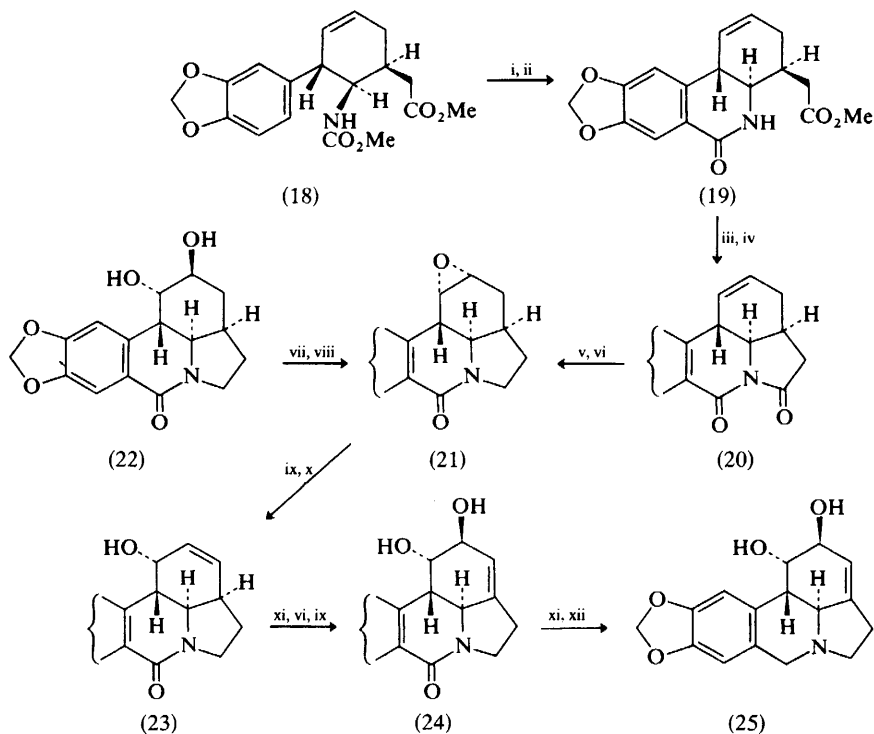
**Scheme 1**

Treatment with methanolic ammonia followed by removal of the trifluoroacetyl group resulted in spontaneous cyclization to give the enone (15) without contamination with its diastereomer, presumably owing to the unfavourable steric effects between the C-6 methylene and the amide function in the latter. The amide (15) was transformed into the corresponding nitrile which upon borohydride reduction followed by reductive decyanation, a reaction which appears to have wide applicability,<sup>18</sup> gave (+)-epimartine (16). Epimerization of (16) into (+)-maritine (17) of optical rotation identical with that reported for the natural product was accomplished by treatment with mild acid.

A relay synthesis of lycorine (25) has been accomplished (Scheme 2)<sup>19</sup> starting with the urethane ester (18) which also served as a key intermediate for the synthesis of other Amaryllidaceae alkaloids (see Vol. 5 of these Reports). Compound (18) was cyclized, presumably *via* its imino-ether, into the lactam ester (19) which was hydrolysed to the corresponding acid and cyclized to give the imide (20). Treatment of (20) with LiAlH<sub>4</sub> under carefully controlled conditions led to reduction only of the five-membered-ring carbonyl function. The resulting amide was epoxidized to give

<sup>18</sup> S. Yamada, K. Tomioka, and K. Koga, *Tetrahedron Letters*, 1976, 61.

<sup>19</sup> Y. Tsuda, T. Sano, J. Taga, K. Isobe, J. Toda, H. Irie, H. Tanaka, S. Takagi, M. Yamaki, and M. Murata, *J.C.S. Chem. Comm.*, 1975, 933.



Reagents: i,  $\text{POCl}_3\text{-CH}_2\text{Cl}_2$ ; ii,  $\text{SnCl}_4\text{-CH}_2\text{Cl}_2$ ; iii, 5%  $\text{HCl-HOAc}$ ; iv,  $\text{Ac}_2\text{O}$ , heat; v,  $\text{LiAlH}_4\text{-Et}_2\text{O}$ ,  $0^\circ\text{C}$ ; vi,  $m\text{-ClC}_6\text{H}_4\text{CO}_3\text{H-CH}_2\text{Cl}_2$ ; vii,  $\text{TsCl-py}$ ; viii,  $\text{NaOAc}$ ; ix,  $(\text{PhSe})_2\text{-NaBH}_4\text{-EtOH}$ ; x,  $\text{NaIO}_4$ ; xi,  $\text{Ac}_2\text{O-py}$ ; xii,  $\text{LiAlH}_4$ .

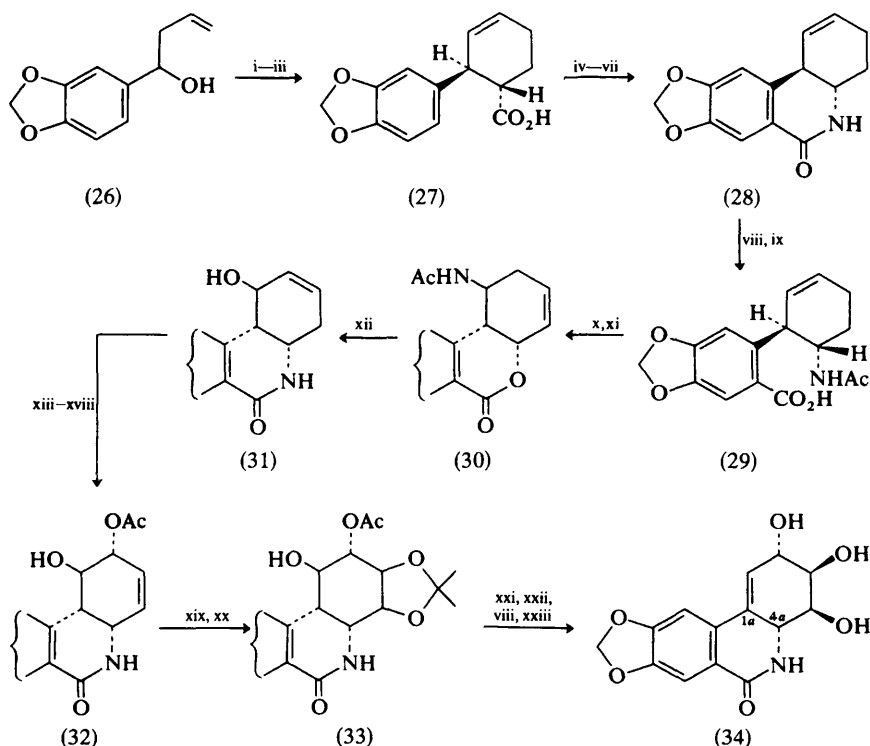
**Scheme 2**

compound (21) which was also obtained in optically active form from natural dihydrolycorine lactam (22) as shown. The relay chiral epoxide (21) was subjected to reaction with diphenyl diselenide followed by oxidation with sodium periodate to give the allylic alcohol (23). The alcohol was successively acetylated and epoxidized and again treated with, in sequence, diphenyl diselenide and sodium periodate to give the lycorine lactam (24). Reduction of the diacetate of (24) finally gave lycorine (25).

The first total synthesis of  $(\pm)$ -lycoridine margetine (33), a member of the non-basic alkaloids which possess antimutagenic activity has been achieved (Scheme 3).<sup>20</sup> The homoallylic alcohol (26) served as a latent diene in a Diels-Alder reaction with ethyl acrylate to give a diastereomeric mixture of adducts which upon base equilibration and hydrolysis provided the *trans*-acid (27). Modified Curtius reaction on (27) afforded the corresponding isocyanate which was cyclized to the lactam (28) in 89% yield by a new method using boron trifluoride etherate. Compound (28) was converted into an *N*-acetyl derivative which upon basic hydrolysis gave the acid (29). Treatment of (29) with NBS followed by reflux in pyridine solution gave the lactone

<sup>20</sup> S. Ohta, and S. Kimoto, *Tetrahedron Letters*, 1975, 2279.

(30); the NBS reaction represents an anchimerically assisted solvolysis of the initially formed bromonium ion by the carboxylic acid function. The lactam ring was reconstituted by treatment of (30) with aqueous sodium hydroxide to give compound (31). The allylic alcohol function of (31) was protected as its tetrahydropyranyl ether and the resulting product was successively epoxidized and subjected to the Sharpless procedure [*cf.* (21)  $\rightarrow$  (23) and (23)  $\rightarrow$  (24), Scheme 2] to give, after acylation and hydrolysis, the diol monoacetate (32). Osmium tetroxide treatment followed by reaction under standard conditions for acetonide formation gave compound (33) which by unexceptional steps led to ( $\pm$ )-lycoricidine (34).

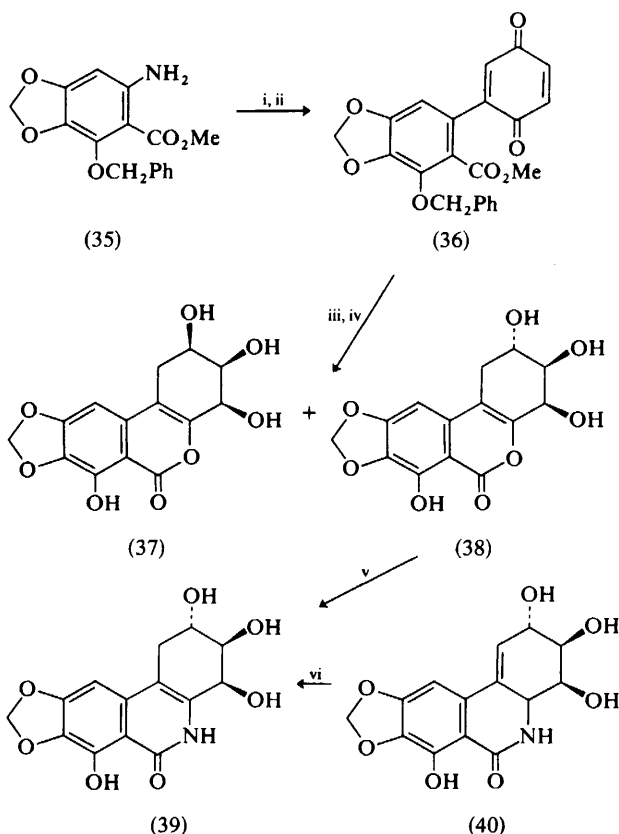


Reagents: i,  $\text{CH}_2=\text{CHCO}_2\text{Et}$ ,  $80^\circ\text{C}$ ; ii,  $\text{NaOEt-EtOH}$ ; iii,  $\text{OH}^-$ ; iv,  $\text{ClCO}_2\text{Et-Et}_3\text{N}$ ,  $\text{Me}_2\text{CO-H}_2\text{O}$ ; v,  $\text{NaN}_3$ ; vi,  $\text{PhMe}$ , heat; vii,  $\text{BF}_3\cdot\text{Et}_2\text{O}$ , room temp.; viii,  $\text{Ac}_2\text{O-py}$ ; ix,  $\text{KOH-MeOH-H}_2\text{O}$ ; x,  $\text{NBS-THF}$ ; xi,  $\text{py}$ , heat; xii,  $\text{NaOH-H}_2\text{O}$ ,  $90^\circ\text{C}$ ; xiii,  $\text{TsOH-dihydropyran-CHCl}_3$ ; xiv,  $m\text{-ClC}_6\text{H}_4\text{CO}_3\text{H}$ ; xv,  $(\text{PhSe})_2\text{-NaBH}_4$ ; xvi,  $\text{H}_2\text{O}_2$ ; xvii,  $\text{Ac}_2\text{O}$ ; xviii,  $\text{TsOH}$ ; xix,  $\text{OsO}_4\text{-py}$ ; xx,  $\text{Me}_2\text{C(OMe)}_2\text{-DMF-TsOH}$ ; xxi,  $\text{SOCl}_2\text{-py}$ ,  $0^\circ\text{C}$ ; xxii,  $\text{TsOH}$ ,  $\text{H}_2\text{O-MeOH-CHCl}_3$ ; xxiii,  $\text{NH}_3\text{-MeOH}$ , room temp.

**Scheme 3**

A strategically different successful synthesis of the related alkaloids isolycoricidine [*cf.* (34; C-1a—C-4a double bond)] and and isonarclasin (39) has been described (Scheme 4).<sup>21</sup> Coupling of the diazotized anthranilate (35) with *p*-benzoquinone

<sup>21</sup> K. Krohn and A. Mondon, *Chem. Ber.*, 1976, **109**, 855.



Reagents: i,  $\text{NaNO}_2\text{-HCl}$ ; ii,  $p$ -benzoquinone- $\text{NaHCO}_3\text{-H}_2\text{O}$ ; iii,  $\text{OsO}_4\text{-NaClO}_4\text{-THF}$ ; iv,  $\text{H}_2\text{-Pd/C-MeOH}$ ; v,  $\text{NH}_3\text{-MeOH}$ ; vi,  $\text{H}_2\text{-Pd/CaCo}_3\text{-EtOH}$ .

**Scheme 4**

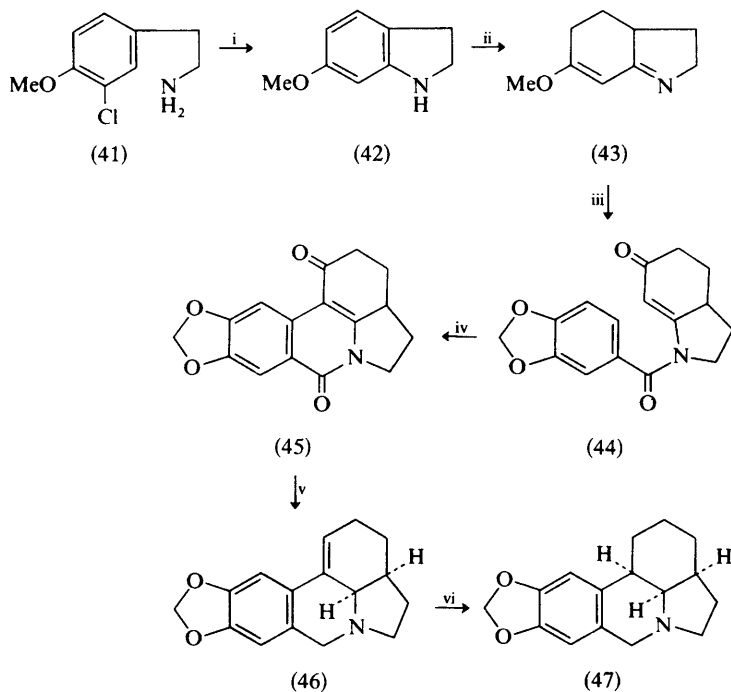
gave the arylated quinone (36) which upon hydroxylation followed by catalytic hydrogenation until hydrogen uptake ceased gave the all-*cis*-triol lactone (37) as the major product together with minor amounts of the epimeric (38) and a ring A aromatized derivative. Compound (38), isolated as its tetra-acetate, was treated with ammonia to give ( $\pm$ )-isonarciclasine (39) whose i.r. spectrum was shown to be identical with that of authentic material. Isonarciclasine has been previously obtained as a by-product from the catalytic hydrogenation of narciclapine (40).<sup>22</sup> Related reactions of the latter alkaloid are also described in this report.<sup>22</sup>

An interesting synthesis of the lycorine-type alkaloids (46) and (47) using the photocyclization of an enamido-ketone (44) as the key step has been reported (Scheme 5).<sup>23,24</sup> Benzyne reaction of the phenethylamine (41) provided the indoline

<sup>22</sup> A. Mondon and K. Krohn, *Chem. Ber.*, 1975, **108**, 445.

<sup>23</sup> H. Iida, S. Aoyagi, and C. Kibayashi, *J.C.S. Chem. Comm.*, 1974, 499.

<sup>24</sup> H. Iida, S. Aoyagi, and C. Kibayashi, *J.C.S., Perkin I*, 1975, 2502.



Reagents: i,  $\text{PhLi-Et}_2\text{NH-Et}_2\text{O}$ ; ii,  $\text{Li-liq. NH}_3\text{-MeOH-THF}$ ; iii,  $3,4\text{-(OCH}_2\text{O)C}_6\text{H}_3\text{COCl-NaOH}$ ; iv,  $h\nu$ , THF; v,  $\text{LiAlH}_4\text{-THF}$ ; vi,  $\text{H}_2\text{-PtO}_2\text{-HOAc}$ .

**Scheme 5**

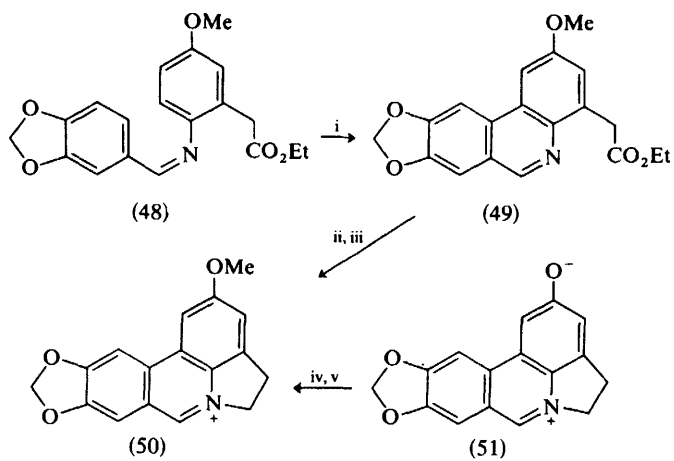
(42) which upon Birch reduction gave the imino-enol ether (43) whose structure was assigned by  $^{13}\text{C}$  n.m.r. spectroscopy. Schotten-Baumann acylation of (43) led to the enamido-ketone (44) which, upon irradiation, gave regioselectively the cyclized product (45) in 70% yield. The photoproduct (45) was reduced by metal hydride to ( $\pm$ )- $\alpha$ -anhydrodihydrocaranine (46), which in turn was catalytically reduced to give  $\gamma$ -lycorane (47).

A photochemical ring construction similar to that described in Scheme 5 was used in the synthesis of the aromatic lycorine alkaloid ungeremine (51) (Scheme 6).<sup>25</sup> Photocyclization of the somewhat inaccessible imine (48) gave the phenanthridine derivative (49) in 21% yield which upon metal hydride reduction and cyclization with phosphorus tribromide afforded the quaternary salt (50) which was shown to be identical with the methyl ether of ungeremine (51) obtained as shown.

Pretazettine (4), in combination with alkylating and DNA-binding agents, has been shown to have an increased beneficial effect in the treatment of certain malignant tumours.<sup>26</sup>

<sup>25</sup> T. Onaka, Y. Kanda, and M. Natsume, *Tetrahedron Letters*, 1974, 1179.

<sup>26</sup> E. Furusawa, N. Suzuki, S. Furusawa, and J. Y. B. Lee, *Proc. Soc. Exp. Biol. Med.*, 1975, **149**, 771.

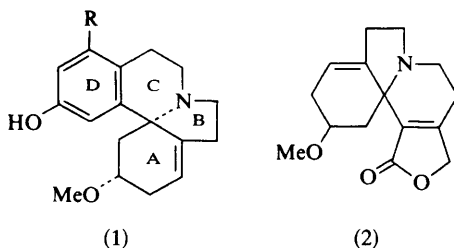


Reagents: i,  $h\nu$ ,  $\text{Et}_2\text{O}-\text{O}_2$ ; ii,  $\text{LiAlH}_4$ ; iii,  $\text{PBr}_3$ ; iv,  $\text{TsOMe}-\text{K}_2\text{CO}_3$ ; v, Amberlite IRA-400 ( $\text{Br}^-$  form).

**Scheme 6**

A comprehensive review concerning the synthesis of the *Cephalotaxus* alkaloids has appeared.<sup>1</sup> Another review incorporates this subject in the context of the synthesis of alkaloids which embody in part a benzazepine framework.<sup>2</sup>

The known alkaloid cocculine (1; R = H) has been isolated from two new sources, *Cocculus carolinus*<sup>3</sup> and *C. trilobus*.<sup>4</sup> *C. carolinus* also yielded cocculolidine (2) while *C. trilobus* was shown to elaborate the new base coccutrine (1; R = OMe). The structure and stereochemistry of cocculine and of coccutrine were established by X-ray crystallographic analysis.<sup>4</sup> Russian workers have advanced the absolute configuration for cocculine enantiomeric with that described by structure (1) on the



basis of an X-ray crystal structure determination of cocculine hydrobromide.<sup>5</sup> It has been pointed out<sup>4</sup> that this assignment is ambiguously represented and does not conform with the previously defined absolute stereochemistry for *Erythrina* alkaloids.

Three reports describing exhaustive chemotaxonomic and chemical investigations of a large number of *Erythrina* species have appeared.<sup>6-8</sup> In the first study,<sup>6</sup> the seeds of 78 of the 107 known species were examined by paper chromatography and electrophoresis for alkaloid content. Interestingly, sections *Breviflorae* and *Edules*

<sup>1</sup> S. M. Weinreb and M. F. Semmelhack, *Accounts Chem. Res.*, 1975, **8**, 158.

<sup>2</sup> T. Kametani and K. Fukumoto, *Heterocycles*, 1975, **3**, 931.

<sup>3</sup> M. A. Elsohly, J. E. Knapp, P. L. Schiff, jun., and D. J. Slatkin, *J. Pharm. Sci.*, 1976, **65**, 132.

<sup>4</sup> A. T. McPhail, K. D. Onan, H. Furukawa, and M. Juichi, *Tetrahedron Letters*, 1976, 485.

<sup>5</sup> A. N. Checklov, Yu. T. Struchkov, and A. I. Kitaigorodskii, *Doklady Akad. Nauk S.S.S.R.*, 1974, **215**, 1394; S. M. Nasirov, V. G. Andrianov, Yu. T. Struchkov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, 395.

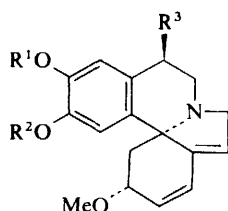
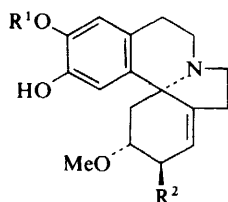
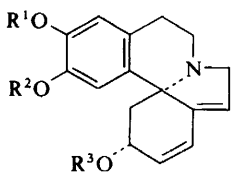
<sup>6</sup> T. Romeo and E. A. Bell, *Lloydia*, 1974, **37**, 543.

<sup>7</sup> R. T. Hargreaves, R. D. Johnson, D. S. Millington, M. H. Mondal, W. Beavers, L. Becker, C. Young, and K. L. Rinehart, jun., *Lloydia*, 1974, **37**, 569.

<sup>8</sup> D. E. Games, A. H. Jackson, N. A. Khan, and D. S. Millington, *Lloydia*, 1974, **37**, 581.



(of subgenus *Erythrina*) have the highest concentration of amino-acids and a corresponding deficiency in alkaloids. *E. edulis*, whose seeds are eaten in Colombia, is devoid of *Erythrina*-type alkaloids. Both  $\alpha$ - and  $\beta$ -erythroidine were shown to be useful chemotaxonomic indicators. In the second paper<sup>7</sup> of this series, 22 American species were analysed by the very powerful g.c.-m.s. technique and the following new alkaloids were isolated: erythravine (3), erysoline (4), erysosalvine (5), erysosalvinone (6), and erysoflorinone (7). Erythravine was found only in *E. folkersii* and *E. steyermarkii*. The only species to yield C-2 ketonic alkaloids, e.g. (6) and (7), was shown to be *E. salviiflora*. In the final report<sup>8</sup> of this series, 18 African, Asian, Polynesian, and Australian species were examined similarly. In agreement with observations made on the American species, erysodine (8) and erysovine (9) were found to be the most abundant alkaloids, and present in all species which were examined. Contrary to the results on plants of American habitat, however, was the presence of 11-oxygenated alkaloids. For example, *E. lysistemon* was shown to elaborate 11-hydroxyerysodine (10) and 11-hydroxyerysovine (11).



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

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

(5)  $R^1 = \text{Me}$ ,  $R^2 = \text{OH}$

(6)  $R^1 = \text{Me}$ ,  $R^2 = \text{=O}$

(7)  $R^1 = \text{H}$ ,  $R^2 = \text{=O}$

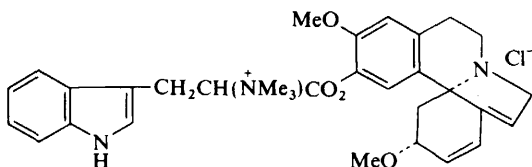
(8)  $R^1 = R^3 = \text{H}$ ,  $R^2 = \text{Me}$

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

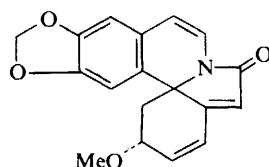
(10)  $R^1 = \text{H}$ ,  $R^2 = \text{Me}$ ,  $R^3 = \text{OH}$

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

Erysophorine (12), an unusual alkaloid obviously of mixed biogenesis, has been isolated from *E. arborescens*.<sup>9</sup> As well as five known bases, *E. crastagalli* has been shown to contain the ring C unsaturated alkaloid crastamine (13).<sup>10</sup> *E. glauca*, *E. poeppigiana*, and *E. variegata* from Singapore have been shown to elaborate a number of known alkaloids.<sup>11</sup>



(12)



(13)

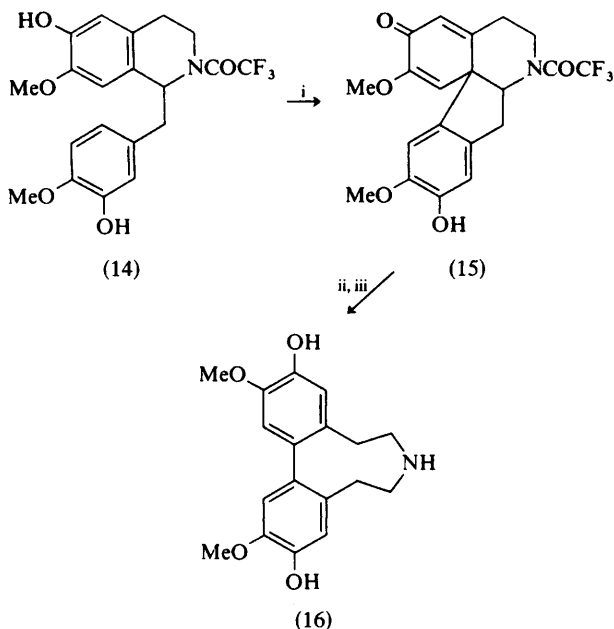
Synthetic work in the *Erythrina* alkaloid area continues unabated. The dibenzazocine (16), a key biosynthetic intermediate, has been neatly prepared (Scheme 1).<sup>12</sup> The readily accessible benzylisoquinoline (14) was subjected to phenol oxida-

<sup>9</sup> S. Ghosal and R. S. Srivastava, *Phytochemistry*, 1974, **13**, 2603.

<sup>10</sup> K. Ito, M. Haruna, Y. Jinno, and H. Furukawa, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 52.

<sup>11</sup> K. Ito, M. Haruna, and H. Furukawa, *Yakugaku Zasshi*, 1975, **95**, 358.

<sup>12</sup> S. Kupchan, C.-K. Kim, and J. T. Lynn, *J.C.S. Chem. Comm.*, 1976, 86.



Reagents: i,  $\text{VOF}_3\text{-CH}_2\text{Cl}_2$ ; ii, 1N-NaOH-anhydrous MeOH, room temp.; iii,  $\text{NaBH}_4$ .

**Scheme 1**

tive coupling conditions using  $\text{VOF}_3$  to give the dienone (15) in 40% yield. Successive base-catalysed hydrolysis and hydride reduction afforded compound (16). Phenol oxidative coupling also plays a key role in the reported synthesis of a homoerythrina-type compound (20) (Scheme 2).<sup>13</sup> The dienone (17), available by  $\text{VOCl}_3$ -promoted coupling of the corresponding phenethylisoquinoline derivative, was subjected to base-catalysed fragmentation followed by borohydride reduction to give the amine (18) in 76% overall yield. Whereas oxidation of the trifluoroacetyl derivative of (18) led to undesired reactions, direct oxidation of the free amine (18) gave clearly the dienone (19) in 45% yield together with compound (20) in 15% yield. The homoerysodianone (20) represents a skeleton presently unknown in Nature. An improvement in yield in the oxidation  $(18) \rightarrow (19)$  using modified conditions has been reported by a different group of workers.<sup>14</sup> This group also obtained the lactam corresponding to (20) by oxidation of the appropriate amide precursor.<sup>15</sup>

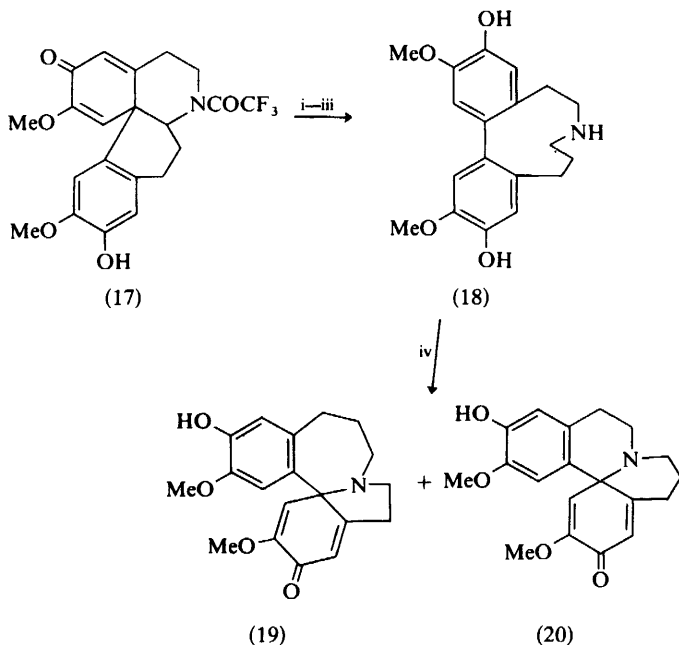
A new approach to the *Erythrina* skeleton involves Birch reduction of the readily available amide (21) and two successive cyclizations,  $(22) \rightarrow (23)$  and  $(23) \rightarrow (24)$  (Scheme 3).<sup>16</sup> Compound (24) was correlated with several known alkaloids and degradation products. A similar acid-catalysed cyclization of the enamido-ketone

<sup>13</sup> J. P. Marino and J. M. Samanen, *J. Org. Chem.*, 1976, **41**, 179.

<sup>14</sup> E. McDonald and A. Suksamrarn, *Tetrahedron Letters*, 1975, 4425.

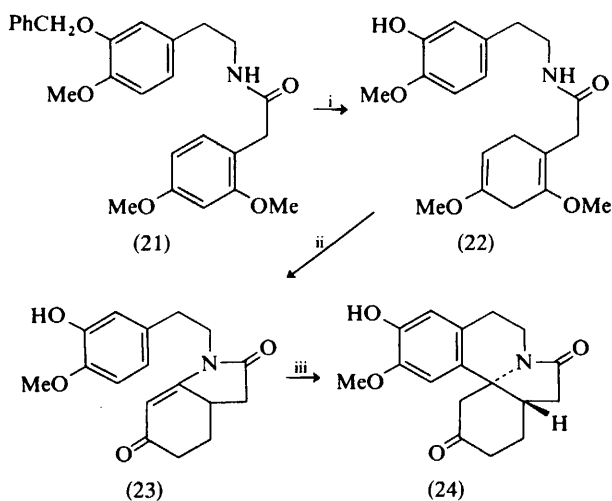
<sup>15</sup> E. McDonald and A. Suksamrarn, *Tetrahedron Letters*, 1973, 4421.

<sup>16</sup> K. Ito, M. Haruna, and H. Furukawa, *J.C.S. Chem. Comm.*, 1975, 681.



Reagents: i, 1N-NaOH-MeOH; ii, HCl-EtOH; iii, NaBH<sub>4</sub>-EtOH; iv, K<sub>3</sub>Fe(CN)<sub>6</sub>-NaHCO<sub>3</sub>, H<sub>2</sub>O-CH<sub>2</sub>Cl<sub>2</sub>.

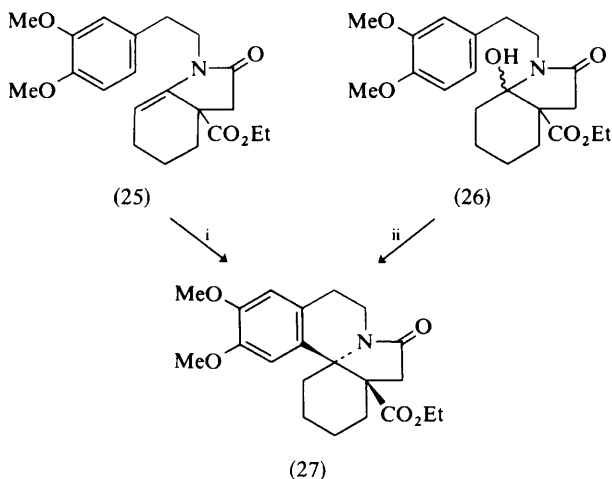
Scheme 2



Reagents: i, Na-liq. NH<sub>3</sub>-MeOH; ii, 10% H<sub>2</sub>SO<sub>4</sub>-DMF; iii, 98% HCO<sub>2</sub>H, 16 h.

Scheme 3

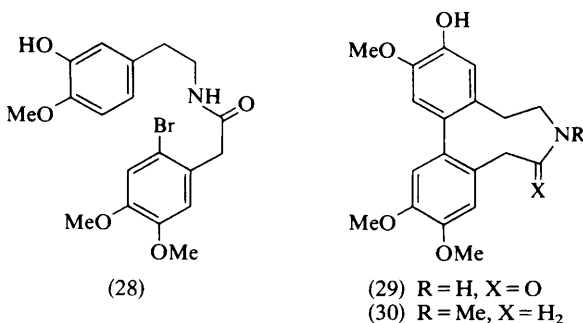
(25) or of the carbinolamine (26) produced the erythrinanone (27), whose structure and stereochemistry were confirmed by an X-ray crystallographic analysis (Scheme 4).<sup>17</sup>



Reagents: i,  $\text{H}_3\text{PO}_4$ , warm; ii,  $\text{HCl}$ -dioxan- $\text{H}_2\text{O}$ , warm.

**Scheme 4**

Erybidine (30) has been prepared by a photochemical route.<sup>18</sup> Irradiation of (28) in basic solution gave in low yields the lactam (29), in addition to an isomeric lactam and the debrominated product corresponding to (29). Sodium borohydride reduction in the presence of boron trifluoride followed by reductive methylation afforded compound (30). Reductive cleavage of the methylenedioxy function of a number of



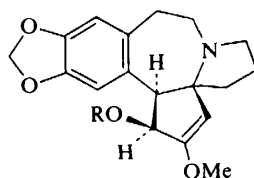
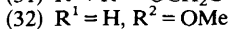
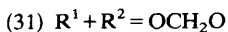
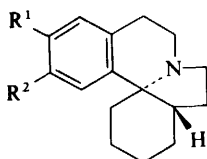
*Erythrina* alkaloids has been examined.<sup>19</sup> For example, treatment of (31) with sodium in liquid ammonia produced the isomeric phenols (32) and (33).

Work which culminated in two total syntheses of cephalotaxine (34; R = H), the major antitumour alkaloid of several species of *Cephalotaxus* (plum-yews), and

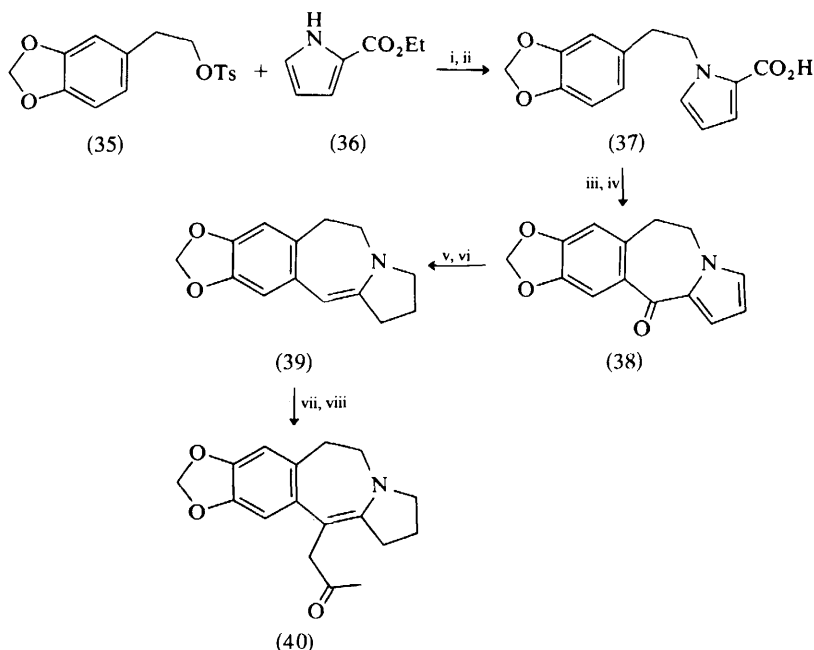
<sup>17</sup> H. J. Wilkens and F. Troxler, *Helv. Chim. Acta*, 1975, **58**, 1512.

<sup>18</sup> K. Ito and H. Tanaka, *Chem. and Pharm. Bull. (Japan)*, 1974, **22**, 2108.

<sup>19</sup> K. Ito, H. Furukawa, M. Haruna, Y. Jinno, and M. Yuasa, *Yakugaku Zasshi*, 1975, **95**, 170.



which has been previously (see Vol. 4 of these reports) and currently<sup>1</sup> reviewed, has been published in detail.<sup>20,21</sup> A synthetic approach which parallels one of these<sup>20</sup> and leads to the enamino-ketone (40) has also appeared (Scheme 5).<sup>22</sup> After several



Reagents: i, NaH-diglyme,  $\text{N}_2$ , 3 days,  $70^\circ\text{C}$ ; ii, 2N-KOH-EtOH, heat; iii,  $(\text{CF}_3\text{CO})_2\text{O}-\text{CH}_2\text{Cl}_2$ ; iv,  $\text{SnCl}_4$ ,  $0^\circ\text{C}$ ; v,  $\text{H}_2$ -Rh/C-EtOH- $\text{HClO}_4$ ; vi,  $\text{Hg}(\text{OAc})_2$ ; vii,  $\text{HC}\equiv\text{CCH}_2\text{Br}$ ; viii,  $\text{Hg}^{2+}$ .

**Scheme 5**

unsuccessful but interesting trials, the tosylate (35) was condensed with 2-ethoxycarbonylpyrrole (36) and the resulting product was hydrolysed to give compound (37). Friedel-Crafts cyclization of (37) gave the pyrrolo[2,1-*b*]-

<sup>20</sup> S. M. Weinreb and J. Auerbach, *J. Amer. Chem. Soc.*, 1975, **97**, 2503.

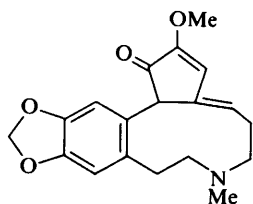
<sup>21</sup> M. F. Semmelhack, B. P. Chong, R. D. Stauffer, T. D. Rogerson, A. Chong, and D. Jones, *J. Amer. Chem. Soc.*, 1975, **97**, 2507.

<sup>22</sup> B. Weinstein and A. R. Craig, *J. Org. Chem.*, 1976, **41**, 875.

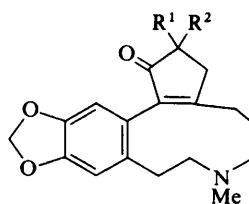
[3]benzazepine derivative (38). Successive catalytic reduction and oxidation with mercuric acetate gave the enamine (39), which had previously served as a key intermediate in the synthesis of cephalotaxine (34; R = H).<sup>20</sup> Alkylation of (39) with propargyl bromide followed by mercury(II)-catalysed hydration apparently gave the enamino-ketone (40) (no experimental conditions are given) which, consistent with the work of Weinreb<sup>20</sup> but contrary to that of Dolby,<sup>23</sup> failed to undergo acid-catalysed cyclization to cyclopentanone-containing products.

Interest has been expressed by the People's Republic of China in the preparation of cephalotaxine ester alkaloids and analogues, no doubt for the purpose of evaluation of antitumour activity.<sup>24,25</sup> Thus a number of esters, *e.g.* (34), (R = Me<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>COCO or PhCOCO), were subjected to Reformatsky reaction with methyl bromoacetate to give, *e.g.*, [34; R = Me<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>C(OH)-(CH<sub>2</sub>CO<sub>2</sub>Me)CO] (deoxyharringtonine) and [34; R = PhC(OH)(CH<sub>2</sub>CO<sub>2</sub>Me)CO].

Two interesting reactions of cephalotaxine (34; R = H) have been discovered during the development of degradative methodology related to biosynthetic experiments.<sup>26</sup> Oppenauer oxidation of cephalotaxine gave the seco-diene (41), which, upon treatment with sodium methoxide, led to the dimethoxyenone (42) in which methanol addition had occurred in an unexpected direction. Similarly, the methoxyenone (43), obtained as a minor product in the Emde degradation of the methiodide of cephalotaxine, underwent anomalous addition of lithium dimethylcuprate to give compound (44). The formation of (42) and (44) requires that



(41)



(42) R<sup>1</sup> = R<sup>2</sup> = OMe  
 (43) R<sup>1</sup> = OMe, R<sup>2</sup> = H  
 (44) R<sup>1</sup> = Me, R<sup>2</sup> = H

nucleophilic addition by methoxide and dimethylcuprate occurs in a 1,6-mode on the cyclopentadienones resulting from base-catalysed isomerization of (41) and methanol loss from (43) respectively. Such addition is predicted by calculations.

<sup>23</sup> L. J. Dolby, S. J. Nelson, and D. Senkovich, *J. Org. Chem.*, 1972, **37**, 3691.

<sup>24</sup> Cancer Chemotherapeutic Agents Research Group, *K'o Hsueh T'ung Pao*, 1975, **20**, 437.

<sup>25</sup> S.-W. Li and J.-Y. Dai, *Hua Hsueh Hsueh Pao*, 1975, **33**, 75.

<sup>26</sup> J. M. Schwab, R. J. Parry, and B. M. Foxman, *J.C.S. Chem. Comm.*, 1975, 906.

## 1 Introduction

The latest volume in the Manske series contains a chapter<sup>1a</sup> on the ergot alkaloids, which surveys this group up to (approximately) the end of 1973. An excellent, comprehensive review by Floss,<sup>1b</sup> ostensibly devoted to the biosynthesis of the ergot alkaloids and related compounds, nevertheless contains a considerable amount of ancillary material concerning the occurrence, structure, chemistry, and pharmacology of the ergot alkaloids and other isoprenoid indolic metabolites of fungi and higher plants. A book devoted to the botany, chemistry, pharmacology and clinical use of the *Catharanthus* alkaloids<sup>2</sup> is a companion volume to one already published on the *Vinca* alkaloids. Other recently published reviews include one on the indole alkaloids of Japanese plants (principally those investigated by Sakai's group),<sup>3</sup> and a survey of natural product chemistry from 1950 by Djerassi,<sup>4</sup> which naturally contains a substantial amount of indole alkaloid chemistry. In another lecture presented at the same Symposium Harley-Mason<sup>5</sup> describes his own contributions in the area of *Strychnos* alkaloid synthesis. Accounts of yohimbine synthesis by the Budapest group,<sup>6</sup> and approaches to camptothecin,<sup>7</sup> are also available. Two reviews are concerned with curare alkaloids,<sup>8,9</sup> emphasis in the latter review being given to their pharmacology and curarising activity. A chapter in the same volume with similar emphasis on pharmacology is devoted to reserpine.<sup>10</sup> Other review articles include one on the pharmaceutical chemistry of reserpine,<sup>11</sup> one on the pharmacology of the *Vinca* alkaloids,<sup>12</sup> and one on selected potential anticancer plant principles,<sup>13</sup> which contains a substantial section on the *Catharanthus* alkaloids.

<sup>1</sup> (a) P. A. Stadler and P. Stütz, in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1975, Vol. XV, Chapter 1, pp. 1—40, (b) H. G. Floss, *Tetrahedron*, 1976, **32**, 873.

<sup>2</sup> The *Catharanthus* Alkaloids, ed. W. I. Taylor and N. R. Farnsworth, Dekker, New York, 1975.

<sup>3</sup> S. Sakai, *Heterocycles*, 1976, **4**, 131.

<sup>4</sup> C. Djerassi, *Pure Appl. Chem.*, 1975, **41**, 113.

<sup>5</sup> J. Harley-Mason, *Pure Appl. Chem.*, 1975, **41**, 167.

<sup>6</sup> L. Töke and Cs. Szántay, *Heterocycles*, 1976, **4**, 251.

<sup>7</sup> E. Winterfeldt, in 'Recent Developments in the Chemistry of Natural Carbon Compounds', ed. R. Bognar, V. Bruckner, and Cs. Szántay, Akadémiai Kiadó, Budapest, 1975, Chapter 1, pp. 11—34.

<sup>8</sup> G. B. Marini-Bettolo, *Comment., Pontif. Acad. Sci.*, 1975, **2**, 25.

<sup>9</sup> J. del Castillo and M. Anderson in 'Neuropoisons: Their Pathophysiological Actions. Vol. 2, Poisons of Plant Origin', ed. L. L. Simpson and D. R. Curtis, Plenum Press, New York, 1974, Chapter 3, pp. 99—156.

<sup>10</sup> T. A. Slotkin, in ref. 9, Chapter 1, pp. 1—60.

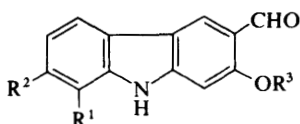
<sup>11</sup> R. E. Schirmer, *Anal. Profiles Drug Subst.*, 1975, **4**, 384.

<sup>12</sup> W. A. Creasey, *Handb. Exp. Pharmacol.*, 1975, **38**, 670 (*Chem. Abs.*, 1975, **83**, 188 096).

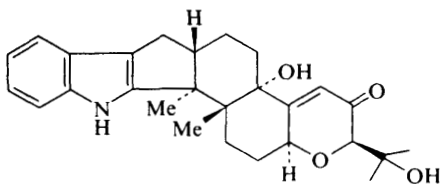
<sup>13</sup> G. A. Cordell and N. R. Farnsworth, *Heterocycles*, 1976, **4**, 393.

## 2 Simple Alkaloids

**Non-tryptamines.**—Details of the structure elucidation of seven pyranocarbazole alkaloids of *Murraya koenigii* [mahanimbine, koenimbine, (–)-mahanine, koenine, koenigine, koenidine, and (+)-isomahanimbine] have now been published.<sup>14</sup> Murrayacine, a minor alkaloid of the same plant, has been isolated<sup>15</sup> from the roots of *Clausena heptaphylla*. The stems of another *Clausena* species, *C. anisata* Willd., contain atanisatin (1), and the roots contain a second new alkaloid, clausanitin (2).<sup>16</sup>

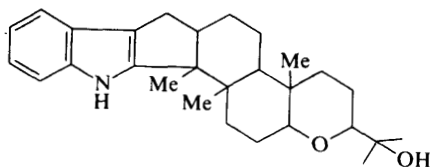


Atanisatin (1)  $R^1 = \text{Me}_2\text{C}=\text{CH} \cdot \text{CH}_2-$   
 $R^2 = \text{H}, R^3 = \text{Me}$

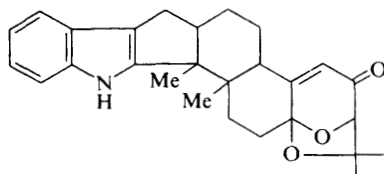


Paxilline (3)

Clausanitin (2)  $R^1 = \text{H}, R^2 = \text{Me}_2\text{C}=\text{CH} \cdot \text{CH}_2-$   
 $R^3 = \text{H}$



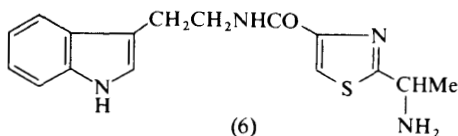
Paspaline (4)



Paspalicine (5)

Paxilline,<sup>17</sup> the tremorgenic metabolite of *Penicillium paxilli* Bainier, proves<sup>18</sup> to have the structure (3), and is almost certainly diterpenoid in origin. That this is so is rendered even more likely by the isolation of the closely related metabolites, paspaline (4) and paspalicine (5),<sup>19</sup> from *Claviceps paspali*; the former of these has an indole residue attached to a regular diterpenoid unit, from which one of the angular methyl groups is missing in paxilline and paspalicine. Although paxilline produces severe tremors in mice it is not highly toxic, in contrast to the other reported tremorgenic metabolites.<sup>18</sup>

**Non-isoprenoid Tryptamines.**—The tryptamide (6) of an aminoethylthiazole carboxylic acid has been isolated<sup>20</sup> from a *Thermoactinomyces* species (strain TM-64).



(6)

<sup>14</sup> N. S. Narasimhan, M. V. Paradkar, V. P. Chitguppi, and S. L. Kelkar, *Indian J. Chem.*, 1975, **13**, 993.

<sup>15</sup> S. Ray and D. P. Chakraborty, *Phytochemistry*, 1976, **15**, 356.

<sup>16</sup> D. O. Okorie, *Phytochemistry*, 1975, **14**, 2720.

<sup>17</sup> R. J. Cole, J. W. Kirksey, and J. M. Wells, *Canad. J. Microbiol.*, 1974, **20**, 1159.

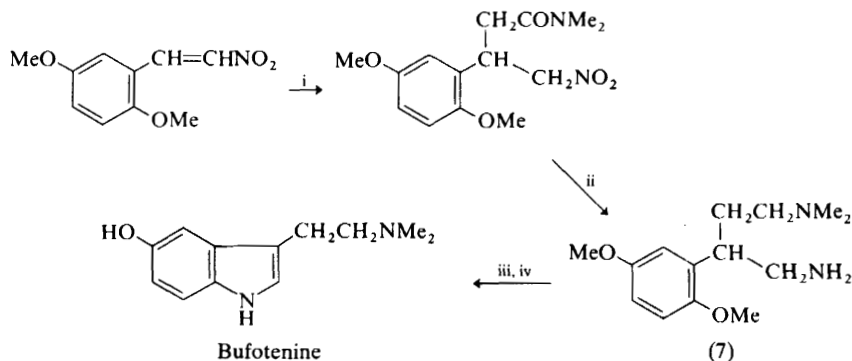
<sup>18</sup> J. P. Springer, J. Clardy, J. M. Wells, R. J. Cole, and J. W. Kirksey, *Tetrahedron Letters*, 1975, 2531.

<sup>19</sup> G. Stamm, R. Gysi, A. Leutwiler, W. Acklin, and D. Arigoni, private communication to authors of ref 18; A. Leutwiler, W. Acklin, and D. Arigoni, private communication to authors of ref. 18.

<sup>20</sup> Y. Konda, Y. Suzuki, S. Omura, and M. Onda, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 92.

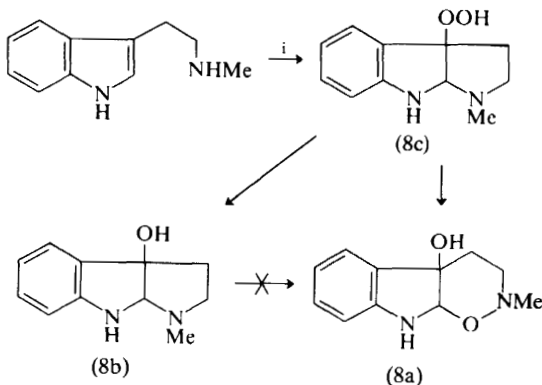


A new preparation<sup>21a</sup> of the diamine (7), by Michael addition of dimethylacetamide to 2,5-dimethoxy- $\omega$ -nitrostyrene followed by reduction of the adduct, constitutes a new synthesis of bufotenine (Scheme 1), since the amine (7) has already been converted<sup>21b</sup> into bufotenine.



Reagents: i, MeCONMe<sub>2</sub>, LiNPr<sub>2</sub><sup>1</sup>, THF, -78 °C; ii, LiAlH<sub>4</sub>-THF-dioxan; iii, HBr; iv, K<sub>3</sub>Fe(CN)<sub>6</sub>, NaHCO<sub>3</sub>, H<sub>2</sub>O.

**Scheme 1**



Reagent:  $h\nu/O_2$ -C<sub>6</sub>H<sub>6</sub>/MeOH-Rose Bengal.

**Scheme 2**

In connection with the synthesis of naturally occurring 3a-hydroxypyrroloindole derivatives, e.g. brevinamide E and sporidesmin A, it is of interest to note that the photosensitized oxidation of *N*<sub>1</sub>-methyltryptamine with singlet oxygen affords<sup>22</sup> the 4a-hydroxyoxazinoindole (8a) and the 3a-hydroxypyrroloindole (8b) via the 3a-hydroperoxy compound (8c) (Scheme 2).

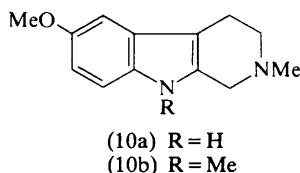
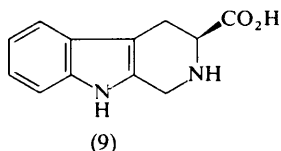
In the  $\beta$ -carboline series the tetrahydro- $\beta$ -carboline carboxylic acid (9) has been isolated<sup>23</sup> from the seeds of *Aleurites fordii* Hemsl. This is the first reported

<sup>21</sup> (a) D. Seebach, H. F. Leitz, and V. Ehrig, *Chem. Ber.*, 1975, **108**, 1924; D. Seebach, V. Ehrig, H. F. Leitz, and R. Henning, *ibid.*, p. 1946; (b) J. Harley-Mason and A. H. Jackson, *J. Chem. Soc.*, 1954, 1165.

<sup>22</sup> M. Nakagawa, K. Yoshikawa, and T. Hino, *J. Amer. Chem. Soc.*, 1975, **97**, 6496.

<sup>23</sup> T. Okuda, T. Yoshida, N. Shiota, and J. Nobuhara, *Phytochemistry*, 1975, **14**, 2304.

occurrence of this amino-acid in a natural source, although the possibility that it is an artifact does not seem to have been definitely excluded. Improved procedures for the isolation and quantitative analysis of the alkaloids of tall fescue (*Festuca arundinacea* Schreb.) and ryegrass (*Lolium perenne* L.) have been reported;<sup>24</sup> the indole alkaloids present are harman and  $\beta$ -carboline. Harman has also been reported to be present in the leaves of *Uncaria attenuata* ssp. *attenuata*, *U. orientalis*, and *U. canescens* ssp. *canescens*,<sup>25a</sup> in the roots of *Strychnos usambarensis*,<sup>25b</sup> and (a less conventional source) in several Georgian wines.<sup>26a</sup> Harmine and harmalol have been extracted<sup>26b</sup> from the stems of Saudi-Arabian samples of *Peganum harmala*. Three new bases isolated<sup>26c</sup> from the leaves and stems of Amazonian *Banisteriopsis caapi* were shown to be harmine *N*<sub>1</sub>-oxide, harmic acid methyl ester, and harmalinic acid. Among the tetrahydro- $\beta$ -carboline derivatives encountered recently are the 2-methyl derivative, which occurs in *Phalaris arundinacea* L. (reed canary grass), together with the 2-methyl-6-methoxy derivative (10a).<sup>27</sup> The 2,9-dimethyl-6-methoxytetrahydro- $\beta$ -carboline (10b) previously isolated<sup>28a</sup> from a variety of this same plant has now been acknowledged<sup>28b</sup> to be a mixture of (10a) and (10b).



A new synthesis<sup>29a</sup> of the eserine ring system (11) (Scheme 3) proceeds *via* a nitrophenylsuccinimide derivative, and is unique among existing syntheses in that ring B, and not ring C, is closed in the final stage.

Complete <sup>13</sup>C n.m.r. assignments for the alkaloids physostigmine, norphysostigmine, eseramine, and physovenine have been added<sup>29b</sup> to the rapidly growing list of available data.

The recently discovered antimicrobial activity of canthin-6-one (12) has provided the impetus for renewed synthetic studies. Of the new, efficient syntheses reported<sup>30</sup> one involves the direct formation of canthin-6-one by a Doebner reaction on  $\beta$ -carboline-1-carboxaldehyde, for which an improved preparation was developed; the overall yield of canthin-6-one from tryptophan is 15%. Alternatively, condensation of  $\beta$ -carboline-1-carboxaldehyde with malonic ester, followed by hydrolysis and decarboxylation of the product, affords canthin-6-one in 19% overall yield from

<sup>24</sup> L. P. Bush and J. A. D. Jeffreys, *J. Chromatog.*, 1975, **111**, 165.

<sup>25</sup> (a) J. D. Phillipson and S. R. Hemingway, *Phytochemistry*, 1975, **14**, 1855; (b) L. Angenot, M. Dubois, Ch. Ginion, W. van Dorsser, and A. Dresse, *Arch. intern. Pharmacodyn.*, 1975, **215**, 246; *Arch. intern. Physiol. Biochim.*, 1974, **82**, 823.

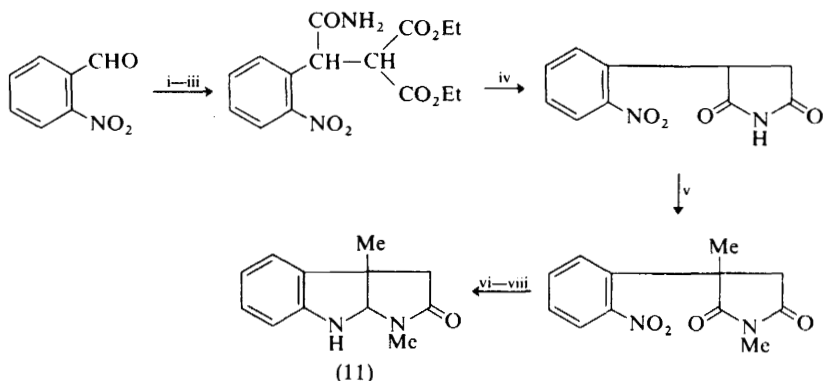
<sup>26</sup> (a) A. D. Lashki and L. A. Mudzhiri, *Vinodel. Vinograd. SSSR*, 1975, 53 (*Chem. Abs.*, 1975, **83**, 41 437); (b) F. J. Muhtadi, A. I. Jado, S. T. Ezmirly, M. M. A. Hassan, and O. A. Jawan, *Bull. Fac. Sci., Riyadh Univ.*, 1974, **6**, 59 (*Chem. Abs.* 1975, **83**, 144 535); (c) Y. Hashimoto and K. Kawanishi, *Phytochemistry*, 1975, **14**, 1633.

<sup>27</sup> J. E. Gander, P. Marum, G. C. Marten, and A. W. Hovin, *Phytochemistry*, 1976, **15**, 737.

<sup>28</sup> (a) R. C. S. Audette, H. M. Vijayanagar, J. Bolan, and K. W. Clark, *Canad. J. Chem.*, 1970, **48**, 149; (b) H. M. Vijayanagar, R. C. S. Audette, J. Bolan, and K. W. Clark, *Lloydia*, 1975, **38**, 442.

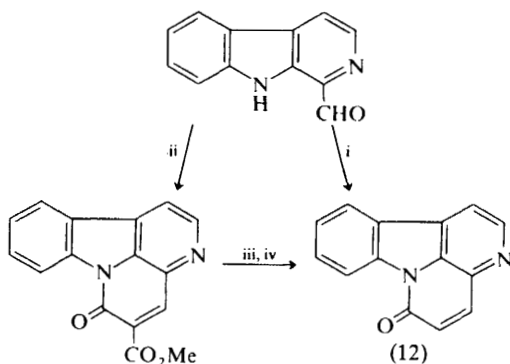
<sup>29</sup> (a) J. B. P. A. Wynberg and W. N. Speckamp, *Tetrahedron Letters*, 1975, 4035; (b) P. A. Crooks, B. Robinson, and O. Meth-Cohn, *Phytochemistry*, 1976, **15**, 1092.

<sup>30</sup> L. A. Mitscher, M. Shipchandler, H. D. H. Showalter, and M. S. Bathala, *Heterocycles*, 1975, **3**, 7.

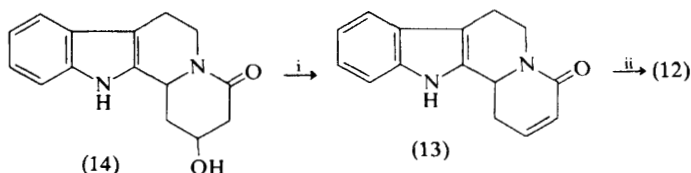
**Scheme 3**

Reagents: i,  $\text{CH}_2(\text{CO}_2\text{Et})_2\text{-TiCl}_4\text{-py}$ ; ii,  $\text{KCN-H}_2\text{O-EtOH-AcOH}$ ; iii, conc.  $\text{H}_2\text{SO}_4$ ,  $0^\circ\text{C}$ ; iv,  $\text{NaCl-DMSO}$ ,  $145^\circ\text{C}$ ; v,  $\text{MeI-K}_2\text{CO}_3\text{-DMF}$ ; vi,  $\text{NaBH}_4$ ; vii,  $\text{Pd/C-H}_2$ ; viii,  $\text{H}^+/\text{EtOH}$ , reflux.

tryptophan (Scheme 4).<sup>30</sup> Another new synthesis which, however, proceeds in low yield only, involves the unsaturated tetracyclic lactam (13), which is prepared by dehydration of the known hydroxylactam (14). Curiously, reaction of (13) with nitrous acid affords canthin-6-one, by a mechanism that is at present obscure (Scheme 5).<sup>31</sup>



Reagents: i,  $\text{CH}_2(\text{CO}_2\text{H})_2\text{-py}$ ; ii,  $\text{CH}_2(\text{CO}_2\text{Me})_2\text{-NEt}_3$ ; iii,  $2\text{N-HCl}$ ,  $100^\circ\text{C}$ , 2h.; iv,  $\text{Cu-py-N}_2$ ,  $80^\circ\text{C}$ .

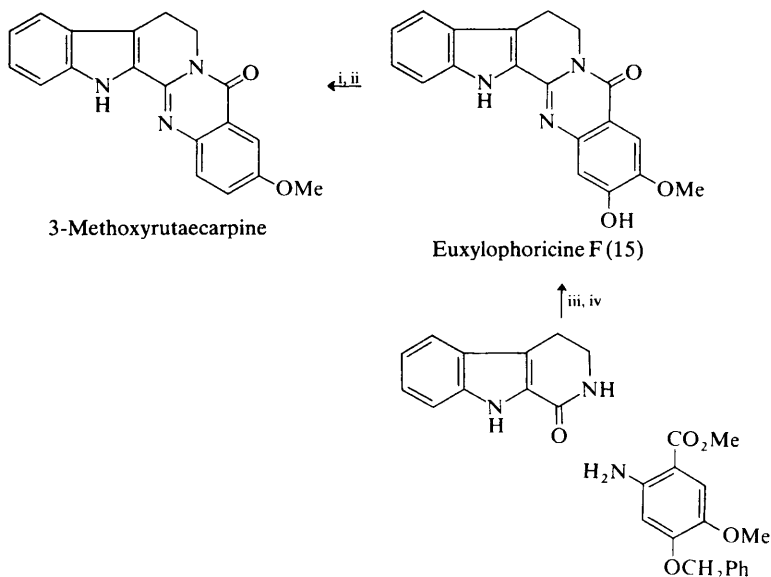
**Scheme 4**

Reagents: i,  $\text{P}_2\text{O}_5\text{-DMF}$ ; ii,  $\text{AcOH-NaNO}_2\text{-H}_2\text{O}$ .

**Scheme 5**

<sup>31</sup> R. Oehl, G. Lenzer, and P. Rosenmund, *Chem. Ber.*, 1976, **109**, 705.

Canthin-6-one occurs<sup>32</sup> in the root bark of *Zanthoxylum flavum* Willd. (*Fagara flava* Krug. et Urb.), together with 3, 14-dihydrorutaecarpine, which has been synthesized<sup>33</sup> by condensation of tryptamine with isoic anhydride, followed by cyclization. A related Ghanaian specis, *Z. dinklagei* Wat&rm. (*Fagara dinklagei* Engl.) also contains indoloquinazoline alkaloids, possibly hydroxy- and methoxy-derivatives of rutaecarpine, but these have not yet been definitely identified.<sup>34a</sup> A new alkaloid of this group which has been definitely identified is euxylophoricine F, a constituent of the yellow bark of *Euxylophora paraënsis* Hub.<sup>34b</sup> The structure of euxylophoricine F (15), deduced by the usual spectroscopic methods, was independently confirmed by correlation with 3-methoxyrutaecarpine, and by total synthesis (Scheme 6).



Reagents: i, PhNCO-NEt<sub>3</sub>-C<sub>6</sub>H<sub>6</sub>; ii, H<sub>2</sub>-Pd/C; iii, POCl<sub>3</sub>-C<sub>6</sub>H<sub>5</sub>Me; iv, H<sub>2</sub>-Pd/C-EtOAc.

**Scheme 6**

A new and very neat synthesis of evodiamine and rutaecarpine is described by the authors<sup>35</sup> as a 'retro mass spectral synthesis', since the original conception was derived from the mode of fragmentation of these alkaloids in the mass spectrometer; this involves a familiar retro Diels-Alder fission of ring C. Evodiamine (16a) was thus constructed by a  $2\pi + 4\pi$  cycloaddition of 3,4-dihydro- $\beta$ -carboline with the keteneimine (17), prepared *in situ* by elimination of sulphur dioxide from the sulphinamide anhydride (18) (Scheme 7). When the anthranilic acid derivative (19) was used the product was rutaecarpine (20) itself, the initially formed dihydro-

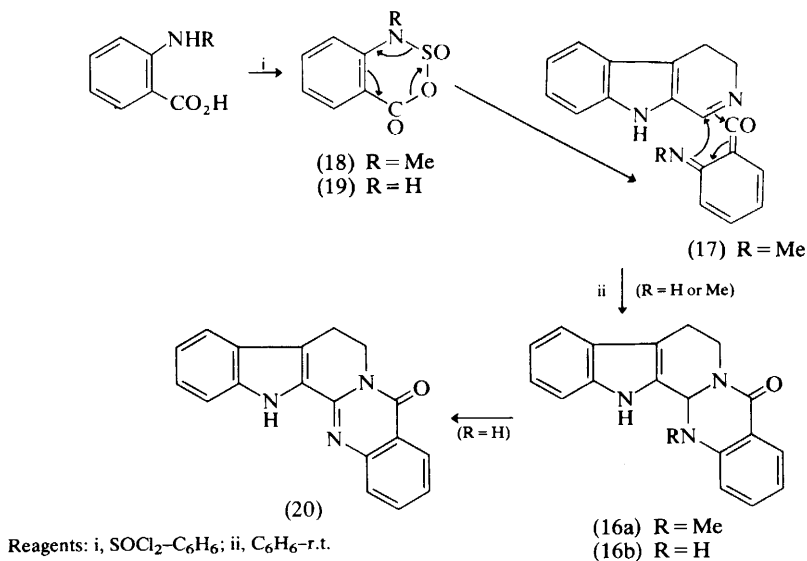
<sup>32</sup> P. G. Waterman, *Phytochemistry*, 1976, **15**, 578.

<sup>33</sup> K. Horvath-Dora and O. Clauder, *Acta Chim. Acad. Sci. Hung.*, 1975, **84**, 93 (*Chem. Abs.*, 1975, **82**, 171 273).

<sup>34</sup> (a) F. Fish, I. A. Meshal, and P. G. Waterman, *Phytochemistry*, 1975, **14**, 2094; (b) B. Danieli, C. Farachi, and G. Palmisano, *Phytochemistry*, 1976, **15**, 1095.

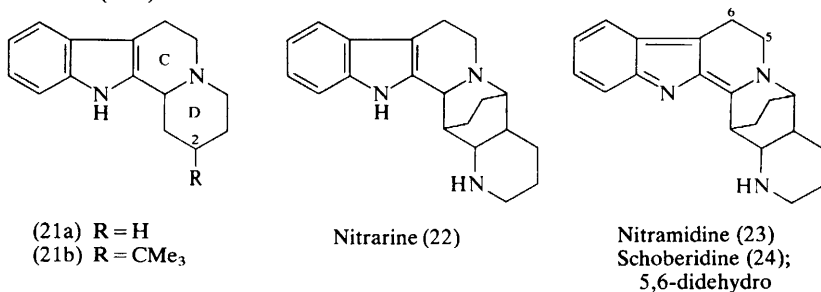
<sup>35</sup> T. Kametani, T. Higa, K. Fukumoto, and M. Koizumi, *Heterocycles*, 1976, **4**, 23.

rutaecarpine (16b) having suffered dehydrogenation under the conditions of the reaction (Scheme 7).



Scheme 7

The  $^{13}\text{C}$  n.m.r. spectrum of 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (21a) has been studied in some detail.<sup>36</sup> Complete assignments were made for (21a) and selectively deuteriated analogues, and the chemical shift differences between the *cis*- and *trans*-C/D isomers were observed with the aid of the 2-*t*-butyl derivatives (21b).



A group of alkaloids having a novel structure has been isolated from *Nitraria schoberi*. The structure of nitrarine (22) was determined by X-ray crystal structure analysis of its dihydrochloride.<sup>37</sup> Nitramidine (23) is a didehydro-derivative, and can be obtained from nitrarine by mercuric acetate oxidation,<sup>38</sup> and schoberidine (24) is

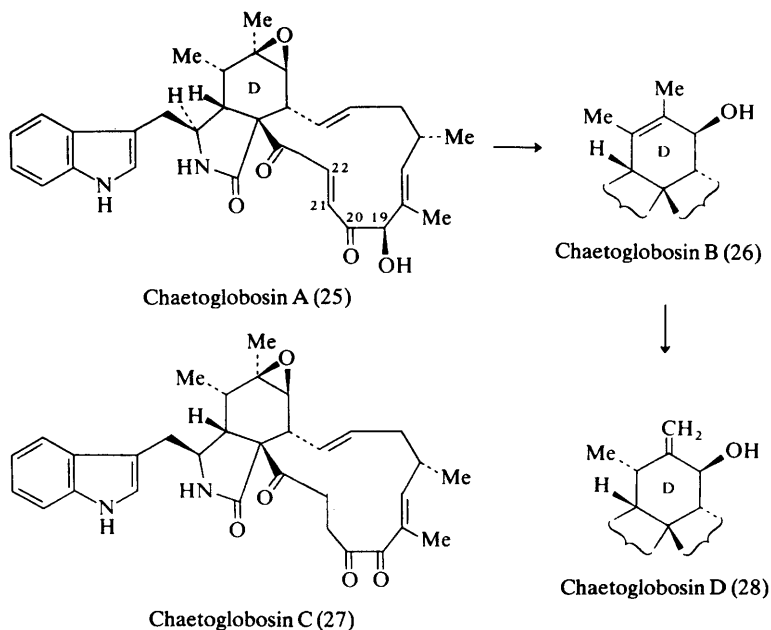
<sup>36</sup> G. W. Gribble, R. B. Nelson, J. L. Johnson, and G. C. Levy, *J. Org. Chem.*, 1975, **40**, 3720.

<sup>37</sup> A. A. Ibragimov, S. M. Nasirov, V. T. Andrianov, S. K. Maekh, Yu. T. Struchkov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, **11**, 273 (*Chem. Abs.*, 1975, **83**, 97673).

<sup>38</sup> A. A. Ibragimov, S. K. Maekh, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, **11**, 275 (*Chem. Abs.*, 1975, **83**, 97674, 97675).

a tetrahydro-derivative. Isonitrarine is the C-3 epimer of nitrarine, and a mixture of these two alkaloids is obtained by Zn-acid reduction of nitramidine; however, the detailed stereochemistry of these alkaloids has not been elucidated.<sup>39</sup>

The chaetoglobosins A-F are cytotoxic, tryptophan-polyacetate derived metabolites of *Chaetomium globosum* Kunz et Fries, belonging to the indol-3-yl-[13]cytochalasan group.<sup>40a,b</sup> The gross structures of chaetoglobosin A (25) and B (26), deduced earlier,<sup>40a</sup> have now been confirmed<sup>41</sup> by X-ray crystal structure analysis of chaetoglobosin A, and the relative stereochemistry implied in (25) has been added. The absolute stereochemistry of (25) and (26) is assumed at present to be the same as that deduced for cytochalasin D and E. Chaetoglobosin C has also been isolated from the fungus *Penicillium aurantio-virens* Biourge found on weevil-infested pecans. Its structure (27) has been similarly deduced<sup>42</sup> by the X-ray method, and also derived by chemical and spectroscopic methods.<sup>43</sup> The isomerization of chaetoglobosin A to chaetoglobosin C by triethylamine in pyridine is simply the result of an obvious series of keto-enol tautomerisms. Similarly the conversion of chaetoglobosin B to chaetoglobosin D (28) by base or the conversion of chaetogloblo-



<sup>39</sup> A. A. Ibragimov, S. K. Maekh, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, **11**, 276 (*Chem. Abs.*, 1976, **84**, 44507).

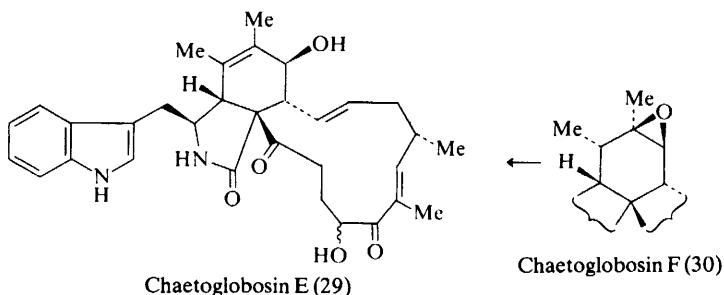
<sup>40</sup> (a) S. Sekita, K. Yoshihira, S. Natori, and H. Kuwano, *Tetrahedron Letters*, 1973, 2109; (b) M. Umeda, K. Ohtsubo, M. Saito, S. Sekita, K. Yoshihira, S. Natori, S. Udagawa, F. Sakabe, and H. Kurata, *Experientia*, 1975, **31**, 435.

<sup>41</sup> J. V. Silverton, T. Akiyama, C. Kabuto, S. Sekita, K. Yoshihira, and S. Natori, *Tetrahedron Letters*, 1976, 1349.

<sup>42</sup> J. P. Springer, J. Clardy, J. M. Wells, R. J. Cole, J. W. Kirksey, R. D. Macfarlane, and D. F. Torgerson, *Tetrahedron Letters*, 1976, 1355.

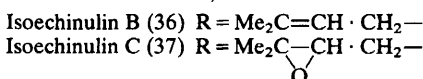
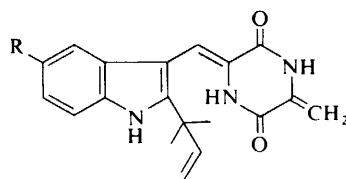
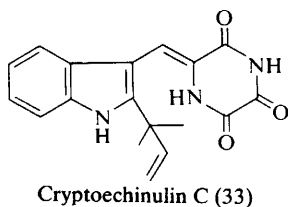
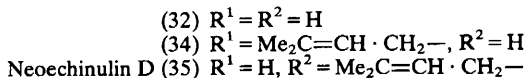
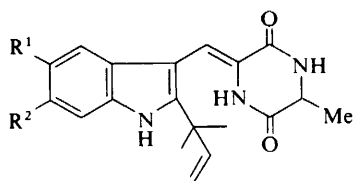
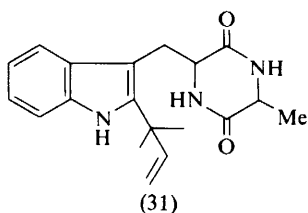
<sup>43</sup> S. Sekita, K. Yoshihira, S. Natori, and H. Kuwano, *Tetrahedron Letters*, 1976, 1351.

sin A into a mixture of B and D by Lewis acid requires a simple prototropic shift. Isomers E (29) and F (30) appear to be dihydro-derivatives of B and A respectively, the 21, 22 double bond having been saturated; in addition the 19, 20 ketol system appears to be reversed.<sup>43</sup>



### 3 Isoprenoid Tryptamine and Tryptophan Alkaloids

**Mould Metabolites.**—Intermediates on the presumed biosynthetic pathway from tryptophan to echinulin and its analogues continue to be isolated. The introduction of a reversed isoprene unit at C-2 leads to L-analyl-2-(1,1-dimethylallyl)-L-tryptophan anhydride (31), a compound which has already been synthesized,<sup>44</sup> and which has now been shown<sup>45</sup> to be a constituent of *Aspergillus chevalieri* (Mangin) Thom et Church IFO 4090. The dehydro-derivative, neocheinulin A (32), recently isolated from *A. amstelodami*,<sup>46</sup> has now been shown to occur in *A. ruber*.<sup>47</sup> A



<sup>44</sup> E. Houghton and J. E. Saxton, *J. Chem. Soc. (C)*, 1969, 1003.

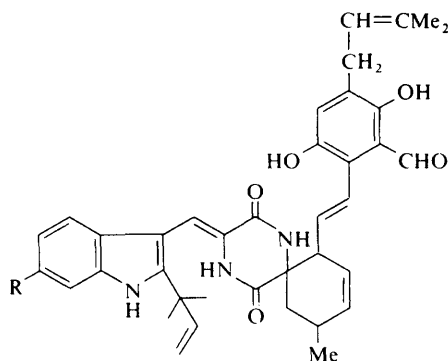
<sup>45</sup> T. Hamasaki, K. Nagayama, and Y. Hatsuda, *Agric. Biol. Chem.*, 1976, **40**, 203.

<sup>46</sup> A. Dossena, R. Marchelli, and A. Pochini, *J.C.S. Chem. Comm.*, 1974, 771.

<sup>47</sup> H. Nagasawa, A. Isogai, K. Ikeda, S. Sato, S. Murakoshi, A. Suzuki, and S. Tamura, *Agric. Biol. Chem.*, 1975, **39**, 1901.

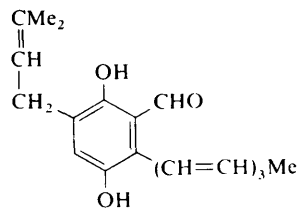
product of further oxidation, cryptoechinulin C (33), occurs in *A. amstelodami*. The 5-prenylated derivative, isoechinulin A (34), to which the isomeric structure (35) was initially<sup>47</sup> assigned, also occurs<sup>49</sup> in *A. ruber*, and appears to be responsible for the growth-inhibiting activity of this mould for silkworm larvae.<sup>47</sup> Other constituents of this same mycelium are isoechinulin B (36) and its epoxide, isoechinulin C (37).<sup>49</sup>

The 6-prenylated series has been encountered again in neoechinulin D (35), a minor metabolite of *A. amstelodami*,<sup>50</sup> which contains<sup>48</sup> four other dehydrotryptophan derivatives, cryptoechinulins B, D, E, and F. Of these, the structures of the last two have still not been elucidated, but cryptoechinulins B (38) and D (39) represent a new structural variant in the echinulin group. Detailed p.m.r. and <sup>13</sup>C n.m.r. studies of these two optically inactive metabolites revealed<sup>51</sup> that they could be derived from auroglaucon (40) and neoechinulin B (41) or C (42), respectively, by

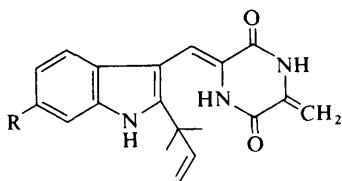


Cryptoechinulin B (38) R = H

Cryptoechinulin D (39) R = CH<sub>2</sub>—CH=CHMe<sub>2</sub>

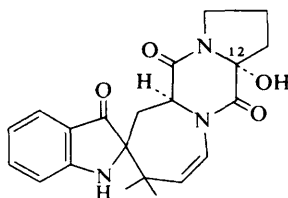


Auroglaucon (40)



Neoechinulin B (41) R = H

Neoechinulin C (42) R = Me<sub>2</sub>C=CH·CH<sub>2</sub>—



12,13-Dihydro-12-hydroxyaustamide (43)

regiospecific Diels–Alder condensation of the terminal diene system of auroglaucon with the exocyclic methylene group of neoechinulin B or C, a proposal rendered all the more probable by the fact that all three compounds (40—42) occur in *Aspergillus amstelodami*. Indeed, condensation of auroglaucon with neoechinulin B at 150 °C afforded a mixture from which cryptoechinulin B (38) was isolated; similarly, condensation of auroglaucon with neoechinulin C afforded<sup>51</sup> cryptoechinulin D (39).

<sup>48</sup> R. Cardillo, C. Fuganti, D. Ghiringhelli, P. Grasselli, and G. Gatti, *J.C.S. Chem. Comm.*, 1975, 778; R. Cardillo, C. Fuganti, D. Ghiringhelli, and P. Grasselli, *Chimica e Industria (Milan)*, 1975, **57**, 678.

<sup>49</sup> H. Nagasawa, A. Isogai, A. Suzuki, and D. Tamura, *Tetrahedron Letters*, 1976, 1601.

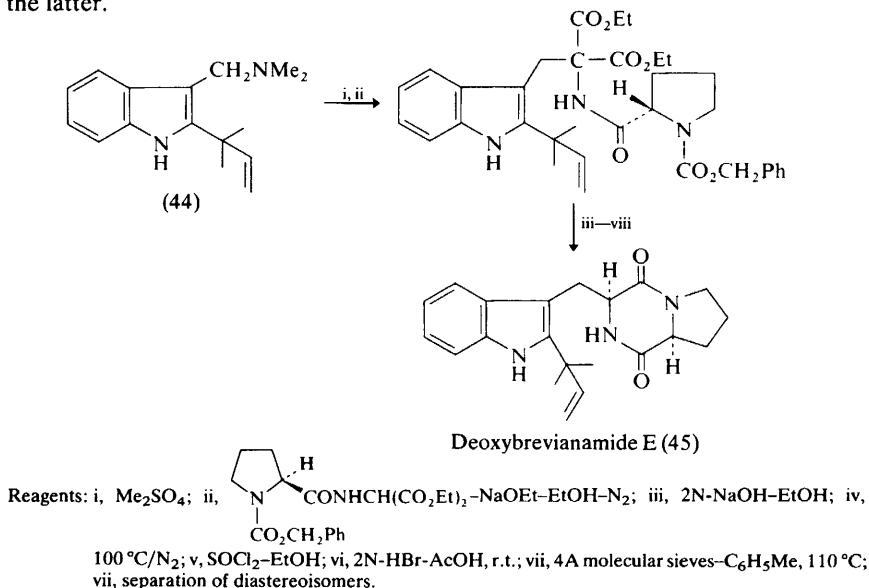
<sup>50</sup> A. Dossena, R. Marchelli, and A. Pochini, *Experientia*, 1975, **31**, 1249.

<sup>51</sup> G. Gatti, R. Cardillo, C. Fuganti, and D. Ghiringhelli, *J.C.S. Chem. Comm.*, 1976, 435.



The fact that these 'metabolites' are optically inactive suggests that they may be artifacts, generated at some stage during the extraction of the fungal mat.

In the brevianamide series brevianamide A has been isolated<sup>52</sup> from *Penicillium ochraceum* Bainier ex Thom., and a new austamide derivative, 12,13-dihydro-12-hydroxyaustamide (43), from *Aspergillus ustus*,<sup>53</sup> which, on the basis of its c.d. spectrum, has been assigned the 2*S*,9*S*,12*R* configuration. The structure (45) assigned to deoxybrevianamide E has been confirmed by synthesis from the gramine derivative (44) (Scheme 8);<sup>54a</sup> since deoxybrevianamide E is slowly converted into brevianamide E on aerial oxidation<sup>54b</sup> this also constitutes a formal total synthesis of the latter.



Scheme 8

The isolation<sup>55</sup> of a new dioxopiperazine derivative, roquefortine (46), from *Penicillium roqueforti* Thom., is of some interest, since its congeners are ergoline derivatives. It is also noteworthy that the molecule contains two unusual features, namely, a reversed isoprene unit at the indole 3-position, and a dehydrohistidine component; the only other naturally occurring molecule known to date which also contains this latter feature is oxaline<sup>56</sup> which, incidentally, also possesses a reversed isoprene unit at the indole  $\beta$ -position. In all probability roquefortine is identical with roquefortine C, isolated independently from the same source by a Japanese group.<sup>37</sup>

<sup>52</sup> J. E. Robbers, J. W. Straus, and J. Tuite, *Lloydia*, 1975, **38**, 355.

<sup>53</sup> P. S. Steyn and R. Vleggaar, *Phytochemistry*, 1976, **15**, 355.

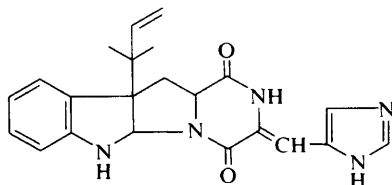
<sup>54</sup> (a) R. Ritchie and J. E. Saxton, *J.C.S. Chem. Comm.*, 1975, 611; (b) P. S. Steyn, private communication (1975).

<sup>55</sup> P. M. Scott, M. A. Merrien, and J. Polonsky, *Experientia*, 1976, **32**, 140.

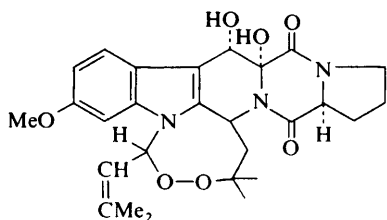
<sup>56</sup> D. W. Nagel, K. G. R. Pachler, P. S. Steyn, P. L. Wessels, G. Gafner, and G. J. Kruger, *J.C.S. Chem. Comm.*, 1974, 1021.

<sup>57</sup> S. Ohmomo, T. Sato, T. Utagawa, and M. Abe, *Agric. Biol. Chem.*, 1975, **39**, 1333; *Nippon Nogei Kagaku Kaishi*, 1975, **49**, 615 (*Chem. Abs.*, 1976, **84**, 86 597).

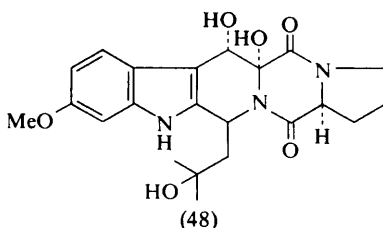
A more detailed account of the isolation of fumitremorgin B and verruculogen (47) from cultures of *Aspergillus caespitosus* Raper et Thom. is now available.<sup>58</sup> Hydrogenation (Pd/C) of verruculogen affords<sup>59a</sup> isovaleraldehyde and a tremorgenic compound designated TR-2 which, as expected, has the structure (48).<sup>59b</sup>



Roquefortine (46)



Verruculogen (47)



(48)

An improved procedure for the production of the tremorgenic mycotoxins tryptoquevaline and tryptoquivalone by *Aspergillus clavatus*, has been reported;<sup>60</sup> this makes use of pearled barley in a procedure based on Hesseltine's solid substrate fermentation technique.

Finally, two toxic, isomeric indole alkaloids of unknown structure have been isolated from a toxigenic fungus identified as *Penicillium islandicum* Sopp., found on freshly dug green peanuts.<sup>61</sup>

**Ergot Alkaloids.**—In connection with the biosynthesis of the ergot alkaloids it is of interest to note that *N*-methyl-4-dimethylallyltryptophan (49) has been isolated from cultures of *Claviceps fusiformis* grown anaerobically;<sup>62</sup> the presence of (49) could not be detected in cultures grown under normal aerobic conditions. An early stage in the biosynthesis of the alkaloids is the introduction of the allylic hydroxy-group, *e.g.* (50) → (51); whether the *N*-methylation precedes or follows hydroxylation is not known, but it seems certain that *N*-methylation occurs before the cyclization-decarboxylation stage that results in formation of the tricyclic chanoclavines.

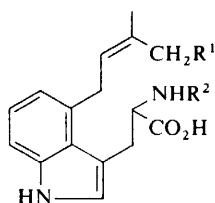
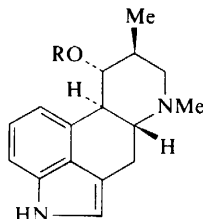
<sup>58</sup> H. W. Schroeder, R. J. Cole, H. Hein, and J. W. Kirksey, *Applied Environmental Microbiology*, 1975, **29**, 857.

<sup>59</sup> (a) R. J. Cole and J. W. Kirksey, *J. Agric. Food Chem.*, 1973, **21**, 927; (b) R. J. Cole, J. W. Kirksey, R. H. Cox, and J. Clardy, *J. Agric. Food Chem.*, 1975, **23**, 1015.

<sup>60</sup> A. L. Demain, N. A. Hunt, V. Malik, B. Kobbe, H. Hawkins, K. Matsuo, and G. N. Wogan, *Applied Environmental Microbiology*, 1976, **31**, 138.

<sup>61</sup> R. J. Cole, J. W. Kirksey, H. G. Cutler, D. M. Wilson, and G. Morgan-Jones, *Canad. J. Microbiol.*, 1976, **22**, 741.

<sup>62</sup> K. D. Barrow and F. R. Quigley, *Tetrahedron Letters*, 1975, 4269.

(49)  $R^1 = H, R^2 = Me$ (50)  $R^1 = R^2 = H$ (51)  $R^1 = OH, R^2 = H$ Isofumigaclavine A (52)  $R = Ac$ Isofumigaclavine B (53)  $R = H$ 

Samples of *Pennisetum typhoides* (pearl millet, *bajra*) contaminated with ergot have been shown<sup>63</sup> to contain mainly agroclavine and elymoclavine, together with smaller quantities of setoclavine, penniclavine, and chanoclavine; peptide alkaloids were entirely absent. Since *bajra* is used as a staple human food in semi-arid regions of India, and is often contaminated with ergot, it is important in the light of this study to re-define the upper limit of ergot contamination permitted, since that at present recommended is based on experience with contaminated rye and wheat, which have been shown to contain mainly the peptidic alkaloid, ergotamine.

*Ipomoea violacea* ('Morning glory') continues to attract attention; of the seeds of three varieties studied, that known as 'Pearly gates' was found to be richest in total and individual ergoline alkaloids.<sup>64</sup> A procedure has been developed<sup>65</sup> for the separation and isolation by t.l.c. of seven alkaloids from small quantities (500 mg) of morning glory leaves; six of these were identified by mass spectrometry as lysergic acid amide, isolysergic acid amide, ergonovine, ergometrinine, agroclavine, and elymoclavine, and the presence of chanoclavine is also postulated.

The ergot fungus parasitic on *Triticale*, an artificial genus resulting from the hybridization of wheat and rye, does not appear previously to have been studied chemically. A reliable method has now been developed<sup>66</sup> for the detection of ergot contamination in ground *Triticale* grain, and two alkaloids, ergonovine and ergocristine, have been identified.

The alkaloid content of *Claviceps purpurea* grown in submerged cultures has been examined,<sup>67</sup> and the nine alkaloids isolated by counter-current distribution were chanoclavine I, isochanoclavine I, elymoclavine, agroclavine, ergotamine, ergocorinine, ergotaminine, ergocryptine, and ergocryptinine.

As well as roquefortine, the mycelium of *Penicillium roqueforti* contains<sup>55</sup> isofumigaclavine A (52), so called because saponification yields a product (53), which is clearly a stereoisomer of fumigaclavine B; in fact, hydroboration of agroclavine yields mainly fumigaclavine B, together with a low yield of isofumigaclavine B. Since the stereochemistry of fumigaclavine B has been established,<sup>68</sup> the stereochemistry of isofumigaclavine B is presumably as given in (53). Isofumigaclavines A and B may

<sup>63</sup> R. V. Bhat, D. R. Roy, and P. G. Tulpule, *Toxicol. Appl. Pharmacol.*, 1976, **36**, 11.

<sup>64</sup> W. L. Witters, *Ohio J. Sci.*, 1975, **75**, 198 (*Chem. Abs.*, 1976, **84**, 28043).

<sup>65</sup> J. M. Weber and T. S. Ma, *Mikrochimica Acta*, 1976, **217**, 227.

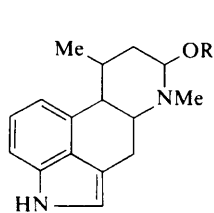
<sup>66</sup> J. E. Robbers, V. M. Krupinski, H. S. Sheriat, and D. M. Huber, *Phytopathology*, 1975, **65**, 455.

<sup>67</sup> C. Galeffi, S. Matosic, and A. Tonolo, *Atti. Acad. Naz. Lincei, Cl. Sci. Fis., Mat. Nat., Rend.*, 1974, **56**, 951 (*Chem. Abs.*, 1976, **84**, 28 044).

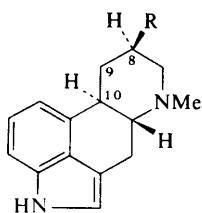
<sup>68</sup> N. J. Bach, H. E. Boaz, E. C. Kornfeld, C. J. Chang, H. G. Floss, E. W. Hagaman, and E. Wenkert, *J. Org. Chem.*, 1974, **39**, 1272.

be identical with roquefortines A and B, isolated<sup>57</sup> from the same source together with festuclavine, although there are discrepancies in the reported physical constants. Tentatively, Ohmomo *et al.* have assigned structures (54) and (55) to roquefortines A and B, but the evidence on which these structures are based is exiguous. In passing it may be noted that roquefortines A and B have been found in insignificant amounts in Roquefort cheeses.<sup>57</sup>

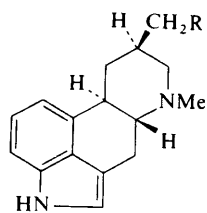
The <sup>13</sup>C n.m.r. spectra (at 22.63 MHz) and the <sup>1</sup>H n.m.r. spectra (at 270 MHz) of the four 10-methoxydihydrolysergic acid methyl esters have been measured, and complete assignments made;<sup>69</sup> the mass spectra of some peptidic ergot alkaloids have also been studied.<sup>70</sup>



(54) R = Ac  
(55) R = H



(56) R = CH<sub>2</sub>OH  
(57) R = CO<sub>2</sub>H



Festuclavine (58) R = H  
(59) R = CN

Transformations and syntheses in this area have been comparatively few in number during the period under review. The first oxidation of a primary alcoholic group in a clavine alkaloid to a carboxy-group has been claimed,<sup>71</sup> but the yields are such that this cannot be claimed to constitute a viable route to the acids. Thus, dihydrolysergol-I (56) affords the dihydrolysergic acid-I (57) in 4.1% yield on oxidation by the Oppenauer method in the presence of cyclohexanone; not surprisingly, the aldol condensation product of the intermediate aldehyde with cyclohexanone is also formed. What is, perhaps, suprising is the reported formation of lysergic acid (57,  $\Delta^{9,10}$ ) from elymoclavine (56,  $\Delta^{8,9}$ ) by the same method, albeit in only 0.25% yield!

The partial synthesis of festuclavine (58) by reduction of agroclavine is unsatisfactory, since it proceeds non-stereospecifically. A much improved partial synthesis has been reported,<sup>72</sup> which simply involves the reductive decyanization of the readily available nitrile (59) by means of potassium in HMPA; alternatively, the unsaturated nitrile (59,  $\Delta^{9,10}$ ) can be used as starting material. In both reactions the yield is stated to be almost quantitative.

Paliclavine (60), the recently isolated metabolite of *Claviceps paspali*, is in a formal sense an allylic rearrangement isomer of the chanoclavine-I isomers (61) and (62), and it was therefore of interest to attempt a partial synthesis of paliclavine from the latter isomers. Attempted rearrangement of chanoclavine-I (61) in the presence of acid under a variety of conditions consistently gave negative results, but a dramatic change was observed when the acidic solution was irradiated with ultraviolet light. In addition to three unidentified, non-polar compounds and some unchanged starting

<sup>69</sup> L. Zetta and G. Gatti, *Tetrahedron*, 1975, **31**, 1403.

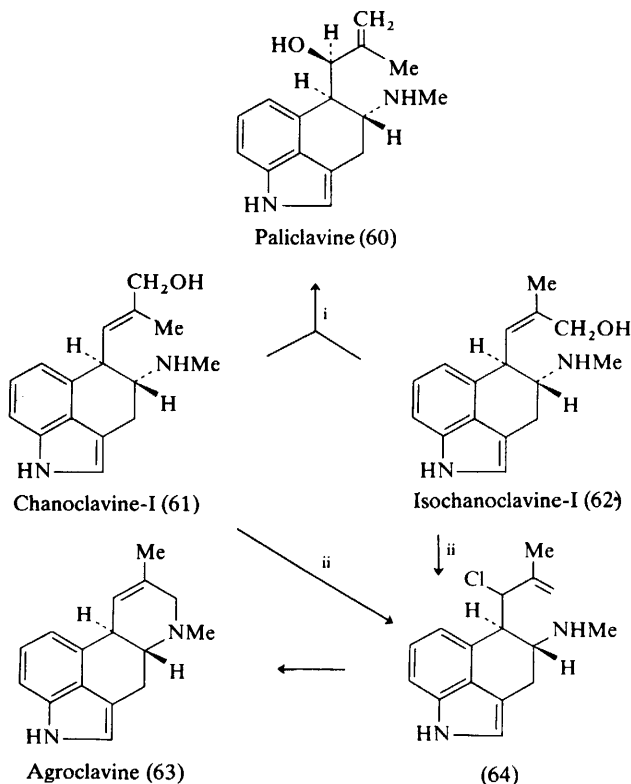
<sup>70</sup> J. Vokoun and Z. Rehacek, *Coll. Czech. Chem. Comm.*, 1975, **40**, 1731.

<sup>71</sup> K. Mayer and E. Eich, *Arch. Pharm.*, 1975, **308**, 819.

<sup>72</sup> J. Křepelka and M. Semonský, *Coll. Czech. Chem. Comm.*, 1976, **41**, 1416.

material, a 25% yield of paliclavine (60) was isolated; contrary to expectations no stereoisomers were obtained. The behaviour of isochanoclavine-I (62) was entirely analogous, and was similarly stereospecific.<sup>73</sup> Further, the equilibrium in these rearrangements appeared to favour paliclavine overwhelmingly, since irradiation of paliclavine in the presence of acid gave only a trace of chanoclavine-I and isochanoclavine-I. A similar irradiation of *N*-methylchanoclavine-I in acid solution gave *N*-methylpaliclavine which, following *O*-acetylation, demethylation with azodicarboxylic ester, and saponification, afforded a second synthesis of paliclavine.<sup>73</sup> The mechanism of this isomerization is at present not clear, but a cyclic transition state involving the basic nitrogen atom may well be implicated, since *N*<sub>6</sub>-acetylchanoclavine-I does not rearrange.

A general synthetic route from elymoclavine (56;  $\Delta^{8,9}$ ) to a variety of substituted  $\Delta^{8,9}$ -ergolenes, by displacement reactions on the related allylic chloride, has been developed.<sup>74</sup> A rather more exciting contribution is the partial synthesis of agroclavine (63) from chanoclavine-I (61) and isochanoclavine-I (62) (Scheme 9);<sup>74</sup> the



Reagents: i,  $h\nu$ -H<sub>2</sub>O-H<sub>2</sub>SO<sub>4</sub>-dioxan; ii, SOCl<sub>2</sub>-dioxan.

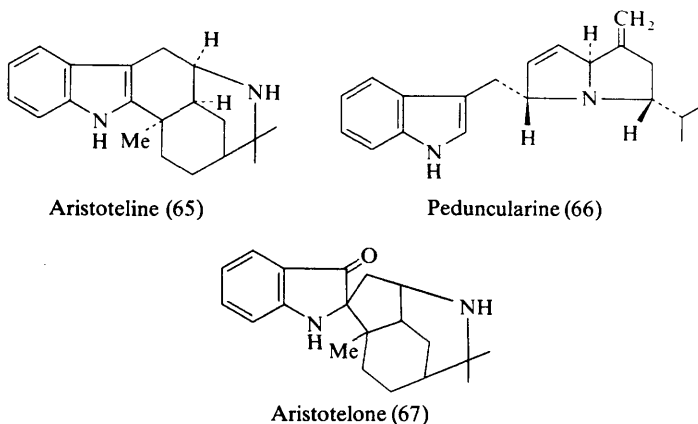
**Scheme 9**

<sup>73</sup> T. Fehr and P. A. Stadler, *Helv. Chim. Acta*, 1975, **58**, 2484.

<sup>74</sup> G. S. Li, J. M. Robinson, H. G. Floss, and J. M. Cassady, *J. Medicin. Chem.*, 1975, **18**, 892.

formation of agroclavine from either isomer suggests that the reaction proceeds *via* an intramolecular  $S_N2'$  displacement on the allylic chloride (64), a route which is obvious enough in principle, but not previously realised in practice.

**Monoterpenoid Alkaloids.**—*Alkaloids of Aristotele species.* Pride of place among the monoterpenoid alkaloids may now be given to aristoteline (65) which occurs, together with peduncularine (66), in the New Zealand wineberry, *Aristotelia serrata* (Elaeocarpaceae),<sup>75</sup> and in the Chilean species *A. chilensis*,<sup>76</sup> in which it occurs in association with aristotelone (67). The structure of aristoteline was determined by detailed mass spectral examination and by X-ray crystal structure determination; the latter method also established the absolute configuration. The minor alkaloid,



aristotelone, exhibits the u.v. and i.r. spectra of a pseudoinoxyl derivative, and the structure (67) rests mainly on mass spectral evidence, owing to paucity of material available. The major point of interest here is that the non-tryptamine component of these two alkaloids constitutes an *unrearranged* monoterpene unit.

**Corynantheine–Heteroyohimbine–Yohimbine Group, and Related Oxindoles.** 5-Oxostrictosidine (68), an early metabolite of vincoside, has been isolated from the neutral glycosides of *Adina rubescens* heartwood.<sup>77</sup> Since the molecule exhibits a positive Cotton effect, C-3 almost certainly has the *S* configuration, the familiar inversion having occurred at this centre during the biosynthesis from vincoside. Cadamine and isocadamine (69) are two non-glycosidic alkaloids from the leaves of *Anthocephalus cadamba*;<sup>78</sup> both alkaloids contain the novel  $N_b$  to C-19 bond found in the major alkaloid, isodihydrocadambine,<sup>79</sup> but in cadamine and isocadamine the dihydropyran ring E is replaced by a pyridine ring, a conversion which has ample biological precedent. It is noteworthy that in the isomers (69) C-3 has the *R* configuration, *i.e.* they are formed from vincoside with retention of configuration at

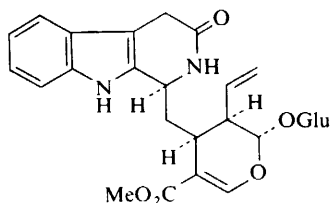
<sup>75</sup> B. F. Anderson, G. B. Robertson, H. P. Avey, W. F. Donovan, I. R. C. Bick, J. B. Bremner, A. J. T. Finney, N. W. Preston, R. T. Gallagher, and G. B. Russell, *J.C.S. Chem. Comm.*, 1975, 511.

<sup>76</sup> D. S. Bhakuni, M. Silva, S. A. Maitlin, and P. G. Sammes, *Phytochemistry*, 1976, 15, 574.

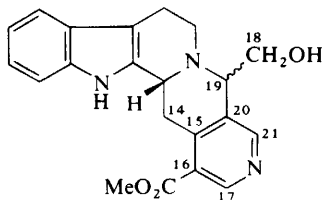
<sup>77</sup> R. T. Brown and A. A. Charalambides, *Experientia*, 1975, 31, 505.

<sup>78</sup> R. T. Brown and C. L. Chapple, *Tetrahedron Letters*, 1976, 1629.

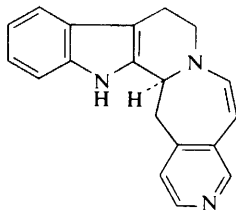
<sup>79</sup> R. T. Brown, S. B. Fraser, and J. Banerji, *Tetrahedron Letters*, 1974, 3335.



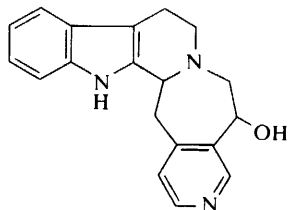
5-Oxostrictosidine (68)



Cadamine and isocadamine (69)



Naufoline (70)



Decarbomethoxynauclechine (71)

C-3. The configuration at C-19 has not been determined, but since the alkaloids show close similarity in all respects, they are presumed to be epimers at this position. Attachment of C-18 instead of C-19 to  $N_b$  results in formation of a seven-membered ring C, exemplified by naufoline (70) and decarbomethoxynauclechine (71), two constituents of the root bark of *Nauclea latifolia* Sm.<sup>80</sup> A *Nauclea* species investigated for the first time is *N. parva* Merrill (*Sarcocephalus parvus*), a small tree indigenous to Sarawak, which contains a number of alkaloids in very low concentrations.<sup>81</sup> The major alkaloid, parvine (72), proves to be identical with nauclefine, previously isolated from *N. latifolia*.<sup>82</sup> The structure of parvine was deduced independently, and confirmed by synthesis from harmalan and nicotinoyl chloride (Scheme 10). A somewhat longer synthesis of nauclefine proceeds<sup>83a</sup> from 4-methylnicotinonitrile, *via* the enol-lactone (73a) and the tryptamide (73b). In both syntheses a spontaneous dehydrogenation occurs during the final stage. An entirely analogous synthesis,<sup>83b</sup> starting with 4-methyl-5-vinylnicotinonitrile, led to angustine (74).

The structure and relative stereochemistry of akagerine (75a) have been confirmed<sup>84</sup> by *X*-ray crystal structure analysis. 6,7-Dihydroflavopereirine (75b) is among the constituents of *Strychnos usambarensis* roots.<sup>25b</sup>

In the corynantheine series dihydrocorynantheine, hirsuteine, hirsutine, and dihydrocorynantheine pseudo-indoxyl have been isolated from samples of *Uncaria attenuata* ssp. *attenuata*,<sup>25a</sup> dihydrocorynantheine and *epiallo*-corynantheine were found in the related subspecies *bulusanensis*. This is the first recorded occurrence in nature of *epiallo*-corynantheine and dihydrocorynantheine pseudindoxyl.<sup>25a</sup>

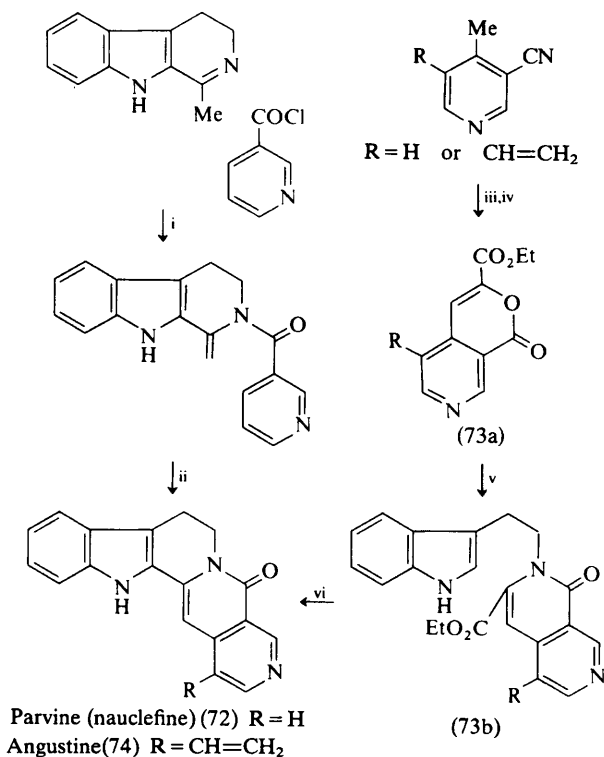
<sup>80</sup> F. Hotellier, P. Delaveau, R. Besselièvre, and J. L. Pousset, *Compt. rend.*, 1976, **282** C, 595.

<sup>81</sup> M. Sainsbury and B. Webb, *Phytochemistry*, 1975, **14**, 2691.

<sup>82</sup> F. Hotellier, P. Delaveau, and J. L. Pousset, *Phytochemistry*, 1975, **14**, 1407.

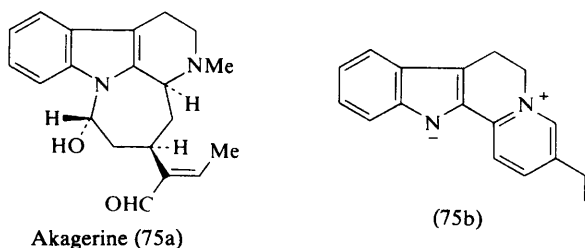
<sup>83</sup> (a) T. Kametani, M. Takeshita, and M. Ihara, *Heterocycles*, 1976, **4**, 247; (b) T. Kametani, M. Takeshita, and M. Ihara, *ibid.*, 1975, **3**, 627.

<sup>84</sup> L. Dupont, O. Dideberg, and L. Angenot, *Acta Cryst.*, 1975, **B31**, 2387.



Reagents: i, DMF, non-aqueous work-up; ii,  $h\nu$ ; iii,  $(CO_2Et)_2$ - $KOBu^t$ - $C_6H_6$ ; iv, dil. HCl; v, tryptamine-AcOH-116 °C, 3 h; vi, HCl-AcOH, high temperature.

Scheme 10



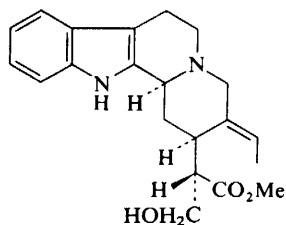
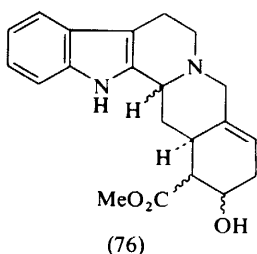
Pleiocarpamine has been found in the bark of *Alstonia vitiensis* (Seeman) var. *novo ebudica monachino*,<sup>85</sup> and 10-methoxygeissoschizol,  $\alpha$ -yohimbine, and alstonine in the leaves and stems<sup>86</sup> of *Rauwolfia obscura*; the stems also contain tetrahydroalstonine and an anhydronium base which, unfortunately, decomposed in the mass spectrometer and was obtained in insufficient amount for structure elucidation.

<sup>85</sup> S. Mamatas-Kalamaras, T. Sévenet, C. Thal, and P. Potier, *Phytochemistry*, 1975, **14**, 1637.

<sup>86</sup> P. Timmins and W. E. Court, *Planta Med.*, 1975, **27**, 105 (*Chem. Abs.*, 1975, **83**, 55 671); *Phytochemistry*, 1976, **15**, 733.



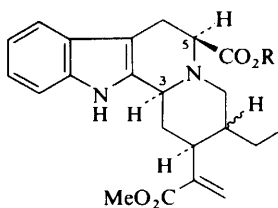
A sixth alkaloid behaves on mass spectral fragmentation as a 19,20-dehydroyohimbine, and since it co-occurs with  $\alpha$ -yohimbine it is formulated as (76), the tentative proposal being that C-3, C-16, and C-17 have the same stereochemistry as in  $\alpha$ -yohimbine.<sup>86</sup>



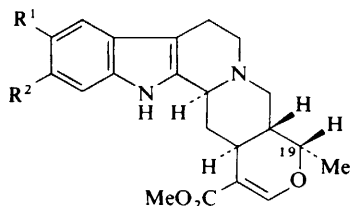
(76)

16-Epi-isositsirikine (77)

Two further ring E *seco* alkaloids have been reported recently. One of these, 16-epi-isositsirikine (77), which occurs in *Aspidosperma cuspa* Blake,<sup>87</sup> may well be identical with an alkaloid isolated earlier from *A. oblongum* A.DC.,<sup>88</sup> but it is now characterized thoroughly for the first time. Its structure becomes apparent from the reduction (NaBH<sub>4</sub>) of geissoschizine, which affords a mixture of isositsirikine and its 16-epimer (77). The other ring E *seco* alkaloid, anhydroadurubine, proves to be the second tetracyclic alkaloid of *Adina rubescens* which is derived from tryptophan, rather than tryptamine;<sup>89</sup> the structure (78) was established by the base-catalysed elimination of acetic acid from methyl adurubine acetate, which afforded anhydroadurubine methyl ester (79). The positive Cotton effect exhibited by (78) indicates that the molecule contains an  $\alpha$ -H at C-3, the presence of Bohlmann bands in the i.r. spectrum suggests that rings C and D constitute a *trans*-quinolizidine system with *cis* hydrogens at C-3 and C-15, and the configurational stability of C-5 argues in favour of an equatorial carboxy-group, *i.e.* that C-5 has the L-tryptophan configuration.<sup>89</sup> Finally, in this group, the isolation of ochromianine (stereoisomer of 10-methoxydihydrocorynantheol) and the related oxindole A, ochromianoxine,<sup>90</sup> together with decarbomethoxydihydrogambirtannine and three bisindole alkaloids, from the bark of *Ochrosia miana*, has been described.<sup>91</sup>



Anhydroadurubine (78) R = H  
(79) R = Me



(80) R<sup>1</sup> = R<sup>2</sup> = H  
(81) R<sup>1</sup> = OMe, R<sup>2</sup> = H  
(82) R<sup>1</sup> = R<sup>2</sup> = OMe

<sup>87</sup> J. C. Simões, B. Gilbert, W. J. Cretney, M. Hearn, and J. P. Kutney, *Phytochemistry*, 1976, **15**, 543.

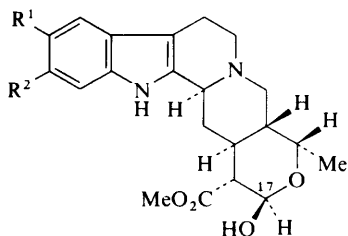
<sup>88</sup> G. Spiteller and M. Spiteller-Friedmann, *Monatsh.*, 1963, **94**, 779.

<sup>89</sup> R. T. Brown and A. A. Charalambides, *Phytochemistry*, 1975, **14**, 2527.

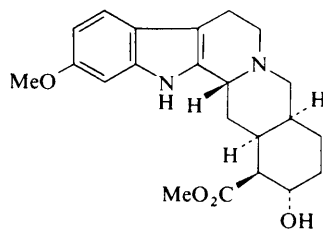
<sup>90</sup> N. Preaux, M. Koch, and M. Plat, *Phytochemistry*, 1974, **13**, 2607.

<sup>91</sup> N. Preaux, M. Koch, M. Plat, and T. Sévenet, *Plant. Med. Phytother.*, 1974, **8**, 250 (*Chem. Abs.*, 1973, **83**, 75 339).

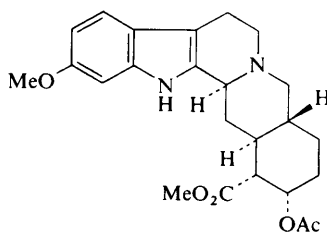
In the heteroyohimbine series ajmalicine (80), cabucine (81), which is 10-methoxyajmalicine, and 10,11-dimethoxyajmalicine (82), have been found<sup>92,93a</sup> in the root bark of *Cabucala striolata* M. Pichon; accompanying these bases in the plant are the related hydroxy-derivatives ajmalicinine (83), cabucinine (84), and 10,11-dimethoxyajmalicinine (85). Treated with toluene-*p*-sulphonyl chloride in pyridine all three alkaloids (83)—(85) dehydrate with formation of the alkaloids (80)—(82). Since the C-17 proton in the *O*-acetyl derivatives of cabucinine (84) and 10,11-dimethoxyajmalicinine (85) gives rise to a doublet having a large coupling constant with the C-16 proton, which is characteristic of a diaxial coupling, the complete stereochemistry of these two alkaloids is as given in (84) and (85); in all probability cabucine (83) has the same stereochemistry.<sup>93a</sup> New reports of natural occurrence include 3-isoajmalicine and akuammigine in *Uncaria attenuata* ssp. *attenuata*, 3-isoajmalicine in *U. orientalis* Guill., and 3-iso-19-epiajmalicine in *U. attenuata* ssp. *bulusanensis*;<sup>25a</sup> this last base has not previously been encountered in a natural source, but has been synthesized by two groups.



- (83)  $R^1 = R^2 = H$   
 (84)  $R^1 = OMe, R^2 = H$   
 (85)  $R^1 = R^2 = OMe$



Quaternatine (86)



Poweridine (87)

*Cabucala torulosa* Pichon, a rare species from the Mandana Forest Reserve in Madagascar, contains (–)tetrahydroalstonine in its leaves, and (–)-aricine and (–)-cabucine (81) in its stem and root bark.<sup>94</sup> A re-examination of elliptamine, isolated some years ago<sup>95</sup> from *Ochrosia poweri* Bail., has shown<sup>96</sup> that it is in fact identical with reserpiline.

<sup>92</sup> L. L. Douzoua, M. Debray, P. Bellet, L. Olivier, and J. Le Men, *Ann. pharm. franc.*, 1972, **30**, 199.

<sup>93</sup> (a) E. Bombardelli, A. Bonati, B. Danieli, B. Gabetta, and G. Mustich, *Fitoterapia*, 1974, **45**, 183; (b) G. A. Cordell and N. R. Farnsworth, *J. Pharm. Sci.*, 1976, **65**, 366.

<sup>94</sup> F. Titeux, B. Richard, M. M. Debray, L. Le Men-Olivier, and J. Le Men, *Phytochemistry*, 1975, **14**, 1648.

<sup>95</sup> F. A. Doy and B. P. Moore, *Austral. J. Chem.*, 1962, **15**, 548; B. Douglas, J. L. Kirkpatrick, B. P. Moore, and J. A. Weisbach, *Austral. J. Chem.*, 1964, **17**, 246.

<sup>96</sup> S. R. Johns, J. A. Lambertson, B. P. Moore, and A. A. Sioumis, *Austral. J. Chem.*, 1975, **28**, 1627.

Yohimbine and pseudoyohimbine have been found<sup>97</sup> in the leaves, stems and bark of *Alstonia quaternata* Heurck et Muell. Arg.; apparently this is the first record of the occurrence of these alkaloids in the *Alstonia* genus. New alkaloids from the same source include a methoxy-yohimbine of unknown structure, and an isomer, quaternatine, for which the complete stereochemistry (86) has been deduced, i.e. 11-methoxy 3-epi- $\alpha$ -yohimbine. Comparison of the n.m.r. data and c.d. curves of 3-epi- $\alpha$ -yohimbine and quaternatine establish that these bases have the same stereochemistry, and the position of the methoxy-group was finally secured by <sup>13</sup>C n.m.r. spectral comparison with poweridine (87) and other methoxy-substituted yohimbine derivatives.<sup>97</sup> Poweridine is the *O*-acetate of a stereoisomer of quaternatine, for which the gross structure (87) was previously deduced;<sup>95</sup> analysis of its <sup>1</sup>H and <sup>13</sup>C n.m.r. spectra and comparison with available models proves that poweridine is 11-methoxyyohimbine *O*-acetate.<sup>96</sup> Pseudoyohimbine and an unidentified yohimbine isomer have been isolated in trace amounts from *Uncaria attenuata* ssp. *attenuata*,<sup>25a</sup> and reserpine has been shown to occur in the root bark of *Cabucala striolata*.<sup>93a</sup> Pseudoyohimbine has also been found in *Catharanthus trichophyllus* (Bak.) Pich. roots.<sup>93b</sup>

In an attempt to confirm identifications of *Uncaria* species made on the basis of morphological and anatomical characteristics the alkaloid content of three species has been very carefully examined;<sup>25a</sup> the results relating to the corynantheine, heteroyohimbine, and yohimbine groups have been mentioned above, but these plants seem to be particularly versatile in their ability to biosynthesize oxindole alkaloids, and the outcome of these investigations is given in Table 1. Not included in the Table is *U. canescens* ssp. *canescens*, of which 18 samples were examined. These samples contained very little alkaloid, consisting of harman and unidentified indole alkaloids, but no oxindole or heteroyohimbine alkaloids. The results listed in the Table are the collected observations from different herbarium specimens; in fact the individual alkaloids present in any given sample often differed from those present in another herbarium sample of the same species. Nevertheless, it is possible to distinguish the species/subspecies on the basis of their alkaloid content, *U. attenuata*, for example, being markedly different from *U. canescens*; the latter, however, shows considerable resemblance to *U. orientalis*, in agreement with the observed morphological affinities.<sup>25a</sup> Of the alkaloids present in *U. perrottetii* (*U. ferrea*) two have been identified<sup>98</sup> as pteropodine and isopteropodine; this is consistent with previous reports on the alkaloid content of *U. ferrea*.

In an earlier communication<sup>99</sup> the isolation of reserpinine and elegantine from *Vinca elegantissima* Hort. was recorded, and a structure deduced for elegantine (88) which, it was subsequently noted,<sup>100</sup> is the same as that derived for isomajdine. The identity of isomajdine and elegantine has now been acknowledged, and the isolation of majdine (89) elegantissine, and isoelegantissine from the same plant has been reported.<sup>101</sup> Since equilibration of isomajdine in aqueous acetic acid affords a mixture of isomajdine, majdine, and the elegantissine isomers, it is clear that these

<sup>97</sup> S. Mamatas-Kalamaras, T. Sévenet, C. Thal, and P. Potier, *Phytochemistry*, 1975, **14**, 1849.

<sup>98</sup> G. C. Lleander and C. L. Herrera, *Philippine J. Sci.*, 1974, **103**, 75 (*Chem. Abs.*, 1975, **83**, 175 457).

<sup>99</sup> J. Bhattacharyya and S. C. Pakrashi, *Tetrahedron Letters*, 1972, 159.

<sup>100</sup> J. A. Joule, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1973, Vol. 3, p. 195.

<sup>101</sup> E. Ali, V. S. Giri, and S. C. Pakrashi, *Experientia*, 1975, **31**, 876.

**Table 1** Oxindole Alkaloids of *Uncaria attenuata*, *U. orientalis* and *U. canescens*.

Alkaloid	Source			
Speciophylline	a	c	d	
Speciophylline <i>N</i> -oxide		c	d	
Rhynchophylline	a	b		
Rhynchophylline <i>N</i> -oxide	a			
Isorhynchophylline	a			
Isorhynchophylline <i>N</i> -oxide	a			
Corynoxine	a			
Isocorynoxine	a			
'A Yohimbine Oxindole'	a			
Rotundifoline	a	b		
Isorotundifoline	a	b		
Uncarine A	a			
Uncarine B	a			
Mitraphylline	a		c	
Mitraphylline <i>N</i> -oxide	a		c	
Isomitraphylline	a		c	
Isomitraphylline <i>N</i> -oxide	a		c	
Speciofoline		b		
Corynoxine B		b		
Isopteropodine			c	d
Isopteropodine <i>N</i> -oxide			c	d
Pteropodine			c	d
Pteropodine <i>N</i> -oxide			c	d
Uncarine F			c	d
Uncarine F <i>N</i> -oxide			c	d

a, *Uncaria attenuata* ssp. *attenuata*; b, *U. attenuata* ssp. *bulusanensis*; c, *U. orientalis*; d, *U. canescens* ssp. *velutina*.

are the four possible allo-epiallo oxindole bases (88)–(91). On the basis of the Cotton effects at 250 and 290 nm, elegantissine (90) is formulated as the epiallo B isomer, *i.e.* majdine 3, and isoelegantissine (91) as the epiallo-A isomer, *i.e.* the majdine 4 of Shellard *et al.*<sup>102</sup> Herboxine, from *Vinca herbacea*, has also been allotted<sup>103</sup> the epiallo stereochemistry, and is stated to be formed by isomerization of majdine; however, the optical rotation reported does not coincide with that reported for either elegantissine or isoelegantissine. 16-Carboxyherbavine, also from *V. herbacea*, is said<sup>104</sup> to have the gross structure of a carboxylic acid corresponding to these ester alkaloids, but details of this work are not readily available.

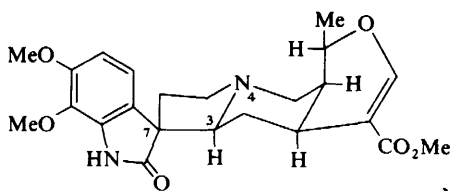
As a preface to the considerable amount of synthetic work that has been carried out in this area during the past year, it may be mentioned that removal of the sugar unit from secologanin (92) and dihydrosecologanin (93), to give the related aglycones, has been achieved<sup>105</sup> by means of  $\beta$ -glucosidase. The aglycones, however, do not contain a free aldehyde group, and are formulated as the hemiacetals (94) and (95). This was supported by the n.m.r. evidence [*e.g.* for (95), a broadened singlet at

<sup>102</sup> E. J. Shellard, J. D. Phillipson, and D. Gupta, *J. Chromatography*, 1968, **32**, 704.

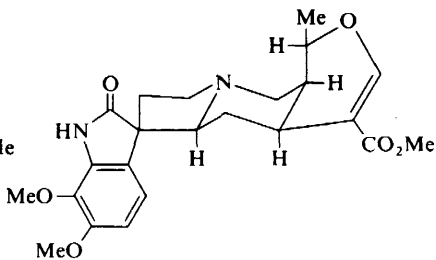
<sup>103</sup> G. V. Chkhivadze, M. M. Khalmirzaev, V. Yu. Vachnadze, V. M. Malikov, and S. Yu. Yunosov, *Khim. prirod. Soedinenii*, 1976, 227.

<sup>104</sup> E. Z. Dzhakeli, K. S. Mudzhiri, and Yu. N. Sheinker, *Izv. Akad. Nauk Gruz. SSR, Ser. Khim.*, 1975, **1**, 142 (*Chem. Abs.*, 1976, **84**, 44 499).

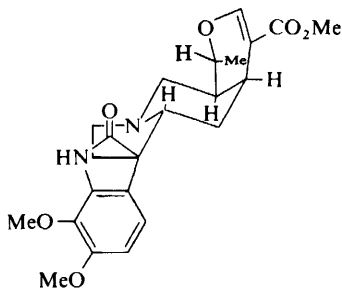
<sup>105</sup> R. T. Brown and C. L. Chapple, *Tetrahedron Letters*, 1976, 787.



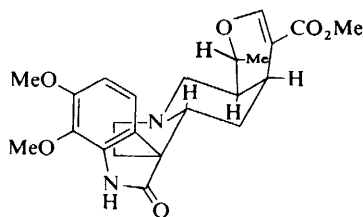
Isomajdine = Elegantine (88)  
(3*S*, 4*R*, 7*S*)



Majdine (89)

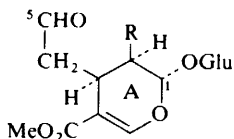


Elegantissine (90)  
(3*R*, 4*S*, 7*R*)

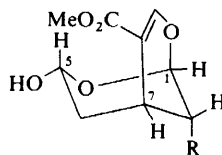


Isoelegantissine (91)  
(3*R*, 4*S*, 7*S*)

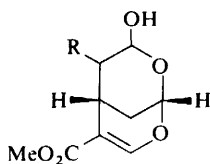
$\tau$  4.68, and a double doublet ( $J = 8, 5$  Hz) at  $\tau$  4.88, which moved downfield to  $\tau$  4.00 on acetylation, attributed to protons at C-1 and C-5 respectively], which also effectively excluded the possible structures (96) and (97). The aglycones (94) and (95) are almost certainly formed by an intramolecular displacement, as shown in (98); the alternative mechanism proceeds *via* the ring-opened dialdehyde, which would be expected to produce at least some (96) or (97). Further, the acyclic aldehyde from secologanin aglycone would almost certainly isomerize to the conjugated aldehyde; the retention of the double bond in the terminal position therefore implies that ring A remains intact.



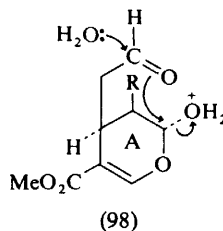
Secologanin (92)  $R = \text{CH}=\text{CH}_2$   
Dihydrosecologanin (93)  $R = \text{Et}$



(94)  $R = \text{CH}=\text{CH}_2$   
(95)  $R = \text{Et}$



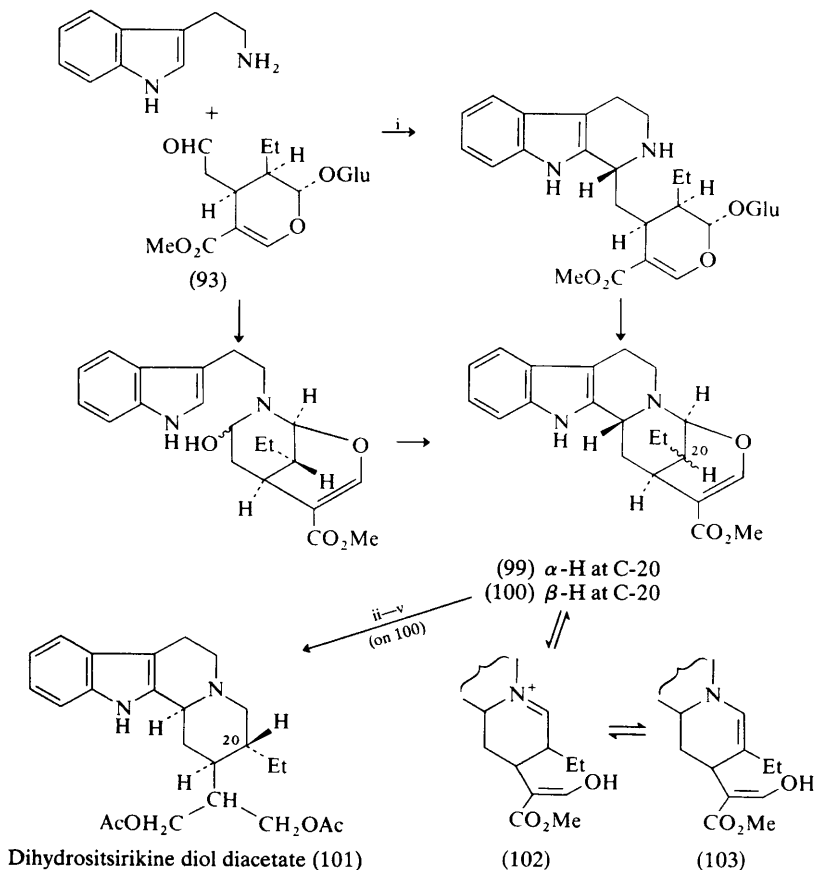
(96)  $R = \text{CH}=\text{CH}_2$   
(97)  $R = \text{Et}$



(98)

The complete stereochemistry and absolute configuration of vincoside have been finally and securely established by the *X*-ray crystal structure analysis of *N*<sub>b</sub>-*p*-bromobenzyltetra-acetylvincoside.<sup>106</sup> As an aid to investigations of the chemistry and metabolism of loganin and later biosynthetic precursors of the indole alkaloids, the complete <sup>13</sup>C n.m.r. data for loganin, loganin penta-acetate, secologanin tetra-acetate, *N*<sub>b</sub>-benzylvincoside, *N*<sub>b</sub>-acetylvincoside, *N*<sub>b</sub>-acetylisovincoside, vincoside lactam tetra-acetate, and isovincoside tetra-acetate have been compiled.<sup>107</sup>

Brown's original synthesis<sup>108</sup> of dihydromancunine (99) started with *N*<sub>b</sub>-benzyl-dihydrovincoside and employed conditions that bore little resemblance to likely *in vivo* processes. However, experience with the secologanin aglycone (see above) suggested a one-pot biomimetic synthesis of dihydromancunine and indeed,



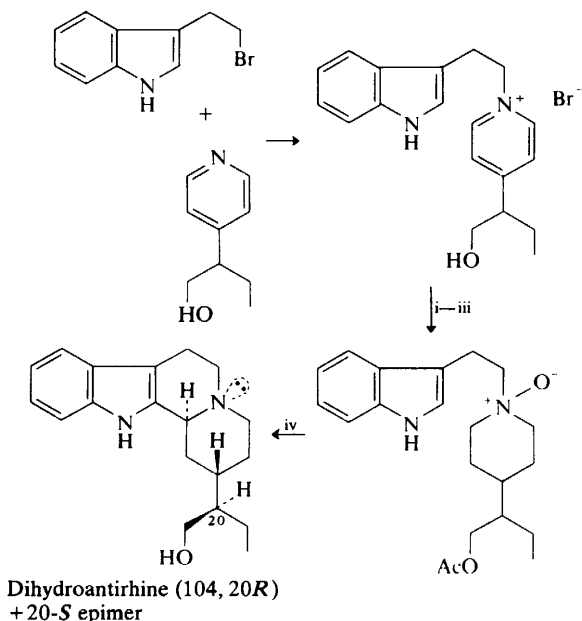
**Scheme 11**

<sup>106</sup> K. C. Mattes, C. R. Hutchinson, J. P. Springer, and J. Clardy, *J. Amer. Chem. Soc.*, 1975, **97**, 6270.

<sup>107</sup> A. H. Heckendorf, K. C. Mattes, C. R. Hutchinson, E. W. Hagaman, and E. Wenkert, *J. Org. Chem.*, 1976, **41**, 2045.

<sup>108</sup> R. T. Brown, C. L. Chapple, and A. A. Charalambides, *J.C.S. Chem. Comm.*, 1974, 756.

treatment of a mixture of dihydrosecologanin (93) and tryptamine with  $\beta$ -glucosidase in a pH 5 buffer at 37 °C afforded dihydromancunine directly, in moderate yield.<sup>109</sup> Notably, the product contained an appreciable amount of the 20 $\beta$ -H epimer (100), in which C-20 had retained its original configuration, a point that was firmly established by conversion of (100) into the known dihydrositsirikine diol diacetate (101) (Scheme 11).<sup>109</sup> As expected, dihydromancunine (100) was considerably less stable than its 20*S*-epimer, and at equilibrium, after only a few hours in solution, only a few per cent of (100) was present. This isomerization is readily explained, as shown in Scheme 11, by the equilibria (99)/(100)  $\rightleftharpoons$  (102)  $\rightleftharpoons$  (103).



Reagents: i, Hydrogenation; ii, acetylation; iii,  $\text{H}_2\text{O}_2$ - $\text{CHCl}_3$ - $\text{EtOH}$ ; iv,  $(\text{CF}_3\text{CO})_2\text{O}$ - $\text{CH}_2\text{Cl}_2$ , then  $\text{N-HCl}/70^\circ\text{C}$ .

### Scheme 12

A new synthesis<sup>110</sup> of ( $\pm$ )-dihydroantirrhine (104) (Scheme 12) makes use of the modified Polonovski reaction for the construction of the indoloquinolizidine ring system; in model experiments it had been established that the preferred stereochemistry of the product formed on closure of ring C was C-3, C-15 *trans*, in contrast to the other available methods of synthesis. However, the product obtained was proved to be an inseparable mixture of (104) and its C-20 epimer.

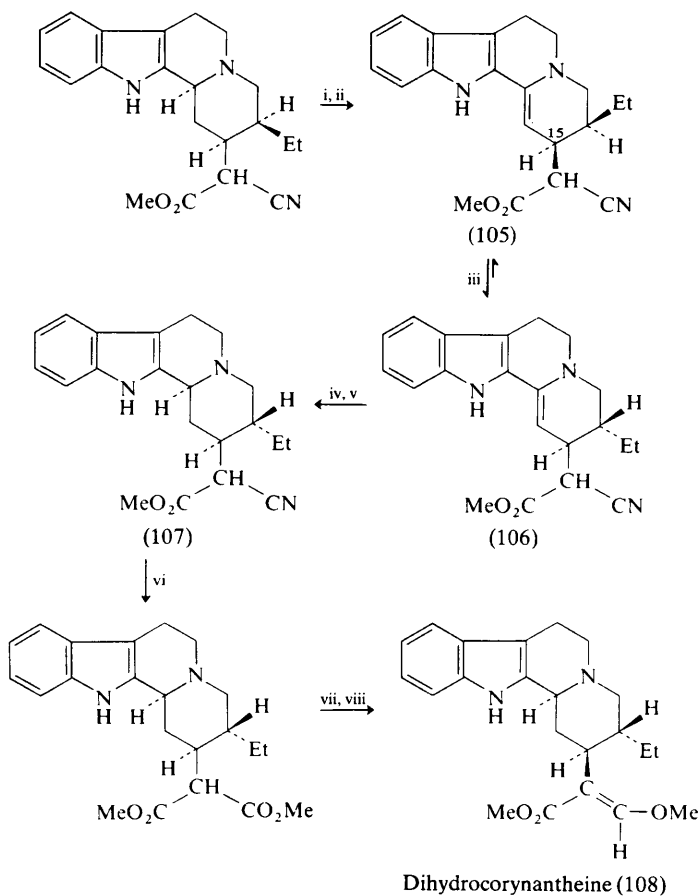
Szántay's synthesis<sup>111</sup> of ( $\pm$ )-dihydrocorynantheine (Scheme 13) takes advantage of an unusual epimerization reaction<sup>112</sup> which occurs in quinolizidine-enamine

<sup>109</sup> R. T. Brown, C. L. Chapple, R. Platt, and S. K. Sleight, *Tetrahedron Letters*, 1976, 1829.

<sup>110</sup> L. Chevolut, H. P. Husson, and P. Potier, *Tetrahedron*, 1975, 31, 2491.

<sup>111</sup> M. Bárczai-Beke, G. Dörnyei, G. Tóth, J. Tamas, and Cs. Szántay, *Tetrahedron*, 1976, **32**, 1153.

<sup>112</sup> M. Bárczai-Beke, G. Dörnyei, M. Kajtár, and Cs. Szántay, *Tetrahedron*, 1976, **32**, 1019.



Reagents: i, HCl, AcOH, Pb(OAc)<sub>4</sub>, then H<sub>2</sub>S; ii, NH<sub>4</sub>OH-H<sub>2</sub>O; iii, CH<sub>2</sub>Cl<sub>2</sub>-argon, 24–48 h; iv, MeOH-HClO<sub>4</sub>; v, NaBH<sub>4</sub>-AcOH-MeOH-CH<sub>2</sub>Cl<sub>2</sub>; vi, MeOH-HCl; vii, LiAlH<sub>4</sub>/–70 °C; viii, MeOH-HCl-CH<sub>2</sub>Cl<sub>2</sub>.

**Scheme 13**

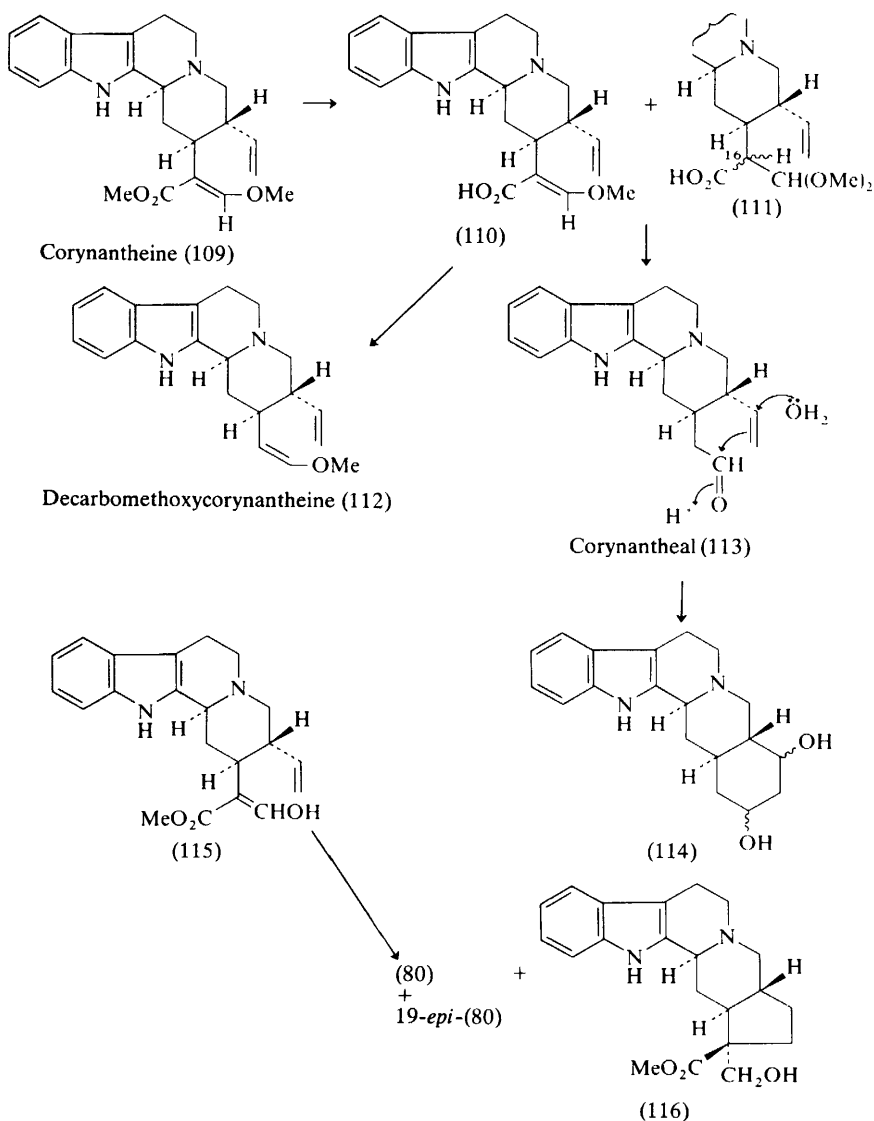
derivatives. For example, on standing in solution the *cis*-isomer (105) slowly isomerizes to the *trans*-isomer (106); in independent experiments with optically active substrates in the benzoquinolizidine series it was established that the carbon atom corresponding to C-15 in (105) was the site of epimerization. The *cis* nitrile-ester, prepared earlier,<sup>113</sup> was thus isomerized to the *trans*-isomer (106), which was reduced to the *normal* ester *via* the immonium ion. Low-temperature reduction of (107) (LiAlH<sub>4</sub>) afforded the corresponding aldehyde-ester which, under the conditions of acetal formation in the presence of a limited amount of methanol, gave the enol ether, (±)-dihydrocorynantheine (108).

In connection with the development of a partial synthesis of heteroyohimbine alkaloids from corynantheine (109), thereby obviating a possibly troublesome

<sup>113</sup> Cs. Szántay and M. Bárczai-Beke, *Tetrahedron Letters*, 1968, 1405; *Chem. Ber.*, 1969, **102**, 3963.



resolution step, Goutarel and his collaborators have carefully re-examined some of the chemistry of corynantheine, and clarified several long-standing obscurities.<sup>114</sup> An improved procedure for the separation of corynantheine and dihydrocorynantheine, and an improved preparation of demethylcorynantheine, have been described, and the course of the saponification of corynantheine in methanol has been elucidated. The product, 'laevorotatory corynantheic acid', is in fact a mixture of corynantheic acid ('dextrorotatory corynantheic acid') (110), and the two C-16



<sup>114</sup> L. A. Djakouré, F. X. Jarreau, and R. Goutarel, *Tetrahedron*, 1975, **31**, 2247.

epimeric acetal acids (111), which when heated with alkali *in vacuo* gives rise to demethoxycarbonylcorynantheine (112). All four compounds, when hydrolysed in acid medium, afford corynantheal (113). In an attempt to improve the yield of (113) the mixture of (110) and (111) from the saponification was heated with acid under conditions necessary to ensure complete decarboxylation but, surprisingly, little corynantheal was obtained. The major products, obtainable<sup>114</sup> also from corynantheal under the same conditions, were two isomers of 17,19-dihydroxy-yohimbane (114), a most interesting closure of the carbocyclic ring E, which in principle may have important biosynthetic implications.

The attempts by the same investigators to realize the synthesis of ajmalicine from corynantheine derivatives, previously reported<sup>115</sup> in brief, have now been published in detail;<sup>116</sup> thus, while oxymercuration of demethylcorynantheine (115) followed by NaBH<sub>4</sub> reduction gave small quantities of ajmalicine (80) and 19-epiajmalicine, the major product was the 18-*abeo* (17 → 16) yohimbane derivative (116).

In continuation of his biomimetic syntheses of heteroyohimbine alkaloids Brown<sup>117</sup> has succeeded in converting secologanin tetra-acetate (117) into elenolic acid (118), and in completing the synthesis of ajmalicine (80) essentially by the route published<sup>118</sup> earlier (Scheme 14). Contrary to the previous workers, who apparently isolated only ajmalicine, Brown *et al.*<sup>117</sup> obtained ajmalicine (80), 19-epiajmalicine (119) and tetrahydroalstonine (120). Since one of the lactams (121) afforded only 19-epiajmalicine (119) and in the general reaction sequence the proportion of (80), (119), and (120) in the final product depended on the length of time allowed for Schiff base formation rather than on the ratio of isomers present in the methyl elenolate [ester of (118)], it is apparent that interconversion of the imines (122) *via* the equilibria shown in Scheme 14 is responsible for the non-stereospecificity of the synthesis.

Kametani's synthesis<sup>119</sup> of yohimbine, mentioned in last year's Report, has now been published in detail.<sup>120</sup> The same group have offered a new synthesis<sup>121</sup> (Scheme 15) from the pentacyclic ester (123), itself prepared by a lengthy sequence, published earlier.<sup>120</sup> Birch reduction of the acid corresponding to (123) was preferred since reduction of the ester itself led to concomitant reduction of the ester function. Re-esterification of the product (124), hydrolysis of the enol ether, and isomerization by acid gave 15,16-dehydroyohimbine (125), which had previously<sup>119</sup> been converted into yohimbine.

Szántay's most recent contribution in this area<sup>122</sup> also involves the enone-ester (125), which was prepared by regioselective Dieckmann cyclization of the dicarboxylic ester (126). Direct reduction of (125) by various reagents, of which two are cited in Scheme 15, gave a separable mixture of yohimbine and  $\beta$ -yohimbine. Alterna-

<sup>115</sup> L. Djakouré, F. X. Jarreau, R. Goutarel, and M. M. Janot, *Compt. rend.*, 1972, **274** C, 1520; M. M. Janot, L. Djakouré, F. X. Jarreau, and R. Goutarel, *ibid.*, p. 2077.

<sup>116</sup> L. A. Djakouré, F. X. Jarreau, and R. Goutarel, *Tetrahedron*, 1975, **31**, 2695.

<sup>117</sup> R. T. Brown, C. L. Chapple, D. M. Duckworth, and R. Platt, *J.C.S. Perkin I*, 1976, 160.

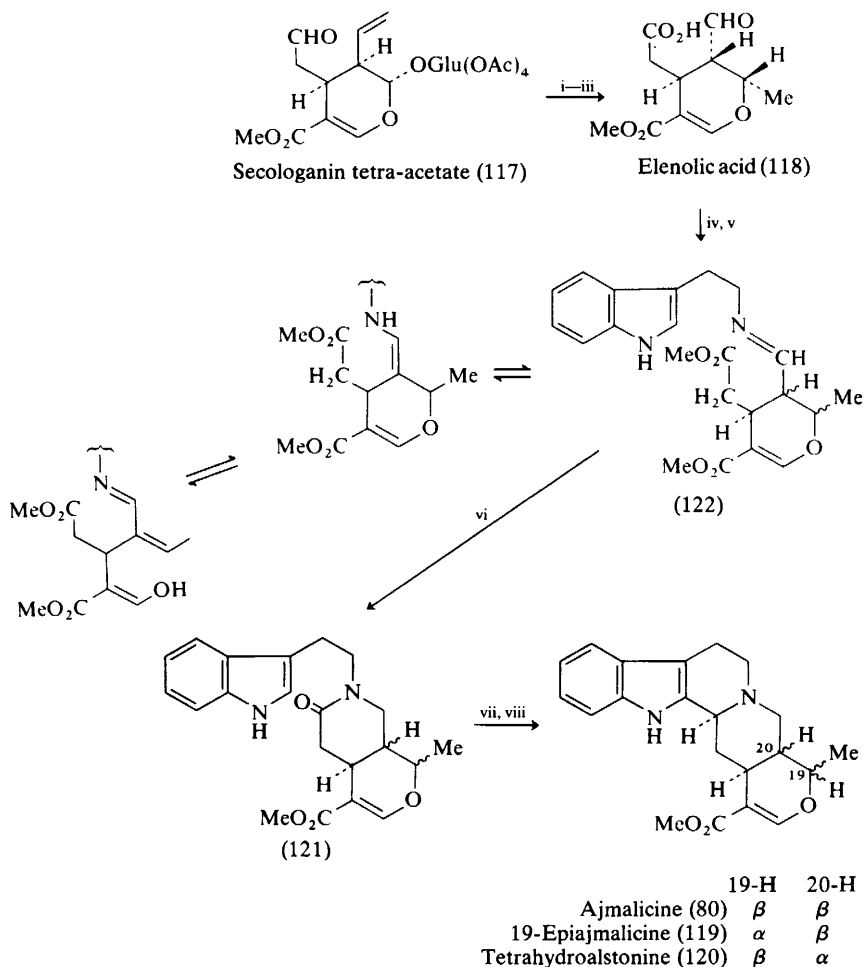
<sup>118</sup> F. A. MacKellar, R. C. Kelly, E. E. van Tamelen, and C. Dorschel, *J. Amer. Chem. Soc.*, 1973, **95**, 7155.

<sup>119</sup> T. Kametani, M. Kajiwara, T. Takahashi, and K. Fukumoto, *Heterocycles*, 1975, **3**, 179.

<sup>120</sup> T. Kametani, Y. Hirai, M. Kajiwara, T. Takahashi, and K. Fukumoto, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 2634.

<sup>121</sup> T. Kametani, Y. Hirai, and K. Fukumoto, *Heterocycles*, 1976, **4**, 29.

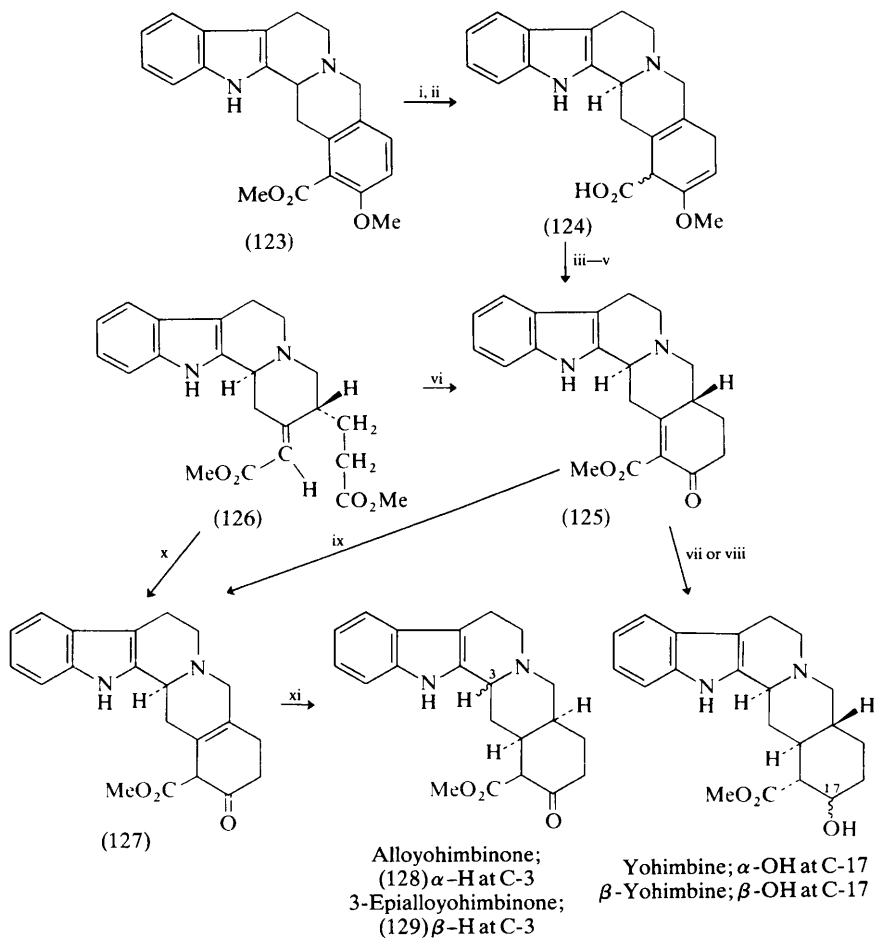
<sup>122</sup> Cs. Szántay, K. Honty, L. Töke, and L. Szabó, *Chem. Ber.*, 1976, **109**, 1737.



Reagents: i, Jones' reagent; ii, deacetylation; iii,  $\beta$ -glucosidase, pH 5 4 days; iv,  $\text{CH}_2\text{N}_2$ ; v, tryptamine- $\text{C}_6\text{H}_6$ ; vi,  $\text{NaBH}_4$ ; vii,  $\text{POCl}_3\text{-C}_6\text{H}_6$ -80 °C-1.5 h; viii,  $\text{NaBH}_4\text{-MeOH}$ .

**Scheme 14**

tively, base-catalysed isomerization of (125), or direct cyclization-isomerization of (126), gave the unconjugated enone-ester (127), whose reduction was thoroughly studied. Reduction with palladized charcoal at atmospheric pressure in the presence of base gave a complex mixture, in which alloyohimbine (128) and 3-epialloyohimbine (129) were accompanied by yohimbine, 17-epicorynanthine (130), and 3-epialloyohimbine (131). Among other reductions of (127) was that using sodium borohydride in propan-2-ol, which afforded a mixture of  $\alpha$ -yohimbine (132), 17-epi- $\alpha$ -yohimbine (133), alloyohimbine (134), and 17-epialloyohimbine (135).<sup>122</sup>



Reagents: i,  $H_2O-MeOH-KOH$ ; ii,  $Li-NH_3-MeCHOHMe-HMPA$ ; iii,  $CH_3N_2-HMPA$ ; iv,  $(CO_2H)_2-H_2O-MeOH$ ,  $40^\circ C$ , 24 h.; v,  $MeOH-HCl$ ; vi,  $NaH-THF$ ; vii,  $H_2-Pt-DMF-AcOH$ ; viii,  $NaBH_4-py$ ,  $0^\circ C$ ; ix,  $KOBu^t-DMSO$ ; x,  $KOBu^t-C_6H_6$ ,  $80^\circ C$ , 1-2 h.; then  $NaOMe-MeOH$ ; xi,  $NaOMe-MeOH-Pd/C-H_2$ , r.t.

**Scheme 15a**

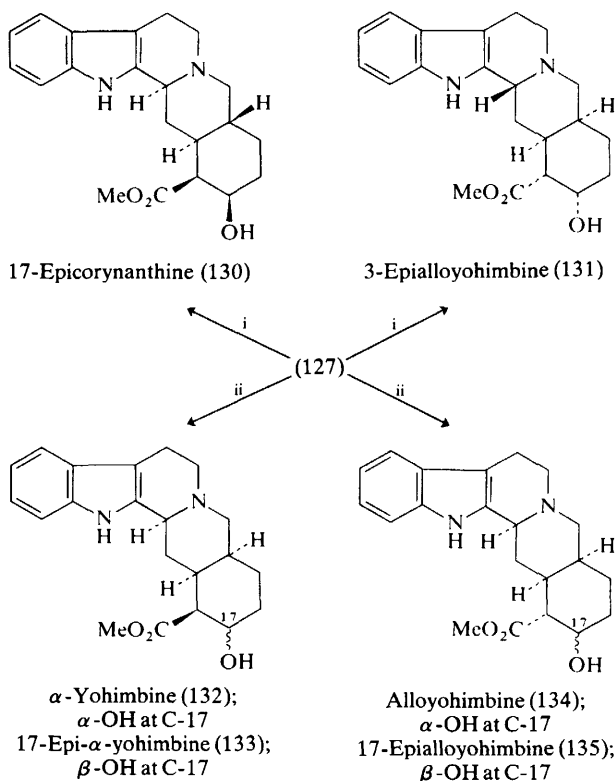
In the oxindole series full details of the syntheses of rhynchophylline, isorhynchophylline, mitraphylline, and formosanine<sup>123</sup> have now been published.<sup>124</sup>

A novel and extremely elegant synthesis<sup>125</sup> of the rhynchophylline isomers uses the recently prepared dihydrosecologanin aglycone (95), which condensed with 2-oxotryptamine to give in >90% yield a product formulated as the oxindole

<sup>123</sup> Y. Ban, M. Seto, and T. Oishi, *Tetrahedron Letters*, 1972, 2113; Y. Ban, N. Taga, and T. Oishi, *ibid.*, 1974, 187.

<sup>124</sup> Y. Ban, M. Seto, and T. Oishi, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 2605; Y. Ban, N. Taga, and T. Oishi, *ibid.*, 1976, **24**, 736.

<sup>125</sup> R. T. Brown, C. L. Chapple, and R. Platt, *Tetrahedron Letters*, 1976, 1401.



Reagents: i, NaOMe-MeOH-Pd/C-H<sub>2</sub>, r.t.; ii, NaBH<sub>4</sub>-MeCHOHMe

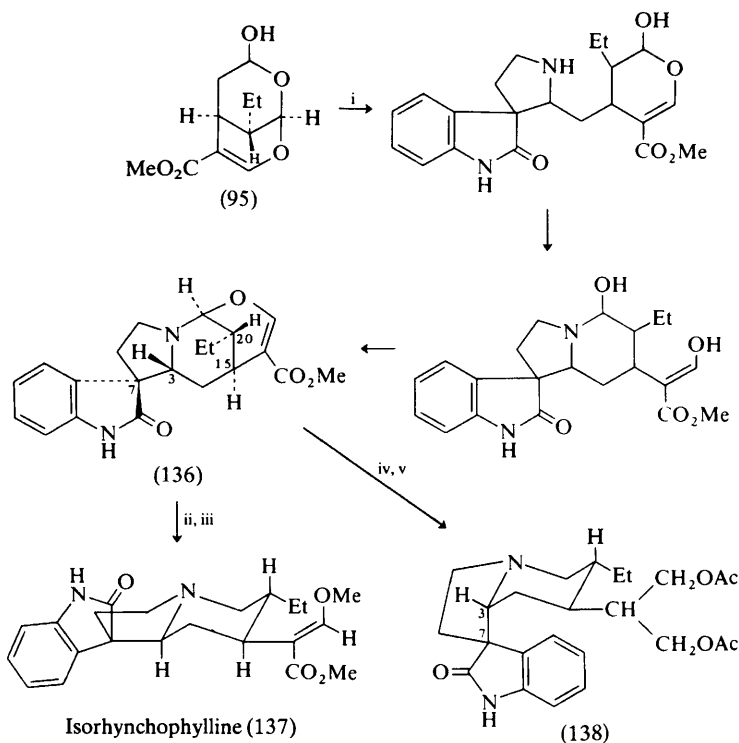
**Scheme 15b**

analogue (136) of dihydromancunine; this is presumably formed as indicated in Scheme 16. Hydrogenation of (136) severed the carbinolamine ether linkage to give an intermediate which, on methylation, gave isorhynchophylline (137) directly; rhynchophylline was then obtained by isomerization of (137) in glacial acetic acid. In principle the configurations at C-3, C-7 and C-20 could all be changed during the conversion of (136) into (137); hence no stereochemical correlation can be deduced with confidence. However, the Cotton effects exhibited by (136) at 290 and 260 nm indicate that C-7 belongs to the B series,<sup>126</sup> and that the C-3 H is  $\beta$ . Analysis of the n.m.r. spectrum indicated that the C-3 hydrogen is *trans* with respect to the C-15 hydrogen, as shown in (136); only the configuration at C-20 remains to be determined.<sup>125</sup>

The further study<sup>127</sup> of the reactions of (136) has led to the preparation of a series of pseudo-oxindole alkaloids which, it was previously thought, were too unstable to exist, owing to steric crowding.<sup>126</sup> Prolonged reduction (NaBH<sub>4</sub>) of (136) gave three

<sup>126</sup> See, for example, J. E. Saxton, in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1973, Vol. 14, Chapter 3.

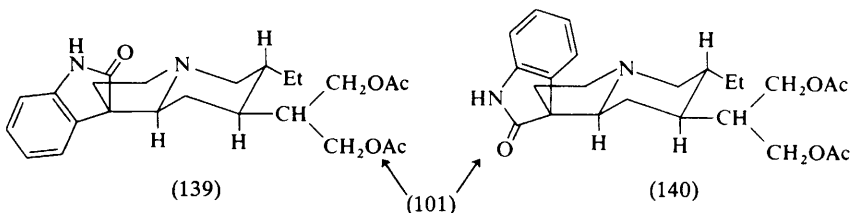
<sup>127</sup> R. T. Brown and R. Platt, *J.C.S. Chem. Comm.*, 1976, 357.



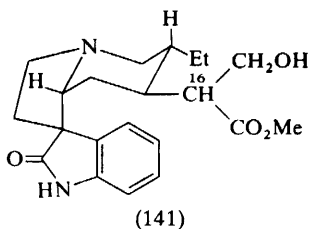
Reagents: i, 2-Oxotryptamine · HCl–EtOH–NEt<sub>3</sub>; ii, H<sub>2</sub>–cat.–MeOH–AcOH; iii, CH<sub>2</sub>N<sub>2</sub>; iv, NaBH<sub>4</sub>–MeOH; v, acetylation.

**Scheme 16**

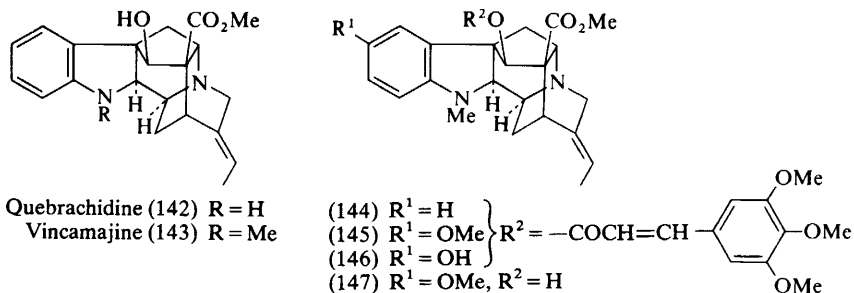
diols, separated and characterized as the acetates (138)–(140). The stereochemistry depicted for these acetates was deduced from their c.d. spectra and confirmed by conversion of dihydrositsirikine diol diacetate (101) and its 20 $\alpha$ -H epimer into the corresponding A/B pairs of oxindoles by chlorination with *t*-butyl hypochlorite and hydrolytic rearrangement. The products from dihydrositsirikine diol diacetate were shown to be identical with (139) and (140), thus establishing the configuration at C-20. The third product from (136), which had been given the pseudo stereochemistry (138), was converted by equilibration in glacial acetic acid into a mixture of (139) and (140), thus confirming the complete stereochemistry (138).



Since the reduction of (136) by sodium borohydride in deuteriomethanol resulted in the incorporation (at C-16) of only one deuterium atom the possibility of inversion at C-20 during the reduction is excluded. The oxindole analogue (136) of dihydromancunine must therefore also belong to the pseudo series, and C-20 retains its configuration in its formation from dihydrosecologanin. A third representative of the pseudo series is obtained by milder reduction of (136), which avoids both reduction of the ester group and inversion at C-3/C-7, and affords both C-16 epimers of the hydroxy-ester (141).<sup>127</sup>



**Sarpagine–Ajmaline–Picraline Group.** (+)-Quebrachidine (142) is one of the minor alkaloids of the root bark of *Cabucala striolata*,<sup>93a</sup> and of the stem and root bark of *C. torulosa*, which also contains (–)-vincamajine (143).<sup>94</sup> *O*-Trimethoxycinnamoylvincamajine (144), a known alkaloid, and six new vincamajine derivatives, have been extracted from the aerial parts of *Alstonia lanceolifera*.<sup>128</sup> Three of the new alkaloids are 10-methoxy-3,4,5-trimethoxycinnamoylvincamajine (145), 10-hydroxy-3,4,5-trimethoxycinnamoylvincamajine (146), and 10-methoxyvincamajine (147); the other three alkaloids are suspected to be the trimethoxybenzoyl



analogues of (144)–(146), but lack of material frustrated a complete structure elucidation. Accompanying these bases in this plant is N<sub>a</sub>-methyl-10-methoxyakuammidine, which was isolated earlier,<sup>129</sup> together with lanciferine and its 10-hydroxy- and 10-methoxy-derivatives. Other recent reports note the presence of vincamajoreine and lochnerine in *Vinca elegantissima*,<sup>101</sup> vomalidine in the stems of *Rauwolfia obscura*,<sup>86</sup> (–)-vobasine (148) in the leaves of *Pandaca minutiflora* Mgf.,<sup>130</sup> affinisine in the root bark of *Peschiera affinis* (Muell. Arg.)

<sup>128</sup> G. Lewin, N. Kunesch, A. Cavé, T. Sévenet, and J. Poisson, *Phytochemistry*, 1975, **14**, 2067.

<sup>129</sup> G. Lewin, N. Kunesch, and J. Poisson, *Compt. rend.*, 1975, **280** C, 987.

<sup>130</sup> N. Petitfrère, A. M. Morfaux, M. M. Debray, L. Le Men-Olivier, and J. Le Men, *Phytochemistry*, 1975, **14**, 1648.

Miers. ( $\equiv$  *Tabernaemontana affinis* Muell. Arg.),<sup>131</sup> dregamine and tabernaemontanine in the root bark of *Tabernaemontana elegans* Stapf.,<sup>132</sup> in the leaves of *T. coronaria* R.Br.,<sup>133</sup> and (together with vobasine) in the bark of *Ervatamia orientalis* (R.Br.) Turrell.<sup>134</sup>

The recent reversal of the configuration originally accepted at C-20 in dregamine and tabernaemontanine relied on the transformation of tabernaemontanine into ervatamine,<sup>135a</sup> whose stereochemistry was established by the X-ray method.<sup>135b</sup> Some supporting chemical evidence for the reversed assignments has now been added;<sup>136</sup> this includes a re-examination and rationalization of the course of hydrogenation of vobasine, and the behaviour of dregamine and tabernaemontanine on base-catalysed equilibration. Thus, the  $\beta$ -face of the piperidine ring in vobasine presents less hindrance to hydrogenation than the  $\alpha$ -face, hence dregamine (149) is the principal product. 16-Epivobasine would be expected to be much more slowly reduced, as indeed is observed; in fact, hydrogenation now occurs from the  $\alpha$ -face to give 16-epitabernaemontanine. In contrast to a previous report dregamine, on treatment with sodium methoxide, gives an epimer in which the ester methyl group is no longer shielded by the indole nucleus; this renders invalid the earlier conclusion that 16-epidregamine is not formed owing to the severe 1,3-diaxial interactions between the ethyl group and the methoxycarbonyl group. The revised configurations are also in accord with the pseudo-first-order rates of methiodide formation from dregamine (149) and tabernaemontanine (150).

A further correlation with a compound of known stereochemistry was achieved by Hofmann degradation of dregamine methiodide, which gave the methine (151) *via* its less stable  $\Delta^{5,16}$ -isomer; reduction of the ketone and ester groups, and formation of the cyclic ether (152) then afforded a compound identical with dihydro-taberpsychine methine (Scheme 17). In independent experiments it was established that C-16 had not suffered epimerization.<sup>136</sup>

Three new alkaloids in this group are accedine (153),  $N_a$ -methyl-16-epiaffinine (154), and  $N_a$ -demethyl-16-epiaccedine (155), obtained from the root bark of *Tabernaemontana accedens* Muell. Arg., which has not previously been investigated.<sup>137</sup> The structures (153) and (154) were confirmed by correlation with vobasine (148) *via* the common transformation product (156), and the structure of (155) was established by reductive methylation to dihydroaffinine (157) and by degradation to the methine base (158), also obtainable from affinine (Scheme 18).<sup>137</sup>

A detailed discussion of the chemical and physical evidence on which the structures of ervatamine, 20-epiervatamine, and 19,20-dehydroervatamine is based<sup>138</sup> has now been published.<sup>139</sup>

<sup>131</sup> F. J. Abreu Matos, R. Braz F., O. R. Gottlieb, F. W. L. Machado, and M. I. L. M. Madruga, *Phytochemistry*, 1976, **15**, 551.

<sup>132</sup> B. Gabetta, E. M. Martinelli, and G. Mustich, *Fitoterapia*, 1975, **46**, 195.

<sup>133</sup> B. Talapatra, A. Patra, and S. K. Talapatra, *Phytochemistry*, 1975, **14**, 1652.

<sup>134</sup> J. R. Knox and J. Slobbe, *Austral. J. Chem.*, 1975, **28**, 1813.

<sup>135</sup> (a) A. Husson, Y. Langlois, C. Riche, H. P. Husson, and P. Potier, *Tetrahedron*, 1973, **29**, 3095; (b) C. Riche, *Acta Cryst.*, 1974, **B30**, 610.

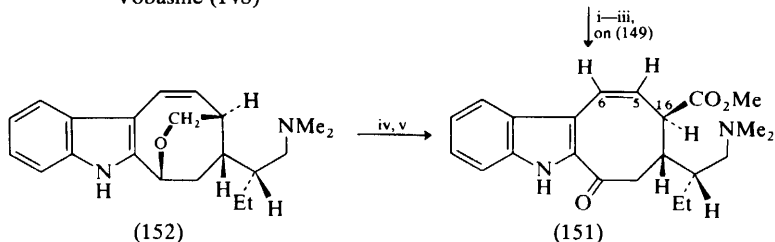
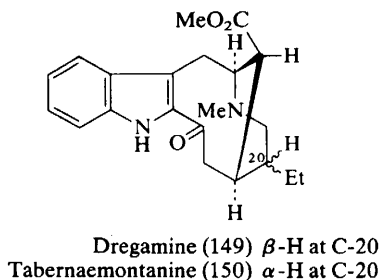
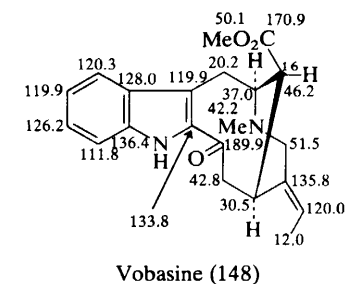
<sup>136</sup> J. R. Knox and J. Slobbe, *Austral. J. Chem.*, 1975, **28**, 1843.

<sup>137</sup> H. Achenbach and E. Schaller, *Chem. Ber.*, 1975, **108**, 3842; *Tetrahedron Letters*, 1976, 351.

<sup>138</sup> J. R. Knox and J. Slobbe, *Tetrahedron Letters*, 1971, 2149.

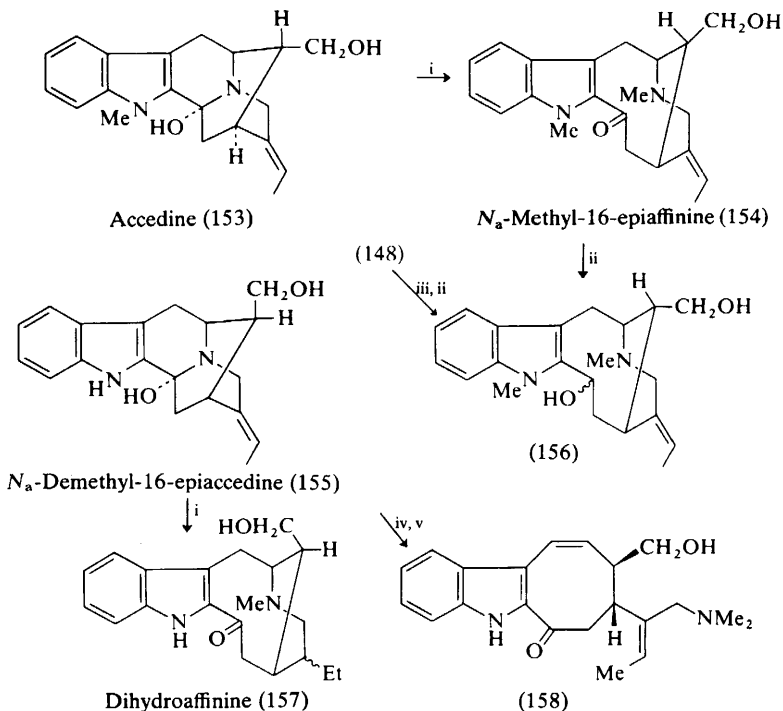
<sup>139</sup> J. R. Knox and J. Slobbe, *Austral. J. Chem.*, 1975, **28**, 1825.





Reagents: i, MeI; ii,  $\text{NH}_4\text{OH-H}_2\text{O}$ ; iii,  $\text{C}_6\text{H}_6$ -reflux; iv,  $\text{LiAlH}_4$ ; v, dil.  $\text{HCl-MeOH}$ -heat.

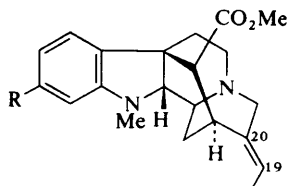
Scheme 17



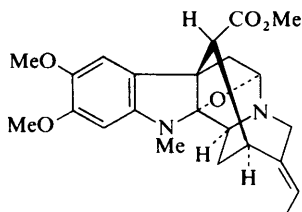
Reagents: i,  $\text{CH}_2\text{O-H}_2/\text{Pd}$ ; ii,  $\text{LiAlH}_4$ ; iii,  $\text{NaH-MeI}$ ; iv,  $\text{MeI-THF-r.t.}$ ; v,  $\text{NaOMe-MeOH}$ , r.t.

Scheme 18

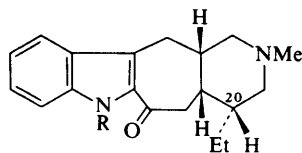
Of the 11 alkaloids so far isolated<sup>97</sup> from New Caledonian *Alstonia quaternata*, four belonging to the yohimbine group have been mentioned above. A fifth alkaloid, tubotaiwine, is a *Strychnos* alkaloid, and a sixth is vincamajine; the remaining five are related to akuammiline or picrinine. These are cathofoline [*N*<sub>a</sub>-methyldeacetyl-deformodihydro-2 $\beta$ -H akuammiline (159)], already known, and four new alkaloids, quaternine [10,11-dimethoxy-*N*<sub>a</sub>-methylpicrinine (160)], quaternidine (a methoxy-*N*<sub>a</sub>-methylpicrinine in which the position of the methoxy-group is uncertain), quaternoxine (the 19,20-epoxide of cathofoline), and quaternoline, a lactone-alcohol base (161) obviously related to quaternoxine.<sup>97</sup> The same group of workers



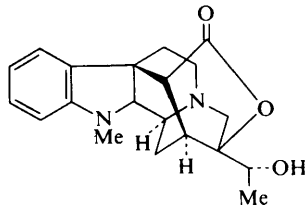
Cathofoline (159) R = H  
Cabucraline (162) R = OMe



Quaternine (160)



(164) R = H  
(165) R = Me



Quaternoline (161)

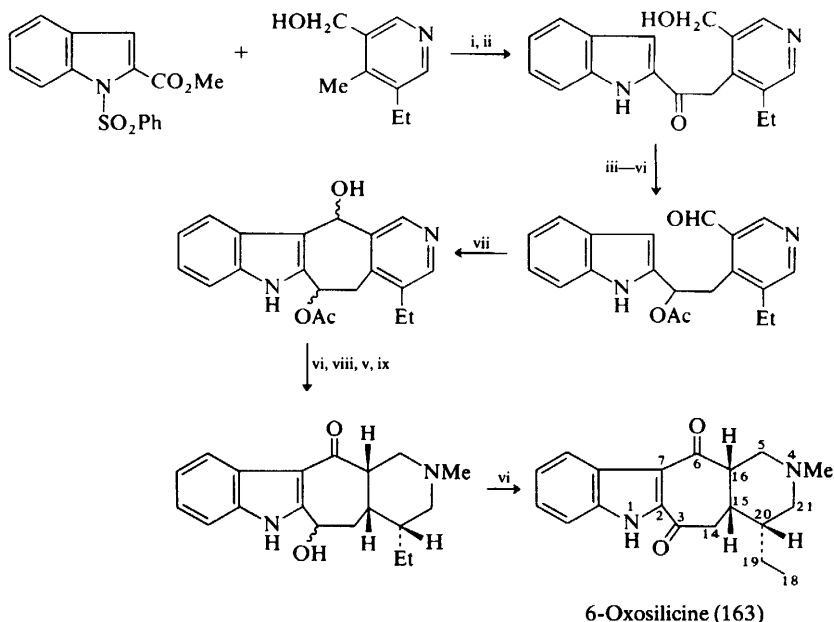
have investigated the constituents of *Alstonia vitiensis* (Seeman) var. *novo ebudica monachino*, from the New Hebrides, which contains in its bark three alkaloids of this group, including quaternoxine and vincorine.<sup>85</sup> The third alkaloid proves to be identical with cabucraline, isolated previously from *Cabucala erythrocarpa*<sup>140</sup> and *C. torulosa*,<sup>94</sup> and now<sup>85</sup> formulated as 11-methoxycathofoline (162), but details of the structure elucidation are not yet available. Aspidodasycarpine, which also belongs in this group, has been isolated from *Aspidosperma cuspa*,<sup>87</sup> and pseudoakuammigine from the root bark of *Alstonia scholaris*.<sup>141</sup>

6-Oxosilicine (163), a new alkaloid of a Malagasy plant, *Hazunta silicicola* Pichon, has an  $\alpha$ -acylindole structure related to 20-epiervatamine. Although details of the isolation are still not available, the synthesis of (163) has already been announced<sup>142</sup> (Scheme 19); this constitutes the first total synthesis of an alkaloid of the dihydrovobasine-ervatamine group. The major feature of the route adopted is that the acylindole linkage is formed at the outset, and the bond to C-7 (indole  $\beta$ -position) formed much later. This route may well be applicable to the synthesis of other 2-acylindole alkaloids.

<sup>140</sup> L. Douzoua, M. Mansour, M. M. Debray, L. Le Men-Olivier, and J. Le Men, *Phytochemistry*, 1974, **13**, 1994.

<sup>141</sup> W. Boonchuay and W. E. Court, *Phytochemistry*, 1976, **15**, 821.

<sup>142</sup> F. Reis, K. Bannai, and H. P. Husson, *Tetrahedron Letters*, 1976, 1085.



Reagents: i,  $\text{Bu}^n\text{Li}$ ; ii,  $\text{OH}^-$ ; iii,  $\text{NaBH}_4\text{-MeOH}$ ; iv,  $\text{Ac}_2\text{O}$ ; v,  $\text{NaBH}_4$ ; vi,  $\text{MnO}_2\text{-THF}$ ; vii,  $\text{Al}_2\text{O}_3$ ; viii,  $\text{MeI}$ ; ix,  $\text{PtO}_2/\text{H}_2$ .

**Scheme 19**

The facile transmethylation which occurs on attempted Hofmann degradation of the methohydroxide of 16-demethoxycarbonyl-20-epiervatamine (164), with formation of the corresponding  $N_\alpha$ -methyl derivative (165), argues in favour of an intramolecular shift which requires a *cis* C/D ring junction. This has now been established by the *X*-ray crystal structure analysis of (164), which has confirmed the stereochemistry shown.<sup>143</sup>

Details of the structure elucidation of gardneramine and 18-demethyl-gardneramine have now been published;<sup>144</sup> these and other *Gardneria* alkaloids figure prominently in an account<sup>3</sup> of Sakai's own investigations on indole alkaloids of Japanese plants.

The  $^{13}\text{C}$  n.m.r. data for dregamine (149), tabernaemontanine (150), vobasine [(148), on which structure the data are quoted], and some related compounds have been compiled, and complete assignments made; the chemical shifts for pairs of epimers, *e.g.* (149) and (150), are discussed in terms of their stereochemistry.<sup>145</sup>

The photochemical oxidation of ajmaline affords a new method of degradation to sarpagine derivatives.<sup>146</sup> For example, irradiation of ajmaline (166) in methanol in the presence of eosin and potassium cyanide leads to an indolic aminonitrile (167),

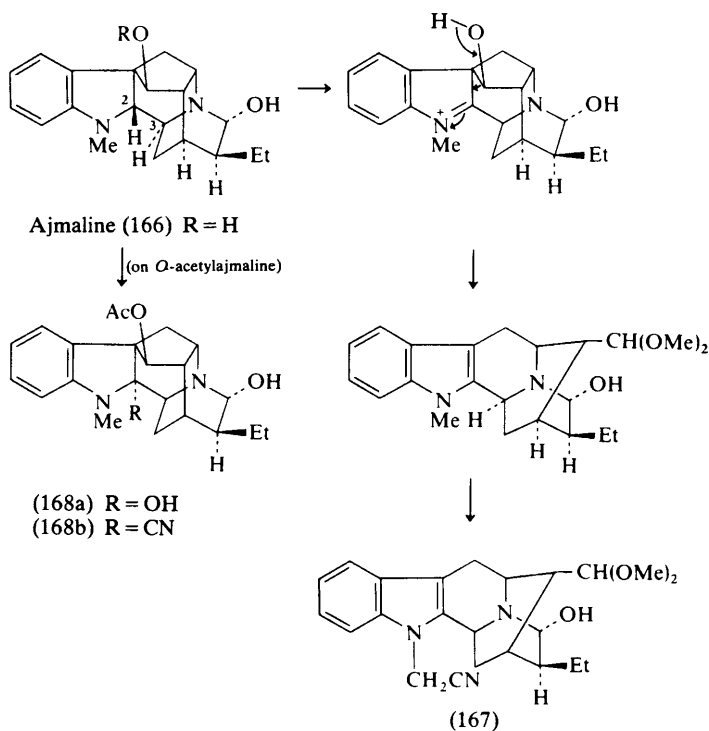
<sup>143</sup> A. Shafiee, A. Ahond, A. M. Bui, Y. Langlois, C. Riche, and P. Potier, *Tetrahedron Letters*, 1976, 921.

<sup>144</sup> S. Sakai, N. Aimi, A. Kubo, M. Kitagawa, M. Hanasawa, K. Kateno, K. Yamaguchi, and J. Haginiwa, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 2805.

<sup>145</sup> A. Ahond, A. M. Bui, P. Potier, E. W. Hagaman, and E. Wenkert, *J. Org. Chem.*, 1976, **41**, 1878.

<sup>146</sup> Y. Hubert-Brierre, D. Herlem, and F. Khuong-Huu, *Tetrahedron*, 1975, **31**, 3049.

whose formation presumably involves oxidation at C-2 (Scheme 20). In consonance with this view, oxidation of 17-acetyljalmaline affords simply the 2 $\alpha$ -hydroxy-compound (168a), and oxidation in the presence of cyanide gives the related nitrile. (168b), also obtained by the action of potassium cyanide on (168a). Formic acid reduction of (168a), followed by saponification, gives a good yield of 2-epiajmaline whose diacetyl derivative gives, on irradiation and gentle saponification, the same 2 $\alpha$ -hydroxy-derivative (168a).



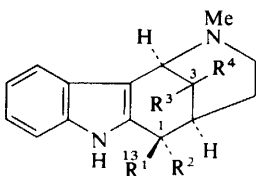
Scheme 20

**Strychnine-Akuammicine-Condyllocarpine-Ellipticine-Uleine Group.** New extractions recorded during the year have resulted in the isolation of (+)-stemmadenine, (+)-condyllocarpine, and (+)-tubotaiwine from *Pandaca minutiflora*; <sup>130</sup> the last alkaloid also occurs in *Alstonia quaternata*. <sup>97</sup> Deacetylretuline, which has not been encountered previously in nature, occurs in the root bark of *Strychnos variabilis* De Wild, together with several bisindole alkaloids of unknown constitution. <sup>147</sup> Retuline itself, and two alkaloids camptine and camptinine, which have as yet only been partially characterized, have been isolated from the root bark of *S. camptoneura*. <sup>148a</sup> *Peschiera affinis* <sup>131</sup> and the bark of *Aspidosperma campus-belus* A. P. Duarte

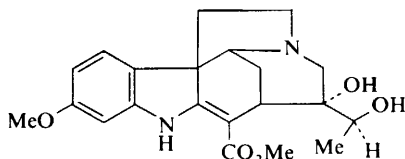
<sup>147</sup> L. Angenot, N. G. Bisset, and M. Franz, *Phytochemistry*, 1975, **14**, 2519.

<sup>148</sup> (a) J. Garnier, M. Koch, and M. Plat, *Plant. Med. Phytother.*, 1974, **8**, 281 (*Chem. Abs.*, 1975, **83**, 93 830); (b) R. F. Garcia, M. and K. S. Brown, *Phytochemistry*, 1976, **15**, 1093.

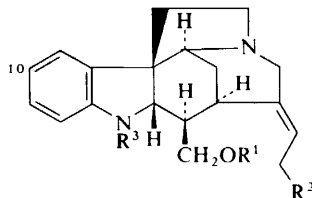
contain olivacine,<sup>148b</sup> the bark of *A. formosanum* A. P. Duarte has yielded uleine (169a), 3-epiuleine (169b), and 1,13-dihydro-13-hydroxyuleine (169c),<sup>148b</sup> and *Ervatamia orientalis* contains apparicine.<sup>134</sup> The bark of *Alstonia vitiensis*<sup>85</sup> contains an alkaloid, alstovine, of akuammicine type, which is formulated as 11-methoxycompactinervine (170). The minor alkaloids of *A. scholaris* root include<sup>141</sup> akuammicine, akuammicine  $N_b$ -metho salt, akuammicine  $N_b$ -oxide,  $N_b$ -demethylechitamine, and tubotaiwine; akuammicine also occurs<sup>93b</sup> in *Catharanthus trichophyllus*. The leaves and branches of *Strychnos henningsii* Gilg. from Madagascar (locally known as 'tsilanimboana') contain<sup>149</sup> ten alkaloids, of which four



Uleine (169a)  $R^1, R^2 = CH_2, R^3 = Et, R^4 = H$   
 3-Epi-uleine (169b)  $R^1, R^2 = CH_2, R^3 = H, R^4 = Et$   
 (169c)  $R^1 = CH_2OH, R^2 = R^4 = H, R^3 = Et.$



Alstovine (170)



(171)  $R^1 = R^2 = R^3 = H$   
 (172)  $R^1 = Ac, R^2 = OH, R^3 = H$   
 (173a)  $R^1 = H, R^2 = OH, R^3 = Ac$   
 (173b)  $R^1 = R^3 = H, R^2 = OH$

derivatives of tsilanine have previously<sup>150</sup> been recorded. The six alkaloids found recently include retuline and five new bases, *N*-deacetylisoretuline (171), *N*-deacetyl-17-*O*-acetyl-18-hydroxyisoretuline (172), 18-hydroxyisoretuline (173a), *N*-deacetyl-18-hydroxyisoretuline (173b), and tsilanibine, which is 10-methoxy-*N*-deacetylisoretuline.

The only synthetic work reported recently in this area involves yet more syntheses of ellipticine (174)<sup>151</sup> and olivacine (175),<sup>152,153</sup> and one of guatambuine (176) (Scheme 21).<sup>153</sup> It should be noted that in Kametani's synthesis<sup>152</sup> the condensation of the dibromide (177) with indole to give olivacine is claimed to be regiospecific.

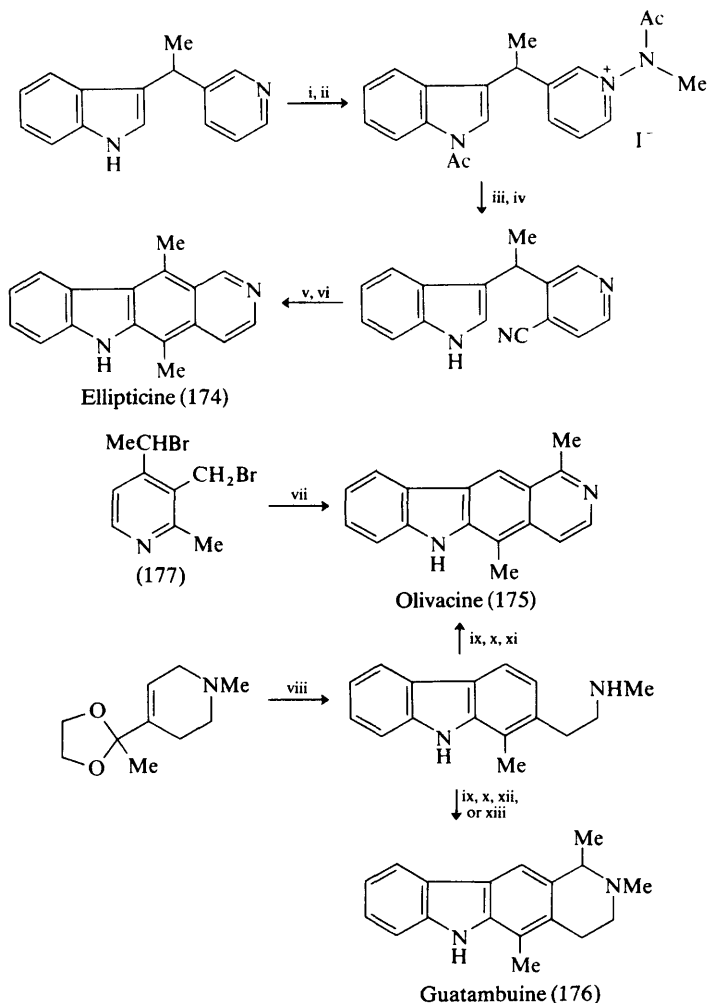
<sup>149</sup> M. Koch, E. Fellion, and M. Plat, *Phytochemistry*, 1976, **15**, 321.

<sup>150</sup> R. Sarfati, M. Pais, and F. X. Jarreau, *Phytochemistry*, 1970, **9**, 1107.

<sup>151</sup> M. Sainsbury and R. F. Schinazi, *J.C.S. Chem. Comm.*, 1975, 540; *J.C.S. Perkin I*, 1976, 1155.

<sup>152</sup> T. Kametani, Y. Ichikawa, T. Suzuki, and K. Fukumoto, *Heterocycles*, 1975, **3**, 401; *J.C.S. Perkin I*, 1975, 2102.

<sup>153</sup> R. Besselièvre and H. P. Husson, *Tetrahedron Letters*, 1976, 1873.



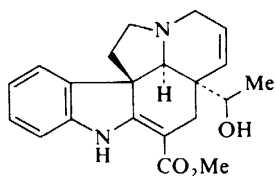
Reagents: i,  $\text{Ac}_2\text{O}-\text{NEt}_3$ ; ii, O-mesitylsulphonylhydroxylamine- $\text{CH}_2\text{Cl}_2$ , then  $\text{Ac}_2\text{O}$ , then MeI; iii, KCN- $\text{NH}_4\text{Cl}$ ; iv,  $\text{Al}_2\text{O}_3$  (basic) chromatography; v, LiMe; vi, 20%  $\text{AcOH}-\text{H}_2\text{O}$ ; vii, indole, HBr, heat; viii, indole,  $\text{AcOH}-\text{H}_2\text{O}$ , reflux; ix, acetylation; x,  $\text{POCl}_3$ ; xi, Pd/C-decalin, reflux; xii,  $\text{NaBH}_4$ ; xiii,  $\text{CH}_3\text{CHO}/\text{H}^+$ .

**Scheme 21**

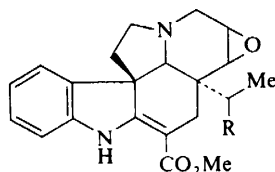
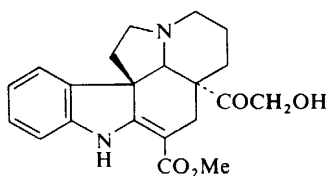
**Aspidospermine-Aspidofractine-Eburnamine Group.** The leaves of *Pandaca minutiflora* contain<sup>154</sup> (+)-vincadiformine, which also occurs<sup>154</sup> in the leaves of *Amsonia tabernaemontana*, together with ten other alkaloids [tabersonine, (+)-1,2-dehydroaspidospermidine, (-)-quebrachamine, lochnericine, ( $\pm$ ) and (-)-vincadine, (-) and ( $\pm$ )-epivincadine, (+)-14,15-dehydrovincadine, and (+)-14,15-dehydroepivincadine]; the roots contain the first four alkaloids and eburnamonine.

<sup>154</sup> B. Zsádon, M. Szilasi, and P. Kaposi, *Herba Hung.*, 1974, **13**, 69 (*Chem. Abs.*, 1975, **83**, 40 171).

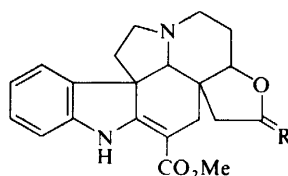
14,15-Dehydro-19-epiminovincinine (178) is a new alkaloid from *Catharanthus lanceus* roots,<sup>155</sup> and minovincine, minovincinine, vindorosine, and (–)echitovenine are among the alkaloids of *Catharanthus trichophyllus*;<sup>93b</sup> this enantiomer of echitovenine has not previously been encountered. The cytotoxic and antitumour properties of this plant may be due in part to lochnericine (179) and hörhammericine (180), also isolated. The remaining alkaloid from this source, cathaphylline (181), belongs to the vincadifformine group; since the additional two oxygen atoms must be in the angular side-chain (mass spectral evidence) and cathaphylline is neither an aldehyde nor an acid it must have the  $\alpha$ -ketol structure (181).<sup>93b</sup> *Vinca herbacea* has been reported<sup>156</sup> to contain *N*-methyl-14,15-dehydroaspidospermidine, and *V. erecta* pseudokopsinine and minovincinine.<sup>157</sup> Other reported occurrences of kopsane derivatives include kopsanone, epikopsanol, and kopsanol in *Aspidosperma cuspa*,<sup>87</sup> a species that does not seem to belong securely in any of the sub-groups of



(178)

(179) R = H  
(180) R = OH

Cathaphylline (181)

Deoxoapodine (182) R = H<sub>2</sub>  
Apodine (183) R = O

the *Aspidosperma* genus. Two other *Aspidosperma* species not previously investigated are *A. formosanum* A. P. Duarte, which elaborates aspidocarpine and the uleine derivatives mentioned above, and *A. desmanthum*, which contains aspidobaline.<sup>148b</sup> Deoxoapodine and apodine, two new constituents of *Tabernaemontana armeniaca*, are claimed<sup>158</sup> to be (182) and (183) respectively, but the evidence on which these structures are based is not readily available. A quaternary alkaloid, Alkaloid Q-2, isolated as the iodide, C<sub>21</sub>H<sub>27</sub>N<sub>2</sub>O<sub>3</sub>I, has been obtained from the bark of *Aspidosperma peroba* F. Allem. ex Sald.,<sup>159</sup> but nothing is known of its structure beyond the fact that it contains a  $\beta$ -anilinoacrylate chromophore.

<sup>155</sup> B. Gabetta, E. M. Martinelli, and G. Mustich, *Fitoterapia*, 1976, **47**, 6.

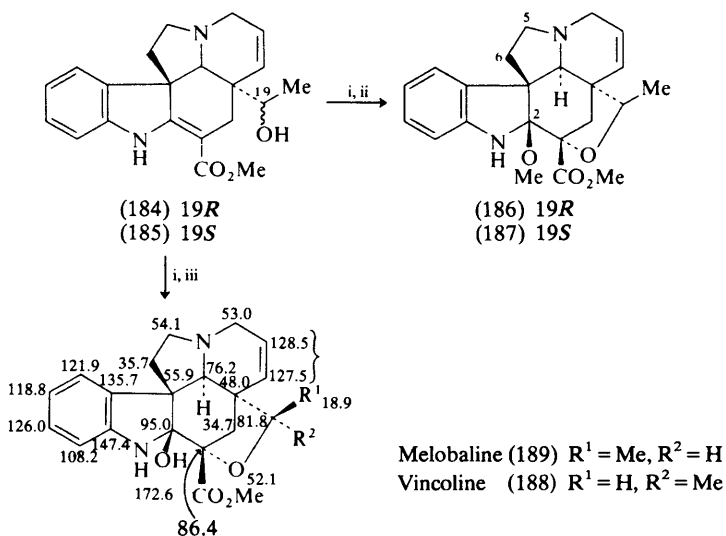
<sup>156</sup> N. A. Babeev, A. M. Aliev, and V. M. Malikov, *Khim. prirod. Soedinenii*, 1975, **11**, 267 (*Chem. Abs.*, 1975, **83**, 128 655).

<sup>157</sup> M. M. Khalmirzaev, V. M. Malikov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, **11**, 264 (*Chem. Abs.*, 1975, **83**, 128 651).

<sup>158</sup> R. Iglesias and L. Diatta, *Rev. Cenic, Cienc. Fis.*, 1975, **6**, 135, 141 (*Chem. Abs.*, 1976, **84**, 44502, 44503).

<sup>159</sup> M. Quaisuddin, *Bangladesh J. Sci. Ind. Res.*, 1974, **19**, 118 (*Chem. Abs.*, 1975, **83**, 114 713).

The oxidative fission of the 2,19-bond in vindoline by means of iodine affords the epimeric 19-iodotabersonines,<sup>160a</sup> which can be converted into the epimeric 19-hydroxy-tabersonines (184) and (185), identical with two new alkaloids isolated from the aerial parts of *Catharanthus ovalis* Mgf.<sup>161</sup> Accompanying these alkaloids in the plant are two further bases, (186) and (187), whose mass spectra show a close similarity to that of vincoline, except that the fragments containing the indole unit are displaced by 14 mass units, *i.e.* (186) and (187) contain a methoxy-group in place of the hydroxy-group of vincoline (188). Analysis of the mass spectrum indicates that the methoxy-group can only be situated at position 2, 5, or 6, but the <sup>1</sup>H n.m.r. spectrum, which contains signals due to the four protons of an unsubstituted ethanamine chain, is only consistent with a methoxy-group at C-2, contrary to the earlier proposal<sup>160b</sup> for vincoline. This was recently confirmed by a partial synthesis of all three alkaloids from the 19-hydroxytabersonines (Scheme 22); the  $\beta$  orientation of the methoxy/hydroxy-group in these alkaloids was deduced on steric grounds



Reagents: i, Pb(OAc)<sub>4</sub>; ii, NaOMe; iii, silica-H<sub>2</sub>O.

Scheme 22

from an examination of molecular models,<sup>161</sup> and is consistent with the inertness of this function in vincoline towards NaBH<sub>4</sub>, or attempts at acetylation.<sup>162</sup> This study also led to a reappraisal of the structure of melobaline, which was originally based on an erroneous structure for vindoline, now corrected.<sup>160a</sup> Melobaline and vincoline behave in all respects as epimers, and on the basis of their <sup>1</sup>H and <sup>13</sup>C n.m.r. spectra are formulated as C-19 epimers. The position of the hydroxy-group is confirmed by the <sup>13</sup>C spectrum, since a signal due to a quaternary carbon at 95.0 p.p.m. is

<sup>160</sup> (a) J. E. Saxton in 'The Alkaloids', ed. M. F. Grondon (Specialist Periodical Reports), The Chemical Society, London, 1976, Vol. 6, p. 234; (b) *ibid.*, p. 235; (c) *ibid.*, p. 227; (d) *ibid.*, p. 226; (e) *ibid.*, p. 243; (f) *ibid.*, p. 249.

<sup>161</sup> R. Z. Andriamialisoa, N. Langlois and P. Potier, *Tetrahedron Letters*, 1976, 163.

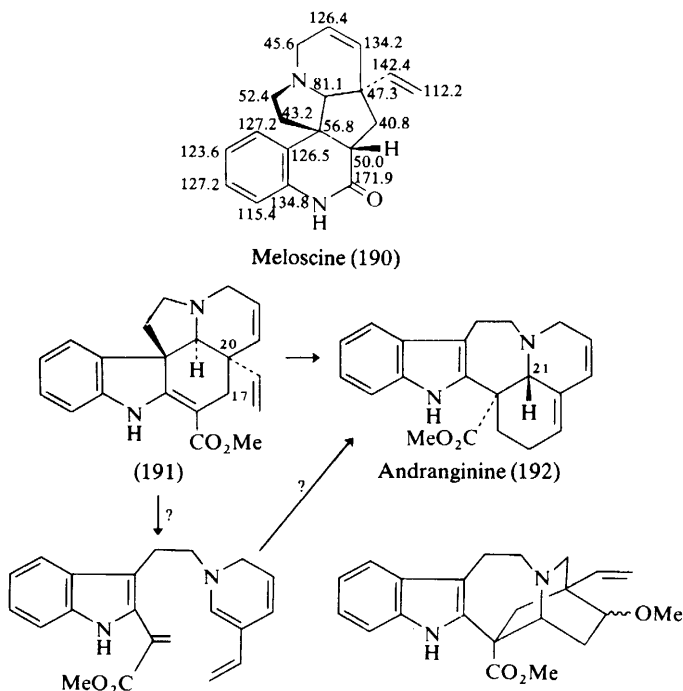
<sup>162</sup> M. Damak, A. Ahond, and P. Potier, *Tetrahedron Letters*, 1976, 167.



consistent only with a carbon atom which carries both nitrogen and oxygen substituents, *i.e.* C-2. Hence vincoline is (188) and melobaline is (189) ( $^{13}\text{C}$  n.m.r. data added).<sup>162</sup>

The meloscine group of alkaloids has been added to the list of those whose  $^{13}\text{C}$  n.m.r. spectra have been thoroughly analysed by a French-American collaboration;<sup>163</sup> as example, the assignments for meloscine (190) are quoted. Details have been given,<sup>164</sup> in a Russian paper, of the X-ray determination of the structure<sup>160b</sup> of pseudokopsinine.

The study of the synthesis and transformations of the *Aspidosperma* alkaloids shows no sign of abating, and much of the fascinating work in this area is concerned with tabersonine, which appears to occupy a central position chemically as well as biosynthetically. One of these investigations<sup>165</sup> involves the thermal rearrangement of  $\Delta^{18}$ -tabersonine (191), obtained from 19-iodotabersonine (178; I in place of OH) by elimination, which affords a mixture of unchanged (191), together with ( $\pm$ )-andranginine (192), ( $\pm$ )-21-epiandranginine, *optically active* 15-methoxy-14,15-dihydro- $\Delta^{18}$ -allocatharanthine (193), and some 1-methyl-2-hydroxycarbazole (Scheme 23). Andranginine has thus been obtained by partial synthesis from both



**Scheme 23**

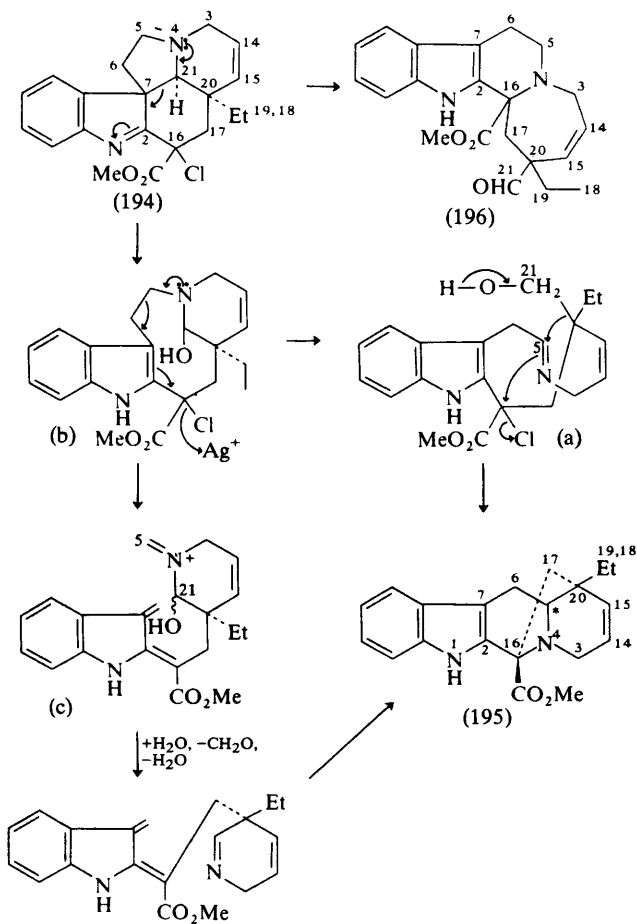
<sup>163</sup> M. Daudon, M. H. Mehri, M. M. Plat, E. W. Hagaman, F. M. Schell, and E. Wenkert, *J. Org. Chem.*, 1975, **40**, 2838.

<sup>164</sup> S. M. Nasirov, V. G. Andrianov, Yu. T. Struchkov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, 197.

<sup>165</sup> R. Z. Andriamialisoa, L. Diatta, P. Rasoanaivo, N. Langlois, and P. Potier, *Tetrahedron*, 1975, **31**, 2347.

precondylocarpine acetate (*Strychnos* group)<sup>160c</sup> and the *Aspidosperma* group. The isolation of both C-21 epimers suggests that even if the reaction proceeds *via* reverse Diels–Alder fission of ring C, the recyclization is not a concerted, stereospecific  $2\pi + 4\pi$  cyclization, but must proceed by a stepwise mechanism. On the other hand, the formation of *optically active* (193) demonstrates that, in this case at least, the 17,20 bond must remain intact during the rearrangement.

An even more remarkable rearrangement occurs when 16-chloro-1,2-dehydrotabersonine (194) is briefly heated,<sup>166</sup> or subjected to silver-ion assisted solvolysis.<sup>167</sup> The product is the tetrahydro- $\beta$ -carboline derivative (195), although the thermal rearrangement also leads to some (196). In Scheme 24 two mechanistic

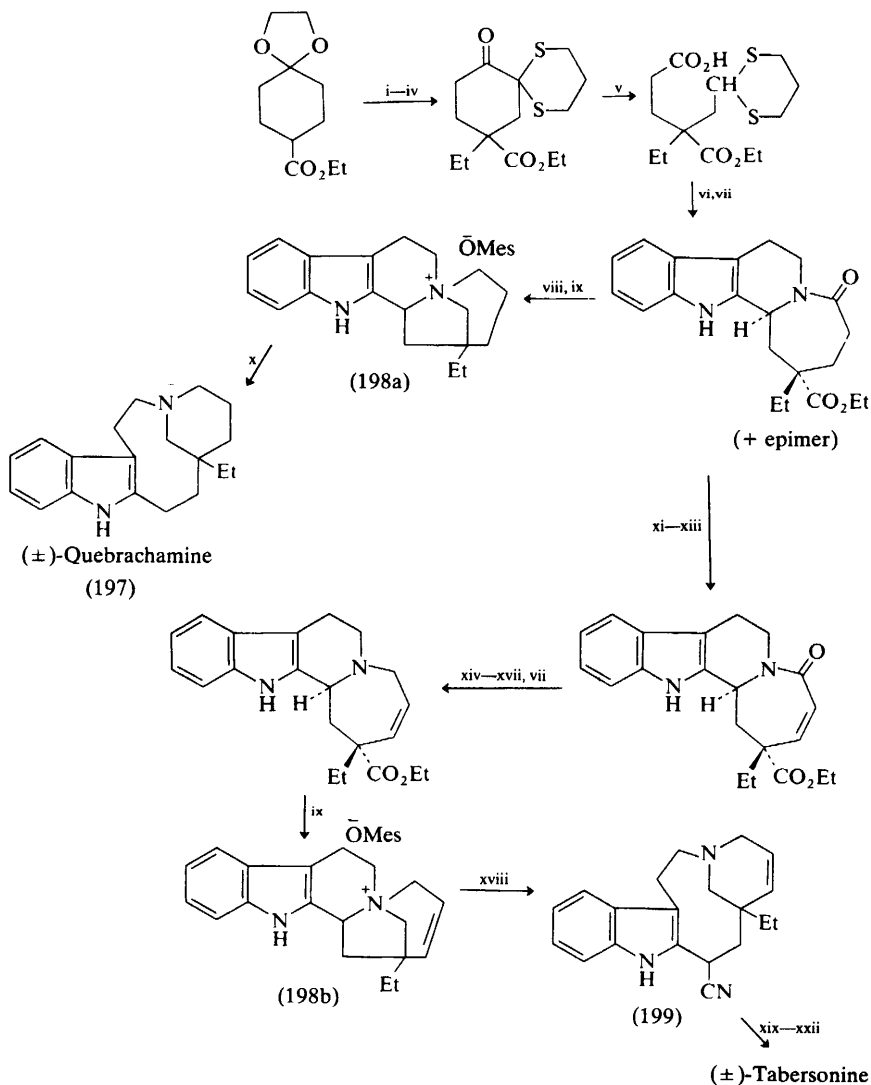


Scheme 24

<sup>166</sup> J. Lévy, C. Pierron, G. Lukacs, G. Massiot, and J. Le Men, *Tetrahedron Letters*, 1976, 669.

<sup>167</sup> W. Hofheinz, P. Schönholzer, and K. Bernauer, *Helv. Chim. Acta*, 1976, **59**, 1213.

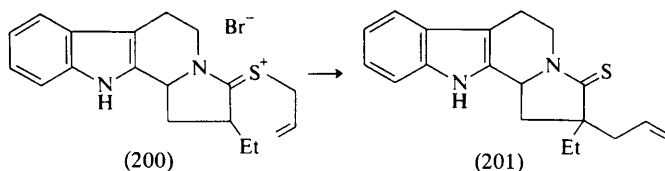
proposals are outlined, the crucial difference between which concerns the origin (C-5 or C-21) of the asterisked carbon atom in (195). Lévy's mechanism, *via* (a), requires expulsion of C-21, hence C\* is C-5, whereas Bernauer's mechanism, *via* (b) and (c), postulates expulsion of C-5, and C\* is therefore C-21.



Reagents: i, LDA-EtBr; ii, dil.  $\text{H}_2\text{SO}_4$ ; iii, pyrrolidine; iv,  $\text{CH}_2(\text{CH}_2\text{SO}_2\text{SC}_6\text{H}_4\text{Me})_2$ ; v,  $\text{NaH}-3 \text{ H}_2\text{O}$ ; vi, tryptamine-DCC; vii, MeI,  $\text{H}_2\text{O}$ , MeCN, reflux; viii,  $\text{LiAlH}_4\text{-THF}$ ; ix,  $\text{MesCl-py}$ ,  $0^\circ\text{C}$ , then heat; x,  $\text{Na-NH}_3$ ; xi,  $\text{LDA-PhSSPh}$ ; xii,  $m\text{-ClC}_6\text{H}_4\text{CO}_3\text{H}$ ; xiii,  $\text{C}_6\text{H}_5\text{Me}-110^\circ\text{C}$ , 30 min; xiv, KOH; xv,  $\text{Cl-CO}_2\text{Et-NEt}_3$ ; xvi,  $\text{NaBH}_4\text{-H}_2\text{O-THF}$ ; xvii,  $\text{Me}_3\text{SiCl-NEt}_3$ ; xviii, KCN; xix, KOH,  $\text{O}(\text{CH}_2\text{CH}_2\text{OH})_2$ ; xx,  $\text{MeOH-HCl}$ ; xxi,  $\text{CH}_2\text{N}_2$ ; xxii,  $\text{Pt/O}_2\text{-EtOAc}$ .

Scheme 25

A new synthesis of ( $\pm$ )-quebrachamine<sup>168a</sup> consists essentially of a new route to the pentacyclic quaternary salt (198a), which has previously been converted into quebrachamine (Scheme 25); similarly, the extension of the route to give the unsaturated salt (198b) constitutes a synthesis of ( $\pm$ )-tabersonine, since Ziegler *et al.* have previously converted this salt, *via* the nitrile (199), into tabersonine. Yet another synthesis of quebrachamine involves as key step the thio-Claisen rearrangement of (200), which presumably gives (201), from which the quaternary salt (198a) can be obtained by obvious methods; however, details of this original approach are not yet available.<sup>168b</sup>



Details of Kutney's syntheses of vincadine, vincaminoreine, vincaminorine, vincadifformine, minovine, and vincaminoridine have now been published.<sup>169</sup>

The total synthesis of *N*-acetylcylindrocarpinol (202), cylindrocarpine (203), and cylindrocarpidine (204), by appropriate modification of Stork's route to aspidospermine, has been reported;<sup>170</sup> this approach involved construction of an aspidospermidine analogue containing an angular allyl group, which could be transformed into the functionalized two-carbon unit present in these alkaloids in the terminal stages of the synthesis (Scheme 26).

The total synthesis of vindoline (205) from the pentacyclic ketone (206), whose formation was discussed in last year's Report,<sup>160d</sup> has now been completed (Scheme 27),<sup>171</sup> essentially according to the route adopted earlier in the synthesis of vindorosine. The reduction of the C-17 ketone function in the penultimate stage with normal hydride reducing agents was not stereospecific. However, this was circumvented by addition of aluminium chloride, which presumably formed a complex involving the C-16 hydroxy-group and N<sub>6</sub>; reduction by a bulky complex hydride then ensured preferential  $\alpha$ -attack with formation of deacetylvindoline.<sup>171</sup>

Ban's synthetic work has been taken a stage further this year with the first total synthesis of aspidofractinine (207) (Scheme 28).<sup>172</sup> The closely related alcohol (208), synthesized previously, could not be converted into aspidofractinine; hence, an alternative synthesis was devised from the important intermediate (209), in which the sixth ring was introduced *via* a Diels-Alder addition of nitroethylene, which was highly regio- and stereo-selective, to the diene (210).

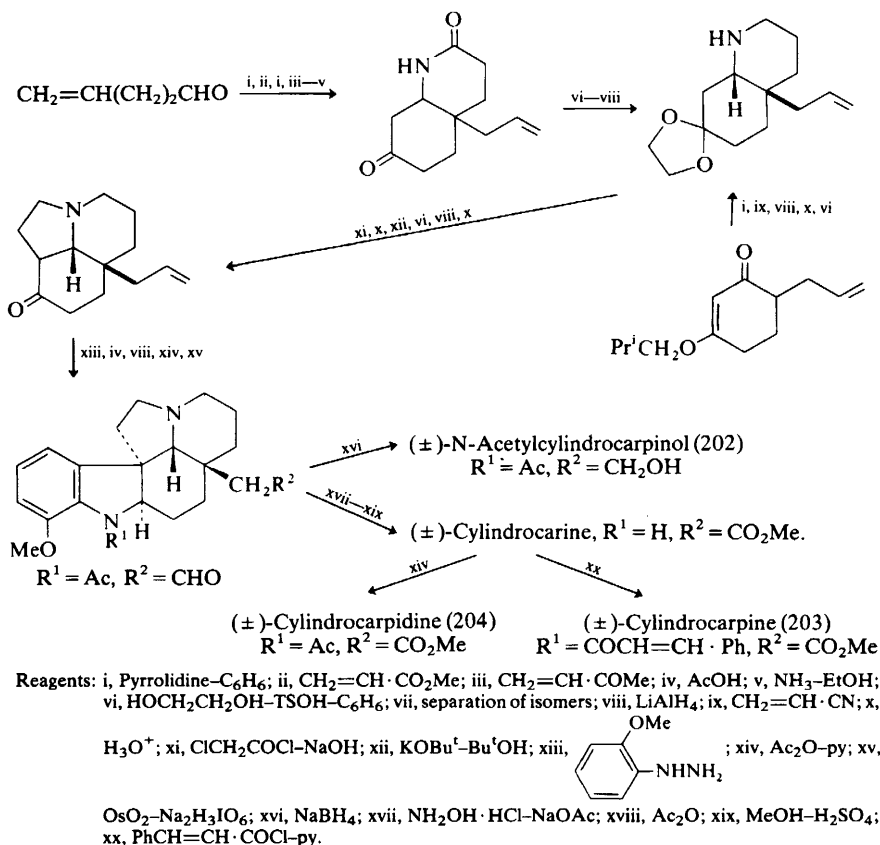
<sup>168</sup> (a) S. Takano, S. Hatakeyama, and K. Ogasawara, *J. Amer. Chem. Soc.*, 1976, **98**, 3022; (b) S. Takano, S. Hatakeyama, M. Hirama, T. Araki, S. Yamada, M. Sato, T. Sugahara, K. Shishido, and K. Ogasawara, *Hukusokan Kagaku Toronkai Koen Yoshishu* 8th 1975, 124 (*Chem. Abs.*, 1976, **84**, 165 085).

<sup>169</sup> J. P. Kutney, K. K. Chan, A. Failli, J. M. Fromson, C. Gletsos, A. Leutwiler, V. R. Nelson, and J. P. de Souza, *Helv. Chim. Acta*, 1975, **58**, 1648.

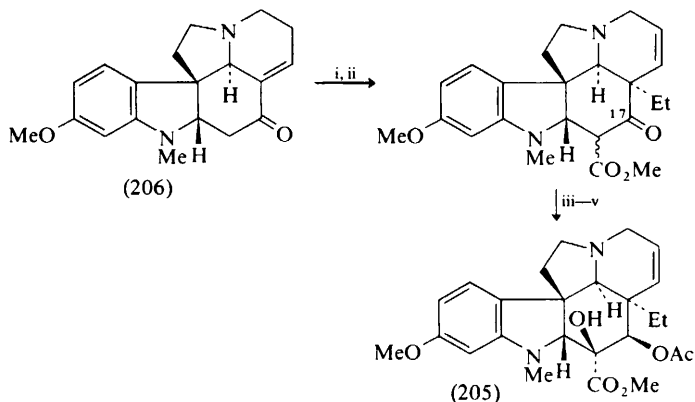
<sup>170</sup> J. E. Saxton, A. J. Smith, and G. Lawton, *Tetrahedron Letters*, 1975, 4161.

<sup>171</sup> M. Ando, G. Büchi, and T. Ohnuma, *J. Amer. Chem. Soc.*, 1975, **97**, 6880.

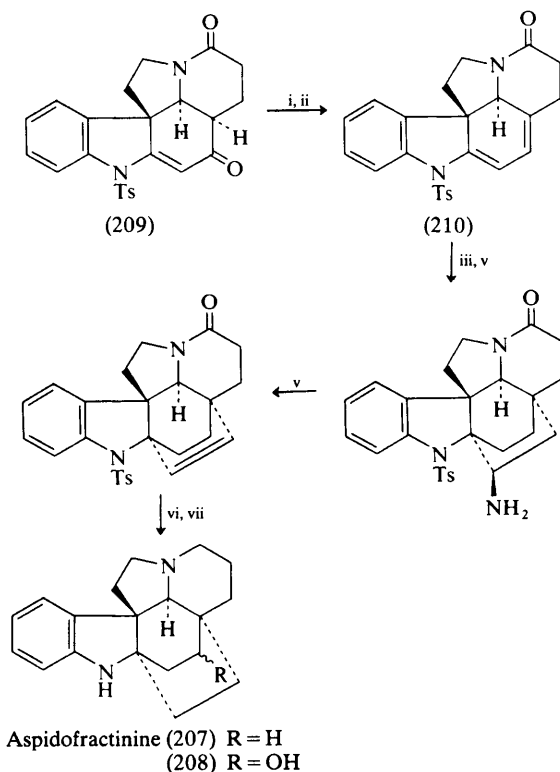
<sup>172</sup> Y. Ban, Y. Honma, and T. Oishi, *Tetrahedron Letters*, 1976, 1111.



Scheme 26



Scheme 27



Reagents: i, NaBH<sub>4</sub>-EtOH-THF; ii, PBr<sub>3</sub>-py-C<sub>6</sub>H<sub>6</sub>; iii, CH<sub>2</sub>=CH-NO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub> r.t.; iv, H<sub>2</sub>/PtO<sub>2</sub>/5·3 atm; v, NaNO<sub>2</sub>-AcOH, 55 °C, 1 h; vi, LiAlH<sub>4</sub>; vii, H<sub>2</sub>/Pt-EtOAc.

**Scheme 28**

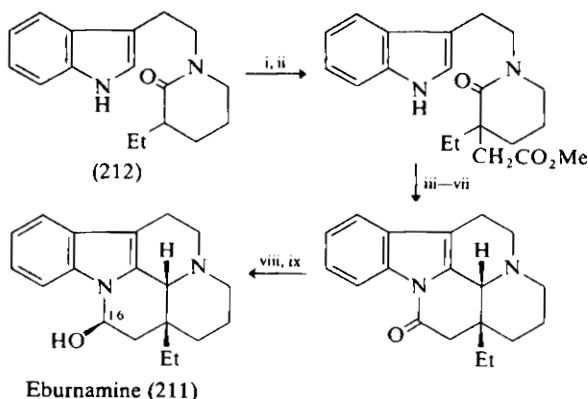
A high-yielding synthesis of (±)-eburnamine (211) employs the known lactam (212), whose dianion is alkylated with methyl bromoacetate as a means of completing the carbon skeleton (Scheme 29); the remaining stages are unexceptional.<sup>173</sup> A second partial synthesis of craspidospermine (213) and criocerine (214) makes use of a photochemical oxidative cyclization of amines (Scheme 30).<sup>174</sup> Thus, Δ<sup>14</sup>-vincine (215) gave craspidospermine directly, but the same procedure applied to vincamine (216a) or vincine (216b) gave the ring-opened products (217, R=H or OMe). However, photochemical oxidation of vincamine in acetone solution yielded criocerine (214), and a similar procedure on Δ<sup>14</sup>-vincine gave an improved yield of craspidospermine.

The demethylation of aspidospermine by an *Actinomyces* culture<sup>175</sup> appears to be the first report of the demethylation of a phenolic ether in the alkaloid series by a

<sup>173</sup> J. L. Herrmann, G. R. Kieczkowski, S. E. Normandin, and R. H. Schlessinger, *Tetrahedron Letters*, 1976, 801.

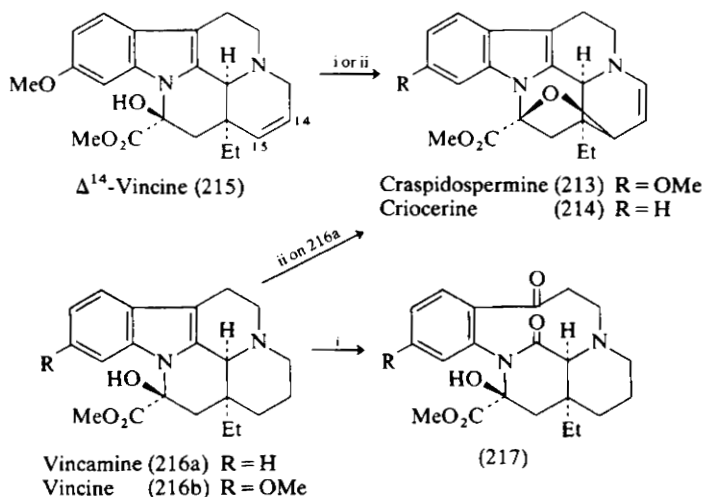
<sup>174</sup> R. Beugelmans, D. Herlem, H. P. Husson, F. Khuong-Huu, and M. T. Le Goff, *Tetrahedron Letters*, 1976, 435.

<sup>175</sup> S. K. Lin, M. Tin-Wa, and E. H. Taylor, *J. Pharm. Sci.*, 1975, **64**, 2021.



Reagents: i,  $\text{LiNPr}_2\text{-THF}/-78^\circ\text{C}$ ; ii,  $\text{BrCH}_2\text{CO}_2\text{Me}/-78^\circ\text{C}$ ; iii,  $\text{POCl}_3\text{-MeCN}$ , reflux; iv,  $\text{LiClO}_4$ ; v,  $\text{H}_2\text{-Pd/C}$ ; vi,  $\text{NaOMe-MeOH}$ ; vii, separation of isomers; viii,  $\text{LiAlH}_4\text{-THF}$ ; ix,  $\text{NaOMe-MeOH}/70^\circ\text{C}$ , 12 h. (epimerization at C-16).

Scheme 29



Reagents: i,  $\text{MeOH}/\text{O}_2$ , methylene blue,  $h\nu$ ; ii, acetone,  $h\nu$ .

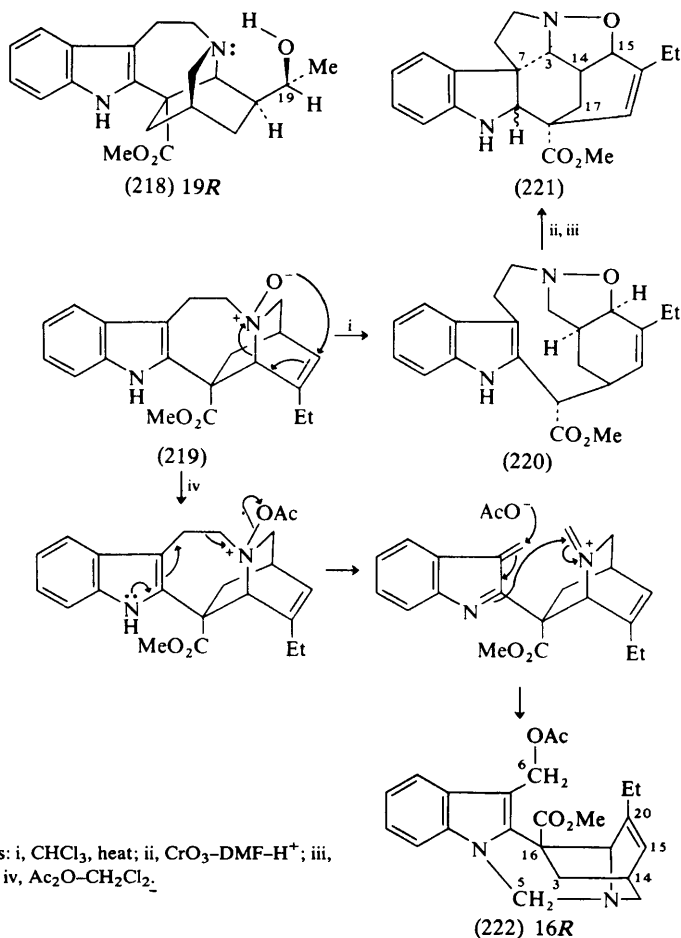
Scheme 30

micro-organism. The *N*-acetyl group may well be involved in the dealkylation since *N*-deacetylaspidospermine and other ethers not containing an *N*<sub>a</sub>-acetyl group were unaffected.

**Ibogamine—Cleavamine Group.** *Ervatamia orientalis* contains alkaloids of at least four sub-groups, including ibogaine, iboxygaine, and voacristine from this group.<sup>134</sup> Coronaridine occurs in *Pandaca minutiflora*,<sup>130</sup> and in the root bark of *Peschiera affinis* (together with the corresponding coronaridine pseudoindoxyl)<sup>131</sup> and the leaves of *Tabernaemontana coronaria*, in which voacristine was also found.<sup>133</sup> In

contrast to these plants *Pandaca mocquersii* (Aug.DC.) Mgf. var. *pendula* Mgf. appears to contain<sup>176</sup> only iboga alkaloids; so far six alkaloids have been isolated, including (–)-coronaridine, (–)-voacangine, (–)-heyneanine, (–)-voacangarine, (–)-19-epivoacangarine, and a new alkaloid, which proves to be (–)-19-epiheyneanine, *i.e.* (–)19*R*-19-hydroxycoronaridine (218). In this series the presence of a hydrogen bond between the hydroxy-group and *N*<sub>6</sub> may well be responsible for a small de-shielding of the methyl group in the 19*R*-isomer, and the deshielding of the C-19 proton in the 19*S*-isomers.

At slightly elevated temperatures (40–60°C) catharanthine *N*<sub>6</sub>-oxide (219) undergoes a facile [2,3]-sigmatropic rearrangement with quantitative conversion into the isoxazolidine derivative (220), whose structure was established by the *X*-ray method.<sup>177</sup> Oxidation at *N*<sub>6</sub> to C-3, followed by Mannich ring-closure, affords an



<sup>176</sup> M. De Bellefon, M. M. Debray, L. Le Men-Olivier, and J. Le Men, *Phytochemistry*, 1975, **14**, 1649.

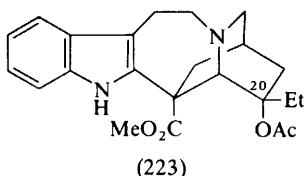
<sup>177</sup> N. Langlois, F. Guérin, R. Z. Andriamialisoa, Y. Langlois, P. Potier, A. Chiaroni, and C. Riche, *Compt. rend.*, 1975, **281** C, 683; *Tetrahedron*, 1976, **32**, 945.



indolenine which on reduction gives an indoline of structure (221). It is apparent from the facility of this rearrangement that catharanthine *N*-oxide, which is useful in bisindole alkaloid synthesis, can only be used with confidence at 0 °C or below, at which temperature rearrangement does not occur.

Another type of rearrangement ensues if the *N*<sub>b</sub>-oxide (219) is treated with a nucleophile.<sup>178</sup> This reaction can be applied to the partial synthesis of bisindole alkaloids (*q.v.*), but in most cases a by-product is obtained. In the simple example in which the nucleophile is acetate, the product obtained is the pentacyclic compound (222), in which the intermediate fragmentation product has cyclized on to *N*<sub>a</sub>. Analogous compounds can also be obtained starting with dihydrocatharanthine or coronaridine.<sup>178</sup>

The Markownikov addition of the elements of water to a cleavamine derivative may also have important application in the synthesis of bisindole alkaloids. Although this appears not to have been achieved, a route to the corresponding derivative of catharanthine has been developed, by use of a modified Prévost reaction.<sup>179</sup> Thus, treatment of catharanthine with iodine and silver acetate in glacial acetic acid afforded an intermediate, which was reduced to the acetate (223) by NaBH<sub>4</sub>. Although formulated otherwise this acetate must be the 20 $\alpha$ -acetate, by reason of its later conversion into vinblastine (*q.v.*).



In last year's Report<sup>160e</sup> the conversion of voacanginol tosylate (224) into voaenamine (225) was discussed. Further investigations have disclosed<sup>180</sup> a most interesting and unexpected rearrangement which occurs when voacanginol tosylate is treated with pyridine and methanol, in the presence of air. The product, voaketone (226), can also be obtained by similar treatment of voaenamine. Scheme 31 includes one proposal for the mechanism of formation of voaketone, whose structure and absolute configuration were established by conventional methods.<sup>180</sup>

Details have been published<sup>181</sup> of the total syntheses of velbanamine, isovelbanamine, cleavamine, 18 $\beta$ -carbomethoxycleavamine, and catharanthine. Rosenmund's route<sup>182</sup> to the iboga alkaloids has now been appropriately modified to yield ibogamine and ibogaine, in addition to epi-ibogamine, and details of this work are also available.<sup>183</sup> Hydroboration-oxidation of (227), presumably obtained by a thio-Claisen rearrangement [cf. (200)  $\rightarrow$  (201)] affords the alcohol (228) which is a key intermediate in a Kutney-type synthesis of cleavamine; however, details of the synthesis are not yet available.<sup>168b</sup>

<sup>178</sup> N. Langlois, F. Guéritte, Y. Langlois, and P. Potier, *Tetrahedron Letters*, 1976, 1487.

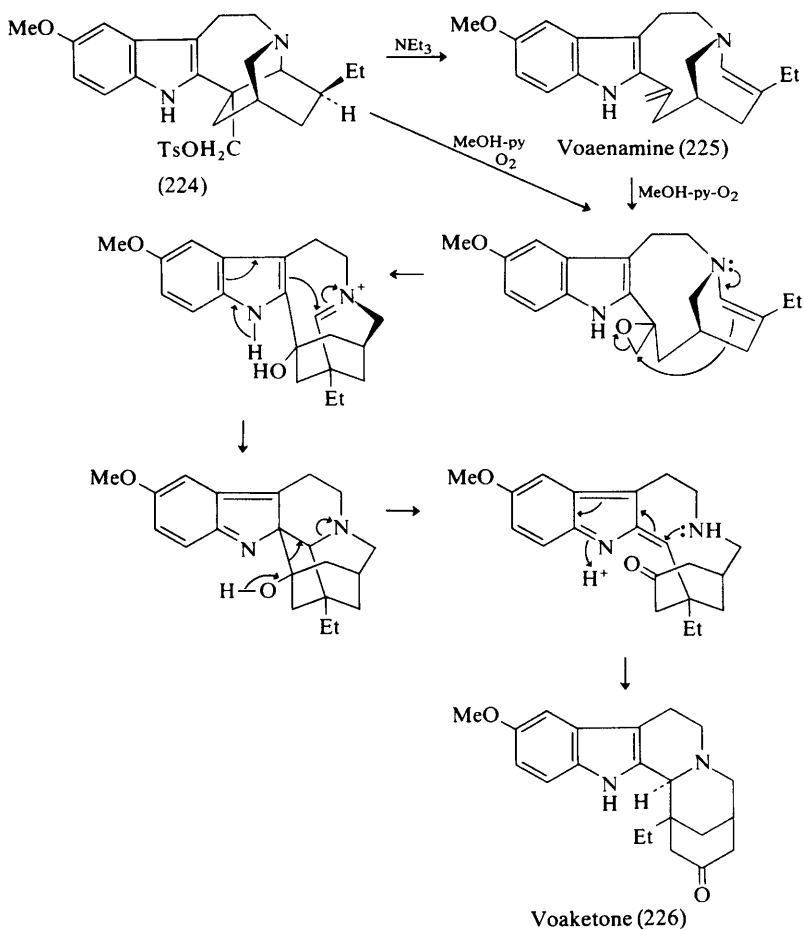
<sup>179</sup> Atta-ur-Rahman, N. Waheed, and M. Ghazala, *Z. naturforsch.*, 1976, **31b**, 265.

<sup>180</sup> Y. Morita, M. Hesse, U. Renner, and H. Schmid, *Helv. Chim. Acta*, 1976, **59**, 532.

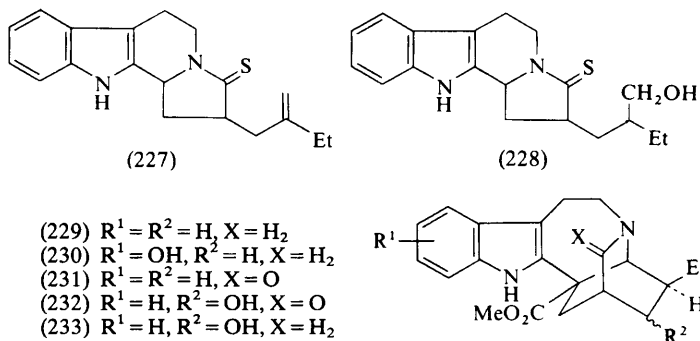
<sup>181</sup> J. P. Kutney and F. Bylsma, *Helv. Chim. Acta*, 1975, **58**, 1672.

<sup>182</sup> P. Rosenmund, W. H. Haase, and J. Bauer, *Tetrahedron Letters*, 1969, 4121.

<sup>183</sup> P. Rosenmund, W. H. Haase, J. Bauer, and R. Frische, *Chem. Ber.*, 1975, **108**, 1871.



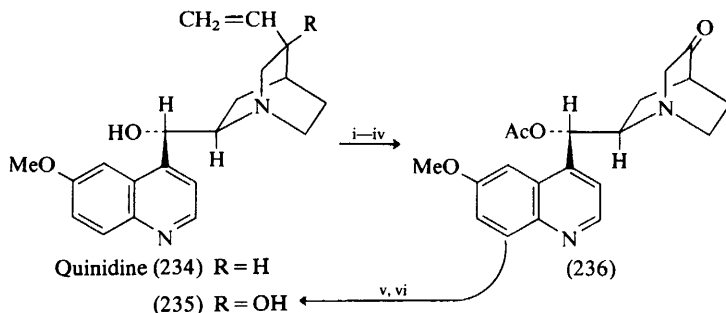
Scheme 31



The microbiological oxidation of coronaridine (229) by means of *Sporotrichum sulfurescens* affords<sup>184</sup> a phenolic derivative (230) of uncertain orientation, together with a lactam (231) identical with an alkaloid previously isolated from *Conopharyngia jollyana* Stapf., and a hydroxylactam, provisionally formulated as (232). The action of *Cunninghamella blakesleana* Lendner leads to a hydroxycoronaridine, which is suspected to be (233).

#### 4 Biogenetically Related Quinoline Alkaloids

Perhaps the only contribution of much chemical interest in the *Cinchona* group during the year concerns the biotransformation of quinidine (234) in man, and the partial synthesis of one of the metabolites.<sup>185</sup> The two metabolites identified were 3-hydroxyquinidine (235) and 2'-quinidinone, the 2-quinolone analogue of quinidine; the former of these was prepared from quinidine by degradation to the ketone (236) (not previously prepared), and re-introduction of the vinyl group by a Grignard synthesis (Scheme 32).



Reagents: i, HBr/0°C; ii, DBU-DMSO/90°C, 2 h; iii, Ac<sub>2</sub>O-py; iv, OsO<sub>4</sub>-NaIO<sub>4</sub>-AcOH-H<sub>2</sub>O; v, CH<sub>2</sub>=CH·MgBr·THF; vi, separation of epimers.

Scheme 32

There has recently been another crop of publications devoted to camptothecin synthesis. Corey's synthesis<sup>186</sup> includes a resolution at an early stage, and is the first synthesis of optically active 20*S*-camptothecin (237) (Scheme 33); unfortunately the yield in the vital coupling-cyclization step (xxi—xxii) is very low indeed (6.5%).

Büchi's shorter synthesis<sup>187</sup> of (±)-camptothecin (Scheme 34) consists essentially of a five-stage synthesis of the pyridone (239), which has previously been converted into camptothecin in two stages by other workers.

Two more formal syntheses have also been reported. The first of these is a synthesis of de-ethyldeoxycamptothecin,<sup>188</sup> and the second, a contribution from Shanghai,<sup>189</sup> constitutes a synthesis of deoxycamptothecin; details of this Chinese

<sup>184</sup> J. Garnier, *Ann. pharm. franc.*, 1975, **33**, 183.

<sup>185</sup> F. I. Carroll, A. Philip, and M. C. Coleman, *Tetrahedron Letters*, 1976, 1757.

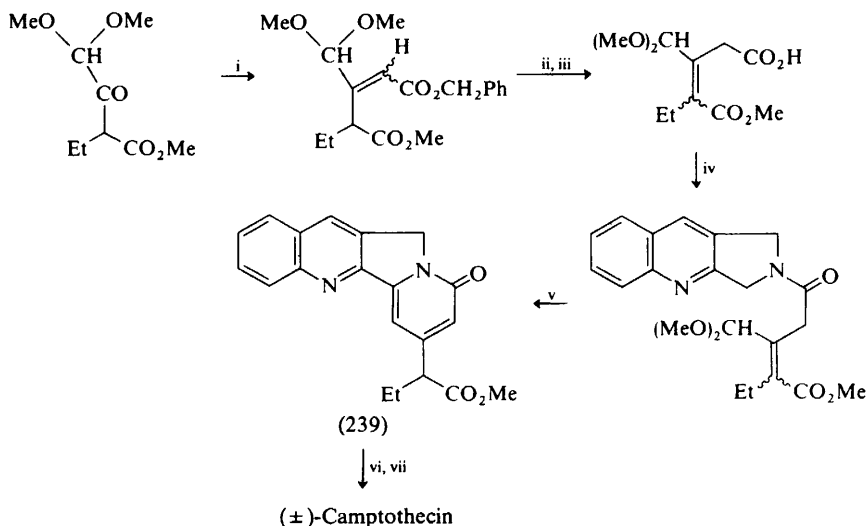
<sup>186</sup> E. J. Corey, D. N. Crouse, and J. E. Anderson, *J. Org. Chem.*, 1975, **40**, 2140.

<sup>187</sup> J. C. Bradley and G. Büchi, *J. Org. Chem.*, 1976, **41**, 699.

<sup>188</sup> H. G. M. Walraven and U. K. Pandit, *Tetrahedron Letters*, 1975, 4507.

<sup>189</sup> Shanghai Fifth Pharmaceutical Plant, K'O. Hsueh T'ung Pao, 1976, **21**, 40 (*Chem. Abs.* 1976, **84**, 122100).





Reagents: i,  $\text{PhCH}_2\text{OCOCH}_2\text{PO}(\text{OMe})_2$ ; ii,  $\text{KOBu}^t$ -THF; iii,  $\text{Pd/C-H}_2$ -MeOH; iv, (238) + DCC; v,  $\text{BF}_3\text{Et}_2\text{O}$ , then  $\text{PhMe-TFA}/110^\circ\text{C}$ ; vi,  $(\text{CH}_2\text{O})_n$ - $\text{H}_2\text{O}$ - $\text{H}_2\text{SO}_4$ -dioxan; vii,  $\text{O}_2$ - $\text{Cu}^{\text{II}}$ -DMF.

Scheme 34

## 5 Bis-indole Alkaloids

Calycanthine has been isolated<sup>191</sup> from the leaves and stems of *Palicourea alpina* (SW.) DC.; this is the first record of the occurrence of this alkaloid in a member of the Rubiaceae. *Strychnos camptoneura* has been reported to contain a new dimeric alkaloid, but little is known of its structure.<sup>192</sup> *S. usambarensis*, from Rwanda, contains usambarensine, 3,4-dihydrousambarensine, and their  $N_b$ -methyl quaternary derivatives, together with dihydrotoxiferine, curarine, calebassine, and a new alkaloid, afrocurarine; these last four alkaloids exhibit potent curarizing activity, hence such alkaloids are not confined to Latin America.<sup>25b</sup> Four closely-related usambarine-like alkaloids have also been reported to be present in the leaves of *Rauwolfia obscura*.<sup>86</sup> The structure and absolute configuration of usambarensine (240) have been established by X-ray crystal structure analysis,<sup>193</sup> and the structure and stereochemistry of (±)-3',4'-dihydrousambarensine (241) by a brief synthesis (Scheme 35),<sup>194</sup> starting from (±)-geissoschizoic acid (242).

Tetrahydrosecamine occurs in *Amsonia elliptica*,<sup>195</sup> and a diastereoisomer of (−)-5,6,5',6'-tetrahydropresecamine in *Pandaca minutiflora*.<sup>130</sup>

Another group of alkaloids subjected to complete  $^{13}\text{C}$  n.m.r. analysis are the ochrolifuanines A and B, which occur, together with a hydroxyochrolifuanine, in

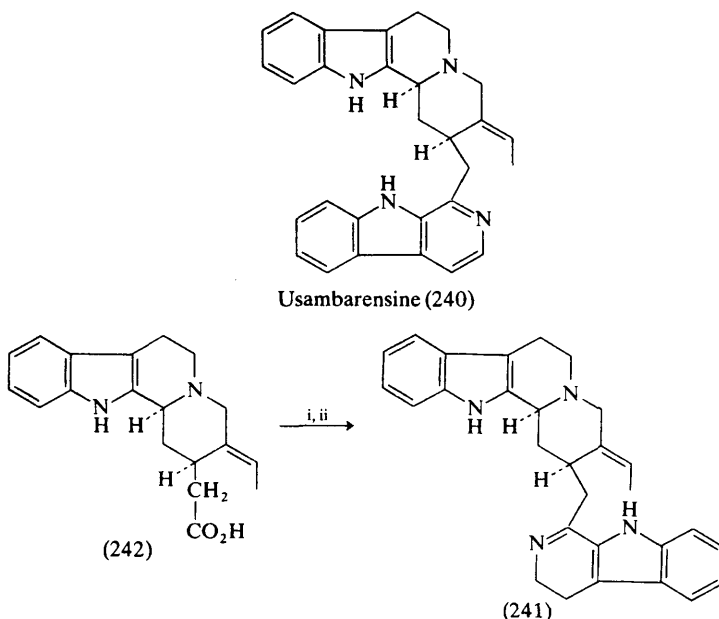
<sup>191</sup> R. B. Woo-Ming and K. L. Stuart, *Phytochemistry*, 1975, **14**, 2529.

<sup>192</sup> R. Verpoorte and A. B. Svendsen, *Acta Pharm. Suecica*, 1975, **12**, 455.

<sup>193</sup> O. Dideberg, L. Dupont, and L. Angenot, *Acta Cryst.*, 1975, **B31**, 1571.

<sup>194</sup> K. Yamada, K. Aoki, and D. Uemura, *J. Org. Chem.*, 1975, **40**, 2572.

<sup>195</sup> S. Sakai, N. Aimi, K. Kato, H. Ido, K. Masuda, Y. Watanabe, and J. Haginiwa, *Yakugaku Zasshi*, 1975, **95**, 1152.



Reagents: i, Tryptamine-DCC-DME-DMF-r.t.; ii,  $\text{POCl}_3\text{-CHCl}_3$ .

**Scheme 35**

*Ochrosia miana*;<sup>91</sup> in the n.m.r. study the spectrum of emetine was also recorded, and complete assignments were made.<sup>196</sup>

The revised structure of haplophytine base, proposed<sup>197</sup> in 1973, has now been confirmed by an X-ray crystal structure determination.<sup>198</sup>

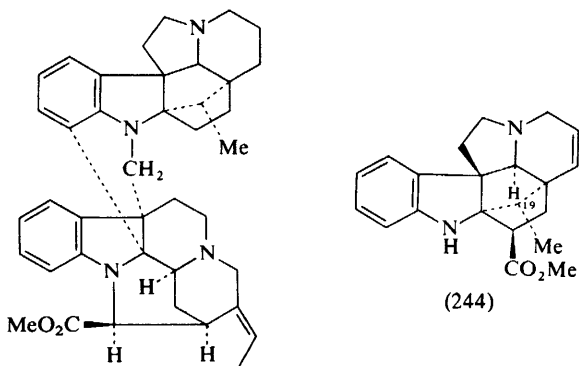
14'-15'-Dihydropycnanthine, an alkaloid composed of demethoxycarbonyl-14',15'-dihydrovindolinine and pleiocarpamine components, has been found in the leaves of *Gonioma malagasy* Mgf. et P.Bt.<sup>199</sup> The recent revision of the structure of vindolinine clearly necessitates a revision also of the structure of dihydropycnanthine, which is now formulated as (243). This structure was derived by extensive comparison of the <sup>13</sup>C n.m.r. spectra of (243), villalstonine, 19*R*-vindolinine, and 19*S*-vindolinine (244). The <sup>13</sup>C n.m.r. signals for the 2,7-dihydropleiocarpamine unit were recognized in the spectra of both 14',15'-dihydropycnanthine and villalstonine.<sup>160f</sup> Subtraction of these signals from the spectrum of (243) gave a set of signals entirely consistent with the presence of a demethoxycarbonyl-14',15'-dihydrovindolinine unit in which C-19 has the *S* configuration, and the attachment of the second component was at C-12' and *via* a methylene group attached to *N*'<sub>a</sub>. The absolute stereochemistry of the *cis* linkage of the two monomers is not known, but is represented as in (243) by analogy with other related bisindole alkaloids.<sup>199</sup>

<sup>196</sup> M. C. Koch, M. M. Plat, N. Préaux, H. E. Gottlieb, E. W. Hagaman, F. M. Schell, and E. Wenkert, *J. Org. Chem.*, 1975, **40**, 2836.

<sup>197</sup> P. Yates, F. N. MacLachlan, I. D. Rae, M. Rosenberger, A. G. Szabo, C. R. Willis, M. P. Cava, M. Bechforouz, M. V. Lakshmikantham, and W. Zeiger, *J. Amer. Chem. Soc.*, 1973, **95**, 7842.

<sup>198</sup> P. T. Cheng, S. C. Nyburg, F. N. MacLachlan, and P. Yates, *Canad. J. Chem.*, 1976, **54**, 726.

<sup>199</sup> P. Rasoanaivo and G. Lukacs, *J. Org. Chem.*, 1976, **41**, 376.



14',15'-Dihydropycnanthine (243)

Several closely related bisindole alkaloids of the vobasine–catharanthine group occur in *Ervatamia* and *Tabernaemontana* species. Thus *E. orientalis* contains<sup>134</sup> 16-demethoxycarbonyldihydrovoacamine (245) and its 20'-epimer (246). The presence of an ibogaine component in these alkaloids was established by the isolation of ibogaine from the acid treatment of (246). Although the alkaloids were clearly C-20 epimers, the spectral evidence did not permit unequivocal assignment of the two structures; hence a solution to this problem was found in a partial synthesis. Condensation of dregaminol (149; C=O → >CHOH) with ibogaine in dilute methanolic HCl afforded 16-demethoxycarbonyldihydrovoacamine (245), and an analogous condensation of tabernaemontaninol (150; C=O → CHOH) gave 16-demethoxycarbonyl-20'-epidihydrovoacamine (246), identical with the two *Ervatamia* alkaloids.<sup>134</sup> The position of attachment of the dregaminol/tabernaemontaninol component is presumed to be C-10 by analogy with known condensations of this type, and is also in agreement with the clearly discernible broadened singlets owing to protons at C-9 and C-12 in the n.m.r. spectra.

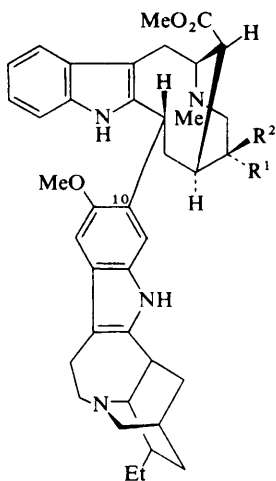
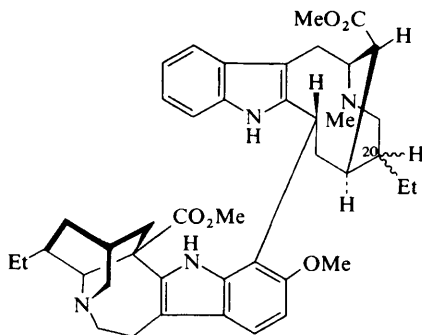
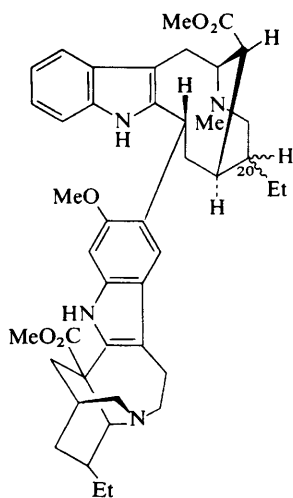
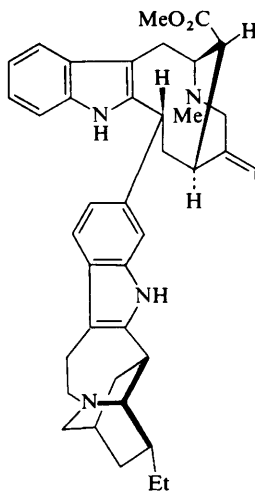
A very similar situation was encountered with the structure of tabernaemine, a cytotoxic alkaloid of *Tabernaemontana johnstonii* Pichon, from Kenya.<sup>200</sup> Acid cleavage of tabernaemine (247) gave ibogamine, and the gross structure of the alkaloid was confirmed by condensation of ibogamine with vobasinol (148; C=O → CHOH).

Conoduramine occurs<sup>132</sup> in the root bark of *Tabernaemontana elegans*, together with seven new bisindole alkaloids, tabernaeelegantines A–D, tabernaeelegantinines A and B, and tabernaeelegantinidine. tabernaeelegantines A–D are formulated as the two pairs of C-20 epimers (248)–(251), but the detailed evidence on which these structures are based is not yet available.<sup>132</sup>

An alkaloid of a less familiar type, containing isovoacangine and hydrocanthine components, is bonafousine (252), the major alkaloid of a genus not previously investigated, *Bonafousia tetraestachya* (Humboldt, Bonpland, and Kunth) Markgraf.<sup>201</sup> The structure was determined by the X-ray method, and the absolute configuration from the c.d. spectrum of its *O*-methyl ether.

<sup>200</sup> D. G. I. Kingston, B. B. Gerhart, and F. Ionescu, *Tetrahedron Letters*, 1976, 649.

<sup>201</sup> M. Damak, A. Ahond, H. Doucerain, and C. Riche, *J.C.S. Chem. Comm.*, 1976, 510.

(245)  $R^1 = \text{Et}$ ,  $R^2 = \text{H}$ (246)  $R^1 = \text{H}$ ,  $R^2 = \text{Et}$ Tabernaelegantine A (248)  $\alpha\text{-H}$  at C-20Tabernaelegantine C (250)  $\beta\text{-H}$  at C-20Tabernaelegantine B (249)  $\alpha\text{-H}$  at C-20Tabernaelegantine D (251)  $\beta\text{-H}$  at C-20

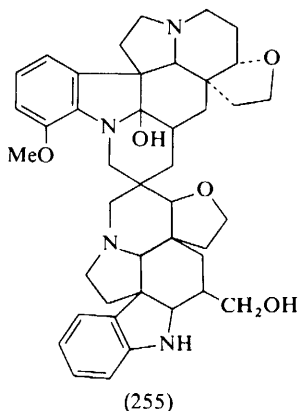
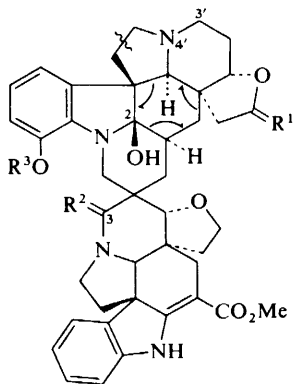
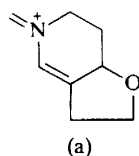
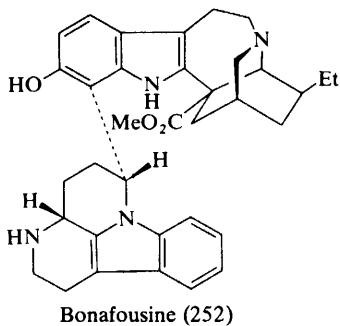
Tabernaemine (247)

Of the 12 bisindole alkaloids isolated earlier<sup>202</sup> from *Voacanga thouarsii* three [vobtusine, vobtusine lactone, and subessiline (amataine)] were already known. Four more of these alkaloids, also related to vobtusine (253), have now been identified.<sup>203</sup> Of these Alkaloid A exhibits spectra very similar to those of vobtusine, except that the i.r. spectrum contains an additional carbonyl band at  $1650\text{ cm}^{-1}$ , due

<sup>202</sup> Y. Rolland, G. Croquelois, N. Kunesch, P. Boiteau, M. Debray, J. Pecher, and J. Poisson, *Phytochemistry*, 1973, **12**, 2039.

<sup>203</sup> Y. Rolland, N. Kunesch, F. Libot, J. Poisson, and H. Budzikiewicz, *Bull. soc. chim. France*, 1975, 2503.





Vobtusine (253)  $R^1 = R^2 = H_2$ ,  $R^3 = Me$

Alkaloid A (254)  $R^1 = H_2$ ,  $R^2 = O$ ,  $R^3 = Me$

Demethylvobtusine (256)  $R^1 = R^2 = H_2$ ,  $R^3 = H$

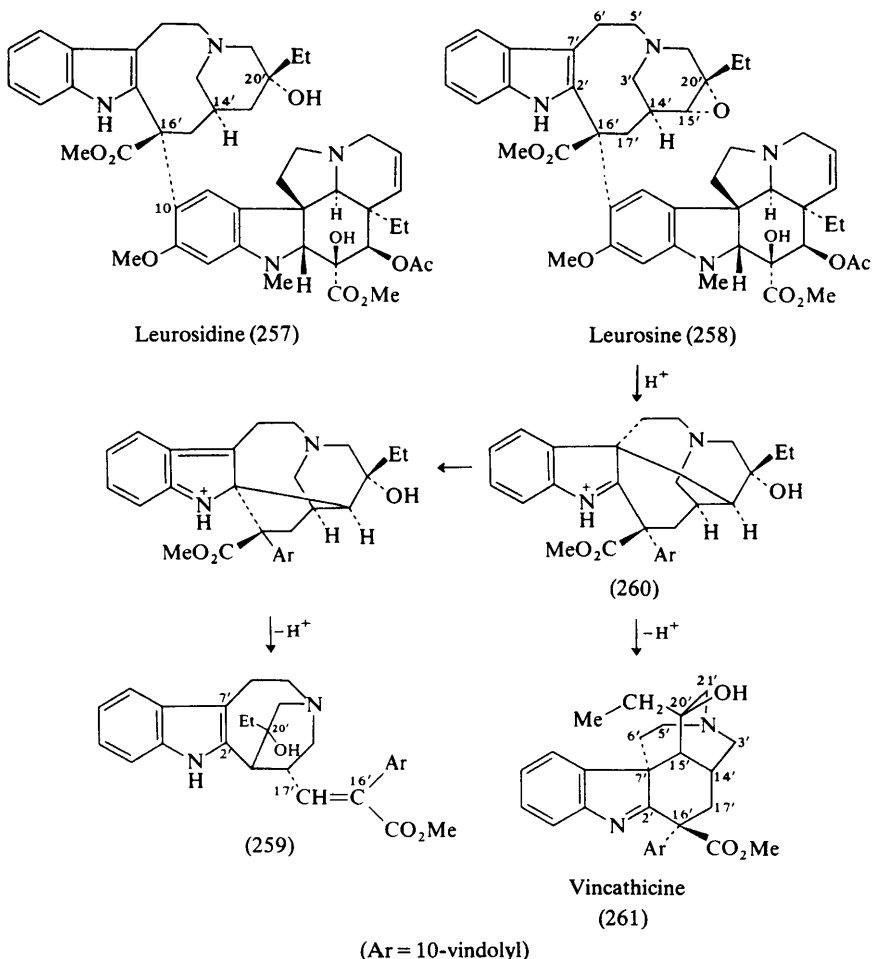
to a  $\delta$ -lactam function. Since the mass spectrum contains a prominent ion at  $m/e$  138 (a) the carbonyl group cannot be situated at C-3' (see 253) and must therefore be at C-3. This was neatly proved by reduction of Alkaloid A and vobtusine with sodium cyanoborohydride followed by  $LiAlH_4$ , which afforded the same reduction product (255). Alkaloid A is therefore vobtusine-lactam (vobtusine-3-one) (254). Alkaloid B is readily reduced by iron and acetic acid to vobtusine-lactam, and is simply vobtusine-lactam  $N_4$ -oxide. Alkaloid D contains one oxygen fewer than Alkaloid A, but exhibits very similar spectra, including the  $\delta$ -lactam carbonyl band in the i.r. spectrum. For these reasons, and the close similarity of its mass spectrum to that of 2'-deoxyvobtusine, Alkaloid A is regarded as 2'-deoxyvobtusine-lactam, i.e. (254), but lacking the C-2 hydroxy-group. However, the lack of a chemical correlation with vobtusine renders this proposal tentative. Alkaloid F is a phenolic base identical with demethylvobtusine (256), isolated earlier<sup>204</sup> from *Hedranthera barteri*.

In the vinblastine sub-group complete  $^{13}C$  n.m.r. assignments have been made for vinblastine, leurosine, and leurosine.<sup>205</sup> This study brought to light the inadequacy

<sup>204</sup> J. Naranjo, M. Hesse, and H. Schmid, *Helv. Chim. Acta*, 1972, **55**, 1849.

<sup>205</sup> E. Wenkert, E. W. Hagaman, B. Lal, G. E. Gutowski, A. S. Katner, J. C. Miller, and N. Neuss, *Helv. Chim. Acta*, 1975, **58**, 1560.

of the earlier structure for leurosidine, which is now shown to be simply the C-20' epimer (257) of vinblastine, a conclusion that substantiates the recent report<sup>206</sup> that vinblastine can be epimerized to leurosidine.

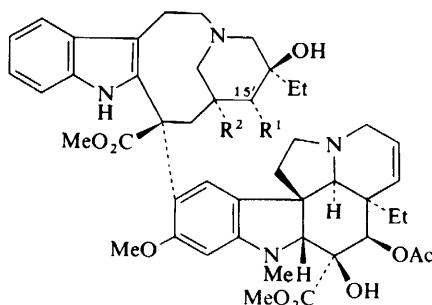


The isomeric product obtained by treatment of leurosine (258) with acid has also been reinvestigated. Whereas the vindoline component of the molecule remains intact, the velbanamine unit suffers a drastic change, with appearance of an  $\alpha,\beta$ -disubstituted acrylate function and an ethyldialkylmethanol unit in which the protons of the methyl group are very strongly shielded, presumably by the aromatic ring. These features are incorporated in the tentative structure (259) for the product of this rearrangement, a possible mechanism for which is illustrated.<sup>205</sup> The intermediate (260) in this rearrangement might be expected, on deprotonation, to afford a

<sup>206</sup> G. E. Gutowski, A. S. Katner, and J. C. Miller, unpublished work, reported in ref. 205.

reasonably stable indolenine derivative (261), which is now shown<sup>207</sup> to be identical with vincathicine, a constituent of *Vinca rosea*, first isolated<sup>208</sup> in 1964, and already shown to be obtainable from leurosine by treatment with acid. In this independent study the constitution of vincathicine was established mainly from its <sup>13</sup>C n.m.r. spectrum, which clearly indicated attachment of C-7' to C-15' rather than to C-20'. The conversion of leurosine into (259) and (261) also supports the  $\alpha$ -orientation of the epoxide function in leurosine. The c.d. spectra of the natural vinblastine alkaloids and their synthetic C-16' epimers show clear differences; hence the c.d. spectrum provides a rapid diagnostic test for the chirality at C-16' in this series.<sup>209</sup> Details of the X-ray crystal structure analysis of catharine have now been published.<sup>210</sup>

Among the new alkaloids in this group is vincadioline (262) which would appear from the structure proposed to be a diol related to the epoxide leurosine.<sup>211</sup> Presumably it is the *trans*-diol that would be expected to be obtained from leurosine, but it should be noted that the evidence concerning the configuration of the diol function in (262) has not yet been divulged.



Vincadioline (262)  $R^1 = \text{OH}, R^2 = \text{H}$

Leurocolombine (263)  $R^1 = \text{H}, R^2 = \text{OH}$

Leurocolombine (263), an isomer of vincadioline, is one of three new dimeric alkaloids of *Catharanthus roseus* (*Vinca rosea*).<sup>212</sup> The additional oxygen atom present in leurocolombine above those present in vinblastine is presumably present in a hydroxy-group, since leurocolombine also contains one more exchangeable hydrogen atom. Since all the vindoline carbon atoms could be identified in the c.m.r. spectrum the hydroxy-group is presumably in the velbanamine unit; this was confirmed by identifying all the n.m.r. signals except that owing to C-14'. Hence the hydroxy-group is placed on C-14', and the complete structure for leurocolombine is (263).

Vinamidine (264), the second alkaloid, also contains an intact vindoline component (c.m.r. spectrum), but the velbanamine unit contains ketone and formamide

<sup>207</sup> S. S. Tafur, J. L. Ocolowit, T. K. Elzey, J. W. Paschal, and D. E. Dorman, *J. Org. Chem.*, 1976, **41**, 1001.

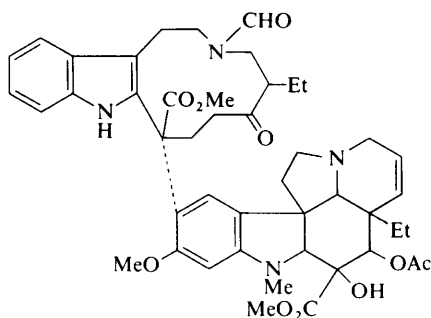
<sup>208</sup> G. H. Svoboda and A. J. Barnes, *J. Pharm. Sci.*, 1964, **53**, 1227.

<sup>209</sup> J. P. Kutney, D. E. Gregonis, R. Imhof, I. Itoh, E. Jahngen, A. I. Scott, and W. K. Chan, *J. Amer. Chem. Soc.*, 1975, **97**, 5013.

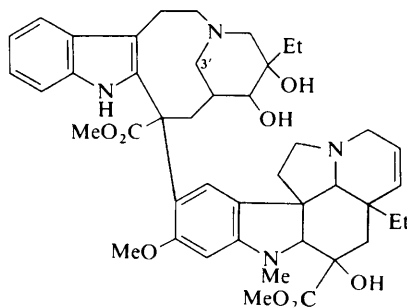
<sup>210</sup> J. Guilhem, A. Ducruix, C. Riche, and C. Pascard, *Acta Cryst.*, 1976, **B32**, 936.

<sup>211</sup> W. E. Jones and G. J. Cullinan, U.S.P. 3,887,545 (*Chem. Abs.*, 1975, **83**, 97687; 1976, **84**, 5230).

<sup>212</sup> S. Tafur, W. E. Jones, D. E. Dorman, E. E. Logsdon, and G. H. Svoboda, *J. Pharm. Sci.*, 1975, **64**, 1953.



Vinamidine (264)



Pseudovincaleukoblastine diol (265)

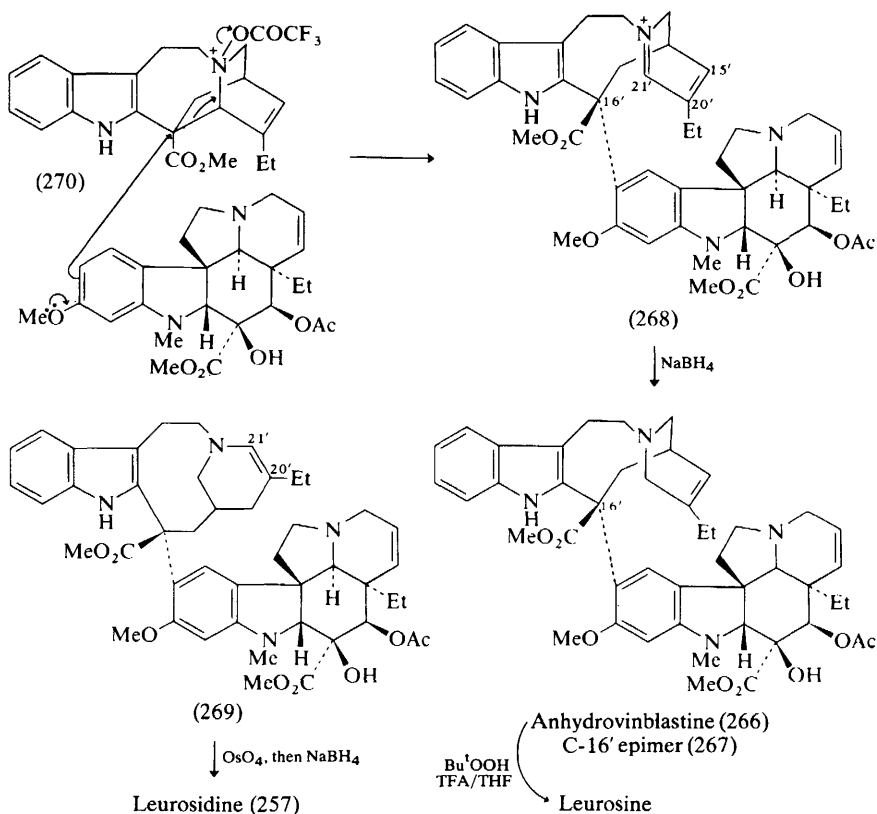
functions. The ketone group is not placed at C-14', the biogenetically preferred position, but at C-15' to account for a small shielding of the C-18' methyl group, and the failure of vinamidine to form a lactone on reduction of the ketone group. This contrasts with catharine, in which the ketone group is situated at C-14'; in any event, vinamidine is not identical with dihydrocatharine.<sup>212</sup>

The third alkaloid, pseudovincaleukoblastine diol, is isomeric with deacetylvinblastine, but the mass spectral evidence indicates that it is in fact a derivative of deacetoxyvinblastine. The remaining oxygen atom is contained in a secondary hydroxy-group (n.m.r. evidence) in the velbanamine portion of the molecule, and since the alkaloid and its acetate show similarities with vincadioline and its acetate, pseudovincaleukoblastine is formulated<sup>212</sup> as (265); however, a carbinolamine structure (OH at C-3') cannot at present be firmly excluded.

There has naturally been a considerable amount of attention devoted to the synthesis of alkaloids related to vinblastine, but whereas all the early attempts resulted in the formation of the 'unnatural' C-16' epimeric series (for details of one group's synthetic endeavours, see ref. 213), the most recent attempts have met with conspicuous success. The major breakthrough was achieved by Potier's group,<sup>214</sup> who applied the modified Polonovski reaction already used with success in the partial synthesis of other alkaloids. In this approach catharanthine was used, rather than a velbanamine derivative, since it was expected that attachment of a good leaving group to N<sub>6</sub> would result in fragmentation, with fission of the C-16' to C-21' bond, leaving C-16' susceptible to attack by a nucleophile. In the event, reaction of catharanthine N<sub>6</sub>-oxide with trifluoroacetic anhydride in the presence of vindoline, followed by reduction (NaBH<sub>4</sub>) (Scheme 36), gave a mixture of (266) and (267). The former (266) was shown to be anhydrovinblastine by deacetylation, the product being identical with the product of dehydration-deacetylation of vinblastine with sulphuric acid. Other partial syntheses successfully carried out included the condensation of 20*S*-dihydrocatharanthine, coronaridine, allocatharanthine, or dihydroallocatharanthine with vindoline or 2,16-dihydro-11-methoxytabersonine.<sup>214</sup> The product from 20*S*-dihydrocatharanthine and vindoline, which is the 15,20*S*-dihydro-derivative of (268), is in equilibrium with the enamine (269); in principle, the

<sup>213</sup> J. P. Kutney, J. Beck, F. Bylsma, J. Cook, W. J. Cretney, K. Fuji, R. Imhof, and A. M. Treasurywala, *Helv. Chim. Acta*, 1975, **58**, 1690.

<sup>214</sup> P. Potier, N. Langlois, Y. Langlois, and F. Guérrette, *J.C.S. Chem. Comm.*, 1975, 670.



Scheme 36

enamine (20', 21') double bond should be much more reactive towards electrophiles than the vindoline double bond, and hence an obvious opportunity for the synthesis of the vinblastine alkaloids presents itself. In fact, hydroxylation of (269) with osmium tetroxide followed by reduction of the carbinolamine function with sodium borohydride afforded a single product, identified<sup>215</sup> as leurosine (257). Subsequently, other workers<sup>216,218</sup> have adopted the same approach to the synthesis of vinblastine derivatives, but in all the examples so far studied<sup>214,216</sup> it is stressed that the configuration of the coupling product obtained ('natural' or C-16' epi series) is remarkably sensitive to the exact experimental conditions employed; it would appear that a *concerted* fragmentation-coupling process, as depicted in (270), yields the 'natural' series, whereas a fragmentation *followed* by coupling is more likely to yield the 16'-epi series.

<sup>215</sup> N. Langlois and P. Potier, *Tetrahedron Letters*, 1976, 1099.

<sup>216</sup> J. P. Kutney, A. H. Ratcliffe, A. M. Treasurywala, and S. Wunderly, *Heterocycles*, 1975, 3, 639.

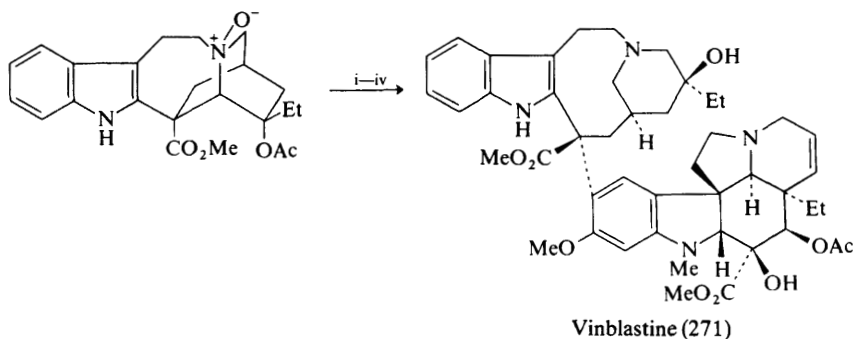
<sup>217</sup> J. P. Kutney, J. Balsevich, G. H. Bokelman, T. Hibino, I. Itoh, and A. H. Ratcliffe, *Heterocycles*, 1976, 4, 997.

<sup>218</sup> Atta-ur-Rahman, A. Basha, and M. Ghazala, *Tetrahedron Letters*, 1976, 2351.

The Canadian group have also followed their synthesis of anhydrovinblastine (266) by studying the introduction of oxygen substituents to positions 15' and/or 20'. Oxidation of anhydrovinblastine with *t*-butyl hydroperoxide afforded a moderate yield of leurosine;<sup>217</sup> following experience with other substrates in this reaction Kutney *et al.* formulate leurosine as the  $\beta$ -epoxide, rather than the  $\alpha$ -epoxide (258) favoured<sup>205,207</sup> by other workers. However, both formulations are at present tentative, and it will be interesting to note which one ultimately proves to be correct.

Hydroxylation of the 15', 20' double bond in (266) by means of osmium tetroxide could not be accomplished satisfactorily; however, osmylation of the  $N_b$ -oxide of (266) followed by reductive ( $H_2S$ ) work-up afforded a hydroxyvinblastine formulated as the  $\beta$ -diol, *i.e.* the C-15' epimer of (262). Since the stereochemical assignments are at present tentative, it is unfortunate that an authentic specimen of vincadioline was not available for direct comparison.<sup>217</sup>

The partial synthesis<sup>218</sup> of vinblastine itself makes use of 20-acetoxycatharanthine (223), prepared<sup>179</sup> from catharanthine as described earlier. The modified Polonovski reaction in the presence of vindoline gave an intermediate immonium ion, which was reduced to 20'-acetylvinblastine (Scheme 37). Mild alkaline hydrolysis afforded deacetylvinblastine, the secondary hydroxy-group of which could be re-acetylated preferentially, with formation of vinblastine (271).<sup>218</sup>

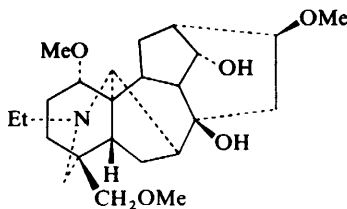


Reagents: i,  $(CCl_3 \cdot CO)_2O$ -vindoline; ii,  $NaBH_4$ ; iii, mild alkaline hydrolysis; iv,  $Ac_2O$ - $NaOAc$ .

**Scheme 37**

### 1 Introduction

Research on diterpenoid alkaloids published during the past year has continued to expand the body of structural and synthetic information available on these complex plant bases. The structures of ten new alkaloids from *Aconitum* and *Delphinium* species, including seven new bisditerpenoid alkaloids, have been reported. The most significant progress in methods of structure elucidation has been the very successful applications of  $^{13}\text{C}$  n.m.r. to the study of complex diterpenoid alkaloids. The New Brunswick group under Professor Karel Wiesner has continued its progress toward the syntheses of the  $\text{C}_{19}$ -aconitine-type alkaloids. An historical account of the synthesis of talatisamine (1), the first synthesis of a hexacyclic aconite alkaloid, has been published.<sup>1</sup> This work was reviewed in a previous Report.<sup>2</sup>



Talatisamine (1)

Six new alkaloids have been isolated from *Daphniphyllum* species. Two reviews of the literature to 1974 on the chemistry of the *Daphniphyllum* alkaloids have appeared.<sup>3,4</sup>

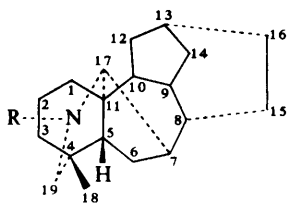
The numbering systems for the lycoctonine and atisine skeletons discussed in this review are indicated in structures (A) and (B), respectively.

<sup>1</sup> K. Wiesner, *Pure Appl. Chem.*, 1975, **41**, 93.

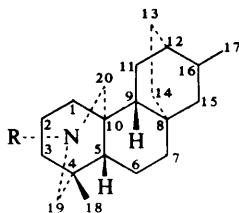
<sup>2</sup> S. W. Pelletier and S. W. Page; in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1974, Vol. 5, Ch. 13.

<sup>3</sup> S. Yamamura and Y. Hirata, in 'The Alkaloids; Chemistry and Physiology', ed. R. H. F. Manske, Academic Press, New York, 1975, vol. 15, Ch. 2, pp. 41—81.

<sup>4</sup> Y. Hirata, *Pure Appl. Chem.*, 1975, **41**, 175.



(A) Lycoponine skeleton



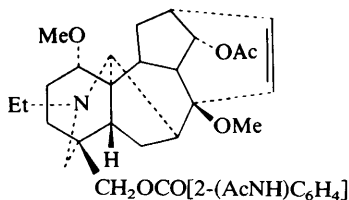
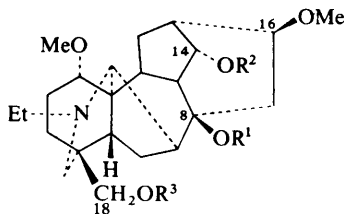
(B) Atisine skeleton

## 2 C<sub>19</sub> Diterpenoid Alkaloids

**Aconorine.**—This amorphous base, C<sub>32</sub>H<sub>44</sub>H<sub>2</sub>O<sub>7</sub>, has been isolated from the roots of *Aconitum orientale* Mill.<sup>5</sup> It formed a perchlorate salt, m.p. 237°C, and on the basis of spectral and chemical evidence was assigned structure (2).

Alkaline hydrolysis of aconorine was found to give the base (3) and *N*-acetylanthranilic acid, whereas the diacetate derivative (4) yielded isopyroacetylaconorine (5) on pyrolysis. This reaction is analogous to the reported pyrolytic rearrangement of talatisamine (1),<sup>6</sup> and from these data the positions of the C-8 hydroxy- and C-16 methoxy-groups were assigned. The position of the second hydroxy-group at C-14 and the point of attachment of the *N*-acetylanthranilate moiety on the C-18 hydroxy-group were determined from the <sup>1</sup>H n.m.r. spectra of aconorine and its hydrolysis product (3).

The Russian workers reported<sup>5</sup> that an alkaloid, columbianine, having the same structure as (3) had been isolated from *Aconitum columbianum* by Professor O. E. Edwards' group at the National Research Council of Canada.



- Aconorine (2) R<sup>1</sup> = R<sup>2</sup> = H; R<sup>3</sup> = 2-(AcNH)C<sub>6</sub>H<sub>4</sub>CO  
 (3) R<sup>1</sup> = R<sup>2</sup> = R<sup>3</sup> = H  
 (4) R<sup>1</sup> = R<sup>2</sup> = Ac; R<sup>3</sup> = 2-(AcNH)C<sub>6</sub>H<sub>4</sub>CO

(5)

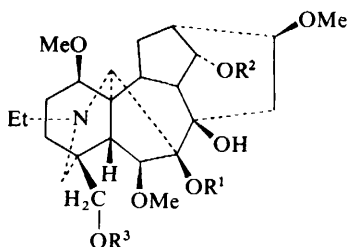
**Delectine.**—A new diterpenoid alkaloid, delectine, has been isolated from *Delphinium dictyocarpum*.<sup>7</sup> This base, C<sub>31</sub>H<sub>44</sub>N<sub>2</sub>O<sub>8</sub>, m.p. 107—109°C, was shown to be the anthranilate ester (6) by chemical and spectral studies and by conversion into *OO*-dimethyl-lycotonine (7). Acetylation of delectine gave an *NO*-diacetyl derivative (8). On alkaline hydrolysis of delectine, anthranilic acid and the alkamine (9) were obtained. Methylation of (9) with methyl iodide–sodium hydride gave (7), which was

<sup>5</sup> V. A. Tel'nov, M. S. Yunusov, S. Yu. Yunusov, and B. Sh. Ibragimov, *Khim. prirod. Soedinenii*, 1975, **11**, 814.

<sup>6</sup> M. S. Yunusov and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1970, **6**, 90.

<sup>7</sup> B. T. Salimov, M. S. Yunusov, S. Yu. Yunusov, and A. S. Narzullaev, *Khim. prirod. Soedinenii*, 1975, **11**, 665.



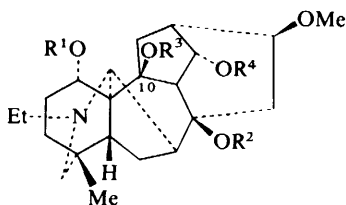


- Delectine (6)  $R^1 = R^2 = H$ ;  $R^3 = 2-(NH_2)C_6H_4CO$   
 (7)  $R^1 = R^2 = R^3 = Me$   
 (8)  $R^1 = H$ ;  $R^2 = Ac$ ;  $R^3 = 2-(AcNH)C_6H_4CO$   
 (9)  $R^1 = R^2 = R^3 = H$

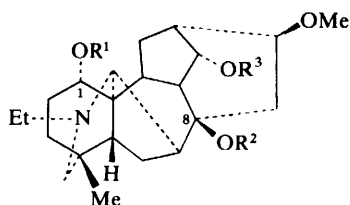
shown to be identical to *OO*-dimethyl-lycoctonine, also isolated from the same species. The positional and stereochemical assignments were made on the basis of comparisons of mass and  $^1H$  n.m.r. spectra with those of other lycoctonine-type diterpenoid alkaloids.

**Karakolidine.**—A full report on the investigations of the structure of karakolidine has appeared.<sup>8</sup> This alkaloid,  $C_{22}H_{35}NO_5$ , m.p. 222–224 °C, had been assigned structure (10) in earlier work.<sup>9</sup> Karakolidine differs from karakoline (11) only by an additional hydroxy-group at C-10. On acetylation with acetic anhydride–pyridine, a diacetate derivative (12) was obtained, whereas acetylation with acetyl chloride afforded the tetra-acetate (13). Pyrolysis of this tetra-acetate followed by hydrolysis, gave pyrokarakolidine (14) as the main product and isopyrokarakolidine (15). The same rearrangement product (15) could also be obtained by treatment of (14) with methanolic hydrochloric acid. Oxidation of karakolidine with Kiliani reagent gave a diketo-derivative (16). Permanganate oxidation of karakolidine yielded the internal carbinolamine ether (17). These structural assignments were based on the i.r.,  $^1H$  n.m.r., and mass spectral data.

This paper included a study of the mass spectra of triacetyl-isotalatizidine (18), triacetyl-karakoline (19), dibenzoylmonoacetyl-karakoline (20), and monobenzoyl-diacetylkarakoline (21). With the acyloxy-groups present at C-1 and C-8, the major



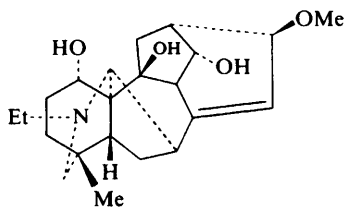
- Karakolidine (10)  $R^1 = R^2 = R^3 = R^4 = H$   
 (12)  $R^1 = R^4 = Ac$ ;  $R^2 = R^3 = H$   
 (13)  $R^1 = R^2 = R^3 = R^4 = Ac$



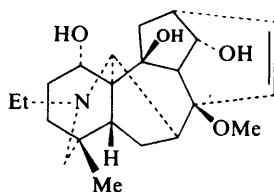
- Karakoline (11)  $R^1 = R^2 = R^3 = H$   
 (19)  $R^1 = R^2 = R^3 = Ac$   
 (20)  $R^1 = R^3 = Bz$ ;  $R^2 = Ac$   
 (21)  $R^1 = Bz$ ;  $R^2 = R^3 = Ac$

<sup>8</sup> M. N. Sultankhodzhaev, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, **11**, 481.

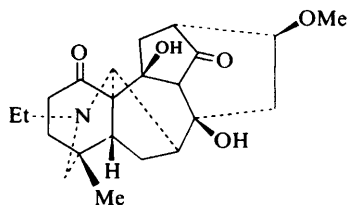
<sup>9</sup> M. N. Sultankhodzhaev, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1973, **9**, 127.



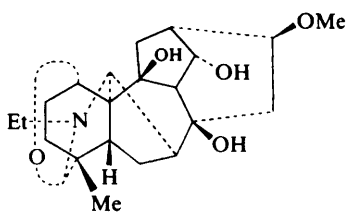
(14)



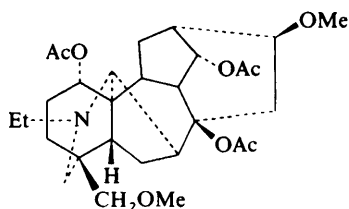
(15)



(16)



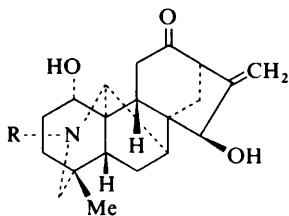
(17)



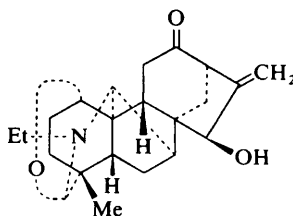
(18)

fragmentation patterns involved the loss of the acyloxy-group from C-1 and the elimination of a molecule of acetic acid to form a  $\Delta^{8,15}$  double bond. In the case of compound (13) there was an additional loss of a molecule of acetic acid from C-10. Mass spectral fragmentation pathways for the pyro products (14) and (15) were also proposed.

**Alkaloids from *Aconitum monticola*.**—In studies of the alkaloid fraction from plants of *Aconitum monticola*, songorine (22), songoramine (23), nor-songorine (24), and a



Songorine (22) R = Et  
Nor-songorine (24) R = H



Songoramine (23)

new base, acomonine,  $C_{25}H_{41}NO_7$ , m.p. 208—210 °C, were isolated.<sup>10</sup> Three alkaloids of undetermined structure were also found: an amorphous compound,  $C_{22}H_{35}NO_6$ , and two crystalline alkaloids,  $C_{22}H_{33}NO_6$ , m.p. 166—167 °C, and  $C_{22}H_{33}NO_5$ , m.p. 161—164 °C.<sup>11</sup> Further structural investigations of acomonine that support the assignment of its structure as (25) have been reported.<sup>11</sup> The preliminary spectral evidence accounted for the presence of an *N*-ethyl, three hydroxy-, and four methoxy-groups. Reaction of acomonine with toluene-*p*-sulphonyl chloride gave anhydroacomonine (26). Oxidation of (26) with periodic acid yielded (27). This reaction has a firm precedent in studies of the C-7–C-8 diol systems of other diterpenoid alkaloids. Hydrogenation of (26) with Adams' catalyst gave desoxoacomonine (28), which was oxidized with potassium permanganate to the lactam (29). Acetylation of acomonine with acetic anhydride yielded the monoacetate derivative (30). The <sup>1</sup>H n.m.r. and mass spectral data for acomonine and the monoacetate enabled the assignment of the secondary hydroxy-group at C-3. The  $\alpha$ -orientation of the hydroxy-group was determined by the oxidation of acomonine with potassium permanganate to give the inner ether (31), which could be further oxidized to (32) with sodium metaperiodate. Borohydride reduction of (31) regenerated acomonine. The positions and configurations of the remaining functional groups were assigned from the <sup>1</sup>H n.m.r. and mass spectral data of these products and related transformation products from other lycotonine-type alkaloids. Acomonine is the first lycotonine-type alkaloid which contains no oxygen function at C-1.

**Iliensine.**—This alkaloid,  $C_{24}H_{39}NO_7$ , m.p. 202—203 °C, was isolated from the aerial parts of *Delphinium bitematum*.<sup>12</sup> A second report on the structure (33) of this alkaline has appeared.<sup>13</sup> The partial formula  $C_{19}H_{21}(NEt)(OH)_4(OMe)_3$  was assigned from the spectral data. Reaction of iliensine with acetic anhydride gave a diacetyl derivative (34), whereas oxidation with potassium permanganate in aqueous acetone afforded the desethyl carbinolamine ether (35). This compound formed an *NO*-diacetyl derivative (36) on acetylation, which could be hydrolysed to (37) with methanolic sodium hydroxide. Reaction of iliensine with toluene-*p*-sulphonyl chloride gave anhydroiliensine (38). Comparison of the <sup>1</sup>H n.m.r. spectra of iliensine and its derivatives with acomonine and the analogous products enabled assignment of an  $\alpha$ -hydroxy-group at C-3. Hydrogenation of anhydroiliensine gave (39), which could be oxidized to the lactam (40) with potassium permanganate. The seco product (41) was obtained by treatment of (40) with sodium metaperiodate. For additional structural conformation, acomonine and iliensine were both methylated with methyl iodide/sodium hydride to yield the identical derivative (42).

**Excelsine.**—The complete results of the X-ray crystallographic study of the monohydrate-hydriodide derivative of (+)-excelsine (43) have been published<sup>14</sup> (cf. Vol. 6, p. 260). This paper includes all positional parameters, bond angles and lengths, and other pertinent inter- and intra-molecular atomic distances.

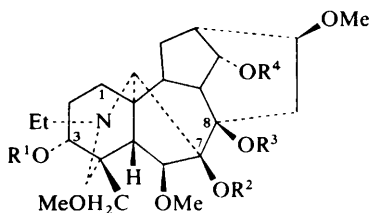
<sup>10</sup> V. E. Nezhevenko, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1974, **10**, 409.

<sup>11</sup> V. E. Nezhevenko, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, **11**, 389.

<sup>12</sup> M. S. Yunusov, V. E. Nezhevenko, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, **11**, 107.

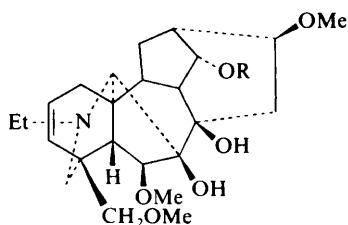
<sup>13</sup> M. S. Yunusov, V. E. Nezhevenko, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, **11**, 770.

<sup>14</sup> S. M. Nasirov, V. G. Andrianov, Yu. T. Rashkes, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1976, **12**, 206.

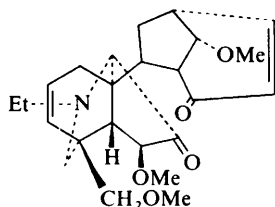


Acomonine (25)  $R^1=R^2=R^3=H$ ;  $R^4=Me$   
 (30)  $R^1=Ac$ ;  $R^2=R^3=H$ ,  
 $R^4=Me$

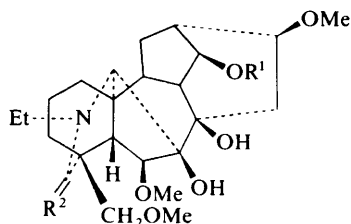
Iliensine (33)  $R^1=R^2=R^3=R^4=H$   
 (34)  $R^1=R^4=Ac$ ;  $R^2=R^3=H$   
 (42)  $R^1=R^4=Me$ ;  $R^2=R^3=H$



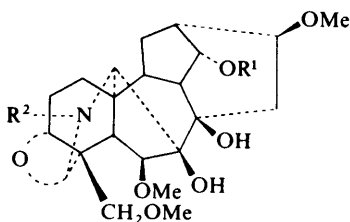
(26)  $R=Me$   
 (38)  $R=H$



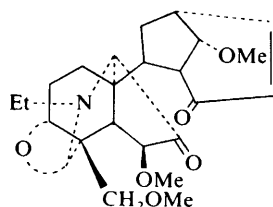
(27)



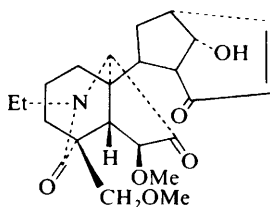
(28)  $R^1=Me$ ;  $R^2=H_2$   
 (29)  $R^1=Me$ ;  $R^2=O$   
 (39)  $R^1=H$ ;  $R^2=H_2$   
 (40)  $R^1=H$ ;  $R^2=O$



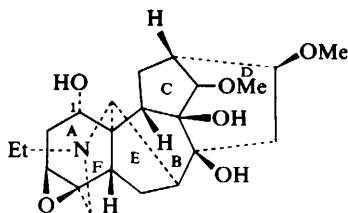
(31)  $R^1=Me$ ;  $R^2=Et$   
 (35)  $R^1=R^2=H$   
 (36)  $R^1=R^2=Ac$   
 (37)  $R^1=H$ ;  $R^2=Ac$



(32)

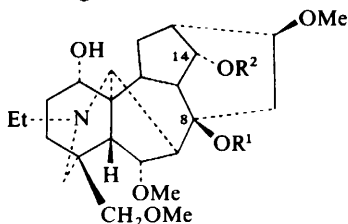


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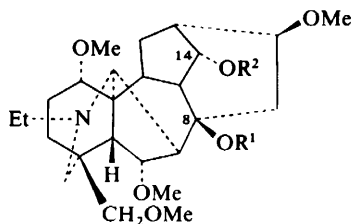


(+) -Excelsine (43)

**Delphisine, Neoline, Chasmanine, and Homochasmanine.**—The full report on the structures and stereochemistry of delphisine (44), neoline (45), chasmanine (46), and homochasmanine (47) has been published<sup>15</sup> (cf. Vol. 6, p. 258). An X-ray crystallographic study of the 14 $\alpha$ -benzoate hydrochloride derivative (48) of chasmanine confirmed the structure of the alkaloid.<sup>16</sup> Using direct methods, the final *R* was 0.048 based on 2493 reflections. As in the previous examples with a C-1  $\alpha$ -hydroxy-group, ring A was found to be in a boat form stabilized by intramolecular hydrogen bonding.



Delphisine (44)  $R^1 = R^2 = \text{Ac}$   
 Neoline (45)  $R^1 = R^2 = \text{H}$



Chasmanine (46)  $R^1 = R^2 = \text{H}$   
 Homochasmanine (47)  $R^1 = \text{Me}; R^2 = \text{H}$   
 (48)  $R^1 = \text{H}; R^2 = \text{Bz(HCl)}$

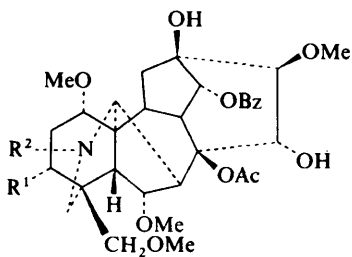
**<sup>13</sup>C N.M.R. Studies of the Aconitine-type Alkaloids.**—A comprehensive <sup>13</sup>C n.m.r. study of nine aconitine-type alkaloids and seventeen related derivatives has been published.<sup>17</sup> The chemical shifts for the carbon atoms in the following alkaloids were assigned: aconitine (49), mesaconitine (50), deoxyaconitine (51), delphinine (52), chasmanine (46), delphisine (44), neoline (45), condelphine (53), and isotalatizidine (54). A most important observation was the consistency of the chemical shifts for the quarternary carbon atoms in these alkaloids. Assignment of the chemical shifts was greatly facilitated by the differences in the oxygen substituents in the molecules. In addition, the oxygen functionalities were shown to cause chemical shifts of the carbons  $\alpha$  and  $\beta$  to the carbon of direct attachment, which assisted in the calculation of chemical shifts using additivity relationships. Tables of the chemical shifts of these alkaloids and their derivatives are presented. The data support the previous structural assignments for these compounds, and corrections of several of the <sup>13</sup>C chemical-shift assignments made by Jones and Benn<sup>18</sup> for delphonine (55) and isotalatizidine (54) are included.

<sup>15</sup> S. W. Pelletier, Z. Djarmati, S. Lajšić, and W. H. De Camp, *J. Amer. Chem. Soc.*, 1976, **98**, 2617.

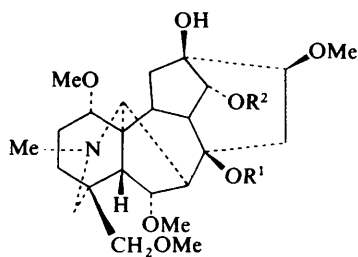
<sup>16</sup> S. W. Pelletier, W. H. De Camp, and Z. Djarmati, *J.C.S. Chem. Comm.*, 1976, 253.

<sup>17</sup> S. W. Pelletier and Z. Djarmati, *J. Amer. Chem. Soc.*, 1976, **98**, 2626.

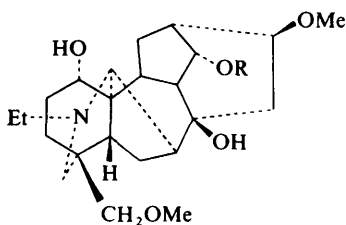
<sup>18</sup> A. J. Jones and M. N. Benn, *Canad. J. Chem.*, 1973, **51**, 486.



Aconitine (49)  $R^1 = \text{OH}$ ;  $R^2 = \text{Et}$   
 Mesaconitine (50)  $R^1 = \text{OH}$ ;  $R^2 = \text{Me}$   
 Deoxyaconitine (51)  $R^1 = \text{H}$ ;  $R^2 = \text{Et}$

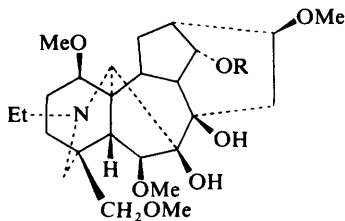


Delphinine (52)  $R^1 = \text{Ac}$ ;  $R^2 = \text{Bz}$   
 Delphonine (55)  $R^1 = R^2 = \text{H}$



Condelphine (53)  $R = \text{Ac}$   
 Isotalatizidine (54)  $R = \text{H}$

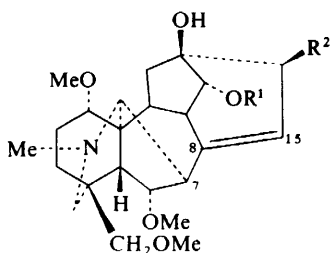
The problem of the incorrect assignment of the structure of chasmanine based on the chasmanine–browniine–lycoctonine correlations (*cf.* vol. 6) was examined in view of these  $^{13}\text{C}$  n.m.r. data.<sup>17</sup> Complete assignments for all of the resonances for lycoctonine (56a) and browniine (56b) and their corresponding acetates were made. These data indicated that lycoctonine and browniine had identical stereochemistry in ring A, as have neoline and chasmanine. The reactions of the attempted browniine–chasmanine correlation would not be expected to affect the oxygen function at C-1; it was therefore concluded that this work must be in error.



Lycoctonine (56) a;  $R = \text{Me}$   
 Browniine b;  $R = \text{H}$

As part of the  $^{13}\text{C}$  n.m.r. study, the 'pyrodelphonine chromophore' was examined. The unexpected u.v. absorption of pyrodelphonine (57) at  $\lambda_{\text{max}}$  245 m $\mu$ ,  $\epsilon_{\text{max}}$  6300, which disappears upon acidification, was explained by Wiesner *et al.* to result from a  $\sigma$ -coupled  $\pi$ -electron system between the nitrogen, the C-7–C-17 bond, and the  $\pi$ -system of the C-8–C-15 double bond. They proposed an excited state resem-

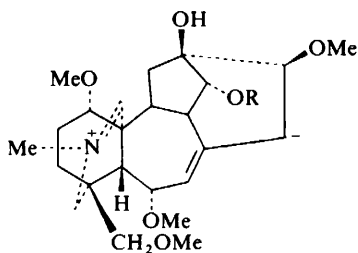
bling (58). This was supported by their subsequent work employing a photoreduction of (59) with sodium borohydride and sodium borodeuteride.<sup>19</sup> The <sup>13</sup>C and <sup>1</sup>H n.m.r. data for pyrodelphinine (60) and pyrodelphinine *N*-oxide (61) in varying concentrations of acetic acid indicated that, even in the electronic ground state of the pyrodelphinine molecule, there is a direct interaction between the free electron pair of the nitrogen and the  $\pi$ -electrons of the C-8—C-15 double bond, as in (62). This conclusion was reached on the basis of the large upfield shift of C-15 and the downfield shift of C-8 on acidification or *N*-oxidation. The C-15 proton signal of pyrodelphonine was also shifted downfield on acidification with hydrochloric acid or on oxidation of the nitrogen.



Pyrodelphonine (57)  $R^1 = H$ ;  $R^2 = OMe$

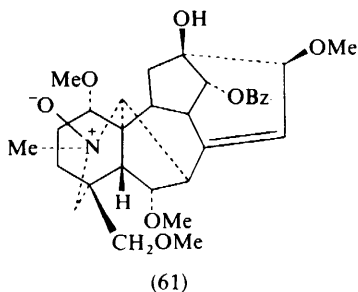
(59)  $R^1 = R^2 = H$

Pyrodelphinine (60)  $R^1 = Bz$ ;  $R^2 = OMe$



(58)  $R = H$

(62)  $R = Bz$



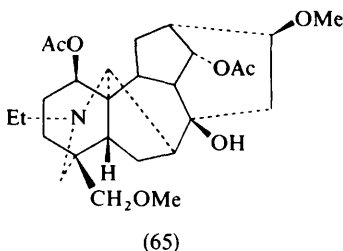
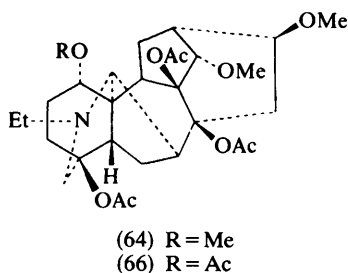
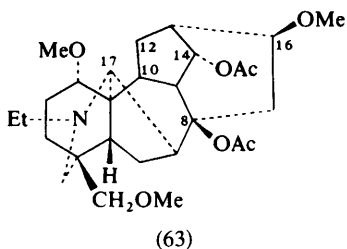
(61)

This work, with the earlier report by Jones and Benn,<sup>18</sup> has established a <sup>13</sup>C n.m.r. data base for the aconitine- and lycoctonine-type alkaloids which should greatly facilitate structural investigations of new bases in these series.

**Acylation and Hydrolysis Studies.**—The relative reactivities of the C-1 and C-14 oxygen functionalities in a series of lycoctonine-type diterpenoid alkaloids have been examined.<sup>20</sup> Diacetyl-talatizamine (63) and triacetyl-lappaconine (64), which contain C-1 methoxyl functions, were saponified approximately three times faster than diacetyl-karakoline (12), diacetyl-talatizidine (65), and tetra-acetyl-lappaconidine (66), all of which contain C-1 acetoxy-groups. In addition, karakoline (11) and karakolidine (10) were selectively mono-acylated at C-1. From these limited data the

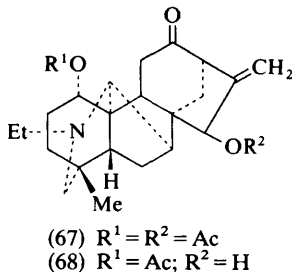
<sup>19</sup> K. Wiesner and T. Inaba, *J. Amer. Chem. Soc.*, 1969, **91**, 1036.

<sup>20</sup> M. N. Sultankhodzhaev, M. S. Yunusov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, **11**, 381.



authors proposed that, on acylation, the C-1 hydroxy-group was less sterically hindered than the C-14 hydroxy-group (*cis*-axial interactions with the substituents at C-8 and C-16). On alkaline hydrolysis, the carbonyl of the C-14 acetoxy-group was reasoned to be sufficiently removed from the ring plane that these interactions would be reduced. Model studies, however, suggested that the carbonyl of the C-1 acetoxy-group would be hindered by the protons at C-10, C-17, and C-12.

It should be noted that steric or simple electronic effects may not be the only factors operating. The  $^{13}\text{C}$  n.m.r. study<sup>17</sup> showed that in the diterpenoid alkaloids with the C-1  $\alpha$ -hydroxy-group, ring A existed in a boat form stabilized by intramolecular hydrogen bonding. On acylation (or methylation) at C-1, this ring converted into the chair form. On the other hand, since the hydrolysis rate of the C-1  $\beta$ -acetoxy-derivative (65) is similar to that of (12) and (66) (with C-1  $\alpha$ -acetoxy-group), the configuration at C-1 evidently has little effect on the hydrolysis rate. The anomalous ready hydrolysis of the C-1 acetoxy-group in di- and tetra-acetyl-karakolidine has been explained as resulting from the influence of the hydroxy-group at C-10. In added proof, the diacetate derivative (67) of songorine, in which the C-1 oxygen functionality has a similar steric environment to that in the aconitine-type alkaloids, was partially hydrolysed, and after 45 minutes the mono-acetyl derivative (68) was isolated.

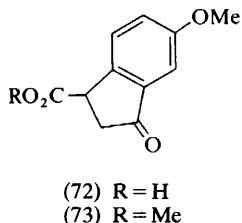
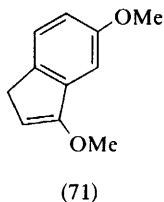
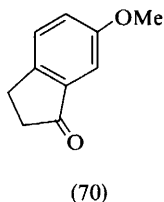
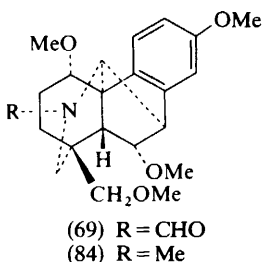




The results of these studies are in agreement with the acylation/hydrolysis studies reported for delphisine.<sup>15</sup>

**Syntheses Directed Toward Chasmanine.**—Outstanding progress toward the total synthesis of the complex hexacyclic diterpenoid alkaloid chasmanine (46) has been reported. The pentacyclic intermediate (69) has been prepared,<sup>21</sup> and, using a model system, the methodology for the conversion of this compound into chasmanine has been developed.<sup>22</sup> These experiments employed many processes developed in the earlier synthetic work, and in a number of instances, considerable improvements in the methods have been made.

For the synthesis of (69), the enol ether (71) from the indanone (70) was carboxylated with  $\text{CO}_2$ -*n*-butyl-lithium in THF at  $-70^\circ\text{C}$  to yield (72). The methyl ester (73) was converted into (75) *via* the maleic anhydride adduct (74), essentially as described in earlier work.<sup>23</sup> Lithium aluminium hydride reduction followed by oxidation with dicyclohexylcarbodi-imide afforded the aldehyde (76). This was condensed with excess (77) to yield a mixture of the diastereomers (78). Oxidation with chromium trioxide-pyridine in methylene dichloride gave (79), which could be converted into the diketone (80) by treatment with excess benzenesulphonylazide. The diketo-lactam (81) was prepared from (80) as described for the synthesis of the analogous intermediate used in the synthesis of napelline.<sup>24</sup> Reduction of (81) with lithium tri-*t*-butoxyaluminumhydride gave the desired dihydroxy-lactam (82). Methylation of (82) with methyl iodide-sodium hydride gave (83). Reduction of this lactam to the amine (84) with lithium aluminium hydride, followed by oxidation with potassium permanganate in acetic acid, gave (69).

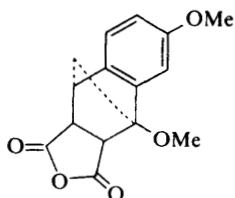


<sup>21</sup> S.-F. Lee, G. M. Sathe, W. W. Sy, P.-T. Ho, and K. Wiesner, *Canad. J. Chem.*, 1976, **54**, 1039.

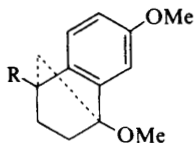
<sup>22</sup> K. Wiesner, P.-T. Ho, W.-C. Liu, and M. N. Shanbhag, *Canad. J. Chem.*, 1975, **53**, 2140.

<sup>23</sup> K. Wiesner, P.-T. Ho, R. C. Jain, S.-F. Lee, S. Oida, and A. Philipp, *Canad. J. Chem.*, 1973, **51**, 1448.

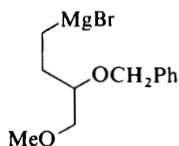
<sup>24</sup> K. Wiesner, P.-T. Ho, D. Chang, Y. K. Lam, C. S. J. Pan, and W. Y. Ren, *Canad. J. Chem.*, 1973, **51**, 3978.



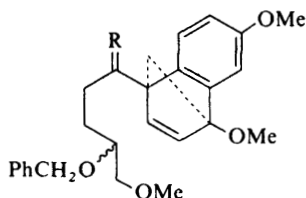
(74)

(75) R = CO<sub>2</sub>Me

(76) R = CHO

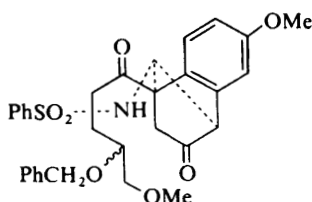


(77)

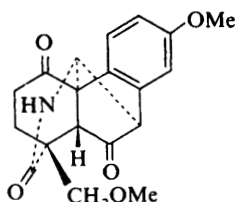


(78) R = H, OH

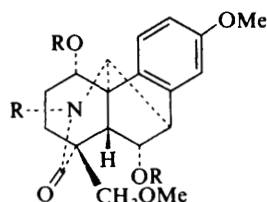
(79) R = O



(80)



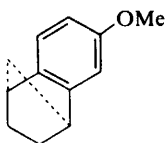
(81)



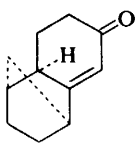
(82) R = H

(83) R = Me

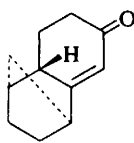
The reactions for the conversion of compound (69) into chasmanine were studied in a model system, starting with (85).<sup>22</sup> Birch reduction followed by acid-catalysed rearrangement gave (86). On equilibration of (86) in methanolic HCl-dioxan for six days, a 2.7 : 1 ratio of (86) to the epimer (87) was obtained. The epimers were separated by column chromatography. Photo-addition of allene to (87) gave (88). Acetalization of the adduct (88), followed sequentially by ozonolysis, sodium borohydride reduction, and acid treatment, yielded the keto-aldehyde (89). Cyclization of (89) with a BF<sub>3</sub> etherate-acetic anhydride-acetic acid mixture gave acetoxy-ketone (90). The equilibrium in this condensation favoured the retroaldol reaction, and therefore this condensation could only be accomplished under acetylating conditions. Reduction of (90) with sodium borohydride gave the acetoxy-alcohol (91), which was methylated with diazomethane-BF<sub>3</sub> etherate. Saponification of the acetoxy-group of (92) followed by oxidation with chromium trioxide produced the ketone (93), which was converted into the acetal (94). Bromination of (94) with pyridine hydrobromide perbromide yielded the bromo-derivative (95). On heating a benzene solution of this bromide with 1,5-diazabicyclo[3,4,0]nonene, the



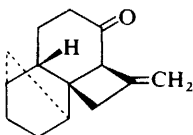
(85)



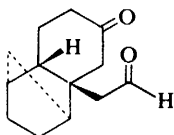
(86)



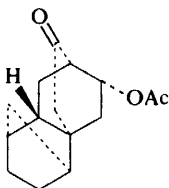
(87)



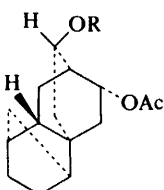
(88)



(89)

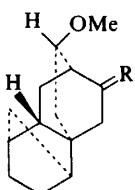


(90)

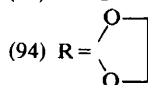


(91) R = H

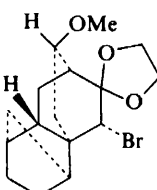
(92) R = Me



(93) R = O

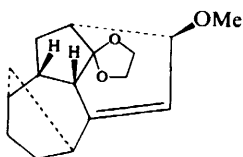


(94) R =

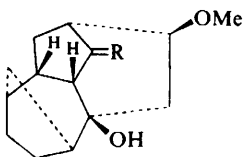


(95)

rearranged product (96) was obtained in a 90% yield. Treatment of (96) with mercuric acetate in aqueous acetone gave (97), which was deacetalized by heating in 50% acetic acid to yield (98). The structure of this ketone was confirmed by a single crystal *X*-ray crystallographic study. On reduction of (98) with sodium borohydride, the alcohol (99) was obtained. It was reasoned that the functionalized groups in (69) should not be affected by any of the reaction conditions employed in the model system. Therefore, the completion of the total synthesis of chasmanine (and other complex delphinine-type alkaloids) may be expected in the near future.

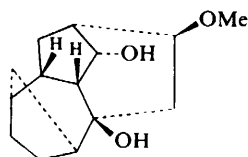


(96)



(97) R =

(98) R = O



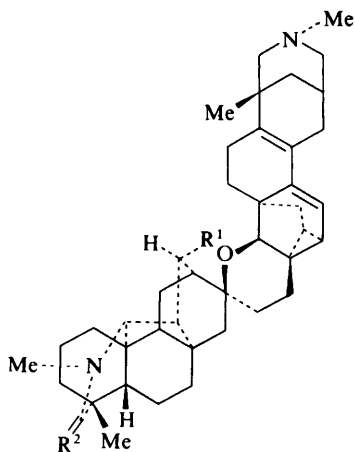
(99)

### 3 C<sub>20</sub> Diterpenoid Alkaloids

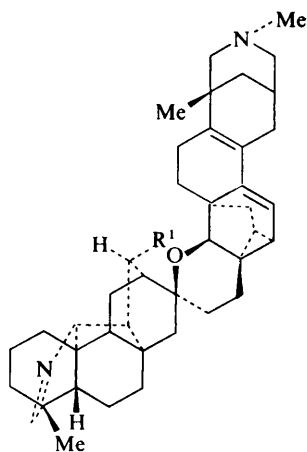
**Bisditerpenoid Alkaloids from *Delphinium staphisagria*.**—Seven new bisditerpenoid alkaloids have been isolated from the mother liquors accumulated during the isolation of delphinine (52) from the seeds of *Delphinium staphisagria*.<sup>25-27</sup> The structures of staphidine (100),<sup>25</sup> staphinine (101),<sup>25</sup> staphimine (102),<sup>25</sup> staphisagnine (103),<sup>26</sup> staphisagrine (104),<sup>26</sup> staphigine (105),<sup>27</sup> and staphirine (106)<sup>27</sup> were assigned primarily by comparisons of their <sup>13</sup>C and <sup>1</sup>H n.m.r. data with those of staphisine, C<sub>43</sub>H<sub>60</sub>N<sub>2</sub>O<sub>2</sub>, m.p. 211—213 °C. Staphisine was previously determined to have structure (107) by an X-ray crystallographic study of its monomethiodide derivative.<sup>28</sup>

Staphidine, C<sub>42</sub>H<sub>58</sub>N<sub>2</sub>O, m.p. 213—216 °C, is the non-methoxy-bearing companion of staphisine; the alkaloid 'staphisine' described by Jacobs and Craig<sup>29</sup> is a mixture of staphisine and staphidine. Staphinine, C<sub>42</sub>H<sub>56</sub>N<sub>2</sub>O<sub>2</sub>, and staphimine, C<sub>41</sub>H<sub>54</sub>N<sub>2</sub>O, were shown to be non-crystalline imine-containing bisditerpenoid alkaloids. Staphimine contains a methoxy-group analogous to staphisine. It was suggested that (101) and (102) might be biogenetic precursors of (107) and (100), respectively.

Staphisagnine, C<sub>44</sub>H<sub>62</sub>N<sub>2</sub>O<sub>3</sub> (resin), and staphisagrine, C<sub>43</sub>H<sub>60</sub>N<sub>2</sub>O<sub>2</sub>, m.p. 229—231 °C, each contain an oxazolidine ring system reminiscent of atisine (108) in one unit of the dimer; they differ only in the methoxy-group at C-13 in staphisagnine.



Staphidine (100) R<sup>1</sup> = H; R<sup>2</sup> = H<sub>2</sub>  
 Staphigine (105) R<sup>1</sup> = OMe; R<sup>2</sup> = O  
 Staphirine (106) R<sup>1</sup> = H; R<sup>2</sup> = O  
 Staphisine (107) R<sup>1</sup> = OMe; R<sup>2</sup> = H<sub>2</sub>



Staphinine (101) R = OMe  
 Staphimine (102) R = H

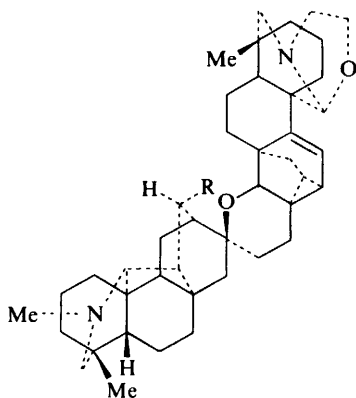
<sup>25</sup> S. W. Pelletier, N. V. Mody, Z. Djarmati, I. V. Mićović, and J. K. Thakkar, *Tetrahedron Letters*, 1976, 1055.

<sup>26</sup> S. W. Pelletier, Z. Djarmati, and N. V. Mody, *Tetrahedron Letters*, 1976, 1949.

<sup>27</sup> S. W. Pelletier, N. V. Mody, Z. Djarmati, and S. D. Lajšić, *J. Org. Chem.*, 1976, **41**, 3042.

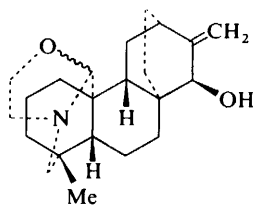
<sup>28</sup> S. W. Pelletier, A. H. Kapadi, L. H. Wright, S. W. Page, and M. G. Newton, *J. Amer. Chem. Soc.*, 1972, **94**, 1754.

<sup>29</sup> W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, 1941, **141**, 67.



Staphisagnine (103) R = OMe

Staphisagrinenine (104) R = H

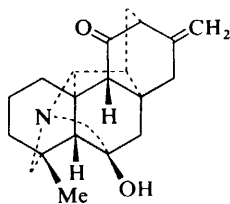


Atisine (108)

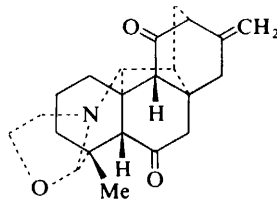
Staphigine,  $C_{43}H_{58}N_2O_3$ , m.p. 225—227 °C, and staphirine,  $C_{42}H_{56}N_2O_2$ , m.p. 222—225 °C, occur in extremely small amounts in the seeds of *D. staphisagria*, and are the C-19 lactam derivatives of staphisine and staphidine, respectively.

In all of the reports on the structures of these novel bisditerpenoid bases the  $^{13}C$  n.m.r. data are tabulated.

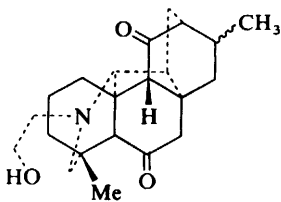
**Spiredine.**—Gorbunov *et al.*<sup>30</sup> have isolated the previously reported<sup>31</sup> spiradine A (109),  $C_{20}H_{25}NO_2$ , m.p. 280—282 °C, and a new alkaloid, spiredine, from *Spiraea japonica*. This new base,  $C_{22}H_{27}NO_3$ , m.p. 163 °C, was assigned structure (110) on the basis of the i.r. and  $^1H$  n.m.r. spectral data and by a chemical correlation with spiradine A. Catalytic hydrogenation of spiredine gave (111), which is identical to the compound obtained by the addition of ethylene oxide to dihydrospiradine A (112).



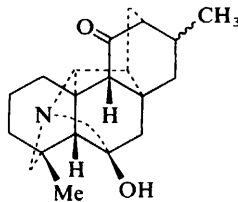
Spiradine A (109)



Spiredine (110)



(111)

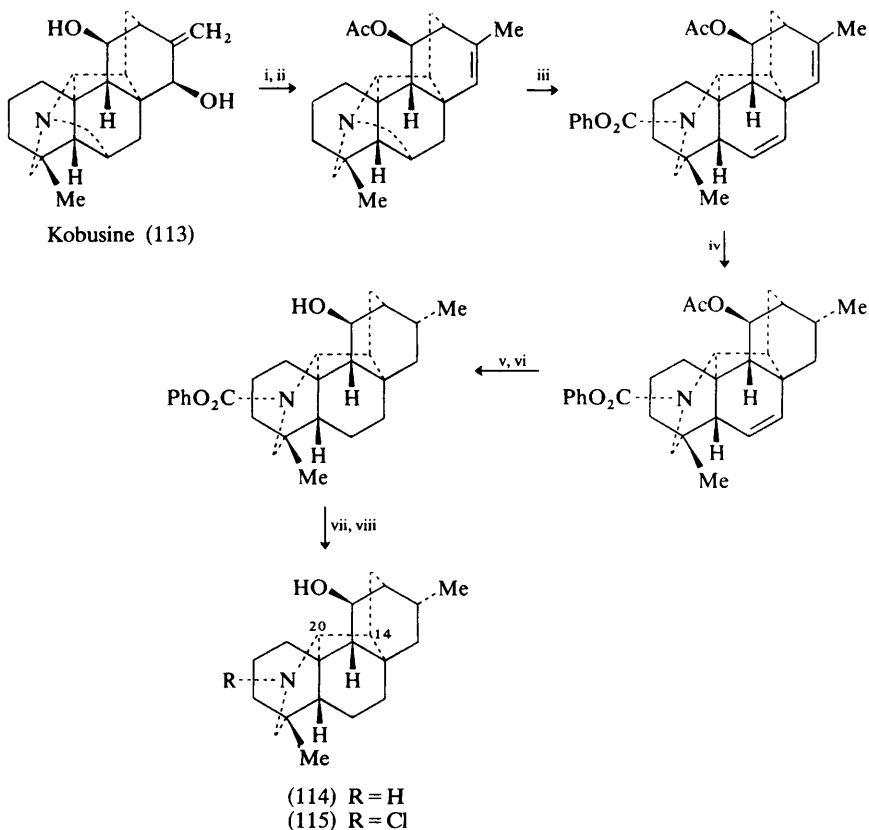


(112)

<sup>30</sup> V. D. Gorbunov, V. I. Sheichenko, and A. I. Ban'kovskii, *Khim. prirod. Soedinenii*, 1976, **12**, 124.

<sup>31</sup> G. Goto, K. Sasaki, N. Sakabe, and Y. Hirata, *Tetrahedron Letters*, 1968, 1369.

**Chemical Conversion of Kobusine.**—In their studies of diterpenoid interconversions, Okamoto and co-workers<sup>32</sup> have reported the conversion of kobusine (113) into the amine (114) (Scheme 1). Chlorination of (114) with *N*-chlorosuccinimide

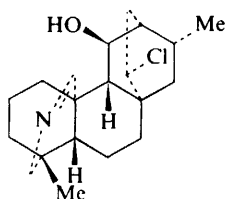


Reagents: i,  $\text{Na}-\text{CH}_3(\text{CH}_2)_2\text{OH}$ ; ii,  $\text{Ac}_2\text{O}$ , pyridine; iii,  $\text{ClCO}_2\text{Ph}$ , *o*-dichlorobenzene; iv,  $\text{H}_2$ -Pd/C, methanol; v,  $\text{H}_2$ -Pt, AcOH; vi, HCl, methanol; vii,  $\text{PhCH}_2\text{OH}$ , NaH, DME; viii,  $\text{H}_2$ -Pd/C-HCl, methanol.

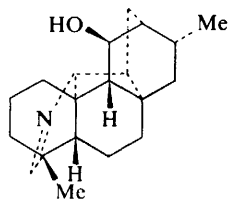
**Scheme 1**

gave (115). On treatment of this chloramine with sodium methoxide, a mixture of (116) (38%), (117) (28%), and (118) (13%) was obtained. The structure and stereochemistry of (116) were determined by an *X*-ray crystallographic study. Reduction of (116) with sodium borohydride, followed by acetylation, hydrolysis, and dechlorination by hydrogenolysis with Raney nickel, gave (119). The cleavage of the C-14—C-20 bond in the chloramine (115) is a novel fragmentation, for which no satisfactory mechanism has been proposed.

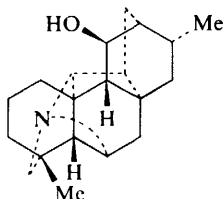
<sup>32</sup> T. Yatsunami, T. Isono, I. Hayakawa, and T. Okamoto, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 3030.



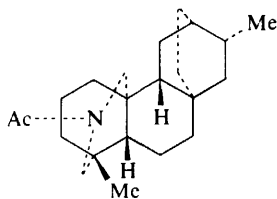
(116)



(117)



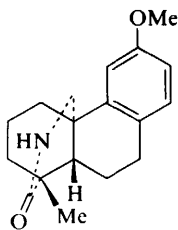
(118)



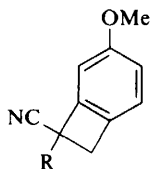
(119)

**Syntheses of Diterpenoid Alkaloid Intermediates.**—In studies of the potential of cycloadditions as a route to intermediates for the syntheses of tetracyclic diterpenoids,<sup>33,34</sup> Kametani and co-workers<sup>34</sup> have prepared the lactam (120). The benzocyclobutene (121) was prepared from *p*-anisaldehyde (122).<sup>35</sup> A Knoevenagel reaction of (122) with cyanoacetic acid gave (123), which could be reduced with sodium borohydride to give the dihydrocinnamic acid (124). Decarboxylation in *NN*-dimethylacetamide at 150 °C followed by treatment of the resulting nitrile (125) with a bromine–sodium acetate–acetic acid mixture yielded (126). This bromonitrile was treated with sodium amide in liquid ammonia to give (121). Condensation of (121) with (127) gave (128). Thermolysis of (128) gave the tricyclic cyanoester (129), whereas on hydrogenation, the tetracyclic lactam (120) was obtained.

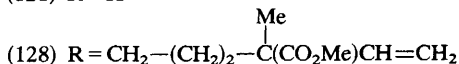
Ghatak and Chakrabarty<sup>36</sup> have published a full report of their synthesis of (130) and (131) *via* the dicarboxylic acids (132) and (133). The tetracyclic acetylamine



(120)



(121) R = H

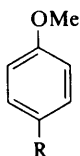
(128) R = CH<sub>2</sub>—(CH<sub>2</sub>)<sub>2</sub>—C(CO<sub>2</sub>Me)CH=CH<sub>2</sub>

<sup>33</sup> T. Kametani, H. Nemoto, and K. Fukumoto, *J.C.S. Chem. Comm.*, 1976, 400.

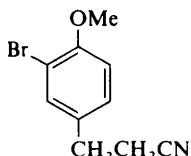
<sup>34</sup> T. Kametani, Y. Kato, T. Honda, and K. Fukumoto, *Heterocycles*, 1976, **4**, 241 (*Chem. Abs.*, 1976, **84**, 165 061b).

<sup>35</sup> T. Kametani, M. Kajiwar, and K. Fukumoto, *Tetrahedron*, 1974, **30**, 1053.

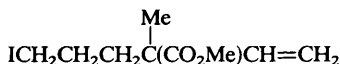
<sup>36</sup> U. R. Ghatak and S. Chakrabarty, *J. Org. Chem.*, 1976, **41**, 1089.



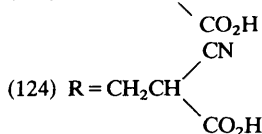
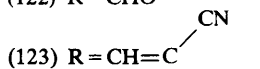
(122) R = CHO



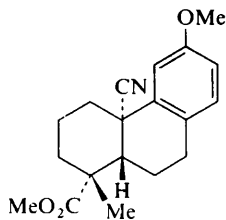
(126)



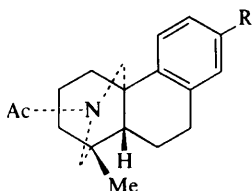
(127)



(125) R = CH2CH2CN

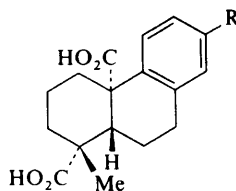


(129)



(130) R = H

(131) R = OMe

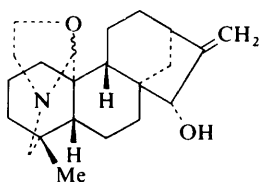


(132) R = H

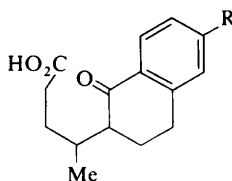
(133) R = OMe

(133) was a key intermediate in the total synthesis of atisine (108) and veatchine (134) reported by Nagata *et al.* (*cf.* Vol. 3, p. 241).

Dutta *et al.*<sup>37</sup> have also reported a synthesis of the diacid (132) and its methoxy-analogue (133). These intermediates were prepared from the oxo-acids (135) and (136), respectively, in thirteen steps. However, considerably different experimental conditions from those used for the synthesis of the model diacid (132) were required in several steps in the synthesis of the methoxy-series.



Veatchine (134)



(135) R = H

(136) R = OMe

<sup>37</sup> A. S. Sarma, A. K. Banerjee, and P. C. Dutta, *J.C.S. Perkin I*, 1976, 722.



4 *Daphniphyllum* Alkaloids

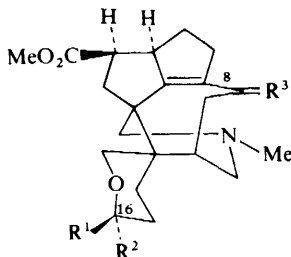
**Alkaloids from *Daphniphyllum gracile*.**—Five new alkaloids were isolated by preparative t.l.c. from the leaves of *Daphniphyllum gracile* Gage, which grows in the Trust Territory of New Guinea.<sup>38</sup>

Daphnigracine (137),  $C_{24}H_{37}NO_4$ , a viscous liquid, and daphnigraciline (138),  $C_{23}H_{35}NO_4$ , m.p. 76—78 °C, were found to differ only by the alkyl group at C-16. On treatment of daphnigraciline methiodide with acetic acid in methanol, yuzurine methiodide<sup>39</sup> (139) was obtained. The  $^1H$  n.m.r. spectra of (137) and (138) indicated that the hydroxy-group at C-16 must be in the axial configuration.

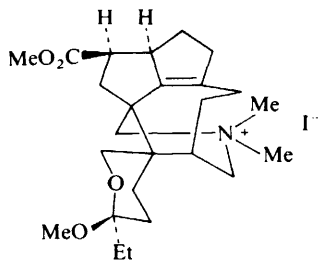
Oxodaphnigracine (140),  $C_{24}H_{35}NO_4$ , m.p. 116—117 °C, and oxodaphnigraciline (141),  $C_{23}H_{33}NO_5$ , m.p. 107—109 °C, were shown from i.r., u.v., and n.m.r. data to be the 8-oxo-derivatives of daphnigracine and daphnigraciline, respectively.

Epi-oxodaphnigraciline (142),  $C_{23}H_{33}NO_5$ , m.p. 102—104 °C, differed from (141) only in the configuration at C-16, as determined from the  $^1H$  n.m.r. spectra.

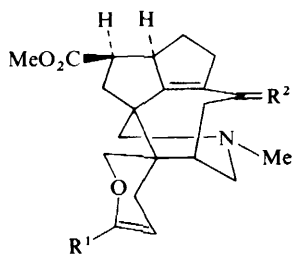
On treatment of (137), (138), and (141) with acetic anhydride–acetic acid, the dehydration products (143), (144), and (145), respectively, were obtained. The structural assignments of these compounds were confirmed by the  $^{13}C$  n.m.r. spectral data.



- Daphnigracine (137)  $R^1 = OH$ ;  $R^2 = Pr^i$ ;  $R^3 = H_2$   
 Daphnigraciline (138)  $R^1 = OH$ ;  $R^2 = Et$ ;  $R^3 = H_2$   
 Oxodaphnigracine (140)  $R^1 = OH$ ;  $R^2 = Pr^i$ ;  $R^3 = O$   
 Oxodaphnigraciline (141)  $R^1 = OH$ ;  $R^2 = Et$ ;  $R^3 = O$   
 Epi-oxodaphnigraciline (142)  $R^1 = Et$ ;  $R^2 = OH$ ;  $R^3 = O$



Yuzurine methiodide (139)

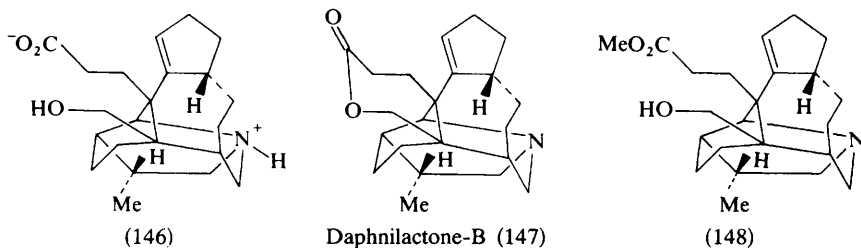


- (143)  $R^1 = Pr^i$ ;  $R^2 = H_2$   
 (144)  $R^1 = Et$ ;  $R^2 = H_2$   
 (145)  $R^1 = Et$ ;  $R^2 = O$

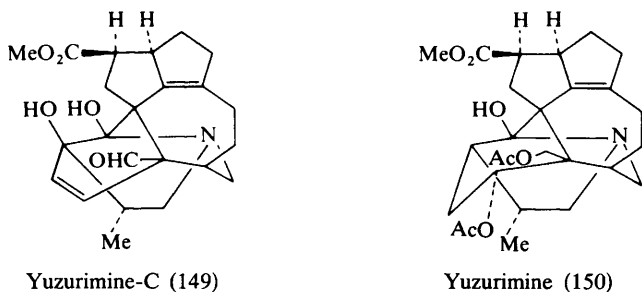
<sup>38</sup> S. Yamamura, J. A. Lamberton, H. Irikawa, Y. Okumura, and Y. Hirata, *Chem. Letters*, 1975, 923.

<sup>39</sup> S. Yamamura, K. Sasaki, M. Toda, and Y. Hirata, *Tetrahedron Letters*, 1974, 2023.

**A Zwitterionic Alkaloid from *Daphniphyllum teijsmanni*.**—This alkaloid,  $C_{22}H_{33}NO_3$ , m.p. 247—248 °C (decomposition), was eluted with ethyl acetate-methanol on alumina in the chromatographic separation of the alkaloid fraction.<sup>40</sup> The i.r. and  $^1H$  n.m.r. spectra indicated the presence of a hydroxymethyl group and a carboxylate group. On treatment of (146) with HCl in anhydrous methanol, a mixture of daphnilactone-B (147)<sup>41</sup> and the methyl ester (148) was obtained. Compound (146) could also be converted into (147) on heating with 90% formic acid. The authors suggested that this alkaloid might be a biogenetic precursor of daphnilactone-B or an artifact produced during the isolation procedures.



**Yuzurimine-C.**—Hirata and co-workers<sup>42</sup> have published additional work confirming the previously proposed structure (149) for yuzurimine-C,<sup>43</sup> the most highly oxygenated yuzurimine-type alkaloid. This base,  $C_{23}H_{29}NO_5$ , m.p. 186—187 °C, was a minor component of *Daphniphyllum macropodum* Miquel, co-occurring with yuzurimine (150). The  $^1H$  n.m.r. and i.r. data for yuzurimine-C showed a secondary methyl group and a carbomethoxyl group analogous to those of yuzurimine. In addition, these data pointed to yuzurimine-C having a tertiary aldehyde instead of an acetoxymethyl group and two olefinic protons.



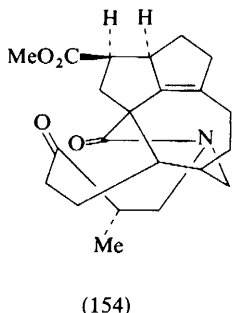
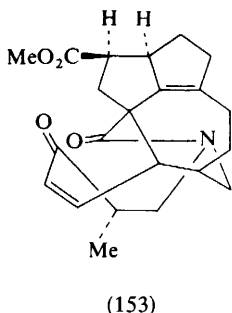
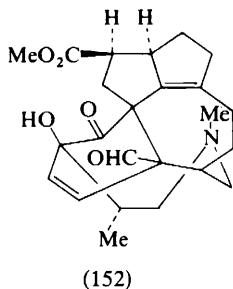
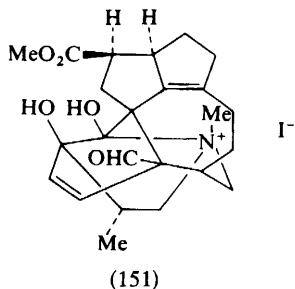
Yuzurimine-C formed the methiodide (151) on heating with methyl iodide in acetone, which, on treatment with aqueous alkaline solution, readily formed the keto-amine (152). This confirmed the location of the tertiary hydroxy-group  $\alpha$  to the nitrogen atom. Oxidation of (149) with sodium metaperiodate gave the keto-lactam (153), which was reduced to (154) by catalytic hydrogenation. Partial reduction of

<sup>40</sup> S. Yamamura, M. Toda, and Y. Hirata, *Bull. Chem. Soc. Japan*, 1976, **49**, 839.

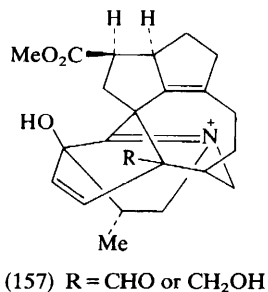
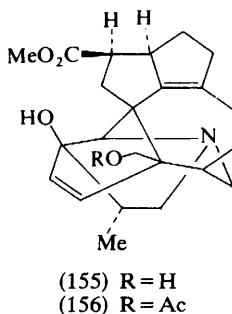
<sup>41</sup> M. Toda, H. Niwa, H. Irikawa, Y. Hirata, and S. Yamamura, *Tetrahedron*, 1974, **30**, 2683.

<sup>42</sup> S. Yamamura, H. Irikawa, Y. Okumura, and Y. Hirata, *Bull. Chem. Soc. Japan*, 1975, **48**, 2120.

<sup>43</sup> M. Toda, Y. Hirata, and S. Yamamura, *Tetrahedron*, 1972, **28**, 1477.



yuzurimine-C with lithium aluminium hydride gave (155), which was acetylated by an acetic anhydride-pyridine mixture at room temperature to form the monoacetate (156). The authors postulated that the imine (157), which violates Brecht's



rule, must be formed as an unstable intermediate in the reduction, analogous to the reduction of yuzurimine.<sup>44</sup> All of these structural assignments were supported by <sup>13</sup>C n.m.r. data. The <sup>13</sup>C chemical shifts of yuzurimine-C, yuzurimine, and four derivatives were presented.

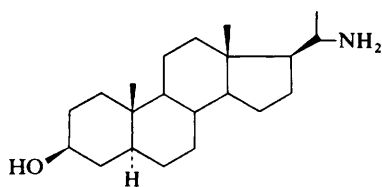
<sup>44</sup> H. Irikawa, S. Yamamura, and Y. Hirata, *Tetrahedron*, 1972, **28**, 3727.

# Steroidal Alkaloids of the Apocynaceae and Buxaceae and Related Compounds

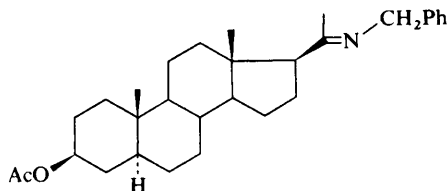
BY F. KHUONG-HUU AND R. GOUTAREL

## 1 Alkaloids of the Apocynaceae

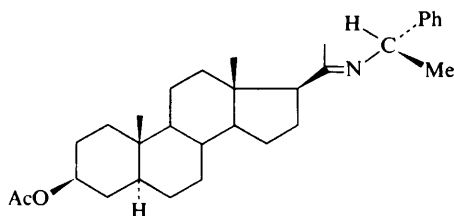
**Steroidal Alkaloids and Amines.**—*Syntheses, Reactions, and Transformations of Steroidal Amines.* A stereospecific synthesis of 20 $\alpha$ -aminopregnan-3 $\beta$ -ol, funtuphyllamine A (1), using reduction of a chiral imine has been described.<sup>1</sup> B<sub>2</sub>H<sub>6</sub> reduction of the 20-benzyliminopregnane (2) (without any chiral centre on the nitrogen atom), followed by debenzylation afforded a mixture of the two epimeric amines at C-20. Similar treatment of the chiral imine (3), prepared by reaction of 3 $\beta$ -acetoxy-5 $\alpha$ -pregnan-20-one with (–)-(S)- $\alpha$ -phenylethylamine in the presence of TsOH, led to the 20 $\alpha$ -amino derivative (1) stereospecifically. On the other hand, the reduction in the same conditions of the imine prepared from (+)-(R)- $\alpha$ -phenylethylamine and 3 $\beta$ -acetoxy-5 $\alpha$ -pregnan-20-one gave after debenzylation 92% of the 20 $\beta$ -amino-derivative and 8% of (1). It was noted that the reduction of the imine (2) with a chiral reagent, (+)-di-3-pinanylborane, gave, after debenzylation, a mixture of the two epimeric amines.



(1)



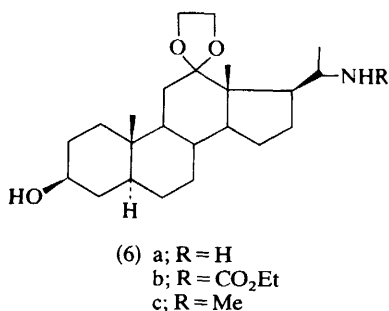
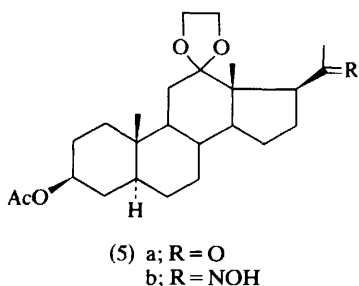
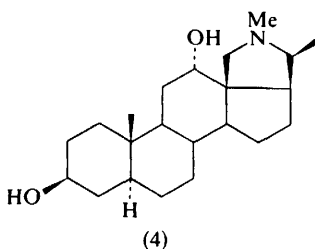
(2)



(3)

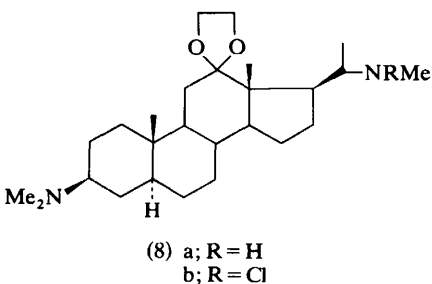
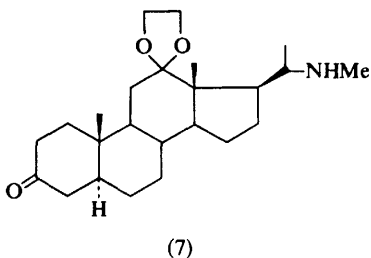
<sup>1</sup> G. Demailly and G. Solladié, *Tetrahedron Letters*, 1975, 2471.

The preparation of 12-oxygenated conanine derivatives and a partial synthesis of dihydroholarrhenine (4) have been reported.<sup>2</sup> 3 $\beta$ -Acetoxy-5 $\alpha$ -pregnan-12,20-dione ethylene acetal (5a), prepared from hecogenine acetate by published procedures, was transformed to the oxime (5b) which was reduced by sodium in propanol to the epimeric 20-amino-derivatives, with hydrolysis of the 3-acetoxy-group. Separation of the 20 $\alpha$ -epimer (6a) was effected by crystallization and column chromatography. Reduction of the cathylate (6b) gave (6c) which was oxidized to the

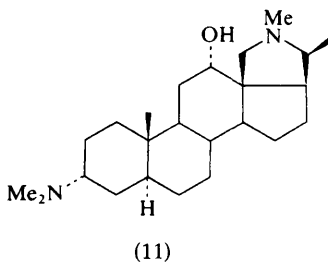
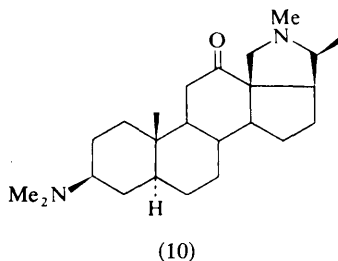
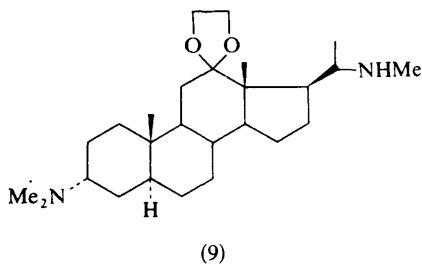


3-ketone (7). Reductive amination of (7) led to the epimeric 3-dimethylamino-compounds (8a) and (9). Hofmann-Löffler cyclization on (8b) afforded 12-oxodihydroconessine (10). Catalytic reduction of (10) over Pd/C furnished (4). Similar treatment of the 3 $\alpha$ -dimethylamino-derivative (9) led to 3-epiholarrhenine (11).

The Hofmann-Löffler reaction on 20 $\beta$ -methylamino-5 $\alpha$ -pregnan-12-one ethylene acetal derivatives failed. The preparation of dihydroconkussine, dihyd-

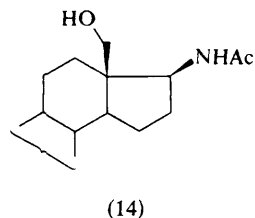
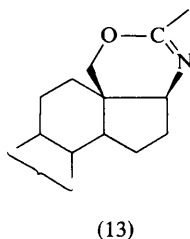
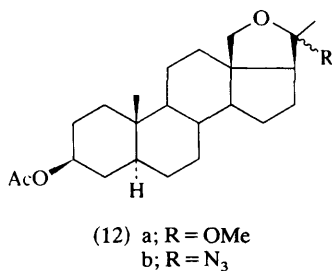


<sup>2</sup> G. Van de Woude and L. Van Hove, *Bull. Soc. chim. belges*, 1975, **84**, 911.



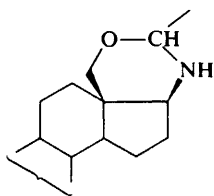
roconessine, dihydroisoconessimine, and 3-epidihydroisoconessimine by reductive amination of 5 $\alpha$ -conan-3-one with dimethylamine and methylamine respectively was also described.

The synthesis of 5,6-dihydro-1,3-oxazines in the androstane series as analogues of steroidal alkaloids has been reported.<sup>3</sup> Treatment of the acetal (12a) with HN<sub>3</sub>-BF<sub>3</sub> etherate gave the dihydro-1,3-oxazine (13) as major product and (14) as minor product. Catalytic hydrogenation, in neutral medium, of (13) led to the tetrahydro-

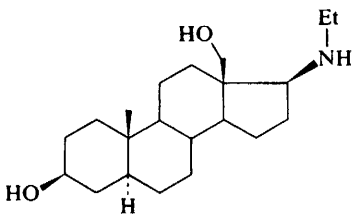


oxazine (15). Derivative (16) was obtained by catalytic hydrogenation in acidic medium of (13), followed by saponification of the 3-acetoxy-group. The structure of (14) was established by identification with the Beckmann rearrangement product of the oxime (17a), obtained from (12a) by NH<sub>2</sub>OH-NaOAc. Reaction of (12a) with HN<sub>3</sub> in benzene containing boric acid gave (12b). On the other hand, the acetal (18) with HN<sub>3</sub>-BF<sub>3</sub>-etherate afforded (19), reduced to (20a) and (21) by NaBH<sub>4</sub>. On filtration on alumina (19) gave (20b). When treated with HN<sub>3</sub> in benzene in the presence of boric acid (18a) led to (18b). The formation of the dihydro-1,3-oxazines

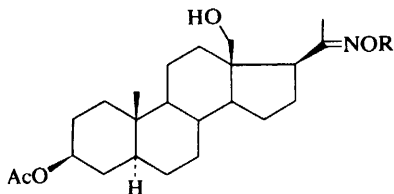
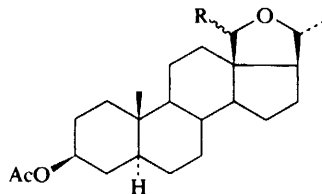
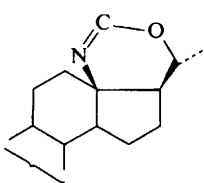
<sup>3</sup> C. Monneret, P. Choay, and Q. Khuong-Huu, *Tetrahedron*, 1975, **31**, 575.



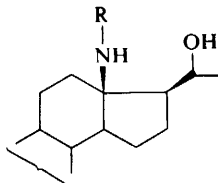
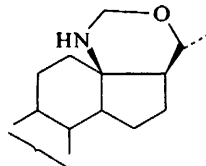
(15)



(16)

(17) a; R = H  
b; R = Ts(18) a; R = OMe  
b; R = N<sub>3</sub>

(19)

(20) a; R = Me  
b; R = CHO

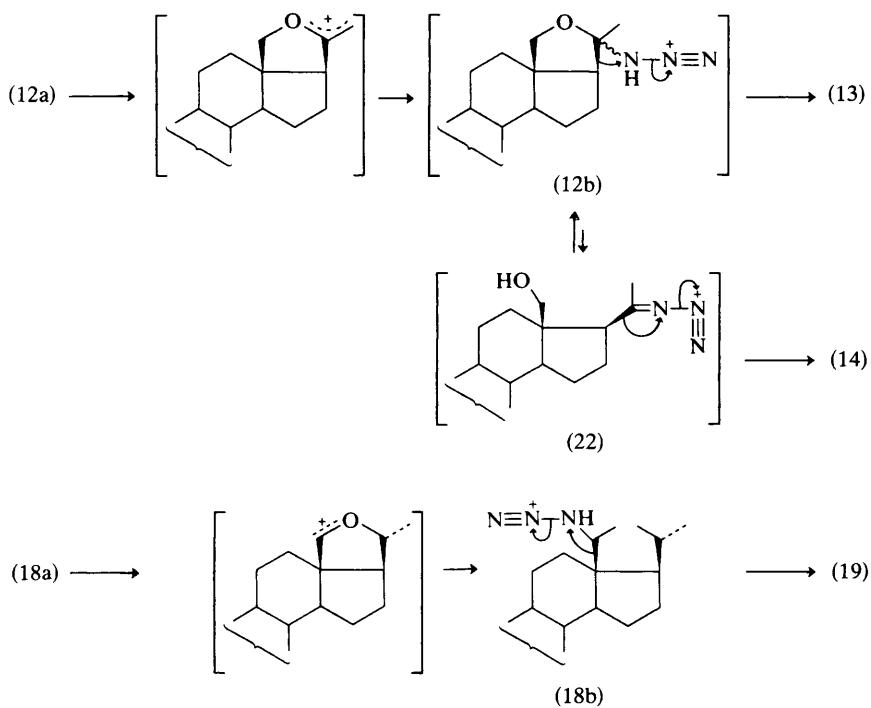
(21)

(13) and (19) was explained by the acid-catalysed decomposition of the azidopregnanes (12b) and (18b) as intermediates. Derivative (14) was explained by rearrangement of the tautomeric form of (12b), (22) (Scheme 1).

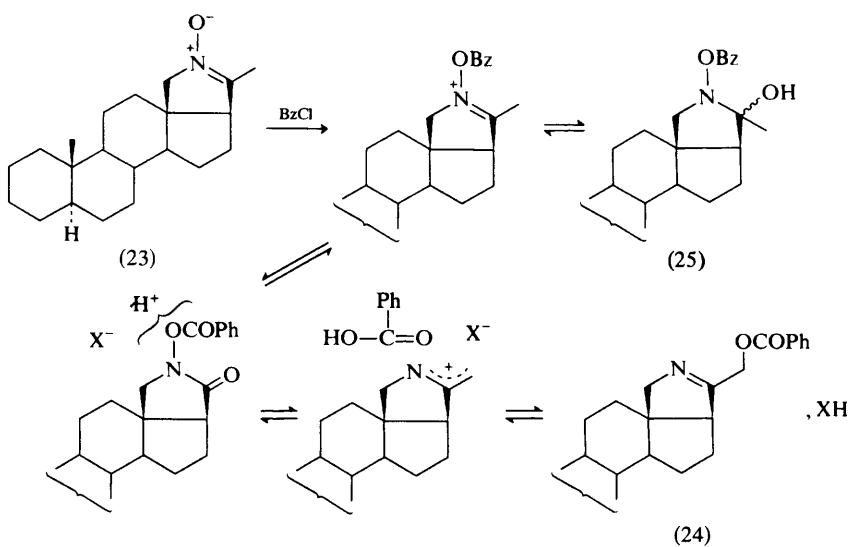
The full paper concerning the reaction of acyl chlorides (benzoyl and toluene-*p*-sulphonyl chlorides) with the steroidal nitron derivative (23) of conanine has been published.<sup>4</sup> Additional information concerning the mechanism of these reactions is given. Thus, it was shown that the formation of the  $\alpha$ -benzyloximine (24) needs acidic conditions which favour the heterolysis of the N—O bond (Scheme 2). At room temperature, under Schotten–Baumann conditions, the epimeric compounds (25) were obtained from (23) with benzoyl chloride. Compound (25) gave (24) on refluxing in neutral solvent or by treatment with acid, whereas (24) was obtained directly from (23) when treated with a benzene solution of benzoyl chloride in the presence of aqueous sulphuric acid.

The structure of (24) was established by the chemical correlation shown in Scheme 3. Reduction of (24) with NaBH<sub>4</sub> gave a mixture of (26), O-to-N acyl migration product, and (27); the latter was methylated to (29) which was identical with the product formed from the enamine (28) by oxidative hydroboration.

<sup>4</sup> J.-P. Alazard, B. Khemis, and X. Lusinch, *Tetrahedron*, 1975, **31**, 1427; J.-P. Alazard, B. Khemis, and X. Lusinch, *Tetrahedron Letters*, 1972, 4795.

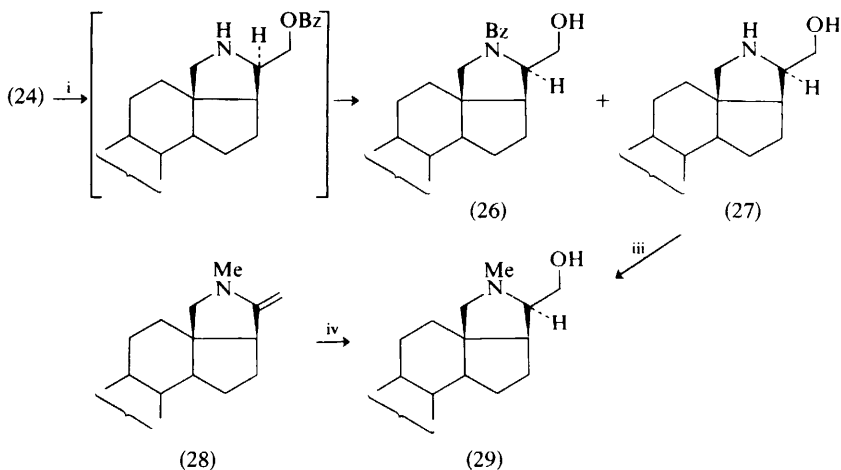


Scheme 1



Scheme 2

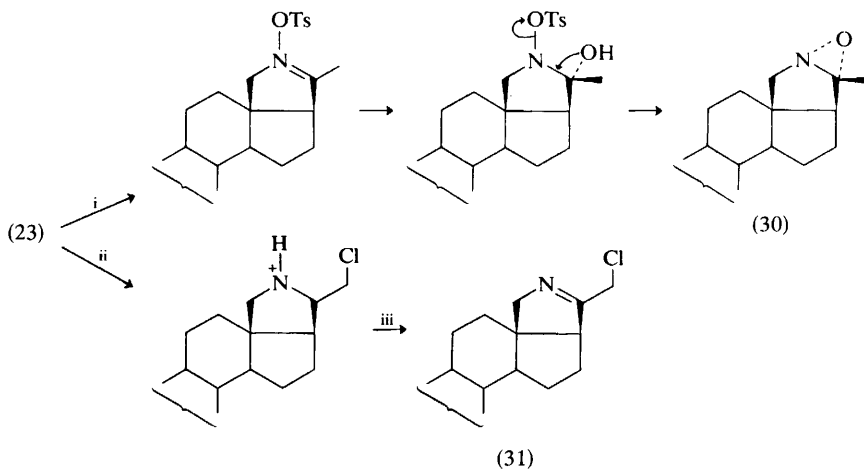




Reagents: i,  $\text{NaBH}_4$ ; ii,  $\text{MeOH}$ ,  $\text{HO}^-$ ; iii,  $\text{HCOOH}$ ,  $\text{HCHO}$ ; iv,  $\text{B}_2\text{H}_6$ ,  $\text{H}_2\text{O}_2$

**Scheme 3**

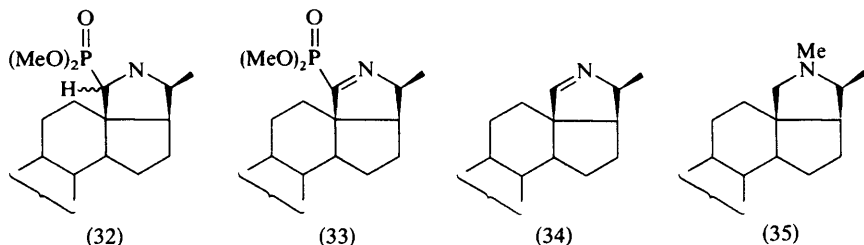
With acetic anhydride, the nitron (23) was unchanged, but with toluene-*p*-sulphonyl chloride in heterogeneous alkaline medium (23) gave the oxaziridine (30), whereas in a neutral solvent it led to (31) (Scheme 4). Conditions for deuteration of the nitron (23) were established: in heterogeneous neutral medium, no deuteration occurred; in homogeneous alkaline medium, quantitative deuteration at C-21 was effected; in heterogeneous alkaline medium, deuteration was incomplete, but in heterogeneous acidic medium, rapid incorporation was observed.<sup>4</sup>



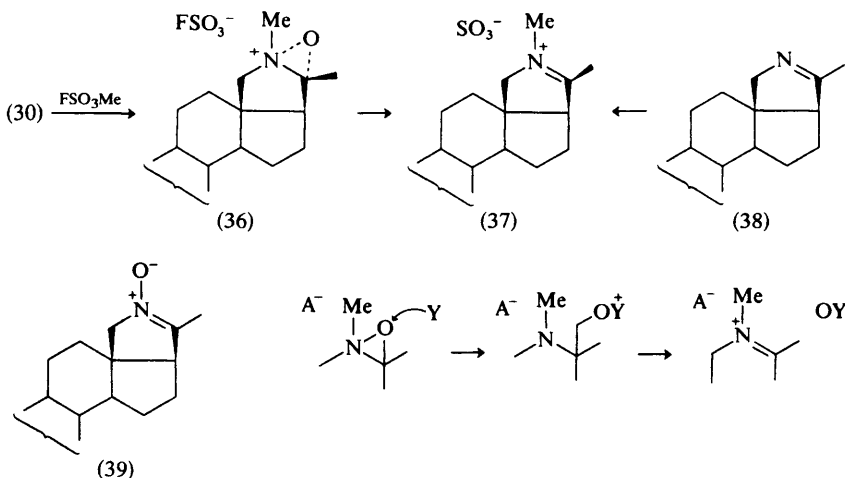
Reagents: i,  $\text{TsCl}$ ,  $\text{H}_2\text{O}$ ,  $\text{HO}^-$ ; ii,  $\text{TsCl}$ ,  $\text{CHCl}_3$ ; iii,  $\text{HO}^-$

**Scheme 4**

The reaction of the nitron (23) with alkyl phosphites has been studied.<sup>5</sup> With trimethyl phosphite in refluxing MeOH (23) afforded a mixture of the epimers (32), whereas in AcOH (33) was obtained. It was shown that (33) was not formed from (32) by loss of MeOH. With triethyl phosphite analogous products were formed, but in this case a large amount of the deoxygenated compound (34) was also obtained. With trimethyl phosphite the formation of an immonium structure, reducible to conanine (35), was suggested by the presence in the n.m.r. spectrum of the reaction mixture of a N—Me group. The structures of these compounds were deduced from their spectral data.



The formation and the oxidative properties of an oxaziridinium salt have been reported.<sup>6</sup> With methyl fluorosulphonate the oxaziridine (30) led to the oxaziridinium salt (36) which was stable as a crystalline product at room temperature, but unstable in solution, giving (37), also obtained from (38) with methyl fluorosulphonate.  $\text{NaBH}_4$  reduction of (36) led to (35). Peroxidic reactivity of (36) was shown by oxygen transfer from (36) to the imine (38) with formation of the nitron (39) (Scheme 5).

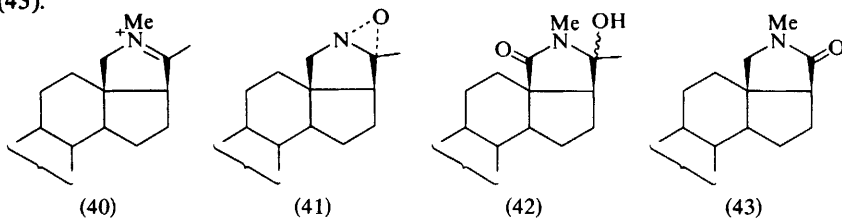


Scheme 5

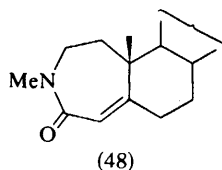
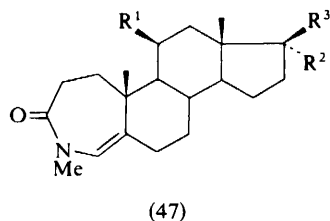
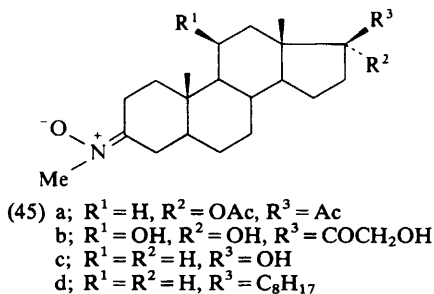
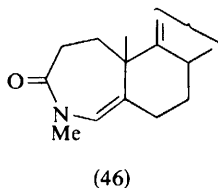
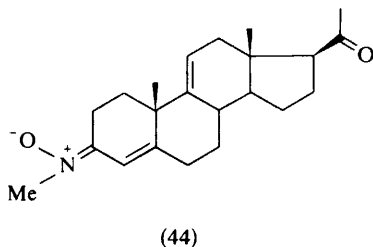
<sup>5</sup> P. Milliet and X. Lusinchi, *Compt. rend.* 1975, **280**, C, 1319.

<sup>6</sup> P. Milliet, A. Picot, and X. Lusinchi, *Tetrahedron Letters*, 1975, 1573.

The action of *p*-nitroperbenzoic acid and hydrogen peroxide on the immonium (40) and the corresponding enamine (28) has been studied and mechanisms have been proposed.<sup>7</sup> With two equivalents of PNPBA, (28) afforded (41), (42), and (43).

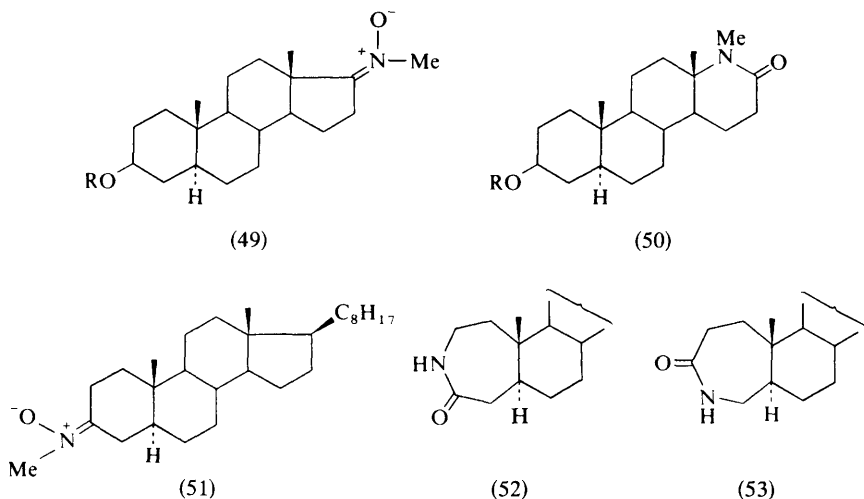


A ready rearrangement of ketonic nitrones to *N*-alkyl derivatives, providing a convenient alternative to the Beckmann rearrangement, has been presented.<sup>8</sup> The nitrones (44) and (45a—d), obtained from the corresponding ketones and hydroxy(methyl)ammonium chloride in pyridine, when treated with toluene-*p*-sulphonyl chloride in pyridine afforded the lactams (46) and (47a—d). In contrast, Beckmann rearrangement of oximes derived from  $\Delta^4$ -3-ketones gave lactams of type (48). In the same conditions, the nitrone (49) gave (50) and the nitrone (51) led to a 1 : 1 mixture of (52) and (53). In contrast to the Beckmann rearrangement, the nitrone rearrangement does not depend on stereochemistry: both *syn*- and *anti*-

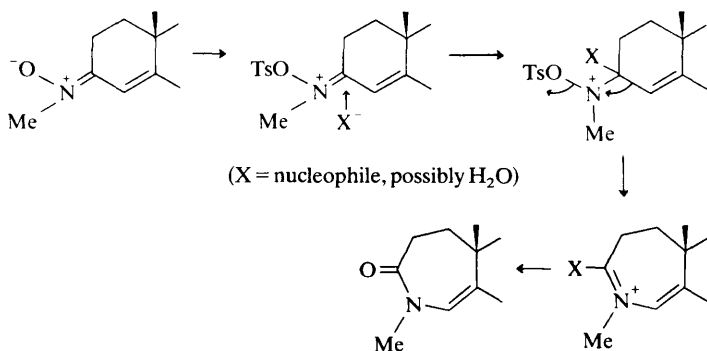


<sup>7</sup> A. Picot, P. Milliet, and X. Lusinchi, *Tetrahedron Letters*, 1975, 1577

<sup>8</sup> D. H. R. Barton, M. J. Day, R. H. Hesse, and M. M. Pechet, *J.C.S. Perkin I*, 1975, 1764.



nitrones gave the same lactam (nitron stereochemistry was assigned from u.v. spectra and confirmed by lanthanide-induced shifts in the n.m.r.). It was shown that *syn-anti* equilibrium occurred in the presence of pyridinium chloride. Lack of steric control, preference for vinyl migration, *syn-anti* equilibration, and increased yields on addition of water led the authors to propose a mechanism for nitron rearrangement (Scheme 6).

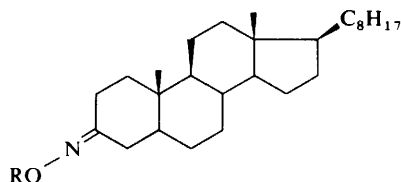


**Scheme 6**

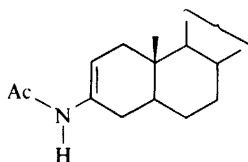
A simple synthesis of enamides from ketoximes has been described and demonstrated with various steroidal derivatives.<sup>9</sup> Thus, 5 $\alpha$ -cholestan-3-one oxime (54a) and its derivatives (54b–e) when refluxing in acetic anhydride and pyridine afforded (55) with 10% of its  $\Delta$ -3 isomer. From crude reaction mixture, the enamide (56) could be isolated by crystallization or silica gel chromatography. Compound (55) was obtained by alumina chromatography and led to (56) with acetic anhydride–

<sup>9</sup> R. B. Boar, J. F. McGhie, M. Robinson, D. H. R. Barton, D. C. Horwell, and R. V. Stick, *J.C.S. Perkin I*, 1975, 1237.

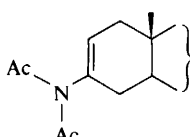
pyridine. With succinic anhydride in pyridine (57) was obtained from (54a). A tentative radical mechanism was proposed (Scheme 7). Limited chemical reactivity in comparison with enamines was found for enamides. However,  $\alpha$ -acetoxylation by reagents such as lead tetra-acetate was efficient. These reactions were applied to a convenient synthesis of the 17 $\alpha$ ,21-diacetoxy-20-oxopregnane side-chain.<sup>10</sup>



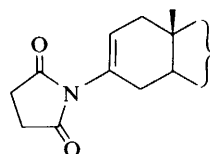
- (54) a; R = H  
 b; R = Ac  
 c; R = PhCO  
 d; R = Me  
 e; R = PhCH<sub>2</sub>



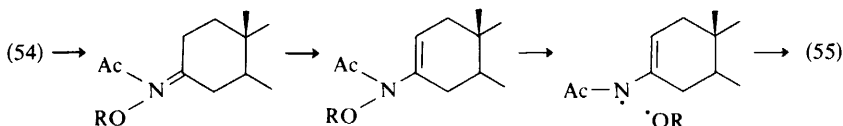
(55)



(56)



(57)



Scheme 7

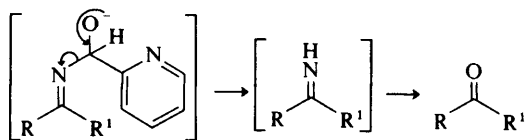
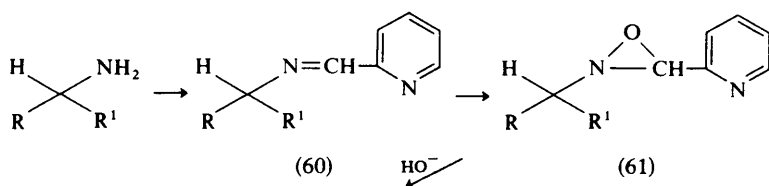
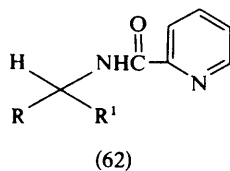
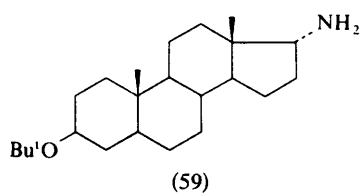
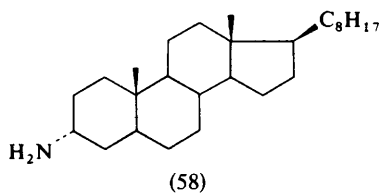
The oxidative deamination of amines to ketones, *via* oxaziridines, was reported as a model for the process found in oxidative deamination of  $\alpha$ -amino-acids to pyruvic acids in biochemical systems.<sup>11</sup> The primary amine, such as (58) or (59) with pyridine-2-carboxaldehyde, was converted into the imine (60) which was oxidized with *m*-chloroperbenzoic acid to the oxaziridine (61). Ring opening of (61) was effected with KOH in MeOH or in DMF (Scheme 8). Acetone was added to trap regenerated pyridine-2-carboxaldehyde. When other bases were used a competing reaction resulting in (62) occurred.

The synthesis of the four epimeric azido-alcohols (63), (65), (67a), and (68a) of oestra-1,3,5(10)-triene 3-methyl ether and the corresponding amino-alcohols (64), (66), (67b), and (68b) has been described.<sup>12</sup> *trans*-Azido-alcohols (63) and (65) were obtained by azidolysis of the 16,17-epoxides (69) and (70) (Scheme 9).

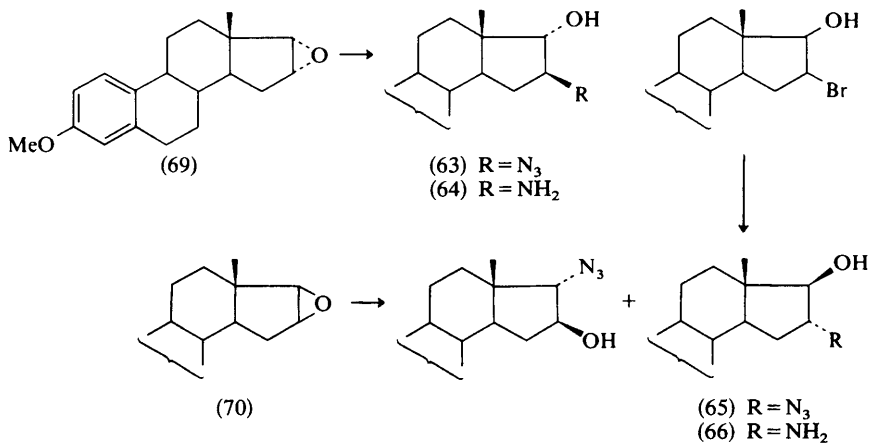
<sup>10</sup> R. B. Boar, J. F. McGhie, M. Robinson, and D. H. R. Barton, *J.C.S. Perkin I*, 1975, 1242.

<sup>11</sup> S. E. Dinizo and D. S. Watt, *J. Amer. Chem. Soc.*, 1975, **97**, 6900.

<sup>12</sup> B. Schoenecker and K. Ponsold, *Tetrahedron*, 1975, **31**, 1113.

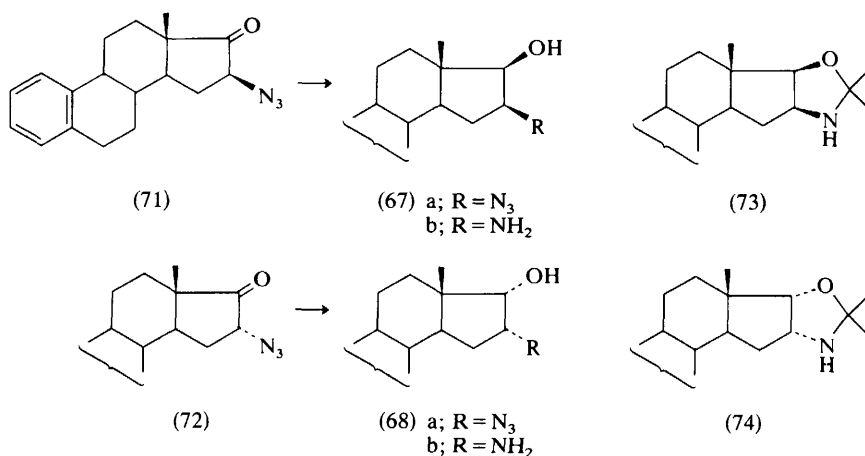


Scheme 8



Scheme 9

*cis*-Azido-alcohols (67a) and (68a) were obtained by reduction of (71) and (72) with  $\text{NaBH}_4$  (Scheme 10). The azido-alcohols were converted into the corresponding amino-alcohols with hydrazine hydrate–Raney nickel. The *cis*-amino-alcohols reacted with acetone to give oxazolidines (73) and (74).



**Scheme 10**

**Circular Dichroism.** The salicylidene-imino chirality rule has been applied to cyclic steroidal amines.<sup>13</sup> This rule was previously used to correlate the absolute configuration of cyclic terpenoid amines with the signs of the observed Cotton effects near 255 and 315 nm in their circular dichroism spectra. Similar considerations were used to interpret the c.d. spectra of *N*-salicylidene derivatives of steroidal cyclic amines. These spectra were reported but no simple interpretation was possible.

**Photochemistry.** Regioselectivity in *N*-dealkylation of tertiary amines by dye-sensitized photo-oxidation has been studied.<sup>14</sup> When irradiated in the presence of methylene blue and oxygen, (75a) led to (75b), (76a) gave a 3 : 2 mixture of (75b) and (76b), (77a) led to (77b), and the amino-ester (75c) afforded (75b), showing the influence of both the degree of substitution of the carbon  $\alpha$  to the nitrogen and the acidity of the hydrogens on the regioselectivity of the reaction, in aliphatic series.

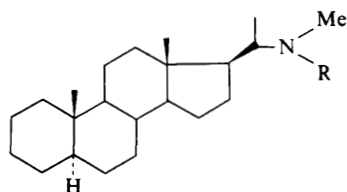
Syntheses and photochemical behaviour of some azido-steroids have been described.<sup>15</sup> Thermolytic and acid-catalysed reactions have also been studied and compared.<sup>16</sup> Photolysis and thermolysis of azido-steroids led to alkyl migration products, endocyclic imines, and 1–2 hydrogen-transfer compounds, exocyclic imines giving ketones by hydrolysis. Pyrrolidine formation through a nitrene intermediate occurred only in the case of 6 $\beta$ -azidopregnene. Mechanistic implications were fully discussed.

<sup>13</sup> H. E. Smith, E. P. Burrows, and F. M. Chen, *J. Org. Chem.*, 1976, **41**, 704.

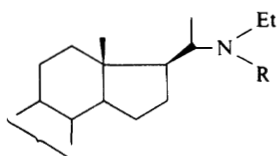
<sup>14</sup> Y. Hubert-Brierre, D. Herlem, and F. Khuong-Huu, *Tetrahedron*, 1975, **31**, 3049.

<sup>15</sup> A. Pancrazi and Q. Khuong-Huu, *Tetrahedron*, 1975, **31**, 2041.

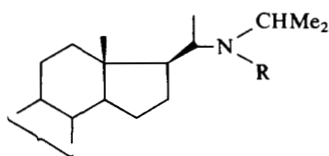
<sup>16</sup> A. Pancrazi and Q. Khuong-Huu, *Tetrahedron*, 1975, **31**, 2049.



(75) a; R = Me  
b; R = H  
c; R = CH<sub>2</sub>CO<sub>2</sub>Et

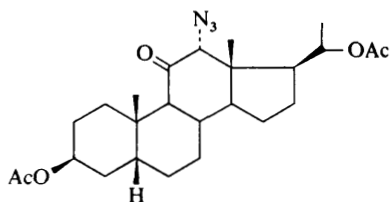


(76) a; R = Me  
b; R = H

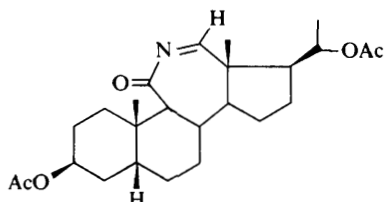


(77) a; R = Me  
b; R = H

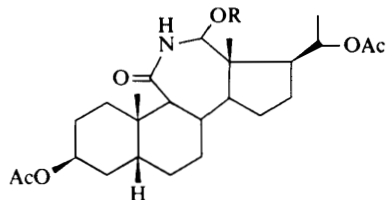
A photochemical technique for the synthesis of *N*-acyl-imines has been reported.<sup>17</sup> Photolysis of the azido-ketone (78) in the presence of pyridine or NEt<sub>3</sub> yielded the *N*-acyl-imine (79) which was hydrated to (80a) on alumina or sulphonic acid ion-exchange resin. Irradiation of (78) in MeOH afforded (80b), (79) being an intermediate. Catalytic reduction of (79) furnished the lactam (81). In refluxing



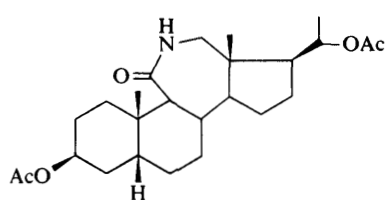
(78)



(79)



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

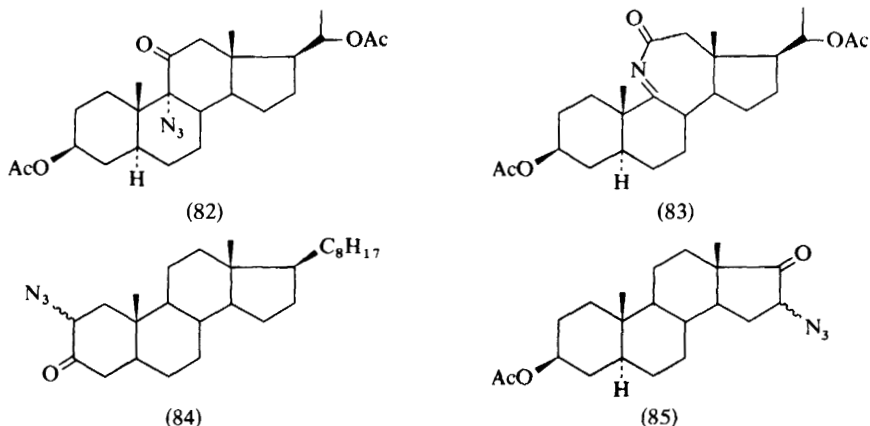


(81)

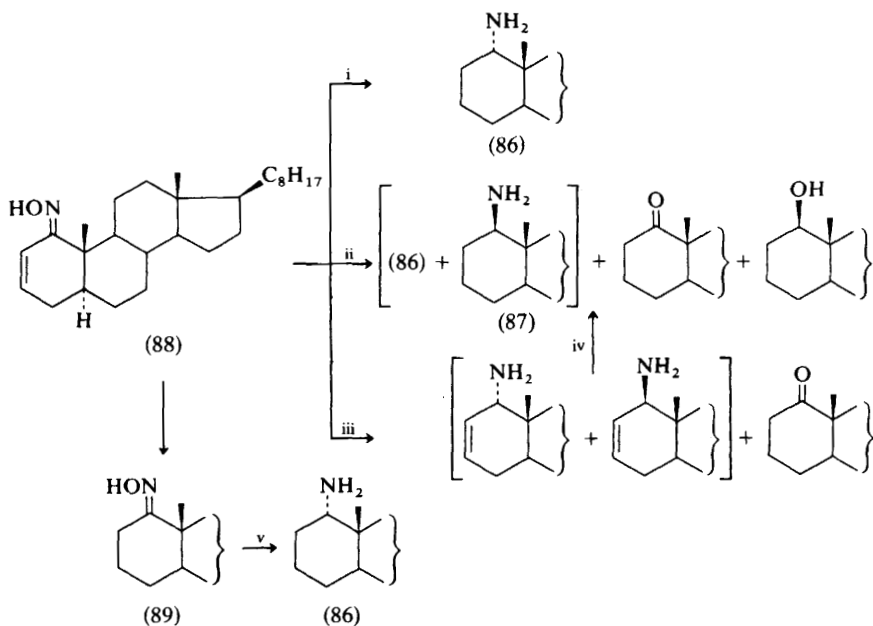
dimethylaniline (78) was also converted into (79). Photolysis of (82) in MeOH produced predominantly (83) but irradiation of (84) and (85) formed complex mixtures containing none or little of the methoxy-lactams.

<sup>17</sup> W. A. Court, O. E. Edwards, C. Grieco, W. Rank, and T. Sano, *Canad. J. Chem.*, 1975, **53**, 463.





**Mass Spectrometry.** The synthesis and mass spectrometry of 1-amino-, 4-amino-, and 2-amino-steroids have been described.<sup>18-20</sup> The synthesis of 1 $\alpha$ - and 1 $\beta$ -amino-cholestane, (86) and (87), was effected by reduction of the oximes, (88) and (89), respectively (Scheme 11); the corresponding methylamino- and dimethylamino-



Reagents: i, Li-EtNH<sub>2</sub>; ii, Pt-H<sub>2</sub>; iii, Zn-AcOH; iv, Pt-H<sub>2</sub>; v, LiAlH<sub>4</sub>, Pt-H<sub>2</sub> or Na-EtOH

**Scheme 11**

<sup>18</sup> C. Marazano and P. Longevialle, *Bull. Soc. chim. France*, 1975, 1307.

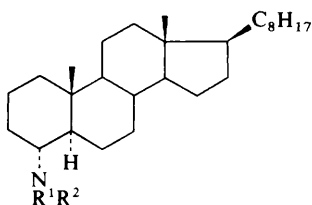
<sup>19</sup> C. Marazano and P. Longevialle, *Org. Mass Spectrometry*, 1975, **10**, 442.

<sup>20</sup> C. Marazano and P. Longevialle, *Org. Mass Spectrometry*, 1975, **10**, 435.

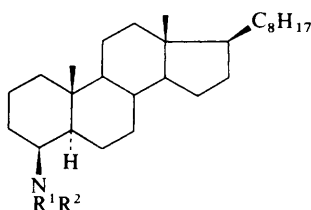
derivatives were prepared from compounds (86) and (87) by standard methods. 1 $\alpha$ -Dimethylamino-4,4'-dimethylcholestane was synthesized by classical procedures from 4,4'-dimethylcholestan-1-one prepared from 4,4'-dimethylcholestan-3 $\beta$ -ol.

The mass spectra of 1-amino-steroids are not affected by the configuration of the amino-group. H-D exchange reactions observed with deuteriated amines were explained by the high activation energy of the last fragmentation leading to the main ion. The relative importance of  $M-43$  ions in the mass spectra of the 1-methylamino-compounds was explained by a conformational effect.

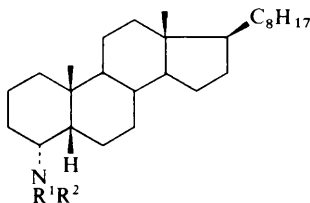
The 4 $\alpha$ - and 4 $\beta$ -amino-steroids (90), (91), and (92) were prepared from 5 $\alpha$ - and 5 $\beta$ -cholestan-4-one by classical procedures, and their mass spectral fragmentations were discussed. The loss of a primary radical in the main fragmentations explained the low rate constant of these reactions and the important intramolecular H-D scrambling observed with a deuteriated derivative.



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



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



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

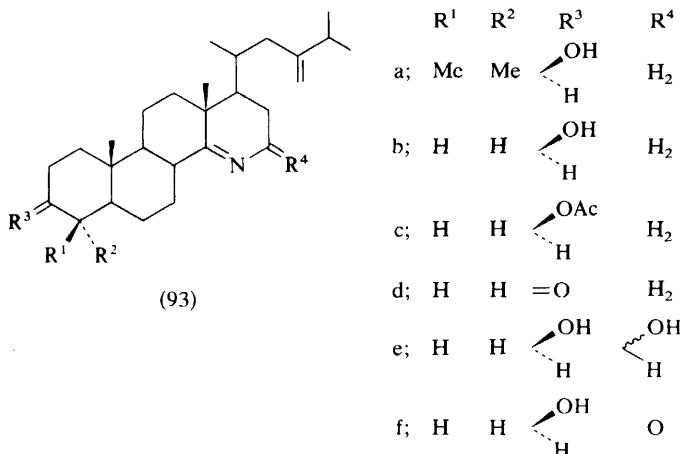
2 $\alpha$ - and 2 $\beta$ -Dimethylaminocholestanes were prepared by classical methods from cholestan-2-one. [1,1',3,3'-<sup>2</sup>H<sub>4</sub>]-2 $\alpha$ -Dimethylaminocholestane and [3,3'-<sup>2</sup>H<sub>2</sub>]-2 $\alpha$ -dimethylaminocholestane were synthesized to confirm the mechanisms of the observed mass spectrometer fragmentations.

Mass spectra of a series of 20-pyridyl steroids were measured,<sup>21</sup> and the fragmentations discussed. Intramolecular hydrogen transfer in mass spectra rearrangements involving the loss of small neutral molecules has been reviewed.<sup>22</sup> The loss of water and ammonia from hydroxy-amino- and amino-steroids was quoted.

<sup>21</sup> D. Voigt, G. Adam, and K. Schreiber, *Pharmazie*, 1975, **30**, 213.

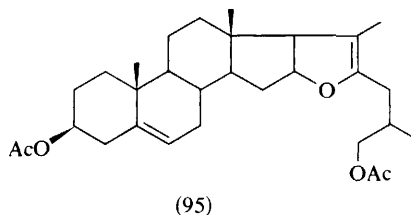
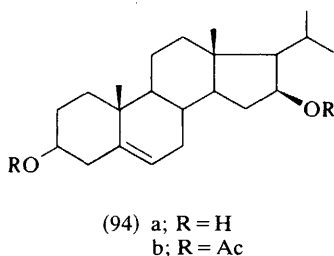
<sup>22</sup> G. I. Knighton, B. W. Hobrock, M. M. Bursey, and J. T. Bursey, *Chem. Rev.*, 1975, **75**, 693.

**Related Compounds.**—Several antibiotic aza-steroids, (93a–f), have been isolated from *Geotrichum flavo-brunneum*.<sup>23</sup> Structures were determined from i.r. and n.m.r. spectra. The most active component (93b) was inhibitory against Gram-positive and -negative bacteria in a range of 0.0312–5.0 mcg ml<sup>-1</sup>. The antibiotic complex was highly active against pathogenic fungi, including *Candida* and *Trichophyton* species.



## 2 *Salamandra* Alkaloids

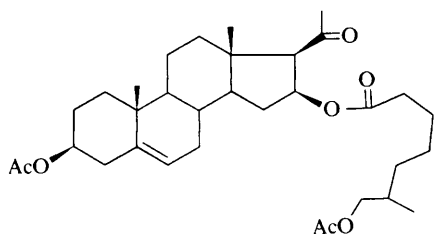
The synthesis of 20-methylpregn-5-ene-3 $\beta$ ,16 $\beta$ -diol (94a) and its diacetate (94b) has been reported.<sup>24</sup> The former compound was required as a possible intermediate for the synthesis of samandinine, a *Salamandra* minor alkaloid. Compound (95),



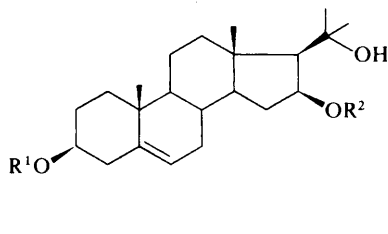
from diosgenin, was oxidized to (96) with KMnO<sub>4</sub>–NaIO<sub>4</sub>. A Grignard reaction with methylmagnesium iodide on (96) afforded (97a) which was acetylated to a mixture of (97b) and (97c). Treatment of (97b) with thionyl chloride in pyridine gave a 1 : 9 mixture of (98a) and (99a) which was transformed with lithium aluminium hydride to (98b) and (99b). Hydrogenation of the 20,21 double bond of (99b) to give (94a) was carried out with a palladium catalyst in the presence of ethyl(di-isopropyl)amine. Palladium-catalysed hydrogenation of (98a) and (99a) afforded a mixture of (94b) and (100).

<sup>23</sup> K. H. Michel, R. L. Hamill, S. H. Larsen, and R. H. Williams, *J. Antibiotics*, 1975, **28**, 102.

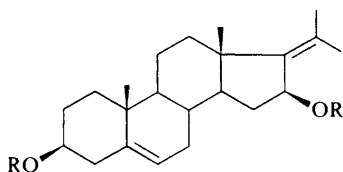
<sup>24</sup> G. Habermehl and H. H. Oh, *Annalen*, 1975, 2331.



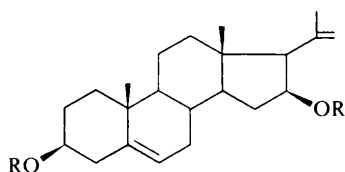
(96)



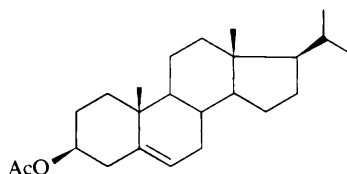
(97) a;  $R^1 = R^2 = H$   
 b;  $R^1 = R^2 = Ac$   
 c;  $R^1 = Ac, R^2 = H$



(98) a;  $R = Ac$   
 b;  $R = H$



(99) a;  $R = Ac$   
 b;  $R = H$



(100)

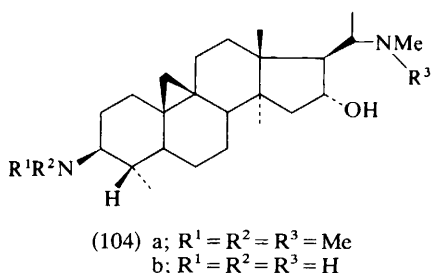
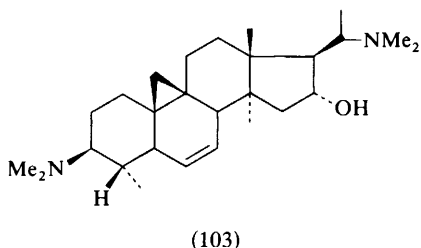
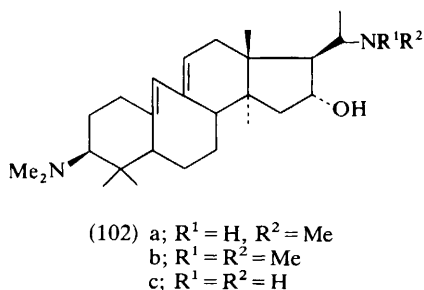
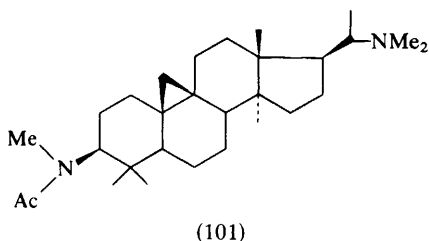
### 3 *Buxus* Alkaloids

*N*<sub>3</sub>-Acetylcycloprotobuxine C (101) [the name buxaline given to this compound was previously used for another type of *Buxus* alkaloid; see (111)] has been isolated from *Buxus sempervirens*.<sup>25</sup> A polybuffer distribution of total alkaloids of *Buxus sempervirens* has been studied.<sup>26</sup> The isolation of some alkaloids, including the novel buxaminol B (102a) and cyclobullatine A (103) from *Buxus sempervirens* var. *bullata* Kirchn., has been described.<sup>27</sup> Methylation of (102a) gave buxaminol A (102b) identical to the methylation product of known buxaminol C (102c). Adams-catalysed hydrogenation of (103) furnished cyclobuxamine A (104a) identical to a sample obtained by Eschweiler-Clarke methylation of cyclobuxamine H (104b). Structures (102a) and (103) were assigned from these reactions together with spectral data.

<sup>25</sup> B. V. Khodzhaev, R. Shakirov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, 176.

<sup>26</sup> B. V. Khodzhaev, R. Shakirov, K. N. Aripov, T. T. Shakirov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, 108.

<sup>27</sup> Z. Voticky, O. Bauerova, and V. Paulik, *Coll. Czech. Chem. Comm.*, 1975, **40**, 3055.



The stereochemistry of the epoxidation of olefins at C-10 in the 9-(10 $\rightarrow$ 19)-*abeo*-4 $\alpha$ -hydroxymethylene-4 $\beta$ ,14 $\alpha$ -dimethyl-5 $\alpha$ -pregnane series has been investigated.<sup>28</sup> With NBA in the presence of perchloric acid, the  $\Delta^{1(10)}$ -olefin (105a), a thermolysis product of *N*-isobutyrylcyclobuxidine F, gave the 1 $\beta$ ,10 $\beta$ -epoxide (106a), isomerized with  $BF_3$ -etherate or sodium hydride to (107). Under the same conditions (105b) led to the epoxide (106b) which on sodium methoxide treatment afforded (108a) by an intramolecular  $S_N2$  type reaction (Scheme 12).

With thionyl chloride (108a) gave (108b) which was transformed to (108c) and (105b) by hydrogenolysis in the presence of palladium charcoal in alkaline medium.

Acetylation and reduction with sodium borohydride of (106a) led to (109) dehydrated to (110). Lithium aluminium hydride reduction of the oxiran ring of (110) afforded the tertiary alcohol (111) identical to *N*-isobutyrylbuxaline F, isolated from *Buxus balearica*<sup>29</sup> whereby structure and stereochemistry were established.

With *p*-nitroperbenzoic acid (112) led to (113), reduced with lithium aluminium hydride to (114). Oxidation of (114) afforded the lactone (115), so demonstrating the 1 $\alpha$ -10 $\alpha$  stereochemistry of the oxiran ring of (113).

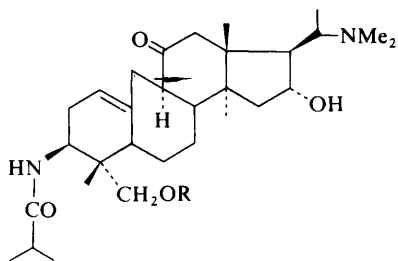
With *p*-nitroperbenzoic acid, (105b) led to (116) which on treatment with triphenylphosphine in benzene afforded (117) as minor product and (118). With sodium methoxide, (118) afforded (119), a cyclopropane derivative in the non-natural 9 $\alpha$ -10 $\alpha$  series, by an intramolecular  $S_N2$ -type reaction (Scheme 13).

The epoxide (121) was obtained regioselectively and stereoselectively from *N*-isobutyrylbuxidienine F (120) on *p*-nitroperbenzoic acid treatment followed by reduction of the *N*-oxy-intermediate with sodium borohydride.

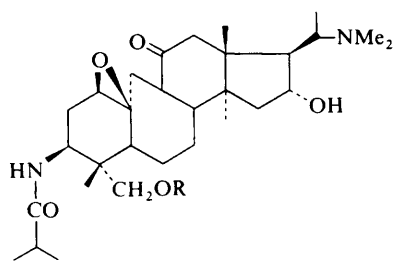
With NBA, the  $\Delta^{5(10)}$ -olefin (122), obtained by acid-catalysed rearrangement of cyclobuxidine A, furnished the bromo-ether (123).

<sup>28</sup> M. Benechie and F. Khuong-Huu, *Tetrahedron*, 1976, **32**, 701.

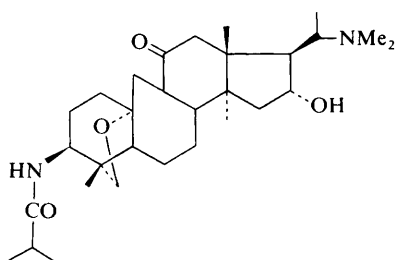
<sup>29</sup> F. Khuong-Huu and D. Herlem, *Tetrahedron*, 1966, **22**, 3321.



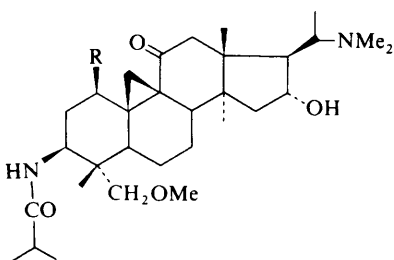
(105) a;  $\text{R} = \text{H}$   
b;  $\text{R} = \text{Me}$



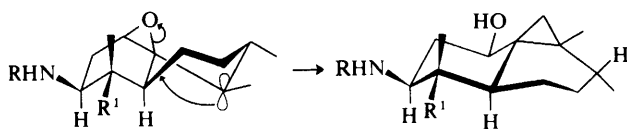
(106) a;  $\text{R} = \text{H}$   
b;  $\text{R} = \text{Me}$



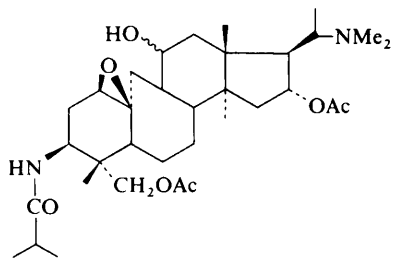
(107)



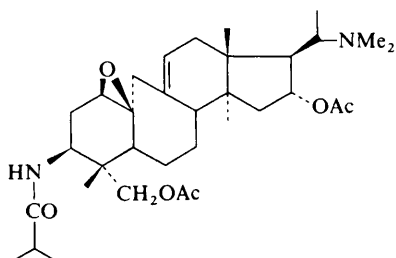
(108) a;  $\text{R} = \text{OH}$   
b;  $\text{R} = \text{Cl}$   
c;  $\text{R} = \text{H}$



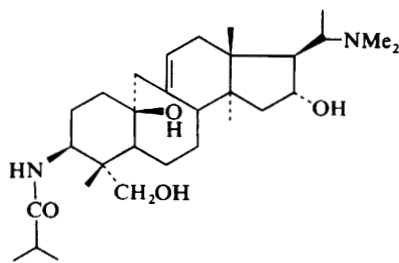
Scheme 12



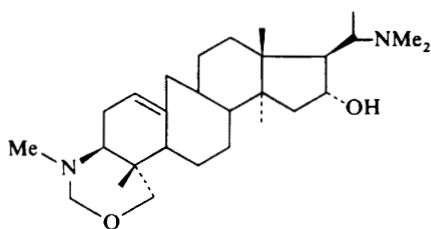
(109)



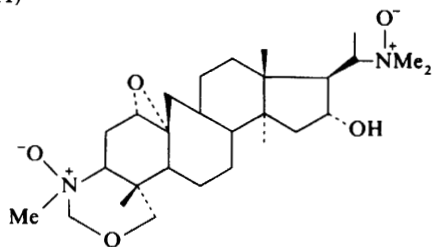
(110)



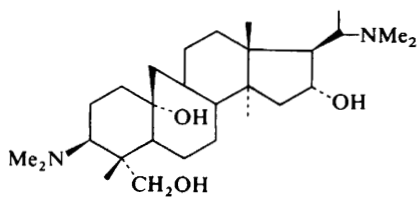
(111)



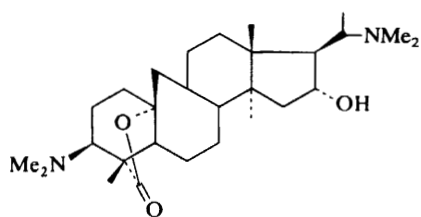
(112)



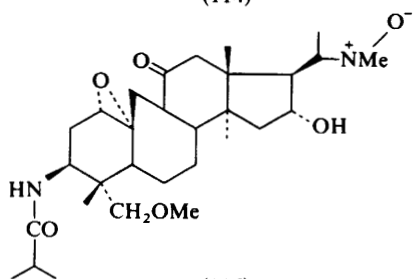
(113)



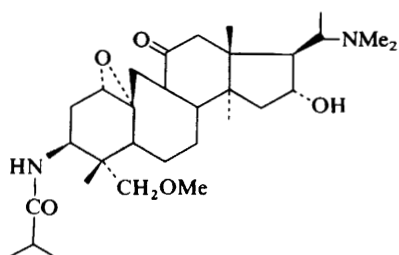
(114)



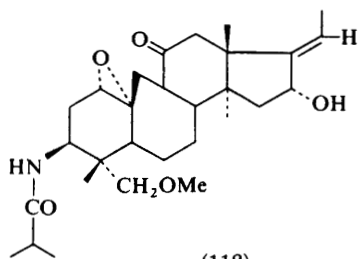
(115)



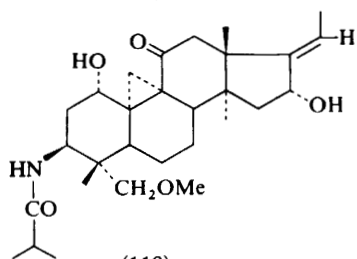
(116)



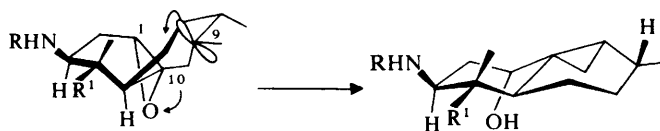
(117)



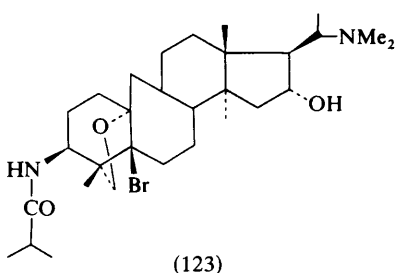
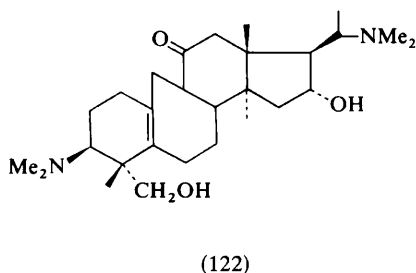
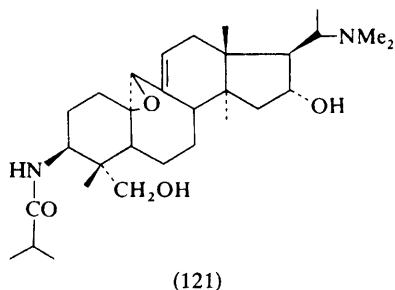
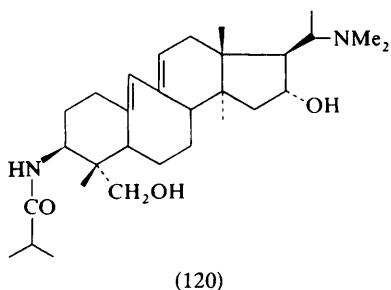
(118)



(119)

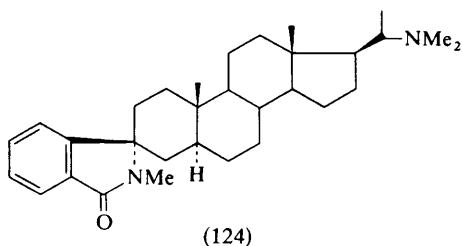


Scheme 13



#### 4 *Pachysandra* Alkaloids

The full paper concerning the structural study of spiropachysine, a major alkaloid of the leaves of *Pachysandra terminalis* Sieb. and Zucc. (124), has been published.<sup>30</sup>



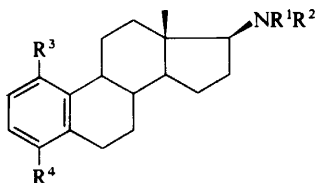
The stereochemistry at the C-3 position was established by a circular dichroism study in comparison with compounds having analogous aromatic chromophores and known absolute stereochemistry, *viz.* hydrastine, narcotine, and oxindole alkaloids.

<sup>30</sup> T. Kikuchi, T. Nishinaga, M. Inagaki, M. Niwa, and K. Kuriyama, *Chem. and Pharm. Bull. (Japan)*, 1975, 23, 416; T. Kikuchi, T. Nishinaga, M. Inagaki, and M. Koyama, *Tetrahedron Letters*, 1968, 2077, reviewed in Vol. 1 of this series.

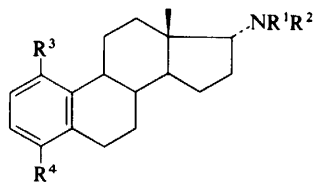


### 5 Biological Notes

Syntheses and antimicrobial activity of some steroidal amines in the 1,3,5(10)-oestratriene series, (125) and (126), have been reported.<sup>31</sup>

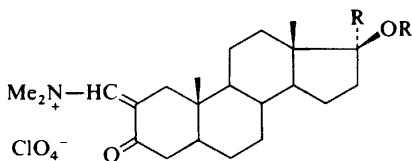


(125)  $R^1 = R^2 = H$   
 $R^1 = R^2 = CH_2CH_2OH$   
 $R^1 = R^2 = CH_2CH_2CN$

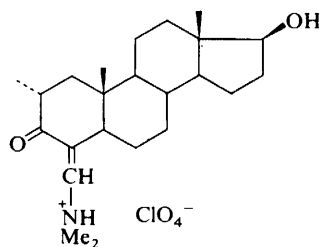


(126)

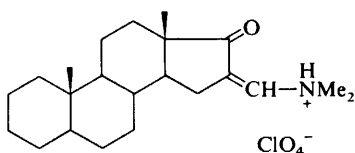
The synthesis of dimethylaminomethylene derivatives of steroidal ketones and lactones such as (127), (128), (129), and (130) has been described.<sup>32</sup> Some compounds of this type possess high anabolic activity.



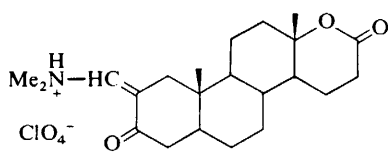
(127)



(128)



(129)



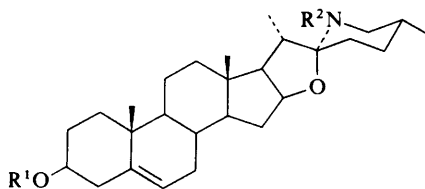
(130)

<sup>31</sup> Y. Hirami, R. Ohuchi, Y. Kurosawa, and H. Mori, *Agric. and Biol. Chem. (Japan)*, 1975, **39**, 843.

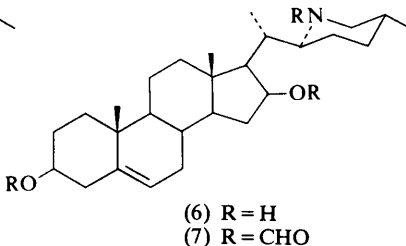
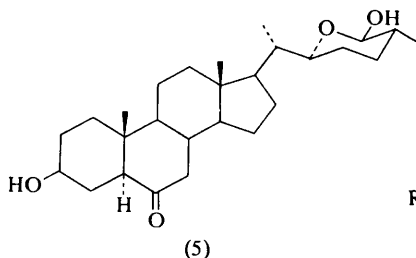
<sup>32</sup> L. N. Volovelsky, M. Y. Yakovlena, and N. V. Popova, *Zhur. obshchei Khim.*, 1975, **45**, 1153.

1 *Solanum* Alkaloids

Solasodine<sup>1</sup> (1) gave two *O*-acetyl-*N*-methyl derivatives, A and B, detected by their distinct n.m.r. spectra.<sup>2</sup> Isomer A was isolated by crystallization and shown to equilibrate with B on heating. It was proposed that A and B both have gross structure (2), are isomeric only in respect of their configurations about the nitrogen atom, and that inversion at nitrogen is unusually slow owing to severe steric hindrance. *O*-Acetylsolasodine also gave two isomeric *N*-formyl derivatives (3). It was suggested that these two derivatives owe their independent existence to pyramidal isomerism on nitrogen<sup>2</sup> rather than to *cis-trans* isomerism about the amide bond, suggested earlier in a related case.<sup>3</sup> Lithium aluminium hydride reduction of one of the *N*-formyl acetates gave a single *N*-methylsolasodine (4) while reduction of the other *N*-formyl acetate gave a mixture of two isomeric *N*-methylsolasodines (4).<sup>2</sup> Clearly a more definitive study of these interesting transformations would be desirable.



- (1)  $R^1 = R^2 = H$
- (2)  $R^1 = Ac, R^2 = Me$
- (3)  $R^1 = Ac, R^2 = CHO$
- (4)  $R^1 = H, R^2 = Me$



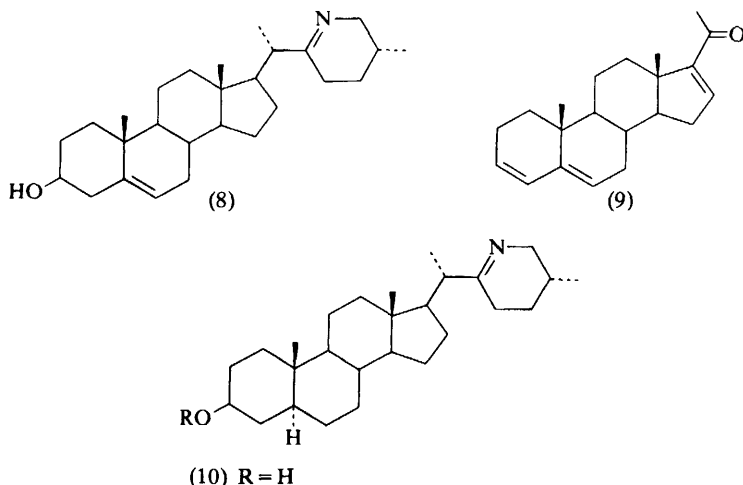
- (6)  $R = H$
- (7)  $R = CHO$

<sup>1</sup> For a comprehensive review of the *Solanum* alkaloids, see K. Schreiber, in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1968, Vol. 10, p. 1.

<sup>2</sup> G. Kusano, T. Takemoto, N. Aimi, H. J. C. Yeh, and D. F. Johnson, *Heterocycles*, 1975, **3**, 697.

<sup>3</sup> L. Toldy and L. Radics, *Tetrahedron Letters*, 1966, 4753.

Osladine aglycone (5) has been synthesized from solasodine *via* dihydrosolasodine A (6), the triformyl derivative (7), and isoverazine (8).<sup>4</sup> The pregnane derivative (9) has been prepared from *N*-acetylsolasodine.<sup>5</sup> Single-crystal *X*-ray diffraction studies on solasodine monohydrate are in progress.<sup>6</sup>



Three glycosides of solacongestidine (10) have been isolated from *Solanum congestiflorum* and partially characterized.<sup>7</sup> Solacongestine<sup>8</sup> gave solacongestidine together with glucose and galactose on acid-catalysed hydrolysis. Similar hydrolysis of  $\alpha$ -solacongestinine gave (10) together with glucose, xylose, and rhamnose, while  $\beta$ -solacongestinine gave (10), glucose, and xylose.<sup>7</sup>

Demissine (11) and a new demissidine glycoside, commersine, have been isolated from *S. commersonii* and *S. chacoense*.<sup>9</sup> Commersine formed a permethyl derivative (mol. wt. 1229), which on acid-catalysed hydrolysis gave demissidine (12) together with 2,3,4,6-tetra-*O*-methylglucose, 4,6-di-*O*-methylglucose, and 2,3,6-tri-*O*-methylgalactose. These partially methylated monosaccharides were identified by combined g.l.c.-mass spectrometry on their derived alditol acetates. This evidence, together with the products of acid-catalysed hydrolysis and partial hydrolysis of commersine, suggested structure (13) for the new glycoside.<sup>9</sup> The proposed structure of the carbohydrate unit in commersine is unique among the *Solanum* glycoalkaloids.<sup>9,10</sup>

<sup>4</sup> M. Havel and V. Černý, *Coll. Czech. Chem. Comm.*, 1975, **40**, 3199. For an earlier synthesis of osladine aglycone from solasodine, see M. Havel and V. Černý, *ibid*, 1975, **40**, 1579; D. M. Harrison, in 'The Alkaloids', ed. M. F. Grondon (Specialist Periodical Reports), The Chemical Society, London, 1976, Vol. 6, p. 287.

<sup>5</sup> G. A. Tolstikov, M. I. Goryaev, and V. P. Yur'ev, U.S.S.R.P. 242 162/1976 (*Chem. Abs.*, 1976, **84**, 105 909).

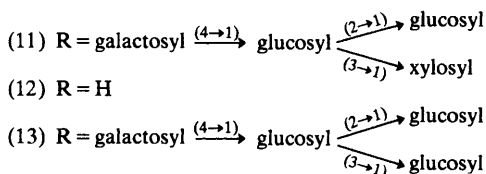
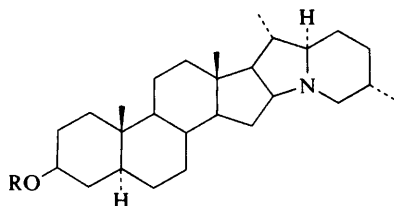
<sup>6</sup> G. C. Bhattacharya, S. A. A. Naqvi, and S. Guha, *Indian J. Phys.*, 1975, **49**, 65 (*Chem. Abs.*, 1975, **83**, 69 453).

<sup>7</sup> R. Katz, N. Aimi, and Y. Sato, *Adv. Front. Plant Sci.*, 1975, **30**, 63.

<sup>8</sup> cf. K. Schreiber, in ref. 1, pp. 18-22.

<sup>9</sup> S. F. Osman, S. F. Herb, T. J. Fitzpatrick, and S. L. Sinden, *Phytochemistry*, 1976, **15**, 1065.

<sup>10</sup> cf. K. Schreiber, in ref. 1, pp. 22-29.



A new glycoside, solapersine, has been isolated from *S. persicum*.<sup>11</sup> Acid-catalysed hydrolysis of the glycoside gave solasodine and the monosaccharides galactose, glucose, and xylose in the molar ratio 1:1:2 respectively. Solasonine and a new glycoalkaloid, solatifoline, were isolated from *S. platanifolium*.<sup>12</sup> Solatifoline gave solasodine, glucose, galactose, and rhamnose on acid-catalysed hydrolysis. The seeds and fruits of the plant yielded in addition the solasodine glycoside solamargine.

Degradative evidence has confirmed<sup>13</sup> the accepted view<sup>10</sup> that solamargine is a  $\beta$ -chacotriose derivative. Solamargine has been isolated from *S. incanum* (fresh berries)<sup>14</sup> and *S. schimperianum*.<sup>15</sup> The latter species also yielded  $\beta$ -solamargine, the tomatidenol glycosides  $\beta$ - and  $\gamma$ -solamarines, and an unidentified solasodine glycoside, which gave glucose and rhamnose (1:1) on acid-catalysed hydrolysis.<sup>15</sup> Extraction of *S. pseudopersicum* gave solasonine, solamargine,  $\beta$ -solamargine, and the soladulcidine glycoside soladulcine.<sup>16</sup>

The alkaloid contents of *S. xanthocarpum* collected in Nepal<sup>17</sup> and France<sup>18</sup> have been compared. Fruits from the French plant were richer in solasodine glycosides than those from the Nepalese plant (yields of solasodine 4.6% and 1.6% respectively). The French plant, in addition, contained traces of tomatidenol glycosides in the stalks.<sup>18</sup>

A number of *Solanum* species have been investigated for their aglycone content. Solasodine was isolated principally from roots and fruits (0.8%) and tomatidenol from fruits (0.04%) of *S. globiferum*.<sup>19</sup> Solasodiene, which was also isolated, is presumably an artifact. Solasodine was detected in Cuban grown *S. eriantum*<sup>20</sup> and

<sup>11</sup> E. N. Novruzov, S. M. Aslanov, N. M. Ismailov, and A. A. Imanova, *Khim. prirod. Soedinenii*, 1975, **11**, 434 (*Chem. Abs.*, 1976, **84**, 40 726).

<sup>12</sup> R. K. Puri and J. K. Bhatnagar, *Phytochemistry*, 1975, **14**, 2096.

<sup>13</sup> L. H. Briggs, R. C. Cambie, and D. M. Hyslop, *J.C.S. Perkin I*, 1975, 2455.

<sup>14</sup> Pan-Ming Hsu and Hsien-Ju Tien, *T'ai-wan Yao Hsueh Tsa Chih*, 1974, **26**, 28 (*Chem. Abs.*, 1976, **84**, 102 338).

<sup>15</sup> C. Coune and A. Denoël, *Plant. Med. Phytother.*, 1975, **9**, 14 (*Chem. Abs.*, 1975, **83**, 93 827).

<sup>16</sup> S. M. Aslanov, *Khim. prirod. Soedinenii*, 1975, **11**, 264 (*Chem. Abs.*, 1975, **83**, 128 652).

<sup>17</sup> J. F. Verbist and R. Monnet, *Plant. Med. Phytother.*, 1974, **8**, 263 (*Chem. Abs.*, 1975, **83**, 75 340).

<sup>18</sup> J. V. Verbist and R. Monnet, *Plant. Med. Phytother.*, 1974, **8**, 269 (*Chem. Abs.*, 1975, **83**, 75 341).

<sup>19</sup> W. Döpke, U. Hess, and G. Padron, *Pharmazie*, 1976, **31**, 133 (*Chem. Abs.*, 1976, **84**, 147 710).

<sup>20</sup> I. Mena, C. Timor, I. Corrales, and V. Fuste, *Rev. Cubana Farm.*, 1974, **8**, 201 (*Chem. Abs.*, 1975, **83**, 4992).

*S. nigrum*,<sup>20</sup> and isolated from *S. laciniatum*.<sup>21</sup> Stems of *S. torvum* gave solasodine (0.06%) and solasodiene.<sup>22</sup> The last three species are known sources of solasodine.<sup>23</sup> Tomatidenol was the only alkaloid isolated from *S. dasyphyllum*.<sup>24</sup>

Solanidine was released from glycoalkaloids in infected *S. tuberosum* tuber tissue.<sup>25</sup> The changes in solasodine content of *S. laciniatum* during growth of the plant have been investigated.<sup>26</sup> The intracellular distribution of  $\alpha$ -tomatine in *Lycopersicon esculentum* has been studied.<sup>27</sup>

The use of gas-liquid chromatography for the identification and estimation of potato glycoalkaloids has been described.<sup>28</sup> The glycosides were rendered sufficiently volatile by conversion into their permethyl ether derivatives. Solasodine and soladulcidine in admixture may be conveniently estimated by thin-layer chromatography after bromination of the former.<sup>29</sup> The detection of steroidal alkaloids on t.l.c. plates<sup>30</sup> and a colorimetric method for the estimation of solasodine<sup>31</sup> have been discussed.

Brief reviews have appeared on the biological aspects of the genus *Solanum*<sup>32</sup> and in particular *S. tuberosum*.<sup>33</sup>

## 2 Veratrum Alkaloids

Details of the total syntheses of verarine and 5 $\alpha$ ,6-dihydroveratramine have now been published.<sup>34,35</sup> The latter compound had previously been converted into veratramine, jervine, veratrobazine, and 11-deoxojervine, and so the present work<sup>34</sup> completes a formal total synthesis of each of these natural products.

Interest continues in the preparation of C-nor-D-homo-steroids from readily available *Veratrum* alkaloids.<sup>36</sup> In this connection the jervine-derived enamine (14) gave the ketone (15) (40%) on sensitized photo-oxygenation.<sup>37</sup> Similarly, enamine (16) gave the expected ketone (17) and the ring-contracted product (18).<sup>37</sup>

<sup>21</sup> C. Timor and B. Pyatin, *Rev. Cubana Farm.*, 1975, **9**, 103 (*Chem. Abs.*, 1976, **84**, 169 586).

<sup>22</sup> W. Döpke, C. Nogueiras, and U. Hess, *Pharmazie*, 1975, **30**, 755 (*Chem. Abs.*, 1976, **84**, 71 442).

<sup>23</sup> K. Schreiber, in ref. 1, pp. 6-18.

<sup>24</sup> C. Coune and A. Denoël, *Planta Med.*, 1975, **28**, 168.

<sup>25</sup> R. M. Zacharius, E. B. Kalan, S. F. Osman, and S. F. Herb, *Physiol. Plant Pathol.*, 1975, **6**, 301 (*Chem. Abs.*, 1976, **84**, 14 768).

<sup>26</sup> J. E. Lancaster and J. D. Mann, *New Zealand J. Agric. Res.*, 1975, **18**, 139 (*Chem. Abs.*, 1975, **83**, 75 524).

<sup>27</sup> J. G. Roddick, *Phytochemistry*, 1976, **15**, 475.

<sup>28</sup> S. F. Herb, T. J. Fitzpatrick, and S. F. Osman, *J. Agric. Food Chem.*, 1975, **23**, 520.

<sup>29</sup> I. Zambo and P. Tetenyi, *Herba Hung.*, 1976, **15**, 107 (*Chem. Abs.*, 1976, **84**, 176 067).

<sup>30</sup> I. R. Hunter, M. K. Walden, J. R. Wagner, and E. Heftmann, *J. Chromatog.*, 1976, **118**, 259.

<sup>31</sup> M. S. Karawya, M. G. Ghourab, and F. H. El-Rakhawy, *J. Assoc. Offic. Analyt. Chemists*, 1975, **58**, 528 (*Chem. Abs.*, 1975, **83**, 24 626).

<sup>32</sup> R. K. Puri and J. K. Bhatnagar, *Pharmacos*, 1974, **19**, 7.

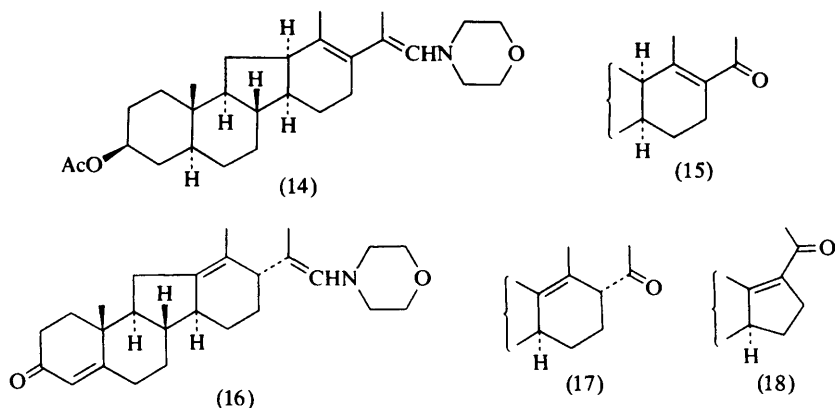
<sup>33</sup> S. J. Jadhav and D. K. Salunkhe, *Adv. Food Res.*, 1975, **21**, 307.

<sup>34</sup> J. P. Kutney, A. By, J. Cable, W. A. F. Gladstone, T. Inaba, S. Y. Leong, P. Roller, E. J. Torupka, and W. D. C. Warnock, *Canad. J. Chem.*, 1975, **53**, 1775; J. P. Kutney, J. Cable, W. A. F. Gladstone, H. W. Hanssen, G. V. Nair, E. J. Torupka, and W. D. C. Warnock, *ibid.*, 1975, **53**, 1796.

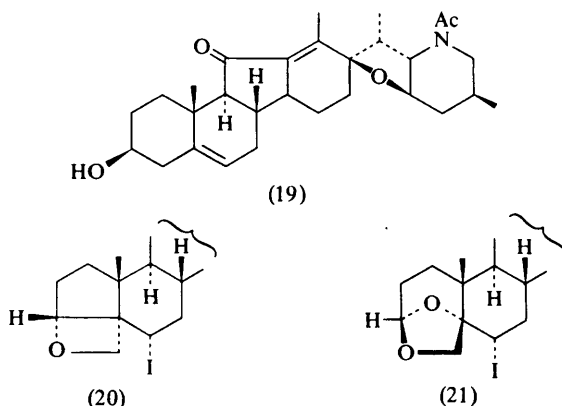
<sup>35</sup> Preliminary communications of this work were reviewed by R. B. Herbert, in 'The Alkaloids', ed. J. E. Saxton, (Specialist Periodical Reports), The Chemical Society, London, 1973, Vol. 3, p. 292.

<sup>36</sup> J. Tomko and Z. Votický, in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1973, Vol. 14, pp. 9-10; R. B. Herbert, in 'The Alkaloids', ed. J. E. Saxton, (Specialist Periodical Reports), The Chemical Society, London, 1974, Vol. 4, p. 392.

<sup>37</sup> A. Murai, C. Sato, H. Sasamori, and T. Masamune, *Bull. Chem. Soc. Japan*, 1976, **49**, 499.



A minor product of the photolysis of the hypoiodite derived from *N*-acetyljervine (19) was originally assigned an oxetan structure (20).<sup>38</sup> The structure of this product has been reassigned by the original authors and is now formulated as the acetal (21).<sup>39</sup>



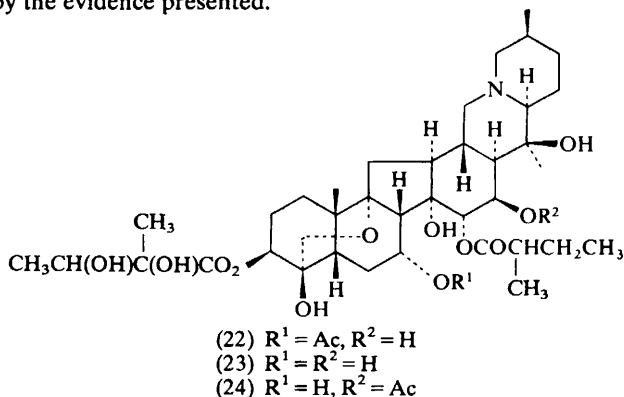
Studies on the alkaloids of *Veratrum lobelianum* continue unabated. Germinalinine<sup>40</sup> was recognized as a germine derivative and assigned the structure (22) on the basis of the following evidence: (a) identification of the products of saponification; (b) an n.m.r. spectrum which indicated the presence of a secondary acetate function (Me at  $\tau$  7.97; H at  $\tau$  4.28, multiplet), but otherwise showed a remarkable similarity to that of germbudine<sup>41</sup> (23); (c) formation of a diacetate derivative which was identical to germbudine triacetate; (d) formation of germbudine on methanolysis. While the structure (22) suggested for germinalinine is probably better

<sup>38</sup> H. Sugimoto, K. Kato, and T. Masamune, *Tetrahedron Letters*, 1974, 1161, 1165; R. B. Herbert, in 'The Alkaloids', ed. J. E. Saxton, (Specialist Periodical Reports), The Chemical Society, London, 1975, Vol. 5, p. 261.

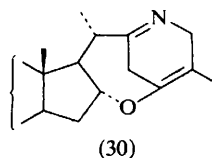
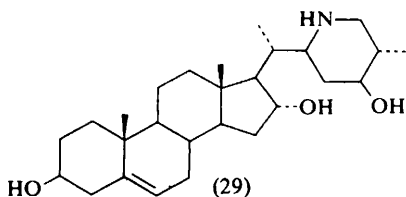
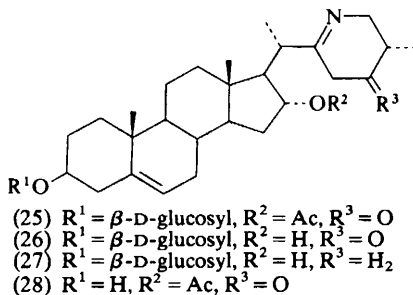
<sup>39</sup> H. Sugimoto, A. Furusaki, K. Kato, and T. Matsumoto, *Tetrahedron Letters*, 1975, 2757.

<sup>40</sup> R. Shakhov and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, 11, 532 (*Chem. Abs.*, 1976, **84**, 59 816).

on biosynthetic grounds,<sup>41</sup> the alternative structure (24) does not seem to be excluded by the evidence presented.<sup>40</sup>



Veralodinine, isolated from *V. lobelianum*, has been assigned structure (25) on the basis of spectroscopic and chemical studies.<sup>42</sup> The glycoside formed a tetra-acetyl derivative while saponification gave a desacetyl derivative (26). Huang–Minlon reduction of the carbonyl group gave desacetylveralosine<sup>43</sup> (27). Hydrogenation of veralodinine gave a tetrahydro-derivative, which on acid-catalysed hydrolysis gave the triol (29), which was also prepared from veralodisine<sup>44</sup> (28). Acid-catalysed hydrolysis of both veralodinine and veralodisine gave the same compound,<sup>42</sup> which was not identical to veralodisinol.<sup>44</sup> This unknown product was assigned the unlikely bicyclo structure (30).<sup>42</sup>



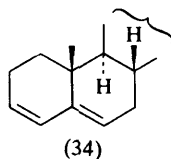
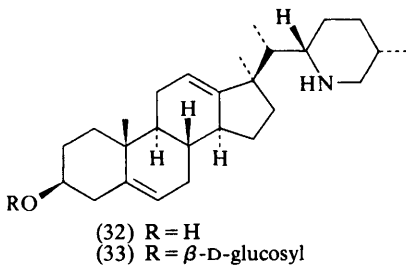
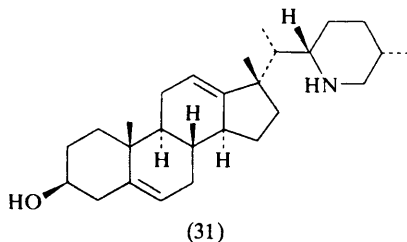
<sup>41</sup> cf. S. M. Kupchan and A. W. By, in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1968, Vol. 10, pp. 217–218.

<sup>42</sup> K. Samikov, R. Shakirov, K. A. Ubaidullaev, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, **11**, 183 (*Chem. Abs.*, 1975, **83**, 79 473).

<sup>43</sup> A. M. Khashimov, R. Shakirov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1970, **6**, 343 (*Chem. Abs.*, 1970, **73**, 99 170).

<sup>44</sup> R. Shakirov, A. M. Khashimov, K. Samikov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1974, **10**, 44 (*Chem. Abs.*, 1974, **80**, 121 205).

Another new glycoside, veralonnine, was isolated from *V. lobelianum*.<sup>45</sup> Acid-catalysed hydrolysis gave D-glucose and two aglycones, veralomidine and veralomidene. The former aglycone gave dihydro- and tetrahydro-derivatives on hydrogenation, and formed a digitonide derivative, demonstrating the presence of a  $3\beta$ -hydroxy-group. Veralomidine gave an *O,N*-diacetal derivative, which was saponified to give an *N*-acetyl derivative. The n.m.r. spectrum of veralomidine showed two tertiary methyl groups, ( $\tau$  9.01 and 9.22), two secondary methyl groups (doublets at  $\tau$  9.24 and 9.08), a secondary hydroxy-group (multiplet at  $\tau$  6.55 for *CHOH*), and two olefinic protons (multiplet at  $\tau$  4.68). The mass spectrum of veralomidine was similar to that of veralinine<sup>46</sup> (31). It was suggested<sup>45</sup> that veralomidine was the C-17 epimer (32) of veralinine. The glycoside veralonnine and aglycone veralomidene were accordingly assigned structures (33) and (34) respectively.<sup>45</sup> Further evidence for these structural assignments would be desirable.



The distribution of alkaloids among the various organs of *V. lobelianum* has been investigated.<sup>47</sup> The isolation of  $\gamma$ -solanine from *V. lobelianum* has been reported.<sup>48</sup>

<sup>45</sup> R. Shakirov, K. A. Ubaidullaev, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, **11**, 527 (*Chem. Abs.*, 1976, **84**, 44 537).

<sup>46</sup> J. Tomko, A. Vassová, G. Adam, and K. Schreiber, *Tetrahedron*, 1968, **24**, 6839.

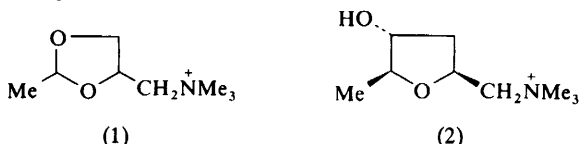
<sup>47</sup> N. V. Bondarenko, A. I. Bondarenko, and Sh. I. Safin, in 'Biol. Akt. Veshchestva Zhizni Rast. Zhivotn.', ed. N. S. Brysov and G. P. Kudryavtsev, "Vysheishaya Shkola", Minsk, U.S.S.R., 1973, 66 (*Chem. Abs.*, 1975, **83**, 75 352).

<sup>48</sup> R. Shakirov and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, **11**, 265 (*Chem. Abs.*, 1975, **83**, 128 653).

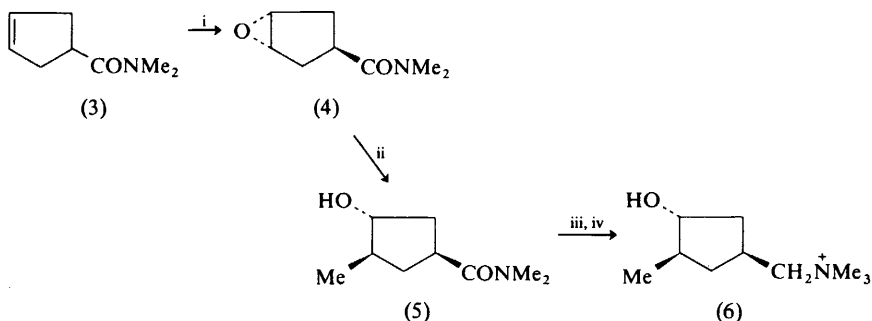


## 1 Muscarine Alkaloids

Hückel MO calculations on several analogues, *e.g.* (1), of muscarine (2) have been carried out, with optimization for the most stable conformations.<sup>1</sup> It was concluded that the distance between the oxygen function and a methyl group of the quaternary nitrogen is the determining factor in cholinergic receptor binding and hence pharmacological activity.



Interest in the synthesis of desether muscarine derivatives (6) has developed owing to their activity and specificity, which parallel those of the muscarines. In order to overcome deficiencies in overall yield of a previous photochemical synthesis,<sup>2</sup> a new stereoselective route has been devised (Scheme 1).<sup>3</sup> The readily available cyclopentene amide (3) was epoxidized to give (4), which upon treatment with lithium dimethylcuprate provided the amido-alcohol (5). Metal hydride reduction followed



Reagents: i, *m*-ClC<sub>6</sub>H<sub>4</sub>CO<sub>3</sub>H, pentane; ii, LiMe<sub>2</sub>Cu; iii, LiAlH<sub>4</sub>; iv, MeI

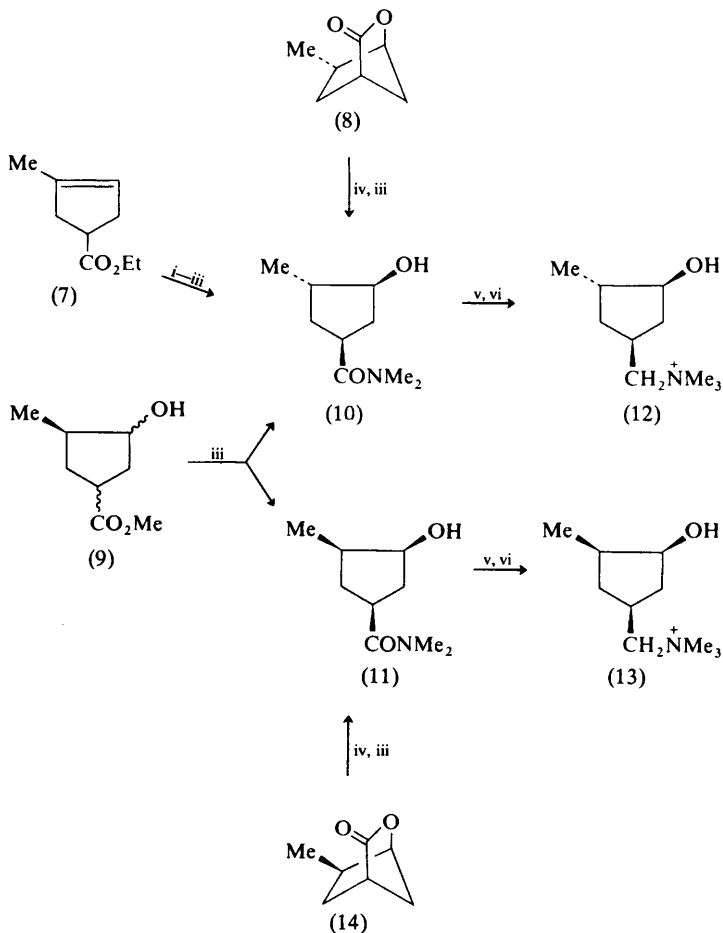
Scheme 1

<sup>1</sup> H. D. Hoeltje, *Arch. Pharm.*, 1974, **307**, 969.

<sup>2</sup> K. G. R. Sunderlin, R. A. Wiley, R. S. Givens, and D. R. Rademacher, *J. Medicin. Chem.*, 1973, **15**, 235.

<sup>3</sup> R. S. Givens, D. R. Rademacher, J. Kongs, and J. Dickerson, *Tetrahedron Letters*, 1974, 3211.

by quaternization with methyl iodide gave the cyclopentane analogue (6) of muscarine in 60% overall yield. The stereoisomeric *allo*- and *epi*-desethermuscarines, (12) and (13), have been prepared in a 1 : 1 ratio by a different route, starting with the ester (9) (mixture of all four isomers) as shown in Scheme 2.<sup>4</sup> Confirmation of



Reagents: i,  $B_2H_6$ , THF,  $0^\circ C$ ; ii,  $H_2O_2$ ,  $OH^-$ ; iii,  $Me_2NH$ ,  $100^\circ C$ ; iv, Na, EtOH; v,  $LiAlH_4$ ; vi, MeI.

**Scheme 2**

the stereochemistry of the two intermediate amides, (10) and (11), was obtained by alternate syntheses from the epimeric lactones (8) and (14) respectively. The hydroxyamide (10) was also obtained as the major product from a hydroboration–amidation sequence on the cyclopentene ester (7). Epimerization at the carbon  $\alpha$  to the ester function occurs in the amidation step owing to the establishment of a favourable

<sup>4</sup> C. Melchiorre, M. Giannella, D. Giardina, and F. Gulatieri, *Synth. Comm.*, 1975, 5, 95.

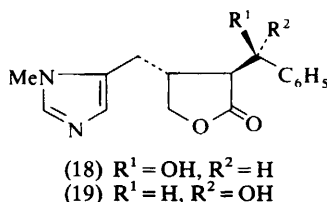
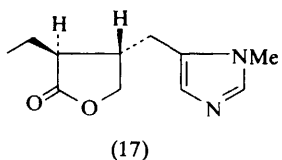
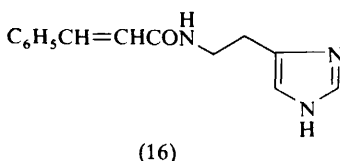
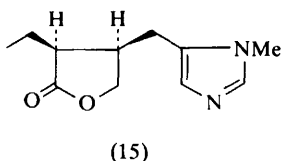
intramolecular hydrogen-bonding situation. Configurations of isomeric esters and amides were established by i.r. and n.m.r. spectral data. Other analogues of desethermuscaine have been prepared and their parasympathomimetic activity evaluated.<sup>5-7</sup>

## 2 Imidazole Alkaloids

A general review on the use of electrochemical methods for the synthesis of N-heterocycles and natural products includes a section on imidazole derivatives.<sup>8</sup> Thin-layer chromatographic methods for the separation of imidazole alkaloids have been briefly reviewed.<sup>9</sup> Pharmacological effects of pilocarpine (15) have been summarized as part of an excellent review on convulsant alkaloids.<sup>10</sup>

*N*<sub>α</sub>-*trans*-Cinnamoylhistamine (16) has been identified in *Acacia spirorbis*.<sup>11</sup> The alkaloid referred to as metapilocarpine has been shown to be identical with (±)-isopilocarpine (17).<sup>12</sup> Its pharmacological effects were found to be similar to that of pilocarpine (15).

The conflict (see Vol. 5 of these Reports) concerning the absolute stereochemistry of (±)-isopilosine (2*S*, 3*R*, 6*R*) (18) and (−)-*epi*-isopilosine (2*S*, 3*R*, 6*S*) (19) has been resolved in favour of these absolute stereoformulae on the basis of high-dilution i.r. studies.<sup>13</sup>



*d*-Pilocarpine specifically labelled with <sup>14</sup>C in the *N*-methyl group ([*N*-Me-<sup>14</sup>C]15) has been synthesized for use in pharmacokinetic studies (Scheme 3).<sup>14</sup> *d*-Homo-

<sup>5</sup> C. Melchiorre, F. Gualtieri, M. Giannella, M. Pigni, M. L. Cingolani, G. Gamba, P. Pigni, and L. Rossini, *Farmaco, Ed. Sci.*, 1975, **30**, 287.

<sup>6</sup> C. Melchiorre, F. Gualtieri, M. Giannella, M. Pigni, M. L. Cingolani, G. Gamba, P. Pigni, and L. Rossini, *Farmaco, Ed. Sci.*, 1975, **30**, 300.

<sup>7</sup> C. Melchiorre, F. Gualtieri, M. Giannella, M. Pigni, M. L. Cingolani, G. Gamba, P. Pigni, L. Re, and L. Rossini, *Farmaco, Ed. Sci.*, 1976, **31**, 218.

<sup>8</sup> R. F. Nelson, *Tech. Chem.*, 1975, **5**, 269.

<sup>9</sup> A. Narbutt-Mering, *Chromatogr. Cienkowiarsztowa Anal. Farm.*, 1973, 230.

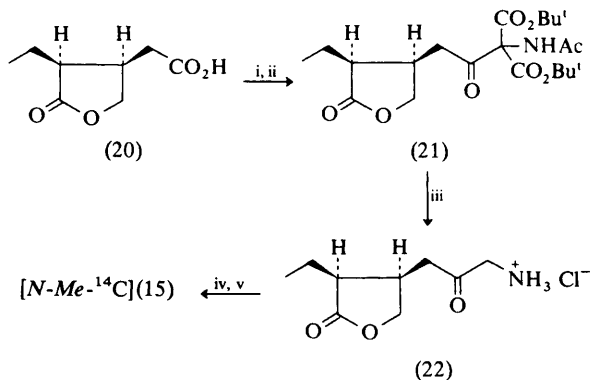
<sup>10</sup> D. R. Curtis, and G. A. R. Johnston, 'Neuropoisons: Their Pathophysiological Actions,' 1974, Vol. 2, p. 207.

<sup>11</sup> C. Poupat and T. Sevenet, *Phytochemistry*, 1975, **14**, 1881.

<sup>12</sup> H. Y. Aboul-Enein, *Acta Pharm. Suecica*, 1974, **11**, 387.

<sup>13</sup> S. Sarel, V. Usieli, and E. Tedeschi, *Tetrahedron Letters*, 1975, **2**, 97.

<sup>14</sup> J. I. DeGraw, J. S. Engstrom, and E. Willis, *J. Pharm. Sci.*, 1975, **64**, 1700.

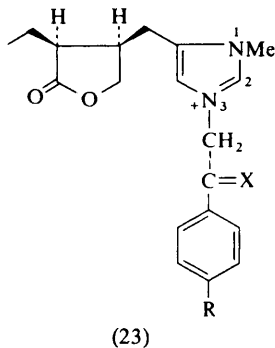


Reagents: i,  $\text{SOCl}_2$ ; ii,  $\text{NaH}$ ,  $\text{AcNHCH}(\text{CO}_2\text{Bu}^t)_2$ ,  $\text{Am}^t\text{OH-C}_6\text{H}_5$ ; iii,  $3\text{N-HCl}$ , heat; iv,  $^{14}\text{CH}_3\text{NCS}$ ,  $\text{K}_2\text{CO}_2$ ,  $\text{THF-H}_2\text{O}$ ; v,  $8\% \text{H}_2\text{O}_2$ .

**Scheme 3**

pilopic acid (20), obtained by resolution of its racemate with (+)- $\alpha$ -methylbenzylamine, was converted into its acid chloride and condensed with di-tert-butylacetamidomalonate to give (21). Compound (21) was hydrolysed and decarboxylated to the  $\alpha$ -aminoketone (22), which upon cyclization with [ $^{14}\text{C}$ ]methyl isothiocyanate followed by hydrogen peroxide-promoted desulphurization yielded *d*-[*N*-Me- $^{14}\text{C}$ ]pilocarpine ([*N*-Me- $^{14}\text{C}$ ] 15). High-performance liquid chromatography showed that the product was contaminated by 2% of isopilocarpine.

A number of pilocarpine salts (23;  $\text{X} = \text{O}$  or  $\text{NOH}$ ;  $\text{R} = \text{NO}_2$ ,  $\text{Br}$ ,  $\text{C}_6\text{H}_5$ , or  $\text{F}$ ) have been subjected to  $\text{D}_2\text{O}$  exchange experiments in [ $^2\text{H}_6$ ]DMSO and under basic conditions.<sup>15</sup> Compounds (23;  $\text{X} = \text{O}$ ) showed rapid exchange of the  $\alpha$ - $\text{CH}_2\text{CO}$  protons. In contrast, oxime derivatives (23;  $\text{X} = \text{NOH}$ ) exhibited exchange at C-2,

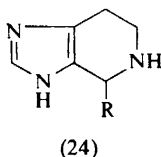


but not at the  $\alpha$ - $\text{CH}_2\text{CO}$  position. Structural and solvent effects on the exchange process were investigated and a mechanism for ring proton exchange *via* the C-2 ylide was suggested. Detailed  $^1\text{H}$  and  $^{13}\text{C}$  n.m.r. spectral studies of pilocarpine (15)

<sup>15</sup> A. A. Ben-Bassat and D. Lavie, *Israel J. Chem.*, 1974, **12**, 845.

and a number of model imidazole derivatives in acid solution have established that the site of protonation is the imine nitrogen in (15).<sup>16</sup>

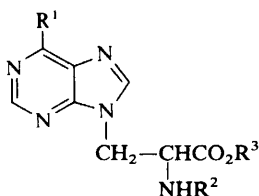
Comparative visual and potentiometric titrations of salts of pilocarpine have been reported.<sup>17</sup> The structurally interesting spinaceamine (24; R = H) and 6-methylspinaceamine (24; R = Me), isolated from amphibian venoms, have been shown to possess antimicrobial activity.<sup>18</sup>



### 3 Purine Alkaloids

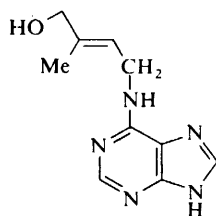
Of more than pure chemical interest is the recent report concerning the implications of consumption of caffeine in common beverages.<sup>19</sup> Although tea and coffee contain approximately the same amount of caffeine (2—5%), the former also contains adenine, which is thought to neutralize the action of caffeine. The presumed reason that children are allowed to drink chocolate and cocoa is that these contain only 0.25% of caffeine! The effects of certain precipitating agents<sup>20</sup> and of variation of the pH during extraction procedures on caffeine and related alkaloids have been studied.<sup>21</sup>

Lupinic acid (25), a metabolite of zeatin (27) in *Lupinus angustifolius*, represents the first example of a naturally occurring purine derivative which exhibits an amino-acid residue on a ring nitrogen.<sup>22</sup> The structure of lupinic acid was inferred from limited spectral data and confirmed by synthesis. Michael reaction of 6-chloropurine with methyl-2-trifluoroacetamidoacrylate followed by selective hydrolysis of the ester group (conditions not given) provided compound (26), which upon condensation with *trans*-4-amino-2-methylbut-2-en-1-ol (for a new synthesis, see below) and detrifluoroacetylation gave lupinic acid (25). This compound could also



(25) R¹ = *trans*-HOCH₂(Me)C=CHCH₂NH,  
R² = R³ = H

(26) R¹ = Cl, R² = COCF₃, R³ = H



(27)

<sup>16</sup> H. Moehrle, J. Tenczer, H. Kessler, and G. Zimmerman, *Arch. Pharm.*, 1975, **308**, 11.

<sup>17</sup> N. A. El-Rabbat and A. A. Abou-Of, *Egypt. J. Pharm. Sci.*, 1974, **15**, 277.

<sup>18</sup> H. J. Preusser, G. Habermehl, M. Sablofski, and D. Schmann-Haury, *Toxicon*, 1975, **13**, 285.

<sup>19</sup> M. Mironescu, *Rev. Fiz. Chim., Ser. A.*, 1974, **11**, 218.

<sup>20</sup> H. Kucerova, M. Kurcera, and C. D. Essien, *Planta Med.*, 1975, **27**, 185.

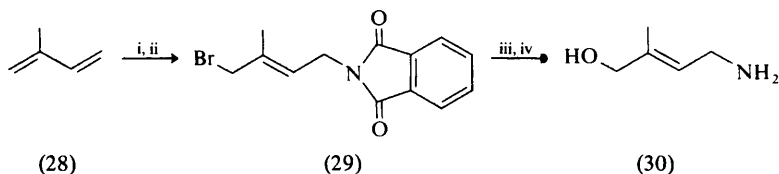
<sup>21</sup> V. F. Kramarenko, *Farmatsiya*, 1974, **23**, 29.

<sup>22</sup> J. K. MacLeod, R. E. Summons, C. W. Parker, and D. S. Letham, *J.C.S. Chem. Comm.*, 1975, 809.

be prepared by treatment of the *O*-acetyl derivative of zeatin (27) with the same Michael acceptor.

$^{13}\text{C}$  N.m.r. spectra of xanthine, theobromine, theophylline, caffeine, and their conjugate acids have been analysed.<sup>23</sup> The *X*-ray crystal structure of (theobromine)<sub>2</sub> H<sub>2</sub>I<sub>8</sub> shows it to be a polyiodide salt with alternating cationic (H-bonded protonated theobromines) and anionic (I<sub>18</sub><sup>-</sup> ions) layers.<sup>24</sup>

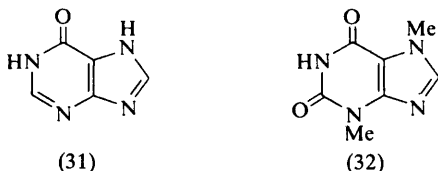
In the synthetic area, a new method for the preparation of *trans*-4-amino-2-methylbut-2-en-1-ol (30) has been reported<sup>25</sup> and offers considerable improvement over the previous procedures, which, incidentally, have not been available in English (see Vol. 5 of these reports). Thus (Scheme 4), bromination of isoprene (28) followed by condensation with potassium phthalimide at low temperature gave compound (29), which upon acetoxylation and base-catalysed hydrolysis afforded (30) in 34% overall yield. As had been previously carried out, treatment of (30) with 6-chloropurine gave zeatin (27).



Reagents: i, Br<sub>2</sub>, CCl<sub>4</sub>, -4 °C; ii, K phthalimide, DMF, -40 °C; iii, C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>NMe<sub>3</sub><sup>+</sup> OAc, Me<sub>2</sub>CO, heat; iv, Ba(OH)<sub>2</sub>, H<sub>2</sub>O.

Scheme 4

A new one-step synthesis of the hypoxanthine skeleton (see also Vol. 3 of these Reports) has been reported.<sup>26</sup> Thus when 2-cyano-2-phenylazoacetamide was hydrogenated over Raney nickel catalyst at high pressure and temperature in the presence of an ammonia-formamide mixture, hypoxanthine (31) was obtained in 60–70% yields. A number of analogues of (31) were similarly prepared. Interestingly, evidence was obtained, from subjecting a number of proposed intermediates to the reaction conditions, that pyrimidine ring closure precedes imidazole ring closure. An improved preparation of theobromine (32) has been reported.<sup>27</sup> A new synthesis of [8- $^{14}\text{C}$ ]theophylline has been achieved, thus facilitating the development of a new radiometric method in the analysis of its metabolism.<sup>28</sup>



<sup>23</sup> C. Nicolau and K. Hildenbrand, *Z. Naturforsch.*, 1974, **29c**, 475.

<sup>24</sup> F. H. Herbstein and M. Kapon, *J.C.S. Chem. Comm.*, 1975, 677.

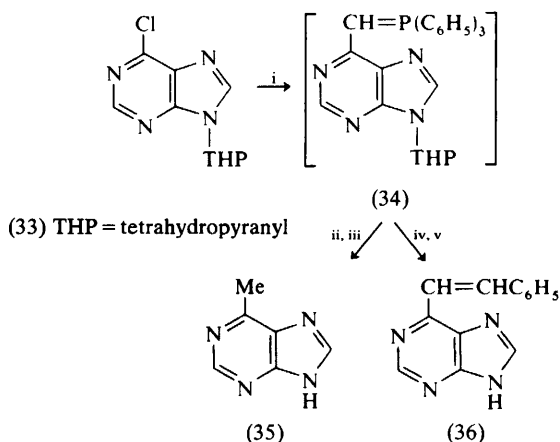
<sup>25</sup> M. Ohsugi, I. Ichimoto, and H. Ueda, *Agric. and Biol. Chem. (Japan)*, 1974, **38**, 1925.

<sup>26</sup> M. Sekiya and J. Suzuki, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 2401.

<sup>27</sup> V. M. Likhacheva, N. G. Zoloznaya, and G. T. Maevskaya, *Khim-Farm. Zhur.*, 1975, **9**, 48.

<sup>28</sup> S. M. Lohmann and R. P. Miech, *J. Labelled Compounds.*, 1975, **11**, 515.

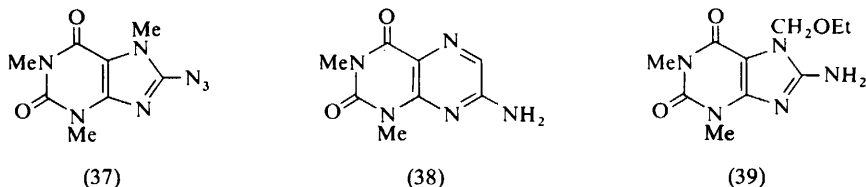
The utility of electrochemical methods for the preparation of purine derivatives has been discussed in a review concerned with broader application of these techniques in N-containing heterocyclic and natural product synthesis.<sup>8</sup> Details concerning the synthesis of cytokinin analogues (36) by a one-pot Wittig route have become available (Scheme 5).<sup>29</sup> Thus treatment of the 6-chloropurine derivative (33) with methylenetriphenylphosphorane, addition of benzaldehyde, and removal of the tetrahydropyranyl protecting group gave compound (36) in 55% yield. On the other hand, similar generation of the presumed ylide (34) intermediate followed by successive base and acid hydrolysis yielded 6-benzylpurine (35). Analogues of both (35) and (36) were also prepared.



Reagents: i, 2 equiv. Bu<sup>n</sup>Li, MeP<sup>+</sup>(C<sub>6</sub>H<sub>5</sub>)<sub>3</sub> Br<sup>-</sup>, DME, -30 °C → room temp; ii, Na<sub>2</sub>CO<sub>3</sub>, H<sub>2</sub>O, heat; iii, 3N-HCl; iv, C<sub>6</sub>H<sub>5</sub>CHO, DME; v, 1N-HCl.

**Scheme 5**

A new procedure for the methylation of a number of purine derivatives has been described.<sup>30</sup> The photolysis and pyrolysis of 8-azidocaffeine (37) has been studied.<sup>31</sup> Noteworthy among the many products isolated from these reactions is the thermally produced pteridine derivative (38) and the photochemically generated (in EtOH) ether (39).

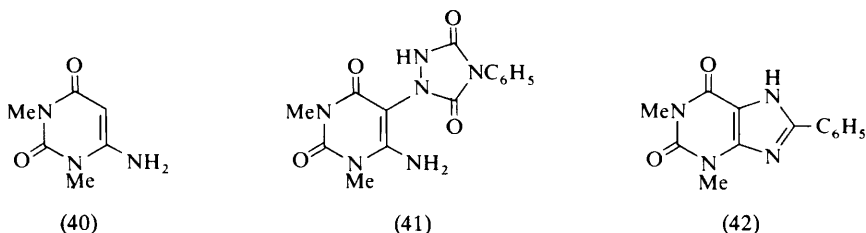


<sup>29</sup> E. C. Taylor and S. F. Martin, *J. Amer. Chem. Soc.*, 1974, **96**, 8095.

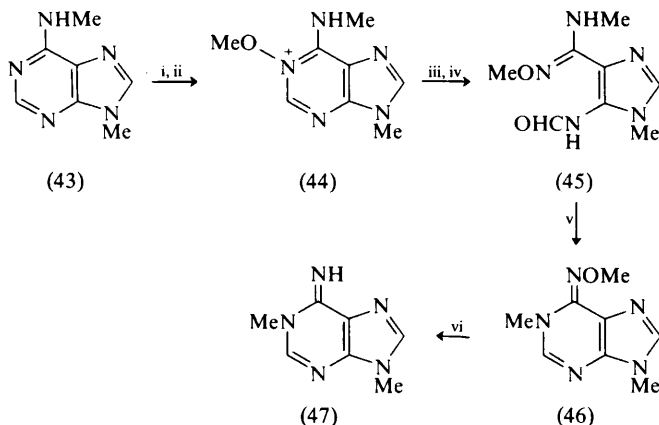
<sup>30</sup> W. F. Bryant and D. Klein, *Analyt. Biochem.*, 1975, **65**, 73.

<sup>31</sup> D. R. Sutherland and J. Pickard, *J. Heterocyclic Chem.*, 1974, **11**, 457.

A new purine ring synthesis has been developed.<sup>32</sup> Treatment of the 6-aminopyrimidine (40) with 4-phenyl-1,2,4-triazoline-3,5-dione in dioxan at room temperature provided the adduct (41) in excellent yield. Fusion of (41) with benzaldehyde at 180 °C gave 8-phenyltheophylline (42). A number of 8-aryl analogues were prepared by this method.



An interesting reaction sequence which formally represents an overall reverse Dimroth rearrangement (43) → (47) has been effected (Scheme 6).<sup>33</sup> *N*-Oxidation



Reagents: i, *m*-ClC<sub>6</sub>H<sub>4</sub>CO<sub>3</sub>H, EtOH; ii, MeI, MeCONMe<sub>2</sub>, 55 °C; iii, Amberlite IRA-402(HCO<sub>3</sub><sup>-</sup>); iv, H<sub>2</sub>O; v, H<sub>2</sub>O, reflux; vi, H<sub>2</sub>, Raney Ni, 50 °C.

**Scheme 6**

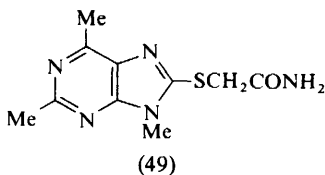
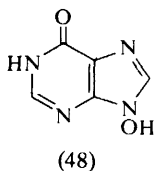
of the adenine derivative (43) followed by methylation gave the *O*-alkylated product (44), which upon basification followed by treatment with water at room temperature furnished the ring-opened intermediate (45). When (45) was subjected to reaction in water at reflux, the Dimroth rearrangement product (46) was obtained, and this compound could also be prepared from (44) under similar conditions. Finally, hydrogenation of (46) provided the imine (47), thus completing the reverse Dimroth rearrangement sequence.

<sup>32</sup> F. Yoneda, S. Matsumoto, and M. Higuchi, *J.C.S. Chem. Comm.*, 1974, 551.

<sup>33</sup> T. Fujii, F. Yanaka, K. Mohri, and T. Itaya, *Chem. and Pharm. Bull. (Japan)*, 1974, **22**, 2211.



Some 9-hydroxypurine derivatives (48) have been prepared.<sup>34</sup> Newly synthesized purine thioacetamides, e.g. (49), have been shown to enhance the antibacterial activity of phleomycin on *Escherichia coli*.<sup>35</sup>



#### 4 Peptide Alkaloids

Excellent reviews dealing with only those alkaloids which incorporate a styrylamine unit have been provided by the leading researcher in this area.<sup>36,37</sup> A further review is not readily accessible.<sup>38</sup>

Mainly as a result of work in Tschesche's laboratories, the discovery of new structural variants of the cyclopeptide alkaloids continues unabated. Some of the reports<sup>39-41</sup> appearing in 1974 and describing the isolation of new alkaloids have been reviewed,<sup>36</sup> and will not be discussed here. In the following summary of new work, the convenient classification of Tschesche will be followed.<sup>36</sup> A number of known 14-membered-ring alkaloids incorporating *p*-hydroxystyrylamine and  $\beta$ -hydroxyleucine units have been isolated from new sources. Thus adouetine Y' has been obtained from *Discaria longispina*<sup>42</sup> and adouetine X and frangulanine have been isolated from *Zizyphus jujuba* var. *inermis*.<sup>43</sup> The previously reported<sup>36,41</sup> presence of scutianine-A (50) and scutianine-B (51) in *Scutia buxifolia* has been confirmed.<sup>42,44</sup> Some confusion has arisen as a result of different names being given to the same alkaloids independently isolated also from *S. buxifolia*. Thus scutianine-C (52) isolated by Tschesche<sup>41</sup> corresponds to scutianine-D obtained by Ruveda<sup>44</sup> and scutiamine-D (53) (Tschesche)<sup>41</sup> shows physical properties in close agreement with scutianine-C (Ruveda).<sup>42</sup> The names suggested by Tschesche will be adopted here. Scutianine-E, a diastereomer of scutianine-D (53), is also known.<sup>41</sup> Furthermore, the new alkaloid scutianene-C (54) has been isolated from *S. buxifolia*.<sup>44</sup> For the sake of consistency, this alkaloid should be renamed scutianene-D, since it may be envisaged as arising from scutianine-D (53) by formal loss of dimethylamine. This process may occur *via* a Hofmann degradation of the corresponding quaternary salt during extraction, leading to the possibility that quaternary peptide alkaloids may be

<sup>34</sup> A. A. Watson, *J. Org. Chem.*, 1974, **39**, 2911.

<sup>35</sup> K. Bhushan, D. J. Vrown, J. H. Lister, L. G. Stephanson, and F. Yoneda, *Austral. J. Chem.*, 1975, **28**, 2553.

<sup>36</sup> R. Tschesche and E. U. Kaussmann, in 'The Alkaloids', ed. R. H. F. Manske, Academic Press, New York, 1975, vol. 15, p. 165.

<sup>37</sup> R. Tschesche, *Heterocycles*, 1976, **4**, 107.

<sup>38</sup> Y. Ogihara, *Nagoya Shiritsu Daigaku Yakugakubu Kenkyu Nempo*, 1974, **22**, 1.

<sup>39</sup> R. Tschesche, H. Wilhelm, E. U. Kaussmann, and G. Eckhardt, *Annalen*, 1974, 1694.

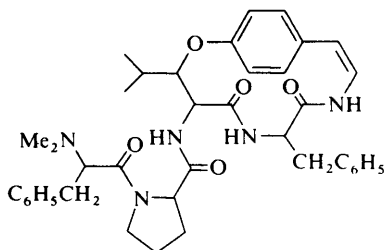
<sup>40</sup> B. K. Cassels, G. Eckhardt, E. U. Kaussmann, and R. Tschesche, *Tetrahedron*, 1974, **30**, 2461.

<sup>41</sup> R. Tschesche and E. Ammermann, *Chem. Ber.*, 1974, **107**, 2274.

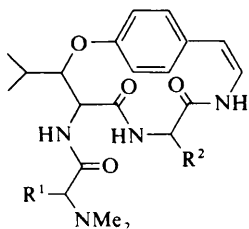
<sup>42</sup> V. M. Merkuza, M. Gonzalez Sierra, O. A. Mascaretti, E. A. Ruveda, C.-J. Chang, and E. Wenkert, *Phytochemistry*, 1974, **13**, 1279.

<sup>43</sup> H. Otsuka, Y. Ogihara, and S. Shibata, *Phytochemistry*, 1974, **13**, 2016.

<sup>44</sup> M. Gonzalez Sierra, O. A. Mascaretti, V. M. Merkuza, E. L. Tosti, E. A. Ruveda, and C.-J. Chang, *Phytochemistry*, 1974, **13**, 2865.



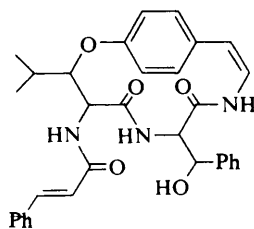
(50) Scutianine-A

(51)  $R^1 = R^2 = \text{CH}_2\text{Ph}$ (52)  $R^1 = \text{CH}(\text{Me})\text{Et}$ ,  $R^2 = \text{CH}_2\text{Ph}$ (53)  $R^1 = \text{CH}_2\text{Ph}$ ,  $R^2 = \text{CH}(\text{OH})\text{Ph}$ 

Scutianine-B

Scutianine-C

Scutianine-D



(54) Scutianene-C

isolated in the future.<sup>44</sup> An additional point of interest is the application of g.l.c. for rapid determination of optical purity of amino-acids obtained by degradation of the alkaloids.<sup>44</sup> Finally, *Zizyphus jujuba* var. *inermis* also yielded three new peptide alkaloids named F, G, and H, whose structures were not determined.<sup>43</sup>

A number of new 14-membered-ring alkaloids incorporating the *p*-hydroxystyrylamine and  $\beta$ -hydroxyphenylalanine structural features have been isolated and structurally elucidated, mainly by application of high-resolution mass spectrometry. Crénatine A (55) has been obtained from *Discaria crenata*<sup>45</sup> while alkaloid A, (feretine) (56) and alkaloid A<sub>2</sub> (57) have been isolated from *Feretia apondanthera*.<sup>46</sup> In addition to four known alkaloids, the root bark of *Zizyphus nummularia* has yielded nummularine-D (58) and nummularine-E (59).<sup>47</sup>

Nummularine-F (60)<sup>47</sup> and zizyphine-G (61),<sup>48</sup> elaborated by *Z. nummularia* and *Z. oenoplia* respectively, represent the only new additions to the 14-membered-ring alkaloid class which exhibit the *p*-hydroxystyrylamine and 3-hydroxyproline units as characteristic features. The known cyclopeptide mauritine-A, together with minor amounts of amphibines-A, -E, and -F, and mauritine-C have been isolated from *Z. spinachristi* of Nigerian origin.<sup>49</sup>

Zizyphine-F (62; R = H), isolated from *Z. oenoplia*, is the first example of a cyclopeptide alkaloid bearing a phenolic hydroxy-group as part of the styrylamine unit.<sup>48</sup> Its structure is based upon spectral data and conversion into the known

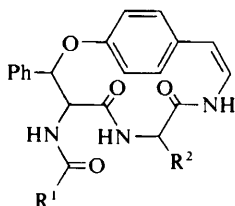
<sup>45</sup> M. Silva, D. S. Bhakuni, P. G. Sammes, M. Pais, and F.-X. Jarreau, *Phytochemistry*, 1974, **13**, 861.

<sup>46</sup> F. Bailleul and P. Delaveau, *Compt. rend.*, 1974, **279**, C, 949.


<sup>47</sup> R. Tschesche, M. Elgamal, G. A. Miana, and G. Eckhardt, *Tetrahedron*, 1975, **31**, 2944.

<sup>48</sup> R. Tschesche, I. Khokhar, C. Spilles, G. Eckhardt, and B. K. Cassels, *Tetrahedron Letters*, 1974, 2941.

<sup>49</sup> R. Tschesche, I. Khokhar, C. Spilles, and M. von Radloff, *Phytochemistry*, 1974, **13**, 1633.




(55)  $R^1 = \text{CH}(\text{NMe}_2)\text{CH}_2\text{CHMe}_2$ ,  $R^2 = \text{CH}_2\text{C}_6\text{H}_5$  Crenatine A

(56)  $R^1 =$    $\text{COCH}(\text{NHMe})\text{CH}_2\text{C}_6\text{H}_5$ ,

$R^2 = \text{CH}_2\text{C}_6\text{H}_5$

Alkaloid A<sub>1</sub>  
(Feretine)

(57)  $R^1 =$    $\text{COCH}(\text{NMe}_2)\text{CH}_2\text{C}_6\text{H}_5$ ,

Alkaloid A<sub>2</sub>

$R^2 = \text{CH}_2\text{C}_6\text{H}_5$

(58)  $R^1 = \text{CH}(\text{NHMe})\text{CH}(\text{Me})\text{Et}$ ,

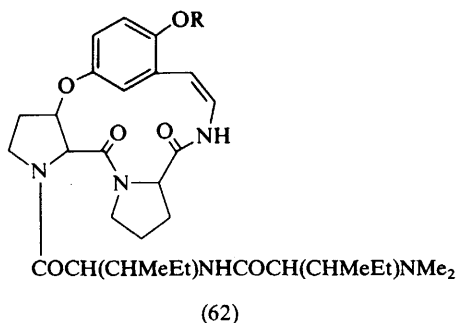
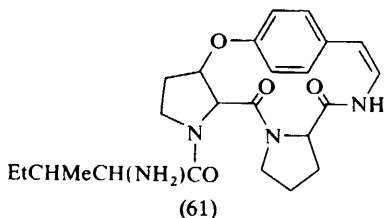
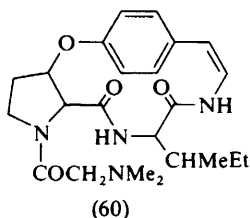
$R^2 = \text{CH}_2\text{CHMe}_2$

Nummularine-D

(59)  $R^2 = \text{CH}(\text{NMe}_2)\text{CH}(\text{OH})\text{Me}$ ,

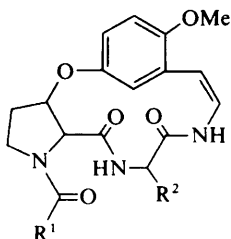
$R^2 = \text{CH}_2\text{CHMe}_2$

Nummularine-E



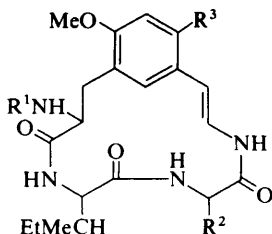
zizyphine-A (62;  $R = \text{Me}$ ) by treatment with diazomethane. Additional new members of the 13-membered-ring alkaloid class which have been structurally elucidated are nummularine-A (63), nummularine-B (64), and nummularine-C (65) obtained from *Z. nummularia*.<sup>50</sup>

<sup>50</sup> R. Tschesche, G. M. Miana, and G. Eckhardt, *Chem. Ber.*, 1974, **107**, 3180.



- (63)  $R^1 = \text{CH}(\text{CH}_2\text{CHMe}_2)\text{NHCOCH}(\text{NHMe})\text{CH}_2\text{C}_6\text{H}_5$ ,  
 $R^2 = \text{CH}(\text{Me})\text{Et}$  Nummularine-A  
 (64)  $R^1 = \text{CH}(\text{CHMe}_2)\text{NHCOCH}(\text{NHMe})\text{Me}$ ,  
 $R^2 = \text{CH}_2\text{C}_6\text{H}_5$  Nummularine-B  
 (65)  $R^1 = \text{CH}(\text{NMe}_2)\text{CH}_2\text{C}_6\text{H}_5$ ,  
 $R^2 = \text{CH}_2\text{CHMe}_2$  Nummularine-C

Finally, the compilation<sup>36</sup> of 15-membered-ring cyclopeptide alkaloids has been expanded by the discovery of mucronine-E (66), mucronine-F (67), mucronine-G (68), and mucronine-H (69) in *Z. mucronata*.<sup>51</sup> The known mucronines-A, -B, -C, and -D were also isolated from this species and, with the exception of mucronine-D, from *Z. abyssinica*.<sup>51</sup> The latter species has been shown for the first time to elaborate the known abyssenines-A, -B, and -C.<sup>52</sup>



- (66)  $R^1 = \text{Me}$ ,  $R^2 = \text{CH}_2\text{CHMe}_2$ ,  $R^3 = \text{OMe}$  Mucronine-E  
 (67)  $R^1 = \text{H}$ ,  $R^2 = \text{CH}_2\text{CHMe}_2$ ,  $R^3 = \text{OMe}$  Mucronine-F  
 (68)  $R^1 = \text{H}$ ,  $R^2 = \text{CH}(\text{Me})\text{Et}$ ,  $R^3 = \text{OMe}$  Mucronine-G  
 (69)  $R^1 = \text{H}$ ,  $R^2 = \text{CH}_2\text{C}_6\text{H}_5$ ,  $R^3 = \text{H}$  Mucronine-H

A detailed analysis of 220 MHz n.m.r. spectra of discarine B (70) and frangulamine has been carried out in order to gain conformational information on cyclopeptide alkaloids.<sup>53</sup> D<sub>2</sub>O-Exchange experiments on discarine B under neutral and acidic conditions and at a variety of temperatures indicate the following order of NH-exchange (see 70):  $\text{H}_\text{A} = \text{H}_\text{B} \gg \text{H}_\text{C} \gg \text{H}_\text{D}$ . The slow rate of exchange of the tryptophan amide  $\text{H}_\text{C}$  may be a consequence of strong intramolecular hydrogen bonding. A solvent-dependence study was also carried out.

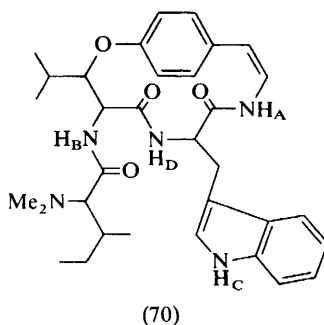
The X-ray crystal structure of tri-*N*-methylfrangulamine methiodide has been determined<sup>54</sup> and shows, in agreement with u.v. data, a conformation in which the

<sup>51</sup> R. Tschesche, S. T. David, R. Zerbes, M. von Radloff, E. U. Kaussmann, and G. Eckhardt, *Annalen*, 1974, 1915.

<sup>52</sup> R. Tschesche, M. Elgama, G. Eckhardt, and M. von Radloff, *Phytochemistry*, 1974, 13, 2328.

<sup>53</sup> C.-J. Chang, E. W. Hagaman, E. Wenkert, M. Gonzalez Sierra, O. A. Mascaretti, V. M. Merkuza, and E. A. Ruveda, *Phytochemistry*, 1974, 13, 7, 1273.

<sup>54</sup> M. Takai, Y. Ogihara, Y. Iitaka, and S. Shibata, *Chem. and Pharm. Bull. (Japan)*, 1975, 23, 2556.



benzene ring and the adjacent double bond are twisted out of plane by 73°. The X-ray picture also predicts which protons should fall in the shielding zone of the benzene ring. Examination of the n.m.r. spectrum of frangulamine confirms these predictions and suggests that the conformation of tri-*N*-methylfrangulamine methiodide is a good approximation for the conformation of the alkaloid.

Details concerning the structural elucidation of codonocarpine and *N*-methylcodonocarpine, *Lunaria*-type alkaloids from *Codonocarpus australis* (see Vol. 3 of these Reports), have become available.<sup>55</sup>

The tripeptide isoleucyl- $\beta$ -hydroxyleucyl-leucyl-tyrosine, a proposed intermediate in the biosynthesis of frangulamine, has been synthesized.<sup>54</sup> A synthesis of amphibine-I (74) has been reported which confirms its structure and allows assignment of configuration (Scheme 7).<sup>56</sup> Homoveratrylamine was coupled with phthalyl-L-alanine in the presence of DCC to give the amide (71), which was cyclized to the dihydroisoquinoline derivative (72) under standard Bischler-Napieralski conditions. Sodium cyanoborohydride reduction followed by Clarke-Eschweiler methylation and dephthaloylation led to the diamine (73), which upon successive coupling with benzyloxycarbonyl-L-valylglycine and catalytic hydrogenolysis produced two diastereomers, one of which was shown to be identical with amphibine-I (74) in all except c.d. spectral data. By c.d. and n.m.r. spectral comparison of the natural and synthetic materials as well as other intermediates and derivatives, it was concluded that amphibine-I consists of a mixture of 1*S*, 9*R*, and 1*R*, 9*S* stereoisomers, with the former configurational form in excess. The terminal valine unit possesses the *S*-configuration in both stereoisomers, as shown by previous degradative experiments.

## 5 Unclassified Alkaloids and Alkaloid-containing Plants

Further extensive alkaloid screening studies (see Vol. 5 of these Reports) have been described.<sup>57</sup> A comprehensive, concise, and thus useful volume on the interpretation of mass spectra of most major classes of alkaloids has been published.<sup>58</sup> Methods of chromatographic analysis of alkaloids from pharmaceutical preparations have been reviewed.<sup>59</sup>

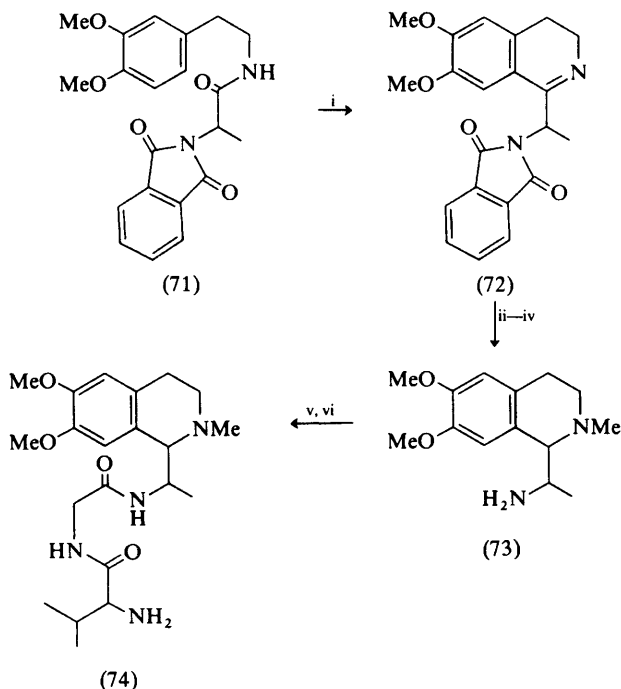
<sup>55</sup> R. W. Doskotch, A. B. Ray, W. Kubelka, E. H. Fairchild, C. D. Hufford, and J. L. Beal, *Tetrahedron*, 1974, **30**, 3229.

<sup>56</sup> R. Tschesche, J. Moch, and C. Spilles, *Chem. Ber.*, 1975, **108**, 2247.

<sup>57</sup> S. J. Smolenski, H. Silinis, and N. R. Farnsworth, *Lloydia*, 1974, **37**, 3, 506.

<sup>58</sup> M. Hesse and H. O. Bernhard, 'Progress in Mass Spectrometry, Volume 3, Alkaloids with the Exception of Indole, Triterpene, and Steroidal Alkaloids', Verlag Chemie, Weinheim, 1975.

<sup>59</sup> K. Macek, 'Pharmaceutical Applications of Thin-Layer and Paper Chromatography', Elsevier, Amsterdam, 1972, p. 431.



Reagents: **i**,  $\text{PCl}_5$ ,  $\text{CHCl}_3$ ; **ii**,  $\text{NaBH}_3\text{CN}$ ,  $\text{MeOH}$ ,  $\text{HCl}$ ; **iii**,  $\text{HCO}_2\text{H}$ ,  $\text{HCHO}$ ,  $90^\circ\text{C}$ ; **iv**,  $\text{NH}_2\text{NH}_2$ ,  $\text{H}_2\text{O}$ - $\text{EtOH}$ ; **v**, benzyloxycarbonyl-L-valylglycine,  $\text{POCl}_3$ ,  $\text{C}_5\text{H}_5\text{N}$ ,  $60^\circ\text{C}$ ; **vi**,  $\text{H}_2$ ,  $\text{Pd-C}$ ,  $\text{EtOH}$ .

**Scheme 7**

Natural sources in which alkaloids have been detected, but not characterized are: *Boerhaavia repens*,<sup>60</sup> *Penicillium corylophilum* and *P. granulatum*,<sup>61</sup> and *Stizolophus balsamita*.<sup>62</sup>

*Antirrhinum hispanicum*, *A. molle*, *A. mollissimum* (Vol. 3, p. 318)

In addition to 4-methyl-2,6-naphthyridine, an unknown alkaloid,  $\text{C}_{16}\text{H}_{13}\text{N}_2\text{O}_2$ , was isolated.<sup>63</sup>

*Beauveria bassiana*, *B. tenella*

These insect-pathogenic fungi produce bassianin ( $75; n = 2$ ) and tenellin ( $75; n = 1$ ), whose structures rest largely on  $^{13}\text{C}$  n.m.r. studies on  $^{13}\text{C}$ - and  $^{15}\text{N}$ -enriched samples obtained by feeding experiments.<sup>64</sup>

*Cannabis sativa* (Vol. 5, p. 279)

The structure of cannabisativine (76), found both in the roots and in the leaves of the plant, has been determined by X-ray crystallographic analysis using a direct

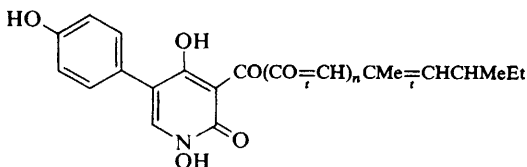
<sup>60</sup> A. Khalique, A. Hannan, J. Rahman, and M. Kiamuddin, *Bangladesh J. Sci. Ind. Res.*, 1974, **9**, 47.

<sup>61</sup> L. V. Penskaya, I. B. Romanova, and O. V. Kruglaya, *Priklad. Biokhim. i Mikrobiol.*, 1975, **11**, 274.

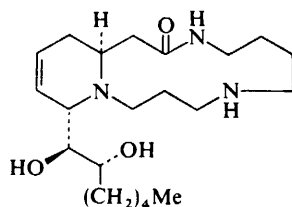
<sup>62</sup> I. Kh. Khaitov, *Aktual. Vopr. Farm.*, 1974, **2**, 7.

<sup>63</sup> S. E. Brooker and K. J. Harkiss, *Planta Med.*, 1974, **26**, 305.

<sup>64</sup> A. G. McInnes, D. G. Smith, C. K. Wat, L. C. Vining, and J. L. C. Wright, *J.C.S. Chem. Comm.*, 1974, 281.



(75)



(76)

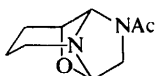
method program.<sup>65</sup> This represents the first report of the isolation of a non-quaternary alkaloid from *C. sativa*.

#### *Clitocybe fasciculata*

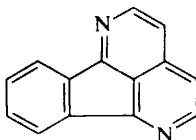
The structure (77) for lepestine has been established by X-ray analysis.<sup>66</sup> Lepistine has structural similarities with pyrrolizidine and *Poranthera* alkaloids.

#### *Eupomatia laurina*

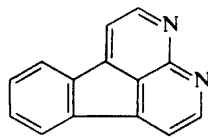
1,6-Diazafluoranthene (78) has been synthesized and shown to be identical with eupolauridine, which had been isolated previously from this species.<sup>67</sup> Two other alkaloids, eupolauramine and hydroxyeupolauramine, were shown not to be related to (78) or synthetic 3,4-diazafluoranthene (79).



(77)



(78)



(79)

#### *Festuca arundinacea* (Vol. 5, p. 280)

Methods for isolation of perloine from this species (tall fescue) have been refined. Perloine appears not to exhibit antibiotic activity but shows marginal anti-tumour properties.<sup>68</sup> A fluorometric analytical method for this alkaloid has been developed.<sup>69</sup>

#### *Lathyrus sativus*

Putrescine, cadaverine, spermidine, spermine, agmatine, and homoagmatine have been isolated.<sup>70</sup> The latter two are guanidoamine derivatives.

#### *Maytenus ovatus*. (Vol. 5, p. 282)

The cyclic carbamate (80), representing a model compound of the anti-tumour macrolide maytansine, has been synthesized (Scheme 8).<sup>71</sup>

<sup>65</sup> H. L. Lotter, D. J. Abraham, C. E. Turner, J. E. Knapp, P. L. Schiff, and D. J. Slatkin, *Tetrahedron Letters*, 1975, 2815.

<sup>66</sup> M. Laing, F. L. Warren, and E. P. White, *Tetrahedron Letters*, 1975, 269.

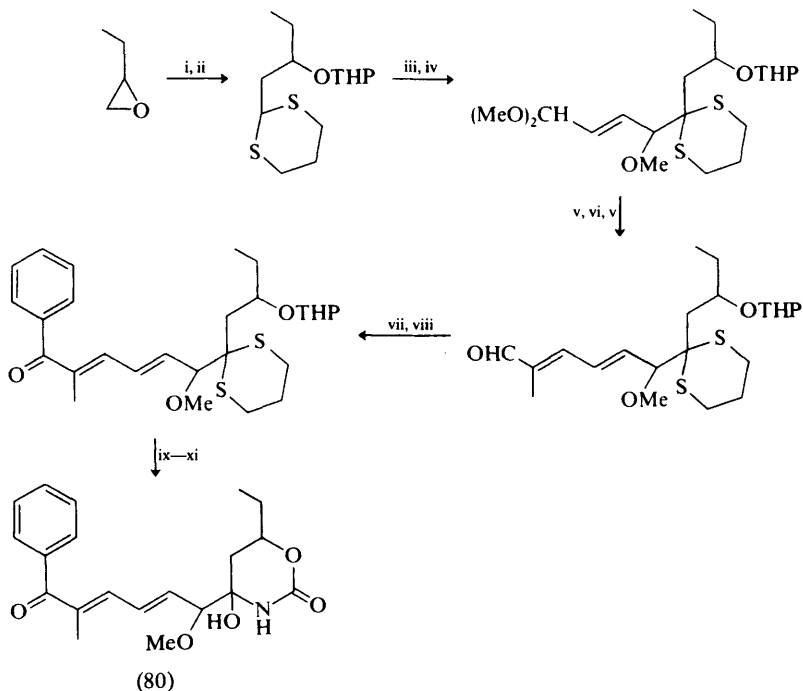
<sup>67</sup> B. F. Bowden, K. Picker, E. Ritchie, and W. C. Taylor, *Austral. J. Chem.*, 1975, **28**, 2681.

<sup>68</sup> S. G. Yates, S. P. Rogovin, L. P. Bush, R. C. Buckner, and J. A. Boling, *Ind. and Eng. Chem. (Product Res. and Development)*, 1975, **14**, 315.

<sup>69</sup> S. R. Shaffer, M. Williams, B. J. Harmon, E. E. Pickett, and G. B. Garner, *J. Agric. Food Chem.*, 1975, **23**, 346.

<sup>70</sup> S. Ramakrishna and P. R. Adiga, *Indian J. Biochem. Biophys.*, 1974, **11**, 128.

<sup>71</sup> A. I. Meyers and R. S. Brinkmeyer, *Tetrahedron Letters*, 1975, 1749.



Reagents: i,  $\text{Bu}^n\text{Li}$ , 1,3-dithian,  $-25^\circ\text{C}$ ; ii, dihydropyran,  $\text{TsOH}$ ,  $\text{Et}_2\text{O}$ ,  $20^\circ\text{C}$ ; iii,  $\text{Bu}^n\text{Li}$ ,  $(\text{MeO})_2\text{CHCH}=\text{CHCHO}$ ,  $-78^\circ\text{C}$ ; iv,  $\text{MeI}$ ,  $\text{HMPA}$ ; v,  $(\text{CO}_2\text{H})_2$ ,  $\text{THF}-\text{H}_2\text{O}$ ,  $5^\circ\text{C}$ ; vi,  $(\text{Pr}^f)_2\text{N}^-\text{Li}$ ,  $\text{C}_6\text{H}_5\text{N}=\text{CHCH}_2\text{Me}$ ,  $-78^\circ\text{C}$ ; vii,  $\text{C}_6\text{H}_5\text{MgBr}$ ,  $\text{Et}_2\text{O}$ ,  $5^\circ\text{C}$ ; viii,  $\text{DDQ}$ ,  $\text{THF}$ ; ix,  $\text{HgCl}_2$ ,  $\text{MeCN}-\text{H}_2\text{O}$ ; x,  $\text{COCl}_2$ , collidine,  $\text{Et}_2\text{O}-\text{C}_6\text{H}_6$ ; xi,  $\text{NH}_3$ ,  $\text{MeOH}$ ,  $-50^\circ\text{C}$ .

**Scheme 8**

*Nitraria schoberi* (Vol. 5, p. 282)

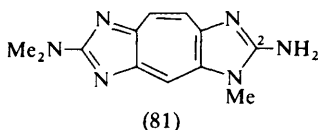
Isonitrarine, a C-3 epimer of nitrarine, has been identified by spectral methods.<sup>72</sup>

*Parazoanthus axinellae* (Vol. 4, p. 424)

The structure (81) of zoanthoxanthin, the major pigment of this Mediterranean zoanthid, has been confirmed by an *X*-ray crystallographic analysis of its 2-chloro-analogue.<sup>73</sup>

*Piper sylvaticum*

Sylvatine (82) has been synthesized by a stereospecific route.<sup>74</sup>

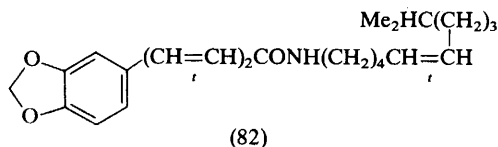


<sup>72</sup> A. A. Ibragimov, S. Kh. Maekh, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1975, **11**, 276.

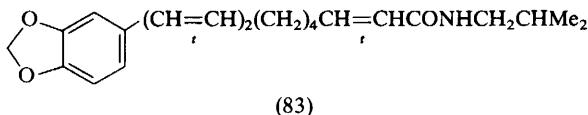
<sup>73</sup> L. Cariello, S. Crescenzi, G. Prota, S. Capasso, F. Giordano, and L. Mazzarella, *Tetrahedron*, 1974, **30**, 3281.

<sup>74</sup> O. P. Vig, A. K. Handa, and S. D. Sharma, *Indian J. Chem.*, 1975, **13**, 225.

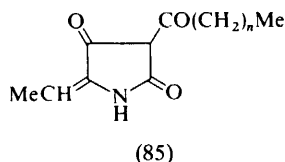
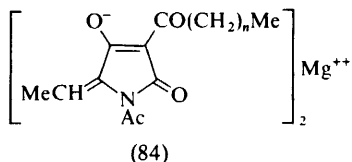


*Piper trichostachyon*

The structure (83) of the new alkaloid piperstachine has been established on the basis of spectral data and the synthesis of its hexahydro-derivative.<sup>75</sup>

*Pseudomonas magnesorubra*

Magnesidin has been shown to be a 1:1 mixture of the salts (84;  $n = 4$ ) and (84;  $n = 6$ ) by spectroscopic and chemical means and by its two-step synthesis ( $\text{MgCl}_2$ ,  $\text{NaOH}$ ;  $\text{Ac}_2\text{O}$ ,  $\text{NaOAc}$ ) from the tetramic acids (85;  $n = 4$ ) and (85;  $n = 6$ ).<sup>76</sup> Magnesidin represents the first magnesium-containing antibiotic substance isolated from natural sources.

*Pseudomonas* sp. (Vol. 3, p. 43)

A number of pyrrolnitrin analogues have been synthesized.<sup>77</sup>

*Rhodotorula pilimanae* (Vol. 5, p. 286)

A new synthesis of rhodotorulic acid (86) has appeared.<sup>78</sup>

*Salvadora persica*

Salvadourea [ $(m\text{-MeOC}_6\text{H}_4\text{CH}_2\text{NH})_2\text{CO}$ ] has been isolated.<sup>79</sup>

*Saxidomus giganteus*

Saxitoxin, the paralytic shellfish poison, has finally revealed its structure as (87) by X-ray crystallographic analysis of its ethyl hemiketal<sup>80</sup> and *p*-bromobenzene-sulphonate<sup>81</sup> derivatives. <sup>13</sup>C n.m.r. studies show that saxitoxin exists primarily as its ketone hydrate in aqueous solution.<sup>80</sup>

<sup>75</sup> B. S. Joshi, N. Viswanathan, D. H. Gawad, and W. von Philipsborn, *Helv. Chim. Acta*, 1975, **58**, 1551.

<sup>76</sup> H. Kohl, S. V. Bhat, J. R. Patell, N. M. Gandhi, J. Nazareth, P. V. Divekar, N. J. DeSouza, H. G. Berscheid, and H. W. Fehlhaber, *Tetrahedron Letters*, 1974, 983.

<sup>77</sup> G. Filacchioni, V. Nacci, G. Stefancieh, and M. Artico, *Farmaco, Ed. Sci.*, 1974, **29**, 872.

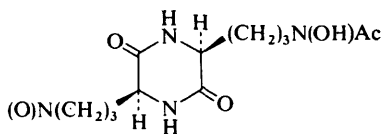
<sup>78</sup> J. Widmer and W. Keller-Schierlein, *Helv. Chim. Acta*, 1974, **57**, 1904.

<sup>79</sup> A. B. Ray, L. Chand, and S. C. Dutta, *Chem. and Ind.*, 1975, **12**, 517.

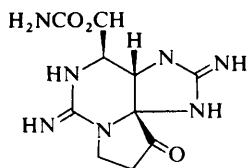
<sup>80</sup> J. Bordner, W. E. Thiessen, H. A. Bates, and H. Rapoport, *J. Amer. Chem. Soc.*, 1975, **97**, 6008.

<sup>81</sup> E. J. Schantz, V. E. Ghazarossian, H. K. Schnoes, F. M. Strong, J. P. Springer, J. O. Pezzanite, and J. Clardy, *J. Amer. Chem. Soc.*, 1975, **97**, 1238.

<sup>82</sup> T. E. Monakhova, O. N. Tol'kachev, M. E. Perel'son, V. S. Kabanov, and N. F. Proskurnina, *Khim. prirod. Soedinenii*, 1974, **6**, 752.



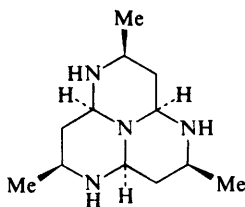
(86)



(87)

*Sophora alopecuroides*

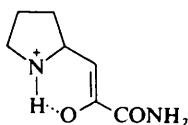
An intriguing structure (88) has been proposed for tricotonyltetramide on the basis of spectral data.<sup>83</sup>



(88)

*Streptomyces evidani*

The metabolite pyracimycin (89) has been isolated and elucidated on the basis of chemical and spectral studies.<sup>83</sup>



(89)

*Streptomyces roseopallidus*

A regioselective and stereoselective synthesis of actinonin (94), the first example of both a naturally occurring hydroxamic acid and a derivative of L-prolinol, has been reported (Scheme 9).<sup>84</sup> Treatment of pentylmaleic anhydride (90) with *O*-benzylhydroxylamine proceeded regioselectively, as expected, to give the maleamic acid (91), which upon dehydration afforded the isomaleimide (92) as the major product. Reaction of (92) with L-valyl-L-prolinol (9) again proceeded with regioselectivity to furnish a bisamide, which upon hydrogenolysis gave actinonin (94). A number of analogues of actinonin have also been prepared.<sup>85</sup>

*Streptomyces* sp.

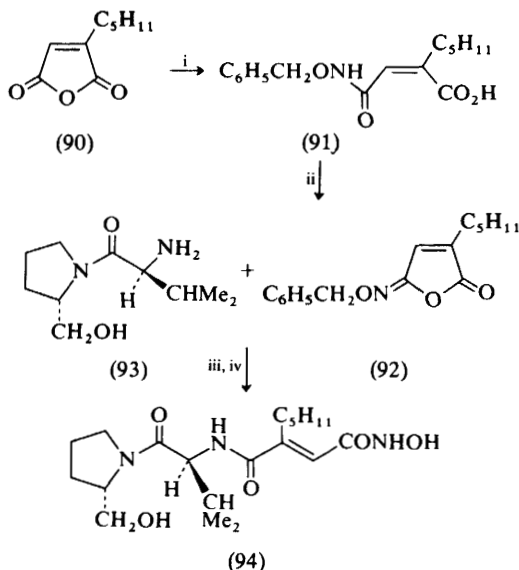
The structure of the broad-spectrum antibiotic naphthyridinomycin (95) has been determined by *X*-ray crystallographic analysis.<sup>86</sup>

<sup>83</sup> G. G. Gallo, C. Coronelli, L. F. Zerilli, B. Cavalleri, and E. Martinelli, *Gazzetta*, 1975, **105**, 51.

<sup>84</sup> N. H. Anderson, W. D. Ollis, J. E. Thorpe, and A. D. Ward, *J.C.S. Chem. Comm.*, 1974, **11**, 420.

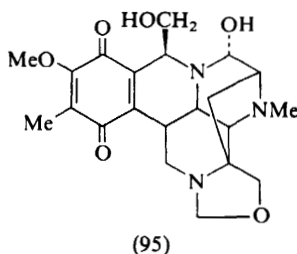
<sup>85</sup> J. P. Devlin, W. D. Ollis, J. E. Thorpe, R. J. Wood, B. J. Broughton, P. J. Warren, K. R. H. Wooldridge, and D. E. Wright, *J.C.S. Chem. Comm.*, 1974, 421.

<sup>86</sup> J. Sygusch, F. Brisse, S. Hanessian, and D. Kluepfel, *Tetrahedron Letters*, 1974, 4021.



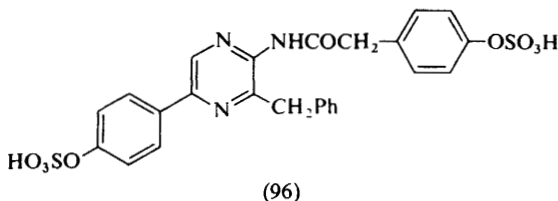
Reagents: i,  $C_6H_5CH_2ONH_2$ ,  $Et_2O$ ,  $0^\circ C$ ; ii, DCC,  $EtOAc$ ,  $0^\circ C$ ; iii,  $EtOAc$ , room temp.; iv,  $H_2$ ,  $Pd-C$ ,  $EtOH$ ,  $C_5H_5N$ .

Scheme 9

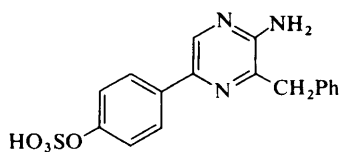


### *Watasenia scintillans*

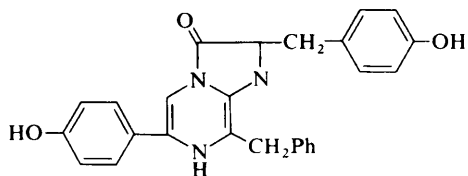
Extraction of the light-emitting organs of this species of squid yielded two fluorescent compounds, which have been shown to possess structures (96) and (97) on the basis of spectroscopic data and synthesis from the corresponding phenols by treatment with chlorosulphonic acid.<sup>87</sup> Recently, the imidopyrazine derivative (98)



<sup>87</sup> T. Goto, H. Iio, S. Inoue, and H. Kakoi, *Tetrahedron Letters*, 1974, 2321.



(97)



(98)

has been isolated from this source.<sup>88</sup> The synthesis of (98), believed to be a precursor of *Watasenia* photoprotein, was also achieved.

<sup>88</sup> S. Inoue, S. Sugiura, H. Kakoi, K. Hasizume, T. Goto, and H. Iio, *Chem. Letters*, 1975, 141.

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