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# **The Alkaloids**

**VOLUME 10**

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**The Alkaloids**

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**Volume 10**





A Specialist Periodical Report

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# The Alkaloids

Volume 10

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A Review of the Literature Published  
between July 1978 and June 1979

Senior Reporter

**M. F. Grundon** *School of Physical Sciences, New University of  
Ulster, Coleraine, Northern Ireland*

Reporters

**W. A. Ayer** *University of Alberta, Canada*

**K. W. Bentley** *University of Technology, Loughborough*

(the late) **J. Butterick** *University of West Virginia, U.S.A.*

**G. Fodor** *University of West Virginia, U.S.A.*

**D. M. Harrison** *New University of Ulster*

**R. B. Herbert** *University of Leeds*

**J. A. Lamberton** *C.S.I.R.O., Melbourne, Australia*

**J. R. Lewis** *University of Aberdeen*

**S. W. Page** *University of Georgia, U.S.A.*

**S. W. Pelletier** *University of Georgia, U.S.A.*

**A. R. Pinder** *Clemson University, South Carolina, U.S.A.*

**D. J. Robins** *Glasgow University*

**J. E. Saxton** *University of Leeds*

**M. Shamma** *Pennsylvania State University, U.S.A.*

The Royal Society of Chemistry  
Burlington House, London W1V 0BN

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## *Foreword*

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The flow of excellent alkaloid research proceeds unabated and for the tenth successive year the contributors to this series have endeavoured to provide a comprehensive review of the literature concerned with the chemistry of alkaloids. We hope to maintain this unique feature of the publication, although the escalating cost of production has resulted in the omission of much background material and occasional more extensive reviews that were provided in earlier volumes. The publication of this volume has been delayed for reasons beyond the control of the contributors and the Royal Society of Chemistry.

With great regret I record the death of one of our authors, Dr. John Butterick.

*October 1980*

M. F. GRUNDON



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## 1 Introduction

Previous practice, of listing earlier Reports in this series as the first references,<sup>1-9</sup> is continued. One of the most recent reviews on alkaloid biosynthesis<sup>10</sup> is again cited for background information; another, more extensive, review has appeared which includes a discussion of the biosynthesis of nitrogenous microbial metabolites, as well as that of plant alkaloids.<sup>11</sup>

This Report is the tenth to have been published. Some perspective has been given to research surveyed in the first five Reports,<sup>5</sup> and it is appropriate to attempt the same for material in succeeding volumes. In the following, liberal reference is made to fuller discussion in previous Reports, and in any case, discussion is curtailed of material appearing again in this Report.

The biosynthetic route to most plant alkaloids and nitrogenous microbial metabolites is quite closely defined by the results of straightforward tracer feeding experiments. For these, work with the enzymes involved provides extra detail, with helpful confirmation for an already deduced sequence (see, *e.g.*, nicotine<sup>12</sup>

<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> R. B. Herbert, in 'The Alkaloids', ed. M. F. Grundon (Specialist Periodical Reports), The Chemical Society, London, 1977, Vol. 7.

<sup>8</sup> R. B. Herbert, in 'The Alkaloids', ed. M. F. Grundon (Specialist Periodical Reports), The Chemical Society, London, 1978, Vol. 8.

<sup>9</sup> R. B. Herbert, in 'The Alkaloids', ed. M. F. Grundon (Specialist Periodical Reports), The Chemical Society, London, 1979, Vol. 9.

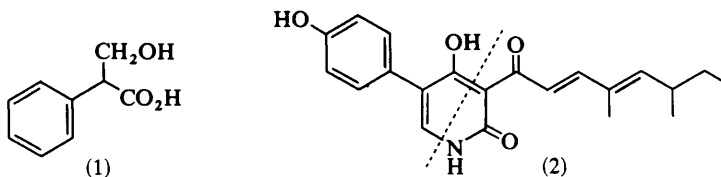
<sup>10</sup> R. B. Herbert, in 'Comprehensive Organic Chemistry', ed. D. H. R. Barton and W. D. Ollis, Pergamon, Oxford, 1978, Vol. 5, p. 1045.

<sup>11</sup> R. B. Herbert, in "Rodd's Chemistry of Carbon Compounds", second edition, ed. S. Coffey, 1980, Vol. IV L, p. 291.

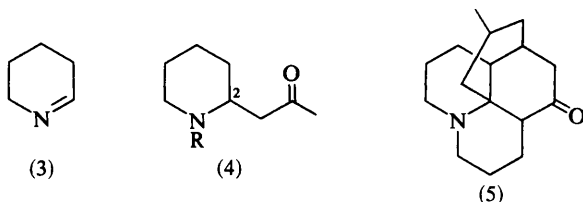
<sup>12</sup> S. Mizusaki, M. Tanabe, M. Noguchi, and E. Tamaki, *Phytochemistry*, 1972, **11**, 2757; *Plant Cell Physiol.*, 1971, **12**, 633; R. B. Herbert, in ref. 4, p. 7.

and coniine<sup>13</sup>). For others it is only with the isolation of the enzymes responsible for the various steps of biosynthesis that a clear statement about the sequence can be made. Not surprisingly, most progress has been made in isolating enzymes responsible for metabolite formation in micro-organisms. Good examples of this are to be found in studies on the biosynthesis of echinulin (this Report p. 24), indolmycin,<sup>14</sup> and benzodiazepine alkaloids.<sup>15,16</sup> It may well be that some of the problems which still defy a solution will only yield to experiments with isolated enzymes.

One such problem concerns the tropic acid moiety (1) found in the tropane alkaloids. It is derived from phenylalanine and its formation involves a 1,2-shift of the carboxy-group in the amino-acid. The mechanism and the substrate for rearrangement are uncertain, however (this Report, p. 12). There is a similar rearranged phenylalanine fragment in the microbial metabolite tenellin (2).<sup>17</sup> That such a rearrangement should be observed both in a plant alkaloid and a microbial metabolite argues for a simple common diversion from phenylalanine metabolism.



The biosynthesis of the *Lycopodium* alkaloids, e.g. lycopodine (5), is still a puzzle. Biosynthesis of these alkaloids from  $\Delta^1$ -piperidine (3) and acetic acid, suggests that these alkaloids are formed by dimerization of a single precursor, for which isopelletierine (4; R = H) is a logical candidate. But, it is quite clear that it is the source for only one half of these molecules.<sup>18</sup> What the precursor for the other half is, remains unknown.



<sup>13</sup> M. F. Roberts, *Phytochemistry*, 1978, **17**, 107; *ibid.*, 1977, **16**, 1381; *ibid.*, 1971, **10**, 3057; *ibid.*, 1974, **13**, 1847; *ibid.*, 1975, **14**, 2393; *J. Pharm. Pharmacol.*, 1975, **27S**, 86P; R. B. Herbert, in ref. 4, p. 10; in ref. 6, p. 7; in ref. 7, p. 4; in ref. 9, p. 2.

<sup>14</sup> M. K. Speedie, U. Hornemann, and H. G. Floss, *J. Biol. Chem.*, 1975, **250**, 7819; R. B. Herbert, in ref. 7, p. 16.

<sup>15</sup> E. A. Aboutabl and M. Luckner, *Phytochemistry*, 1975, **14**, 2573; I. Richter and M. Luckner, *ibid.*, 1976, **15**, 67; L. Nover and M. Luckner, *FEBS Lett.*, 1969, **3**, 292; M. Luckner, *Eur. J. Biochem.*, 1967, **2**, 74; M. Luckner, K. Winter, and J. Reisch, *ibid.*, 1969, **7**, 380; see also this Report, p. 27.

<sup>16</sup> R. B. Herbert, in ref. 8, p. 26; in ref. 7, p. 24; in ref. 5, p. 39.

<sup>17</sup> E. Leete, N. Kowanko, R. A. Newmark, L. C. Vining, A. G. McInnes, and J. L. C. Wright, *Tetrahedron Lett.*, 1975, 4103; R. B. Herbert, in ref. 7, p. 9; in ref. 5, p. 11.

<sup>18</sup> W. D. Marshall, T. T. Nguyen, D. B. MacLean, and I. D. Spenser, *Can. J. Chem.*, 1975, **53**, 41; R. B. Herbert, in ref. 7, p. 3; in ref. 1, p. 5; in ref. 4, p. 1; in ref. 3, p. 28.

There are some difficulties associated with a highly attractive model for piperidine alkaloid biosynthesis (this Report, p. 9). There is still debate about the symmetrical or unsymmetrical incorporation of  $^{13}\text{CO}_2$  into nicotine (this Report, p. 14). Curiously, the nature of the intermediates in quinolizidine alkaloid biosynthesis is unknown, although an attractive hypothesis has been proposed that is based on incorporation of  $\Delta^1$ -piperideine (3).<sup>19</sup>

The terpenoid indole alkaloids are a group of plant bases derived by multiple variation on the strictosidine [(79); p. 20] skeleton. Arguably the most important work in the past five years has been done on these alkaloids with enzyme preparations from plant tissue cultures, and the research is of great potential significance for other studies in alkaloid biosynthesis. The results have allowed close definition of the early stages of biosynthesis (this Report, p. 19). Use of crude enzyme preparations in this way has been extended to the study of benzyloisoquinoline biosynthesis, with enzyme-catalysed formation of norlaudanoline-1-carboxylic acid [(57); p. 16]; this compound had earlier been identified<sup>20</sup> as the first of the benzyloisoquinolines (this Report, p. 15). It seems that amino-acids of this general formula (6) are key intermediates in the biosynthesis of all isoquinoline alkaloids.<sup>20,21</sup> Lophocereine (7) is exceptional in that two routes (from leucine and mevalonate) may lead to it, only one of which potentially involves an acid like (6).<sup>22</sup>

Most remarkable for proving that structural relationships are not always what they seem are anatabine [(34); p. 11] and dioscorine (8). Inspection and experience with other piperidine alkaloids leads one to expect a biosynthesis for the piperidine ring [heavy bonding in (8)] from lysine *via*  $\Delta^1$ -piperideine (3).<sup>10</sup> However, in both cases it turns out that this ring derives from nicotinic acid<sup>23</sup> [the exceptional derivation of the piperidine nuclei of coniine and pinidine (9) from acetate has been known for some time<sup>24</sup>].

The structurally unusual base securinine (10) derives in orthodox manner from lysine *via* (3), the origins of the remaining atoms being in tyrosine.<sup>25</sup> So far no intermediates have been identified, and the alkaloid presents an intriguing biogenetic puzzle.

<sup>19</sup> W. M. Golebiewski and I. D. Spenser, *J. Am. Chem. Soc.*, 1976, **98**, 6726; R. B. Herbert, in ref. 8, p. 3. For other references to work with these alkaloids see R. B. Herbert, in ref. 6, p. 6; in ref. 9, p. 2.

<sup>20</sup> M. L. Wilson and C. J. Coscia, *J. Am. Chem. Soc.*, 1975, **97**, 431; A. R. Battersby, R. C. F. Jones, and R. Kazlauskas, *Tetrahedron Lett.*, 1975, 1873; D. S. Bhakuni, A. N. Singh, S. Tewari, and R. S. Kapil, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1662; R. B. Herbert, in ref. 6, p. 17; in ref. 9, p. 8.

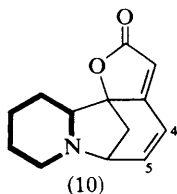
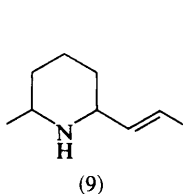
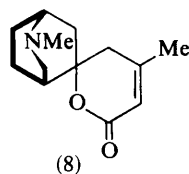
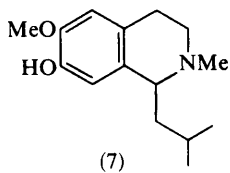
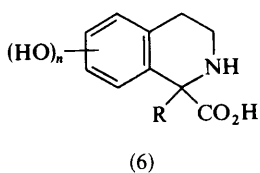
<sup>21</sup> G. J. Kapadia, G. S. Rao, E. Leete, M. B. E. Favez, Y. N. Vaishnav, and H. M. Fales, *J. Am. Chem. Soc.*, 1970, **92**, 6943; J. Staunton, in ref. 2, p. 10; see also this Report, p. 15.

<sup>22</sup> D. G. O'Donovan and E. Barry, *J. Chem. Soc., Perkin Trans. 1*, 1974, 2528; D. G. O'Donovan and H. Horan, *J. Chem. Soc. (C)*, 1968, 2791; H. R. Schütte and G. Seelig, *Justus Liebigs Ann. Chem.*, 1970, **730**, 186; R. B. Herbert, in ref. 1, p. 17; in ref. 6, p. 16.

<sup>23</sup> Dioscorine: see E. Leete, *Phytochemistry*, 1977, **16**, 1705; R. B. Herbert, in ref. 8, p. 1; in ref. 9, p. 1; anatabine: see this Report, p. 11.

<sup>24</sup> E. Leete and J. O. Olsen, *J. Am. Chem. Soc.*, 1972, **94**, 5472; E. Leete and K. N. Juneau, *ibid.*, 1969, **91**, 5614; R. B. Herbert, in ref. 1, p. 1; in ref. 4, p. 10; J. Staunton, in ref. 2, p. 26. For recent work on pinidine, see E. Leete, J. C. Lechleiter, and R. A. Carver, *Tetrahedron Lett.*, 1975, 3779; E. Leete and R. A. Carver, *J. Org. Chem.*, 1975, **40**, 2151; R. B. Herbert, in ref. 7, p. 4.

<sup>25</sup> U. Sankawa, Y. Ebizuka, and K. Yamasaki, *Phytochemistry*, 1977, **16**, 561; R. J. Parry, *Tetrahedron Lett.*, 1974, 307; *J. Chem. Soc., Chem. Commun.*, 1975, 144; W. M. Golebiewski, P. Horwood, and I. D. Spenser, *ibid.*, 1976, 217; R. B. Herbert, in ref. 5, p. 10; in ref. 6, p. 40; in ref. 7, p. 2; in ref. 8, p. 4; this Report, p. 10.



The structurally elaborate phenanthroindolizidine alkaloids of *Tylophora asthmatica*, e.g. tylophorinine (15), have proved to have a biogenesis from (11),<sup>26</sup> which is a common structural element in many pyrrolidine and piperidine alkaloids.<sup>10</sup> A later key intermediate is the diphenol (12), which, by oxidative phenol coupling, affords (13). This dienone then suffers modification to give the *T. asthmatica* bases.<sup>27</sup> Tylophorinine (15) must be formed *via* (14), rearrangement of which involves styryl (as against aryl) migration; a so far unique example among alkaloids formed by oxidative coupling of phenols.

Hasubanonine (18) and protostephanine (17) appear to be benzyloisoquinoline variants, but only after extensive and painstaking research has this been established.<sup>28,29</sup> The key intermediate is the triphenol (16),<sup>29</sup> the crucial (and elusive) feature of which is two hydroxy-groups on ring C; so far, (16) is the only example of a substrate for oxidative coupling of phenols where more than one hydroxy-group must be present on an aromatic ring.

Chelidonine [(66); p. 17] was long suspected as a protoberberine variant. The truth of this has been established by the results of a series of elegant experiments, which also defined the detail of biosynthesis, including the stereochemistry of the proton losses which occur during transformation of protoberberine into chelidonine (this Report, p. 16; see also ref. 30). Corydaline (19) is a methylated protoberberine, and investigation of its biosynthesis suggests an orthodox pathway. The corydaline skeleton appears in modified form in ochotensimine (20).<sup>31</sup>

<sup>26</sup> R. B. Herbert, F. B. Jackson, and I. T. Nicolson, *J. Chem. Soc., Chem. Commun.*, 1976, 865; R. B. Herbert, in ref. 8, p. 6.

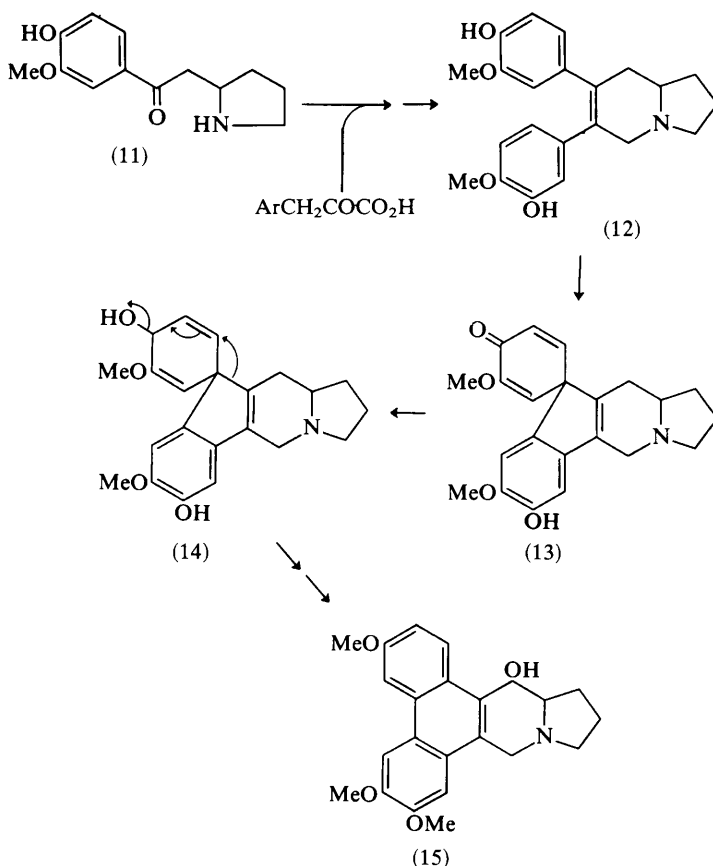
<sup>27</sup> R. B. Herbert and F. B. Jackson, *J. Chem. Soc., Chem. Commun.*, 1977, 955; R. B. Herbert, in ref. 9, p. 5.

<sup>28</sup> A. R. Battersby, R. C. F. Jones, R. Kazlauskas, C. Poupat, C. W. Thornber, S. Ruchirawat, and J. Staunton, *J. Chem. Soc., Chem. Commun.*, 1974, 773; R. B. Herbert, in ref. 6, p. 26.

<sup>29</sup> A. R. Battersby, A. Minta, A. P. Ottridge, and J. Staunton, *Tetrahedron Lett.*, 1977, 1321; R. B. Herbert, in ref. 8, p. 8.

<sup>30</sup> A. Yagi, G. Nonaka, S. Nakayama, and I. Nishioka, *Phytochemistry*, 1977, **16**, 1197; R. B. Herbert, in ref. 9, p. 14.

<sup>31</sup> G. Blaschke, *Arch. Pharm. (Weinheim, Ger.)*, 1968, **301**, 439; *ibid.*, 1970, **303**, 358; H. L. Holland, M. Castillo, D. B. MacLean, and I. D. Spenser, *Can. J. Chem.*, 1974, **52**, 2818; R. B. Herbert, in ref. 1, p. 21; in ref. 6, p. 23.



New investigation of bisbenzylisoquinoline biosynthesis is welcome (see ref. 32; also this Report, p. 16). Although aporphine alkaloids are the simplest developments of the benzylisoquinoline skeleton, their biosynthesis need not, as several examples show,<sup>10,33</sup> be simple. It has, however, been found that the biosynthesis of boldine<sup>34</sup> and isocorydine<sup>35</sup> is straightforward. Further detail has been reported<sup>36</sup> on the biosynthesis of *Erythrina* alkaloids, which were established to be modified benzylisoquinolines some time ago.<sup>37</sup> Further detail on the biosynthesis of morphine (23) and related alkaloids continues to be published.<sup>38</sup> Of particular

<sup>32</sup> R. B. Herbert, in ref. 9, p. 11.

<sup>33</sup> R. B. Herbert, in ref. 5, p. 15; in ref. 4, p. 17; in ref. 1, p. 19; J. Staunton, in ref. 2, p. 12.

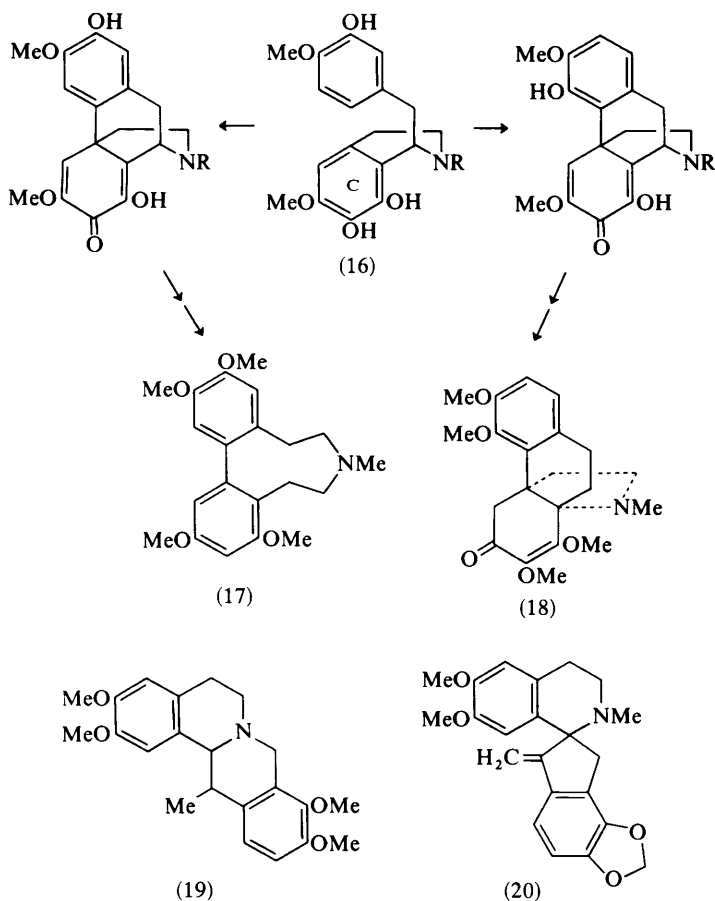
<sup>34</sup> S. Tewari, D. S. Bhakuni, and R. S. Kapil, *J. Chem. Soc., Chem. Commun.*, 1974, 940; R. B. Herbert, in ref. 8, p. 19.

<sup>35</sup> O. Prakash, D. S. Bhakuni, and R. S. Kapil, *J. Chem. Soc., Perkin Trans. 1*, 1978, 622; R. B. Herbert, in ref. 9, p. 14.

<sup>36</sup> D. H. R. Barton, R. D. Bracho, C. J. Potter, and D. A. Widdowson, *J. Chem. Soc., Perkin Trans. 1*, 1974, 2278; D. S. Bhakuni, A. N. Singh, and R. S. Kapil, *J. Chem. Soc., Chem. Commun.*, 1977, 211; D. S. Bhakuni and A. N. Singh, *J. Chem. Soc., Perkin Trans. 1*, 1978, 618; R. B. Herbert, in ref. 6, p. 25; in ref. 8, p. 10; in ref. 9, p. 16.

<sup>37</sup> R. B. Herbert, in ref. 5, p. 24; in ref. 1, p. 22.

<sup>38</sup> R. B. Herbert, in ref. 9, p. 8.



interest is the observation that the demethylation of thebaine (21) to give neopinone (22), which occurs at an intermediate state of biosynthesis, involves retention of oxygen at C-6. This is not expected of normal ether hydrolysis, and an alternative mechanism is shown.<sup>38,39</sup>

The 'homo-*Erythrina*' alkaloid schelhammeridine (24) appears to be derived, as expected, from a phenethylisoquinoline.<sup>40</sup> After some initial doubt the evidence for the biosynthesis of the related base cephalotaxine (25) has been deduced to be consistent with it too being a modified phenethylisoquinoline.<sup>41</sup>

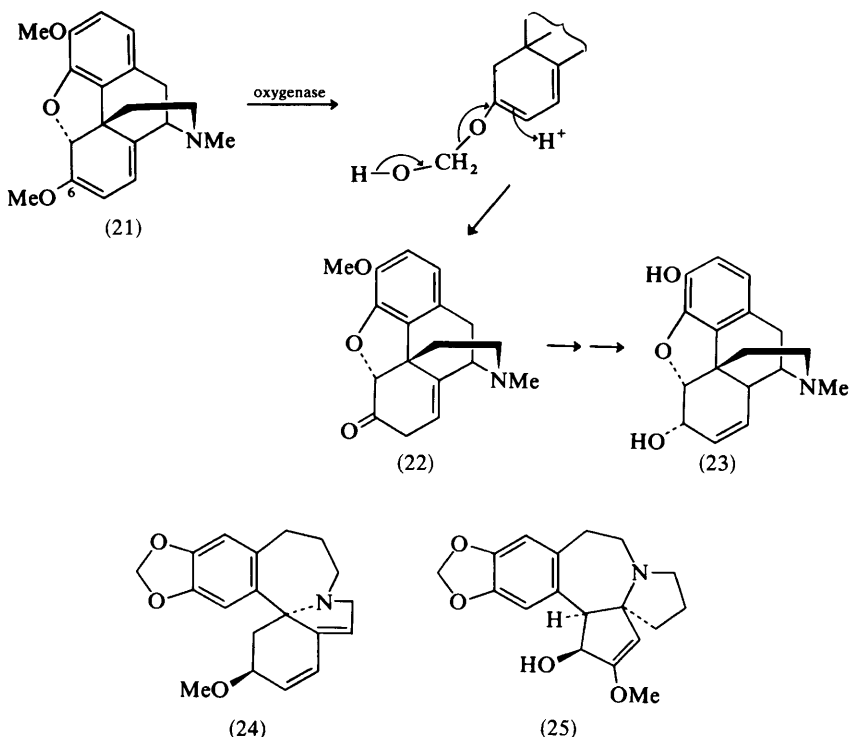
Use of <sup>13</sup>C labels has transformed, especially, the study of polyketide biosynthesis, and this label has found application in the study of the biogenesis of

<sup>39</sup> J. S. Horn, A. G. Paul, and H. Rapoport, *J. Am. Chem. Soc.*, 1978, **100**, 1895.

<sup>40</sup> A. R. Battersby, E. McDonald, J. A. Milner, S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Tetrahedron Lett.*, 1975, 3419; R. B. Herbert, in ref. 7, p. 10.

<sup>41</sup> J. M. Schwab, M. N. T. Chang, and R. J. Parry, *J. Am. Chem. Soc.*, 1977, **99**, 2368; R. B. Herbert, in ref. 8, p. 12.





nitrogenous microbial metabolites, *e.g.* cytochalasins,<sup>42</sup> rifamycins,<sup>43</sup> geldanamycin,<sup>44</sup> prodiginines,<sup>45</sup> and nybomycin.<sup>44</sup> Of particular note is the greater certainty, and more detail generally obtained, with <sup>13</sup>C labelling. (For the biosynthesis of metabolites related to the rifamycins and geldanamycin, namely the mitomycins and streptovaricins, see refs. 46 and 47, respectively.)

With plants, the much lower incorporation generally obtaining has generally precluded the use of stable isotopes. In three studies so far, <sup>13</sup>C labelling has been used where incorporations were favourable: these were camptothecin,<sup>48</sup> colchicine,<sup>49</sup> dioscorine,<sup>23</sup> nicotine (with <sup>13</sup>CO<sub>2</sub>; see this Report, p. 14), and anatabine (this Report, p. 11).

Staple isotopes for biosynthetic studies continue to be <sup>14</sup>C and <sup>3</sup>H, often in combination, to indicate both intact incorporation<sup>26,27,50</sup> and to monitor hydrogen

<sup>42</sup> R. B. Herbert, in ref. 7, p. 29; in ref. 6, p. 44.

<sup>43</sup> R. B. Herbert, in ref. 6, p. 45; see also ref. 9, p. 34, and this Report, p. 29.

<sup>44</sup> R. B. Herbert, in ref. 8, p. 30.

<sup>45</sup> R. B. Herbert, in ref. 6, p. 50; in ref. 9, p. 32; see also ref. 8, p. 36.

<sup>46</sup> R. B. Herbert, in ref. 7, p. 32; in ref. 6, p. 45; in ref. 4, p. 40.

<sup>47</sup> R. B. Herbert, in ref. 7, p. 32; this Report, p. 29.

<sup>48</sup> R. B. Herbert, in ref. 6, p. 36; see also this Report, p. 22.

<sup>49</sup> A. R. Battersby, P. W. Sheldrake, and J. A. Milner, *Tetrahedron Lett.*, 1974, 3315; R. B. Herbert, in ref. 6, p. 28.

<sup>50</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. 23.

loss in the course of biosynthesis, for which there are numerous examples. A combination of these labels in two different precursors has also been used to obtain accurate comparison of the relative efficiencies of incorporation of these precursors.<sup>51,52</sup>

A precursor with  $^{14}\text{C}$  and  $^3\text{H}$  labels is normally made by mixing two singly labelled samples. In some cases it has been observed that subsequent biotransformation leads to an increase in the relative amount of tritium-labelled species. This is explained as the result of preferential metabolism of  $^{14}\text{C}$ -labelled material along other paths.<sup>52,53</sup>

Where incorporations are favourable, deuterium can provide more information than tritium, one example being the biosynthesis of microbial phenazines, where the analysis of deuterium incorporation from  $[2\text{-}^2\text{H}]\text{shikimic acid}$  has allowed clear definition of the way in which shikimic acid is used in the construction of the phenazine ring system.<sup>54</sup>

A number of microbial metabolites whose biosynthesis has been studied are (at least formally) derived from a di- (or tri-)peptide: echinulin and benzodiazepine alkaloids (both referred to already), gliotoxin,<sup>55</sup> mycelianamide,<sup>56</sup> sporidesmin,<sup>57</sup> and the  $\beta$ -lactam antibiotics.<sup>58</sup> In the case of the last mentioned, in spite of extensive work and the accumulation of a wealth of detail on the fates of the individual atoms in the precursor amino-acids, the mechanism of ring formation remains obscure.

A study of the biosynthesis of cyclopiazonic acid<sup>59</sup> is to be noted.

A feature of the biosynthesis of a number of microbial metabolites is the fracture of aromatic rings in the precursor amino-acids: pyrrolnitrin (see this Report, p. 23), anthramycin,<sup>60,61</sup> tomaymycin,<sup>60</sup> and streptonigrin (see this Report, p. 23). This is only observed rarely in the biosynthesis of plant bases, a notable example being the betalains, which are pigments in plants of the order *Centrospermae*.<sup>10,62</sup>

With much of the essential biosynthetic information uncovered, there has been little published work on furoquinoline<sup>63</sup> and Amaryllidaceae<sup>63,64</sup> alkaloids. Although a similarity in structure between mesembrine and Amaryllidaceae alkaloids indicates a similar biogenesis, the evidence is to the contrary. So far, in

<sup>51</sup> E. Leistner, R. N. Gupta, and I. D. Spenser, *J. Am. Chem. Soc.*, 1973, **95**, 4040; R. B. Herbert, in ref. 5, p. 5; N. M. Bale and D. H. G. Crout, *Phytochemistry*, 1975, **14**, 2617.

<sup>52</sup> R. B. Herbert, in ref. 7, p. 1.

<sup>53</sup> A. R. Battersby, R. J. Francis, M. Hirst, E. A. Ruveda, and J. Staunton, *J. Chem. Soc., Perkin Trans. I*, 1975, 1140; A. R. Battersby, J. Staunton, H. R. Wiltshire, R. J. Francis, and R. Southgate, *ibid.*, p. 1147.

<sup>54</sup> R. B. Herbert, F. G. Holliman, and J. B. Sheridan, *Tetrahedron Lett.*, 1976, 639; R. B. Herbert, in ref. 7, p. 27; see also this Report, p. 28; other references are R. B. Herbert, in ref. 8, p. 33; in ref. 9, p. 29.

<sup>55</sup> R. B. Herbert, in ref. 6, p. 37; in ref. 7, p. 24; this Report, p. 27.

<sup>56</sup> R. B. Herbert, in ref. 6, p. 37; in ref. 8, p. 35.

<sup>57</sup> R. B. Herbert, in ref. 6, p. 30.

<sup>58</sup> R. B. Herbert, in ref. 6, p. 49; in ref. 7, p. 30; in ref. 8, p. 35; in ref. 9, p. 33; this Report, p. 29.

<sup>59</sup> R. B. Herbert, in ref. 6, p. 30; in ref. 7, p. 18; in ref. 8, p. 27.

<sup>60</sup> R. B. Herbert, in ref. 7, p. 25; in ref. 5, p. 40.

<sup>61</sup> R. B. Herbert, in ref. 8, p. 24.

<sup>62</sup> R. B. Herbert, in ref. 6, p. 41; and refs. cited therein.

<sup>63</sup> R. B. Herbert, in ref. 6, p. 39.

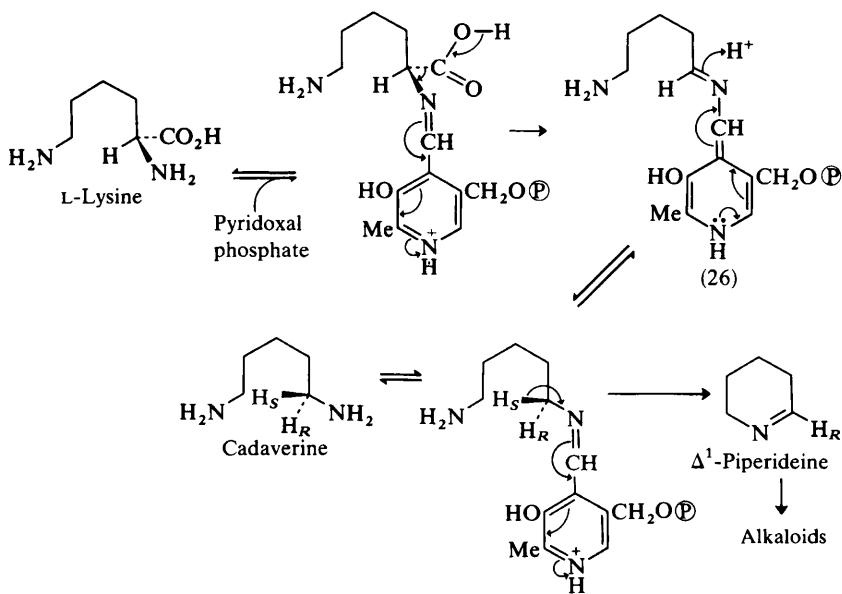
<sup>64</sup> R. B. Herbert, in ref. 8, p. 19.

spite of extensive research, the nature of the key intermediates of mesembrine alkaloid biosynthesis remains obscure.<sup>65</sup>

Study of the biosynthesis of ergot<sup>66</sup> and steroidal<sup>67</sup> alkaloids continues. The biosynthesis of the necic acid components of the pyrrolizidine alkaloids has been elucidated,<sup>68</sup> and attention has turned to the biosynthesis of the pyrrolizidine nucleus, which is largely unknown (see this Report, p. 13).

## 2 Piperidine, Pyridine, and Pyrrolizidine Alkaloids

L-Lysine and cadaverine serve as precursors for the majority of piperidine alkaloids.<sup>10</sup> The experimental results have been interpreted in terms of an attractive series of pyridoxal-linked intermediates derivable independently from both precursors; see Scheme 1. The transformation of cadaverine into alkaloids involves stereospecific removal of one of the protons attached to C-1 (*pro-S* hydrogen) and probably involves a diamine oxidase; *cf.* refs. 5 and 6. Examination of the diamine-oxidase-catalysed oxidation of cadaverine, with enzyme from hog kidney, and analysis by an excellent <sup>2</sup>H n.m.r. method, has shown that this reaction also involves removal of the 1-*pro-S* proton from the diamine;<sup>69</sup> pea seedling diamine oxidase has been found to effect the conversion of benzylamine into benzaldehyde with similar stereochemistry.<sup>70</sup>



Scheme 1

<sup>65</sup> R. B. Herbert, in ref. 7, p. 23; in ref. 8, p. 21; in ref. 9, p. 16.

<sup>66</sup> R. B. Herbert, in ref. 6, p. 31; in ref. 7, p. 20; in ref. 8, p. 27; in ref. 9, p. 26; see also this Report, p. 26.

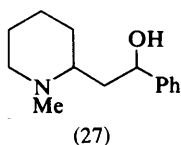
<sup>67</sup> R. B. Herbert, in ref. 6, p. 52; in ref. 7, p. 32; in ref. 8, p. 28; in ref. 9, p. 27.

<sup>68</sup> R. B. Herbert, in ref. 1, p. 8; in ref. 3, p. 40; in ref. 6, p. 11; in ref. 9, p. 4.

<sup>69</sup> J. C. Richards and I. D. Spenser, *J. Am. Chem. Soc.*, 1978, **100**, 7402.

<sup>70</sup> A. R. Battersby, J. Staunton, and M. C. Summers, *J. Chem. Soc., Perkin Trans. 1*, 1976, 1052.

The conversion of lysine into piperidine alkaloids involves retention of hydrogen isotope at C-2.<sup>10</sup> The sequence is suggested to be that shown in Scheme 1, and catalysis of the reaction may be attributed to L-lysine decarboxylase. This enzyme, from the micro-organism *Bacillus cadaveris*, has been found to carry out the conversion of L-lysine into cadaverine with retention of configuration. Decarboxylation of L-[2-<sup>3</sup>H]lysine by this enzyme then affords [1S-<sup>3</sup>H]-cadaverine. When this material is converted into alkaloids, e.g. *N*-methyl-pelletierine (4; R = Me), the tritium attached to what becomes C-2 is lost; cf. refs. 5 and 6. On the other hand, conversion of lysine into sedamine (27) in *Sedum acre* results in retention of the tritium originally present at C-2. The simplest explanation is that protonation of (26) in the micro-organism and plant proceeds with opposite stereochemistry. This is at variance, however, with current ideas on the stereochemistry of reactions that are catalysed by pyridoxal phosphate.<sup>71</sup>



This is disturbing, and so the stereochemistry of the overall reaction L-lysine → cadaverine →  $\Delta^1$ -piperideine has been checked,<sup>72</sup> using L-lysine decarboxylase from *Escherichia coli* and *B. cadaveris*, pea seedling diamine oxidase, and *S. acre* plants, with confirmation of the above deductions; the lysine decarboxylase from the two sources effected decarboxylation with the same stereochemical outcome. Solution of the problem must now await further experiments with the enzymes involved in alkaloid biosynthesis.

**Securinine.**—The C<sub>5</sub>N unit in securinine (10), shown with thickened bonds, is derived from lysine *via*  $\Delta^1$ -piperideine (3); cf. ref. 7. The eight-carbon unit (normal bonding) of (10) derives from tyrosine. Some of the results, published in preliminary form, are now available in full.<sup>73</sup> The mechanism whereby (3) combines with a tyrosine derivative remains an intriguing mystery. *p*-Hydroxyphenylpyruvic acid and *p*-hydroxyphenylacetaldehyde (30)<sup>73</sup> are plausibly involved. A flanking approach in feeding experiments using the more stable 4'-hydroxy-2-phenylethanol and *p*-hydroxyphenylacetic acid, potentially convertible into *p*-hydroxyphenylacetaldehyde, gave, however, negative results.<sup>73</sup> It has been shown that securinine (10) is the biosynthetic precursor for its 4,5-dihydro-derivative *in vivo*.<sup>73</sup>

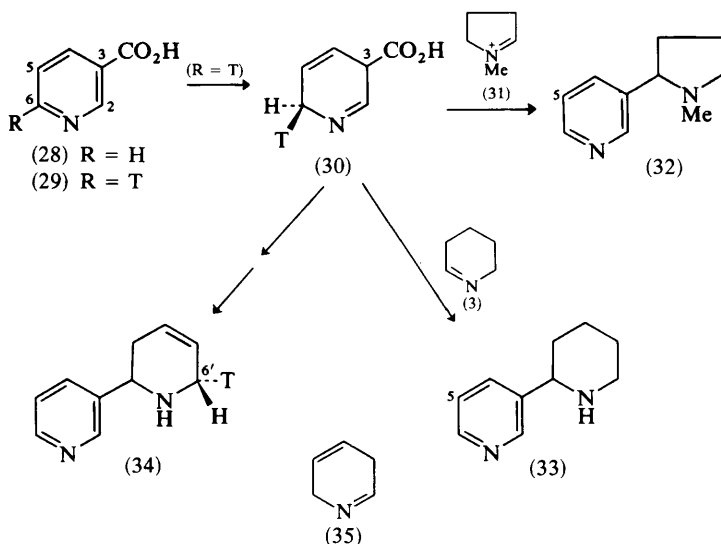
**Anabasine.**—5-Fluoronicotinic acid [as (28)] is one of several unnatural substrates that have been metabolized by plants to alkaloid analogues; cf. refs. 3 and 5. The major alkaloid of *Nicotiana glauca* is anabasine (33); it is essentially racemic. 5-Fluoronicotinic acid has been found recently to be converted into racemic 5-fluoroanabasine [as (33)] in this plant.<sup>74</sup>

<sup>71</sup> H. C. Dunathan and J. G. Voet, *Proc. Natl. Acad. Sci. USA*, 1974, **71**, 3888.

<sup>72</sup> H. J. Gerdes and E. Leistner, *Phytochemistry*, 1979, **18**, 771.

<sup>73</sup> R. J. Parry, *Bio-org. Chem.*, 1978, **7**, 277.

<sup>74</sup> E. Leete, *J. Org. Chem.*, 1979, **44**, 165.



**Anatabine.**—It is known that anabesine (33) is derived from one molecule each of lysine and nicotinic acid (28).<sup>10</sup> In contrast, the co-occurring alkaloid anatabine (34) is derived exclusively from nicotinic acid, both heterocyclic rings being equally labelled by labelled precursor. Furthermore, the labelling results show that the nicotinic-acid fragments couple by the linking of C-3 of one unit to C-2 of the other. In the formation of anabesine (33) and nicotine (32), linkage is to C-3 of the nicotinic-acid fragment, which again gives the pyridine ring in these alkaloids. For these alkaloids, tritium from C-6 of nicotinic acid is lost in the course of biosynthesis; *cf.* refs. 4, 6, and 8.<sup>75</sup> The biosynthesis of the pyridine ring of anatabine is similar in that tritium is again lost from C-6 of nicotinic acid.<sup>75</sup> On the other hand, tritium from C-6 of nicotinic acid is retained in the tetrahydropyridine ring of anatabine, and is located at C-6', as expected; the stereochemistry is *S* [see (34)].

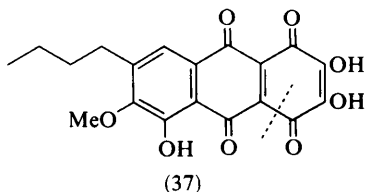
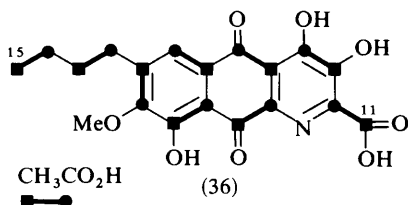
The biosynthesis of nicotine and anabesine can reasonably proceed *via* (30), which will be electrophilic towards (31) and (3), which are intermediates for the other parts of the alkaloids,<sup>10</sup> subsequent aromatization leading to loss of tritium. Coupling of two molecules of (30), decarboxylation, and aromatization would give anatabine, with 50% retention of tritium observed; the stereochemistry of (30) follows from that determined in anatabine (34). [Direct coupling of two molecules of (30) makes use of the higher electrophilicity associated with this molecule (*cf.* fatty acid biosynthesis), and so is preferred to the suggested coupling with two molecules of (35).]

The formation of  $\alpha\beta$ -dipyridyl in *Nicotiana* species occurs from anatabine (34) during drying of the plants prior to isolation of alkaloids.<sup>76</sup>

<sup>75</sup> E. Leete, *J. Chem. Soc., Chem. Commun.*, 1978, 610.

<sup>76</sup> E. Leete, K. C. Ranbom, and R. M. Riddle, *Phytochemistry*, 1979, **18**, 75.

**Phomazarin.**—The structure of phomazarin, an orange pigment produced by *Pyrenochaeta terrestris*, has been defined as (36).<sup>77</sup> It is manifestly polyketide in structure, and the results of experiments with [1-<sup>14</sup>C]- and [2-<sup>14</sup>C]-acetate are in support. Precise definition of the nature of the polyketide precursor follows from experiments with [<sup>13</sup>C]acetate and [<sup>13</sup>C]- and [<sup>14</sup>C]-malonate;<sup>78</sup> [1-<sup>13</sup>C]- and [2-<sup>13</sup>C]-acetate showed alternate and complementary labelling of the carbon atoms of phomazarin. The coupling observed in the n.m.r. spectrum of metabolite derived from [<sup>13</sup>C<sub>2</sub>]acetate established that assembly of phomazarin was from nine intact acetate units, as shown in (36). Observation of a lower level of radioactivity at C-15, but not C-11, relative to other labelled positions in material derived from [2-<sup>13</sup>C]malonate (similar results with <sup>14</sup>C-labelled precursor) indicated that C-15 was the 'starter' acetate unit, and further therefore that only one polyketide chain was involved (C-11 was a potential site for starter acetate in a two-chain precursor). In the course of biosynthesis, this chain must be broken to allow intercalation of the nitrogen atom present in (36), and it has been suggested that this occurs on the bisquinone (37).<sup>78</sup>



**Tropane Alkaloids.**—[3-<sup>14</sup>C]Acetoacetate has been shown<sup>79</sup> to be a precursor for hygrine (38) (in *Nicandra physaloides*), the activity being localized at C-2'. Unfortunately, because of the labelling site in the precursor, it is uncertain whether the acetoacetate was incorporated intact or only after prior degradation to acetate (no comparative levels of incorporation of acetoacetate and acetate were obtained either).

It has been shown recently that (+)-hygrine was much preferred over its enantiomer, in *Datura innoxia*, for the elaboration of tropane bases, but only slightly preferred in the formation of cuscohygrine; cf. ref. 9. On the other hand, in *Physalis alkekengi*, *Atropa belladonna*, and *Hyoscyamus niger*, no stereoselectivity was observed in alkaloid formation.<sup>80</sup>

The possible role of cytochrome *P*450 as an enzyme that can hydroxylate tropane alkaloids has been examined *in vitro* by use of a rat liver microsomal preparation.<sup>81</sup> 3 $\alpha$ -Tigloyloxytropine (40) was converted into meteloidine (41). The reaction was dependent on NADPH and was inhibited by carbon monoxide, thus suggesting that cytochrome *P*450 was the enzyme responsible.

<sup>77</sup> A. J. Birch, D. N. Butler, R. Effenberger, R. W. Rickards, and T. J. Simpson, *J. Chem. Soc., Perkin Trans. 1*, 1979, 807.

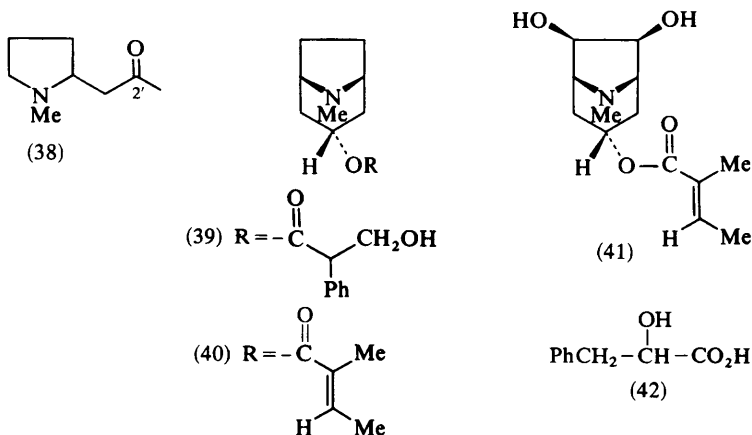
<sup>78</sup> A. J. Birch and T. J. Simpson, *J. Chem. Soc., Perkin Trans. 1*, 1979, 816.

<sup>79</sup> B. A. McGaw and J. G. Woolley, *J. Pharm. Pharmacol.*, 1978, **30**, 83P.

<sup>80</sup> B. A. McGaw and J. G. Woolley, *Phytochemistry*, 1979, **18**, 189.

<sup>81</sup> E. W. T. Major, I. Davies, and J. G. Woolley, *J. Pharm. Pharmacol.*, 1978, **30**, 81P.

The tropic acid moiety (1) found in some tropane alkaloids, *e.g.* (39), is known to be derived from phenylalanine, and the necessary skeletal rearrangement involves intramolecular shift of the carboxy-group of the amino-acid; *cf.* ref. 7. Competitive feeding experiments with phenylpyruvic acid, phenyl-lactic acid (42), and phenylalanine in *Datura stramonium* plants has given results which indicate that phenyl-lactic acid is a later intermediate in the formation of tropic acid than phenylalanine.<sup>82</sup>



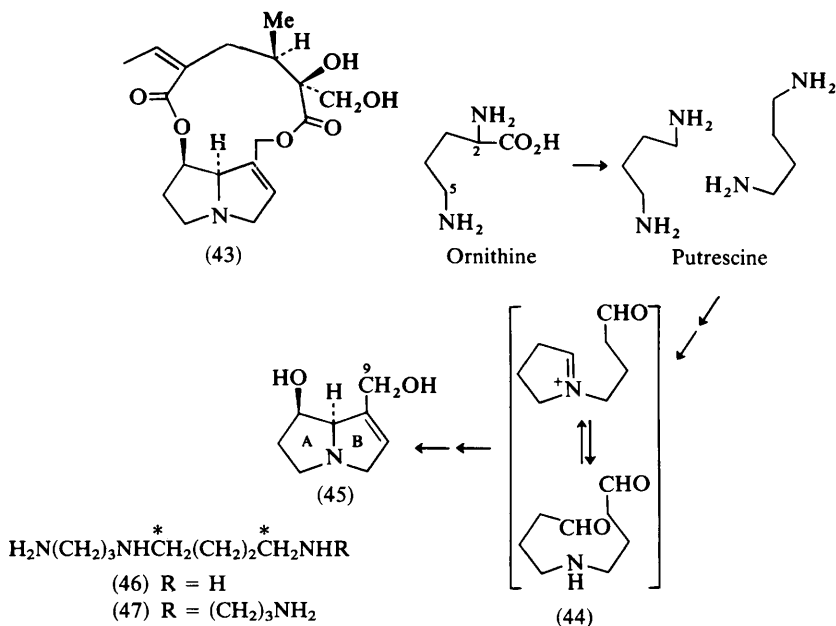
**Pyrrolizidine Alkaloids.**—Welcome new work has been published<sup>83</sup> on the origins of the pyrrolizidine ring system [as (45)], seen in alkaloids such as retrorsine (43). It was known that retronecine (45) is labelled at C-9 with one quarter of the activity from [1,4-<sup>14</sup>C<sub>2</sub>]putrescine, [2-<sup>14</sup>C]ornithine, and [5-<sup>14</sup>C]ornithine. The observation with the latter two precursors indicates that incorporation of ornithine proceeds by way of a symmetrical intermediate, at least for ring B. The new results<sup>83</sup> confirm this conclusion, and establish that ornithine is built into ring A also *via* a symmetrical intermediate. Putrescine was a much better precursor for retrorsine (43) than ornithine (measured in each case against arginine that bore a different isotopic label, fed at the same time), and a similar distribution of activity in the retronecine (45) was observed. This, and the symmetrization of the ornithine label, indicates strongly that retronecine (45) is formed from two molecules of ornithine *via* putrescine.

Incorporations, similar to that for putrescine, were observed<sup>83</sup> for spermine (46) and spermidine (47) (also measured against arginine; <sup>14</sup>C-labels on asterisked carbons), and there was a similar distribution of the label. These amines can, like putrescine, then be converted into pyrrolizidine alkaloids *via* the hypothetical (44); both polyamines are known to be degraded to pyrrolines, resembling (44), plus 1,3-diaminopropane on oxidation with plant polyamine oxidases.

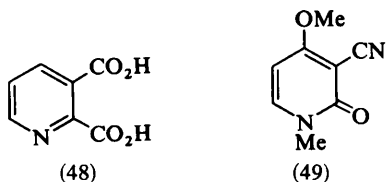
It has also been found<sup>83</sup> that proline, 4-aminobutanoic acid, and glutamic acid were poor precursors for retrorsine (43), and label was scattered over both retronecine and the necic acid fragment.

<sup>82</sup> M. Ansarin and J. G. Woolley, *J. Pharm. Pharmacol.*, 1978, **30**, 82P.

<sup>83</sup> D. J. Robins and J. R. Sweeney, *J. Chem. Soc., Chem. Commun.*, 1979, 120.



**Ricinine.**—Ricinine (49), the alkaloid of castor bean plants, is derived from nicotinic acid (28) and quinolinic acid (48), and its formation is intimately associated with the pyridine nucleotide cycle; *cf.* ref. 6. Quinolinic acid is built from a  $\text{C}_3$  fragment that is formed from glycerol *via* glyceraldehyde and a  $\text{C}_4$  unit that is related to succinic or aspartic acids. A recent investigation has confirmed this pathway for ricinine (49) and indicated that dihydroxyacetone phosphate lies between glycerol and glyceraldehyde (loss of tritium from C-2 of labelled glycerol).<sup>84</sup>



**Nicotine.**—Some uncertainty, associated with an n.m.r. method (*cf.* ref. 8) of analysis on nicotine (32) derived from  $^{13}\text{CO}_2$ , has been resolved in a recent paper.<sup>85</sup> It appears, in agreement with the degradative evidence, that labelling of the pyrrolidine ring of (32) by  $\text{CO}_2$  is symmetrical overall. Not inconsistent with this, unsymmetrical labelling within individual molecules was observed. This may be taken as a reflection of the fact that assembly of the five carbon atoms of the eventual pyrrolidine ring occurs from different sources.

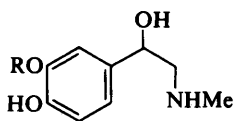
<sup>84</sup> T. Robinson, *Phytochemistry*, 1978, **17**, 1903.

<sup>85</sup> M. Nakane and C. R. Hutchinson, *J. Org. Chem.*, 1978, **43**, 3922.



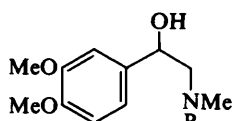
### 3 Phenethylamine and Isoquinoline Alkaloids

**Normacromerine.**—Normacromerine (52) is closely related to simple phenethylamines,<sup>10</sup> and is formed from tyrosine and tyramine *via* epinephrine (50) in the cactus *Coryphantha macomeris*; *cf.* ref. 9. Metanephrine (51), a natural constituent of the cactus, has been shown to be an efficient and specific precursor for normacromerine (52).<sup>86</sup> The previously observed slow conversion of (52) into macromerine (53) has again been noted.<sup>86</sup>



(50) R = H

(51) R = Me



(52) R = H

(53) R = Me

**Peyote Alkaloids.**—An *O*-methyltransferase has been isolated from the peyote cactus. Its ability to catalyse the methylation of various phenolic phenethylamines and isoquinolines, and the site of methylation, has indicated possible biosynthetic relationships within the peyote cactus;<sup>87</sup> *cf.* ref. 3.

**Papaver Alkaloids.**—Biosynthesis of benzyloisoquinoline alkaloids involves the amino-acid dopa, which is in part implicated through decarboxylation to dopamine.<sup>10</sup> The presence of L-dopa decarboxylase in *Papaver orientale* latex has recently been demonstrated.<sup>88</sup>

An early key intermediate in benzyloisoquinoline biosynthesis is (57), which by decarboxylation affords (59); this in turn leads to (61) and on to alkaloids<sup>10,20</sup> (Scheme 2). Confirmation of this pathway has come from a study using cell-free preparations of *P. somniferum* stems and seed capsules.<sup>89</sup> It was found that this preparation catalysed the formation of (57), (59), and (61) from dopamine (54) plus 3,4-dihydroxyphenylpyruvic acid (55); without the addition of *S*-adenosyl-methionine, NADPH, and pyridoxal phosphate, the reaction stopped at (57). The formation of the alkaloids reticuline, thebaine, codeine, and morphine, produced by whole plants, could not be detected with this cell-free system. The results confirm not only the intermediacy of (57) and (59) in benzyloisoquinoline biosynthesis, but also the involvement of (54) and (55).

**Coclaurine.**—Coclaurine (63) is an intermediate of some significance in the biosynthesis of benzyloisoquinoline alkaloids, *e.g.* bisbenzyloisoquinolines (see below). Its biosynthesis, in *Annona reticulata*, has been investigated<sup>90</sup> and found to follow an orthodox pathway,<sup>10</sup> from two molecules of tyrosine. Radioactive tyramine, dopa, and dopamine (54) labelled the phenethylamine portion of (63)

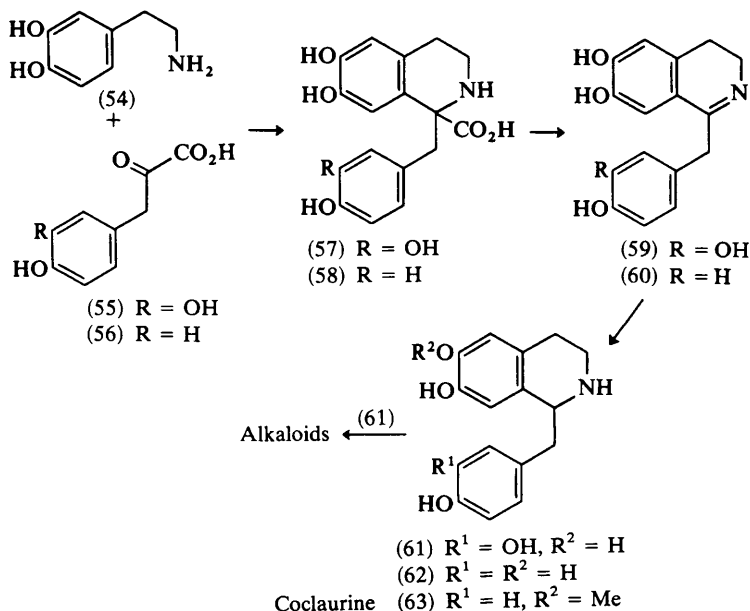
<sup>86</sup> W. J. Keller, *J. Pharm. Sci.*, 1979, **68**, 85.

<sup>87</sup> G. P. Basmadjian, S. F. Hussain, and A. G. Paul, *Lloydia*, 1978, **41**, 375.

<sup>88</sup> M. F. Roberts and M. D. Antoun, *Phytochemistry*, 1978, **17**, 1083.

<sup>89</sup> A. I. Scott, S.-L. Lee, and T. Hirata, *Heterocycles*, 1978, **11**, 159.

<sup>90</sup> O. Prakash, D. S. Bhakuni, and R. S. Kapil, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1515.



Scheme 2

whereas 4-hydroxyphenylpyruvic acid (56) was, like tyrosine, incorporated into both halves. Further orthodoxy is seen in the incorporation of (58) (shown to be specific), (60), and (62) (*cf.* refs. 10 and 20, and Scheme 2).

**Chelidonine.**—Chelidonine (66) has been proved to be a modified benzylisoquinoline arising along a pathway from (*S*)-reticuline, through (*S*)-scoulerine, (*S*)-stylopine (64), and protopine (65) (detailed pathways are given in ref. 7, p. 12, and ref. 8, p. 14). The steps which lie beyond stylopine (64) manifestly involve fracture of the C-14—N and C-6—N bonds in (64). It has been shown that the *pro-S* proton at C-13, as well as the one at C-14, is lost on formation of chelidonine (those at C-5 and C-8 are retained). The most recent results are that in the scission of the C-6—N bond it is again the *pro-S* proton which is lost.<sup>91</sup> It is interesting to note that all three protons are lost from the *si*-face of the molecule.

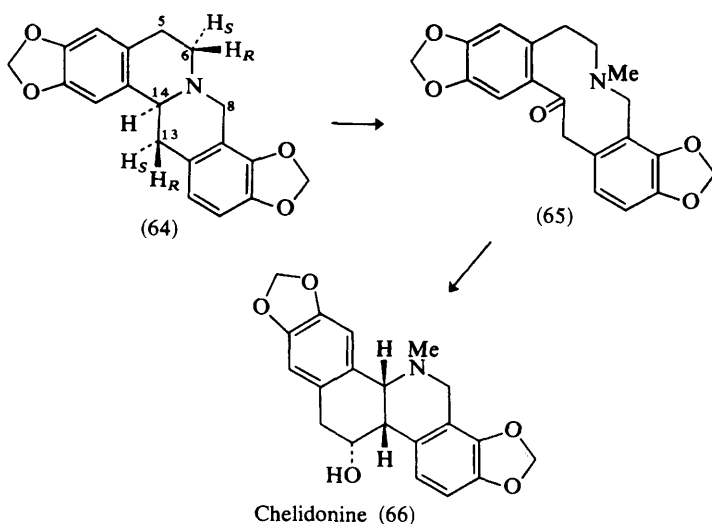
**Bisbenzylisoquinoline Alkaloids.**—The biosynthesis of several bisbenzylisoquinolines has now been investigated. All have been found to be based on coclaurine (63).<sup>92,93</sup> Investigation of the biosynthesis of oxyacanthine (69), in *Cocculus laurifolius*, has given results which show that this alkaloid too arises from coclaurine.<sup>94</sup> Norcoclaurine (62), coclaurine (63), and *N*-methylcoclaurine were

<sup>91</sup> A. R. Battersby, J. Staunton, M. C. Summers, and R. Southgate, *J. Chem. Soc., Perkin Trans. 1*, 1979, 451.

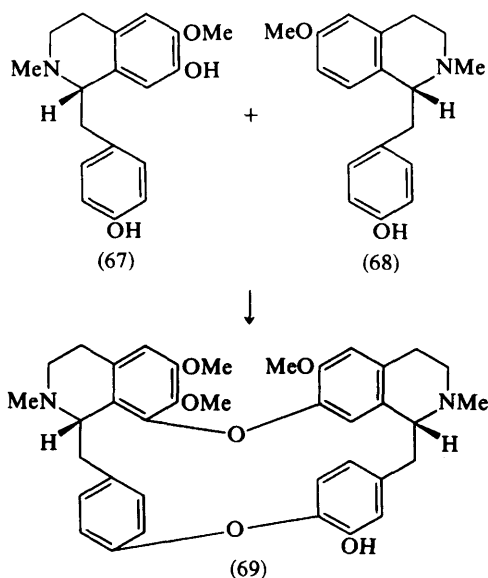
<sup>92</sup> D. H. R. Barton, G. W. Kirby, and A. Wiechers, *J. Chem. Soc. (C)*, 1966, 2313.

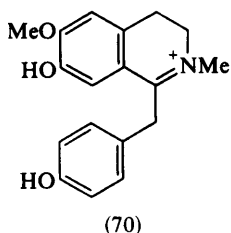
<sup>93</sup> D. S. Bhakuni, A. N. Singh, S. Jain, and R. S. Kapil, *J. Chem. Soc., Chem. Commun.*, 1978, 226; D. S. Bhakuni, V. M. Labroo, A. N. Singh, and R. S. Kapil, *J. Chem. Soc., Perkin Trans. 1*, 1978, 121; D. S. Bhakuni, S. Jain, and A. N. Singh, *ibid.*, p. 380.

<sup>94</sup> D. S. Bhakuni, A. N. Singh, and S. Jain, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1318.



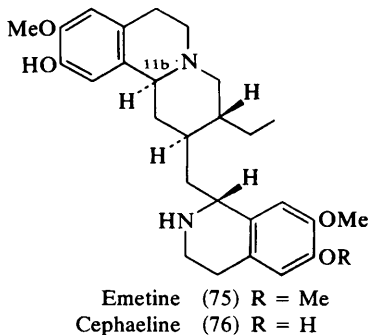
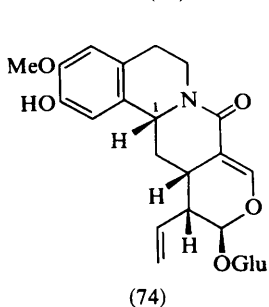
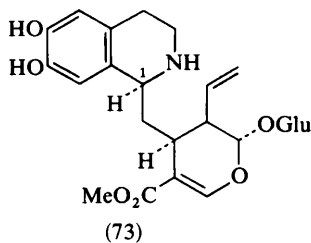
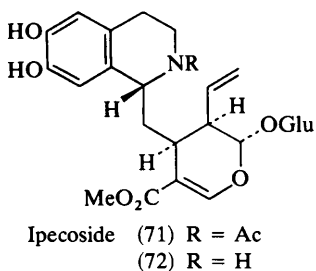
all efficiently incorporated; as expected, *NOO*-trimethylcoclaurine was not utilized for biosynthesis. It was shown further that the incorporation of ( $\pm$ )-*N*-methylcoclaurine was equally into both halves of (69), and without loss of hydrogen label from C-1. Results obtained with chiral samples of *N*-methylcoclaurine are that (*R*)-*N*-methylcoclaurine (68) is built into the right-hand half of (69) only; *i.e.*, the half with the same stereochemistry. Complementary results were obtained with (*S*)-*N*-methylcoclaurine (67). It afforded only the left-hand half, which has (*S*) stereochemistry. It is clear from these results that





stereoisomers of *N*-methylcoclaurine are not interconvertible [*via* (70)] prior to utilization for alkaloid biosynthesis, so the efficient incorporation of (70) that is observed is not by a normal pathway, in agreement with results for other bisbenzylisoquinoline alkaloids.<sup>93</sup>

**Ipecac Alkaloids.**—The stereochemistry of ipecoside (71) is known by *X*-ray analysis, and this has been confirmed.<sup>95</sup> Feeding experiments in *Cephaelis ipecacuanha* have given results which demonstrate that it is not desacetylipecoside (72), as previously supposed (*cf.* ref. 2), but desacetylipecoside (73), with the same stereochemistry at C-1 (= C-11b) as cephaeline (76) and emetine (75), which is the true precursor for these alkaloids.<sup>95,96</sup> Similar results were obtained for cephaeline (76) in *Alangium lamarckii*.<sup>95</sup> On the other hand, desacetylipecoside (72), and not (73), is the precursor for ipecoside (71) (in *C. ipecacu-*



<sup>95</sup> N. Nagakura, G. Höfle, and M. H. Zenk, *J. Chem. Soc., Chem. Commun.*, 1978, 896; N. Nagakura, G. Höfle, D. Coggiola, and M. H. Zenk, *Planta Med.*, 1978, **34**, 381.

<sup>96</sup> A. R. Battersby, N. G. Lewis, and J. M. Tippet, *Tetrahedron Lett.*, 1978, 4849.

*anha*)<sup>95,96</sup> and for alangiside (74) (in *A. lamarckii*),<sup>95</sup> now seen as biosynthetic dead ends. Conversion of either of these precursors into the corresponding alkaloids was with retention of the proton at C-1.<sup>95</sup> Utilization of both epimers in biosynthesis contrasts with the formation of terpenoid indole alkaloids where only one epimer [strictosidine (79), p. 20] is involved in the biosynthesis of alkaloids with both 3 $\alpha$ - and 3 $\beta$ -configurations; cf. ref. 9 [C-3 is equivalent to C-1 in (73)]. The overall picture is consistent, however, for the formation of 3 $\beta$  indole alkaloids, with obvious inversion of configuration, results in the loss of hydrogen isotope from C-3.

#### 4 Alkaloids Derived from Tryptophan

**Terpenoid Indole Alkaloids.**—It has been confirmed recently for ajmalicine (84), vindoline (89), and catharanthine (90), in *Catharanthus roseus* (*Vinca rosea*),<sup>96</sup> that strictosidine (79), and not vincoside (86), is the key intermediate in terpenoid alkaloid biosynthesis (cf. ref. 9).

Cathenamine (82) has been identified as an intermediate after strictosidine (79). The immonium salt (80) lies logically between (79) and (82); see Scheme 3. Evidence in support has been obtained by isolating sitsikirine (91) and isositsikirine (92) as new and exclusive products from a *C. roseus* enzyme preparation incubated with strictosidine (79) and potassium borohydride.<sup>97</sup> (It would be interesting to repeat the experiment with borodeuteride and to determine the sites of labelling.)

The cell-free synthesis of strictosidine (79) and cathenamine (82) has been further explored, and the conditions under which these key compounds are formed have been optimized.<sup>98</sup> Strains from *C. roseus* suspension cultures that were resistant to inhibition of their growth by various tryptophan analogues have been selected.<sup>99</sup> The free tryptophan level in cells of these strains could be 30–40 times higher than in normal cells. Tryptophan at this level did not induce tryptophan decarboxylase, nor the production of alkaloids. It is to be noted, however, that stimulation of alkaloid production by tryptophan and tryptamine<sup>100</sup> in cultures of normal cells has been reported. In the case of tryptamine the two most prominent metabolites were *N*-acetyltryptamine and *NN*-dimethyltryptamine.

5 $\alpha$ -Carboxystrictosidine (88) is a naturally occurring compound. Neither it, nor its C-3 epimer (87), has been found to be a precursor for akuammidine (93), sarpagine (94), ajmaline (95), tetraphyllicine (96), quebrachidine (97), or gelsemine (98),<sup>101</sup> thus reinforcing the already deduced key role of strictosidine (79) in terpenoid indole biosynthesis. 5 $\alpha$ -Carboxystrictosidine (88), on the other hand, is reasonably an intermediate in the formation of alkaloids such as adirubine (99).

It has been found that enzyme systems from *C. roseus* deal inefficiently with geissoschizine (83)<sup>102,103</sup> (cf. ref. 8, p. 27), hitherto believed to be a key

<sup>97</sup> J. Stöckigt, M. Rueffer, M. H. Zenk, and G.-A. Hoyer, *Planta Med.*, 1978, **33**, 188.

<sup>98</sup> J. Stöckigt, *Phytochemistry*, 1979, **18**, 965.

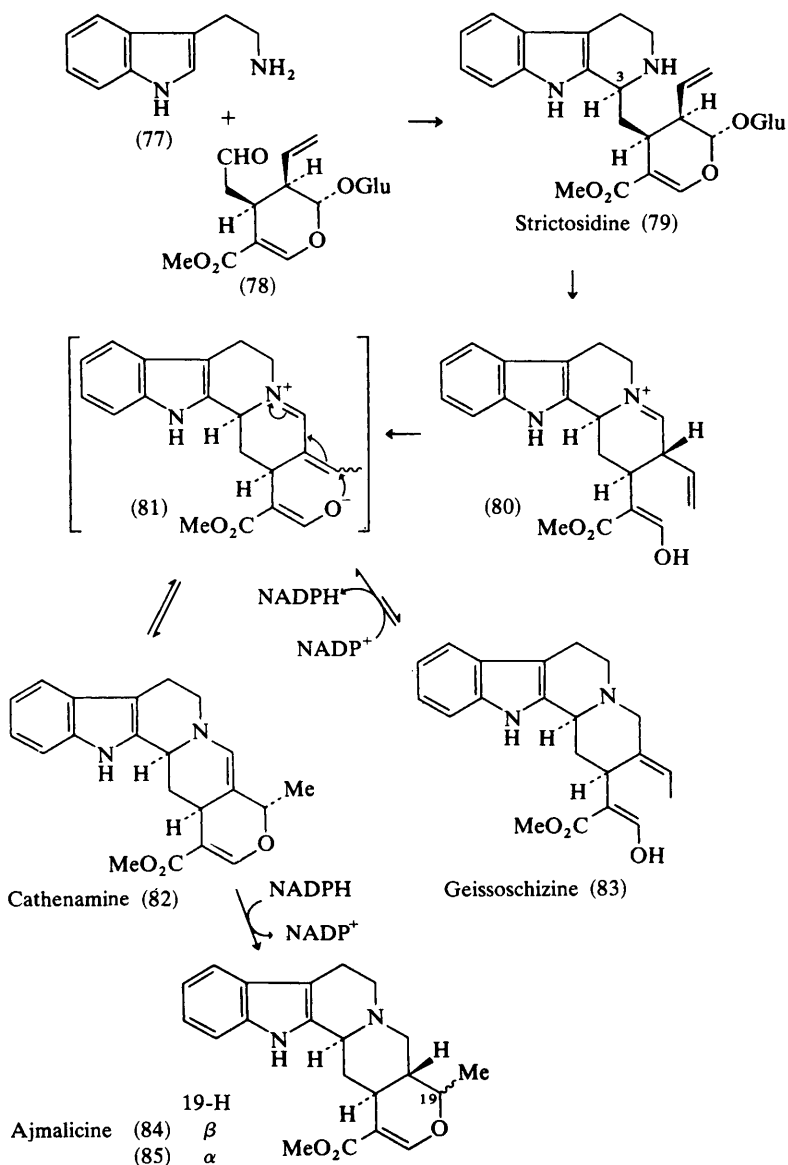
<sup>99</sup> A. I. Scott, H. Mizukami, and S.-L. Lee, *Phytochemistry*, 1979, **18**, 795.

<sup>100</sup> R. J. Krueger and D. P. Carew, *Lloydia*, 1978, **41**, 327.

<sup>101</sup> J. Stöckigt, *Tetrahedron Lett.*, 1979, 2615.

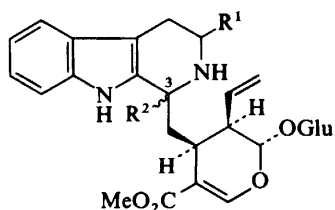
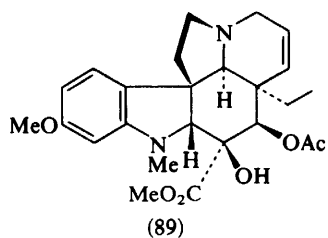
<sup>102</sup> S. L. Lee, T. Hirata, and A. I. Scott, *Tetrahedron Lett.*, 1979, 691.

<sup>103</sup> J. Stöckigt, *J. Chem. Soc., Chem. Commun.*, 1978, 1097.

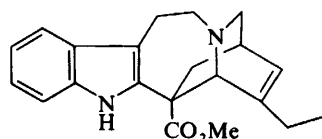


Scheme 3

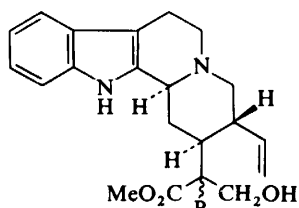
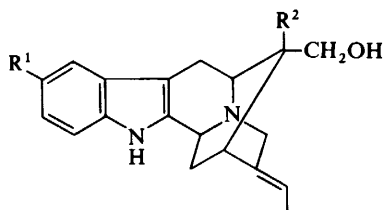
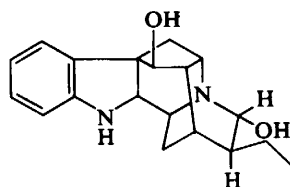
biosynthetic intermediate. Much more efficient conversions of secologanin plus tryptamine into ajmalicine (84) were recorded. The enzymic conversion of geissoschizine (83) into ajmalicine (84) and 19-*epi*-ajmalicine (85) was found to be at least partly independent of the synthesis of these two alkaloids from (77) and (78).<sup>103</sup> The former conversion depended on the presence of NADP<sup>+</sup> as well as

(86)  $R^1 = H, R^2 = \beta-H$ (87)  $R^1 = CO_2H, R^2 = \beta-H$ (88)  $R^1 = CO_2H, R^2 = \alpha-H$ 

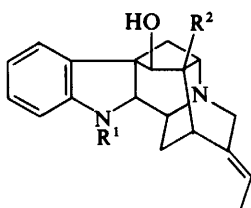
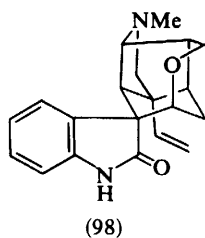
(89)



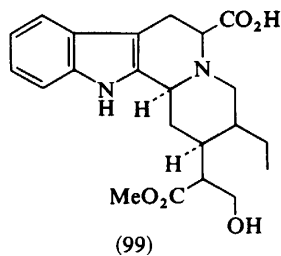
(90)

(91)  $R = \beta-H$ (92)  $R = \alpha-H$ (93)  $R^1 = H, R^2 = CO_2Me$ (94)  $R^1 = OH, R^2 = H$ 

(95)

(96)  $R^1 = Me, R^2 = H$ (97)  $R^1 = H, R^2 = CO_2Me$ 

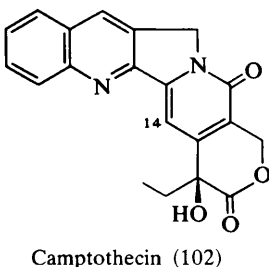
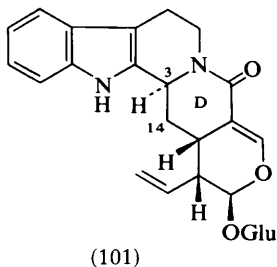
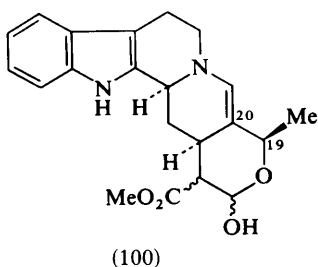
(98)



(99)

NADPH, unlike the latter reaction sequence, which is  $\text{NADP}^+$ -independent. It is clear from these results that geissoschizine is at a shunt from the main pathway to terpenoid indole alkaloids like (84); see Scheme 3.

A new alkaloid (100), related to cathenamine (82), has been isolated from *Guettarda eximia*. It is readily converted chemically into cathenamine (82), presumably *via* (81). It seems likely that (100) has a biosynthetic role, and it may be that access to alkaloids with different stereochemistries at C-19 and C-20 occurs *via* (81)  $\rightleftharpoons$  (100).<sup>104</sup>



The biosynthesis of camptothecin (102) follows that of terpenoid indole alkaloids through strictosidine (79). The lactam (101) derived from (79), and not the C-3 epimer, is the next intermediate.<sup>105</sup> Several unknown steps follow, included in which is dehydrogenation of ring D [see (101)]. In this process a proton is lost from C-14. Tritium label at this site in (101) is retained by a primary isotope effect, the result of non-stereospecific deprotonation.<sup>105</sup> This indicates that removal of the proton is not enzyme-controlled (*cf.* papaverine biosynthesis; *ref.* 8, p. 19).

Although, by inspection, it would seem probable that the dimeric indole alkaloids, such as vinblastine (104), have their genesis in monomeric bases, such as vindoline (89) and catharanthine (90), investigations have been dogged by poor incorporations; *cf.* *ref.* 9. Most recently, however, even more careful work and the employment of cell-free preparations has given positive results.

First, unstable anhydrovinblastine (103) was trapped as a natural product in young *C. roseus* plants.<sup>106</sup> In experiments of a few hours' duration it was shown to

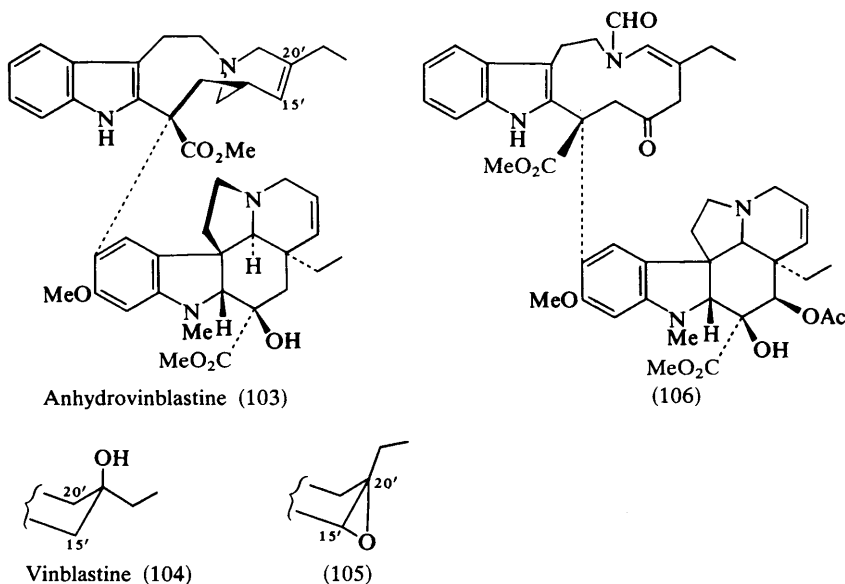
<sup>104</sup> C. Kan-Fan and H.-P. Husson, *J. Chem. Soc., Chem. Commun.*, 1978, 618.

<sup>105</sup> C. R. Hutchinson, A. H. Heckendorf, J. L. Straughn, P. E. Daddona, and D. E. Cane, *J. Am. Chem. Soc.*, 1979, **101**, 3358.

<sup>106</sup> A. I. Scott, F. Gueritte, and S.-L. Lee, *J. Am. Chem. Soc.*, 1978, **100**, 6253.



be labelled specifically and efficiently by radioactive vindoline (89) and catharanthine (90). Vinblastine, however, was but poorly labelled, as before. Significant labelling of leurosine (105) was observed,<sup>106</sup> but ready chemical conversion of (103) into (105) has been noted,<sup>107</sup> so this result must be treated with caution. Using a cell-free extract of *C. roseus* plants, the efficient conversion of (89) and (90) into anhydrovinblastine (103) and leurosine (105) has also been observed.<sup>108</sup>



Secondly, it was shown, using cell-free extracts of *C. roseus*, that anhydrovinblastine (103) is a specific and efficient precursor for vinblastine (104);<sup>109,110</sup> positive incorporations into leurosine were also recorded, but, for the reason stated above, these results must be treated with caution. Leurosine (105) was, however, found to be, like (103), an efficient precursor for catharine (106).<sup>110</sup>

**Pyrrolnitrin.**—Pyrrolnitrin (109) is a metabolite of *Pseudomonas aureofaciens* and is derived from tryptophan. The amino-compound (108) is naturally occurring, and (107) has now also been isolated.<sup>111</sup> This, taken together with evidence from feeding experiments (*cf.* ref. 4, p. 28), indicates the pathway shown in Scheme 4. 3-Chloroanthranilic acid and 7-chloroindoleacetic acid have also been isolated from *P. aureofaciens*.<sup>112</sup>

**Streptonigrin.**—Rings C and D of streptonigrin (111), a metabolite of *Streptomyces flocculus*, originate from tryptophan, and the methyl group at C-3', as

<sup>107</sup> N. Langlois and P. Potier, *J. Chem. Soc., Chem. Commun.*, 1978, 102.

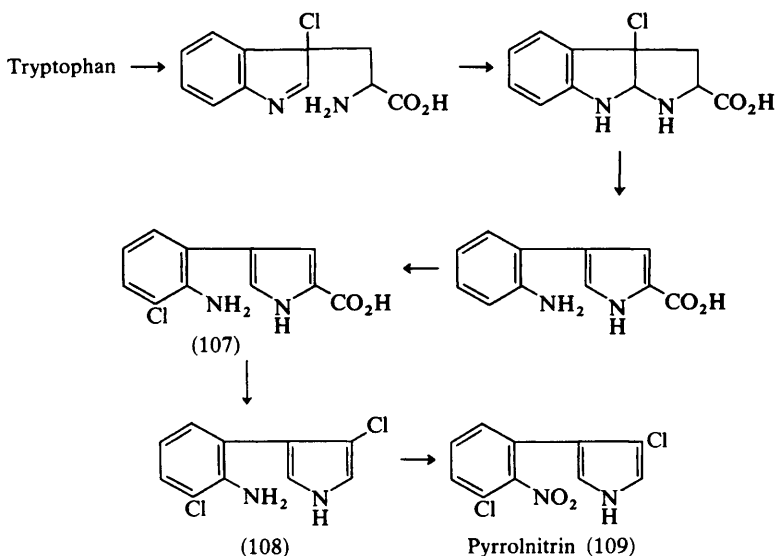
<sup>108</sup> K. L. Stuart, J. P. Kutney, T. Honda, and B. R. Worth, *Heterocycles*, 1978, 9, 1419.

<sup>109</sup> R. L. Baxter, C. A. Dorschel, S.-L. Lee, and A. I. Scott, *J. Chem. Soc., Chem. Commun.*, 1979, 257.

<sup>110</sup> K. L. Stuart, J. P. Kutney, T. Honda, and B. R. Worth, *Heterocycles*, 1978, 9, 1391.

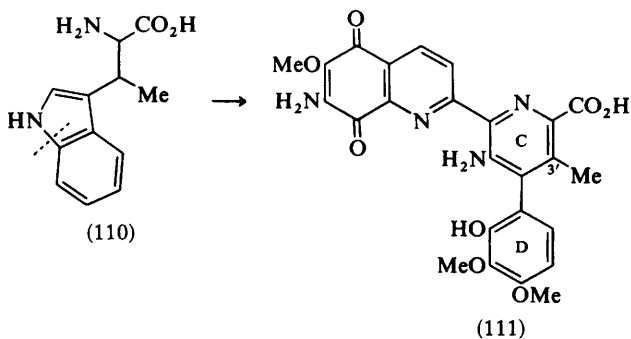
<sup>111</sup> O. Salcher, F. Lingens, and P. Fischer, *Tetrahedron Lett.*, 1978, 3097.

<sup>112</sup> O. Salcher and F. Lingens, *Tetrahedron Lett.*, 1978, 3101.



Scheme 4

well as the methoxy-groups, derive from methionine; *cf.* ref. 9. The *C*-methyl group is introduced at an early stage of biosynthesis, as evidenced by the formation of 3-methyltryptophan (110) in *S. flocculus* cultures and its efficient incorporation into streptonigrin (111).<sup>113</sup>

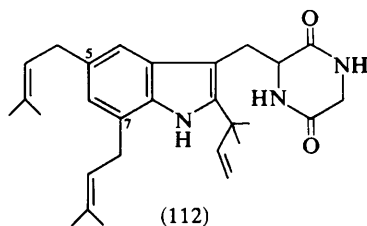


**Echinulin.**—It is known that entry of the dimethylallyl groups at C-5 and C-7 of echinulin (112) occurs with loss of hydrogen from these positions and not from adjacent ones, thus indicating that substitution occurs simply and directly onto these sites; *cf.* ref. 6. The labelling pattern in these groups when echinulin is derived<sup>114</sup> from [1,2-<sup>13</sup>C<sub>2</sub>]acetate indicates that the *E*-methyl group is derived

<sup>113</sup> S. J. Gould and D. S. Darling, *Tetrahedron Lett.*, 1978, 3207.

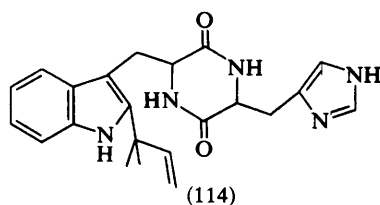
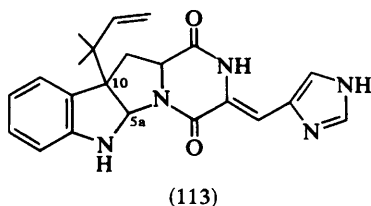
<sup>114</sup> J. K. Allen, K. D. Barrow, and A. J. Jones, *J. Chem. Soc., Chem. Commun.*, 1979, 280.

from C-2 of mevalonate, as expected of a normal biogenesis; similar results have been observed with the isoprenylated phenol flavoglaucin.<sup>115</sup> Thus echinulin is formed without isomerization of the double bonds of the dimethylallyl group. Moreover, the isoprenylation at C-5 and at C-7 occurs with unexceptional inversion of configuration, as monitored<sup>114</sup> with mevalonate that is chirally tritiated at C-5. This indicates again that the dimethylallyl groups are introduced by simple direct substitution.



Incorporation of leucine into the C<sub>5</sub> isoprene units of echinulin (112) through catabolism to mevalonate is thought to proceed *via* acetoacetate; *cf.* ref. 9. Loss of C-2 of leucine is required in this pathway, which is supported by loss of <sup>14</sup>C label from [2-<sup>14</sup>C, 5-<sup>3</sup>H]leucine on incorporation into echinulin (also some loss of tritium, measured in another experiment).<sup>116</sup>

**Roquefortine.**—Roquefortine (113), isolated from *Penicillium roqueforti*, is a member of the group of diketopiperazine metabolites, other representatives of which are echinulin (112), gliotoxin [(122), p. 27], *etc.* Satisfactory incorporations (no degradations though) of radioactive tryptophan, mevalonic acid lactone, and histidine into roquefortine confirm the expected origins for the metabolite.<sup>117</sup> Use of a mutant of *P. roqueforti*, unable to grow in the absence of tryptophan, allowed the use of deuteriated tryptophan as a precursor, yielding (113) with high deuterium enrichment, since the mutant was not producing any tryptophan. The derived metabolite showed complete loss of deuterium from C-2 of tryptophan [equivalent to C-5a in (113)], which indicates that the C<sub>5</sub> isoprene unit at C-10b of (113) may have arrived at this site *via* C-5a, with (114) as a possible intermediate [*cf.* echinulin (112) above].

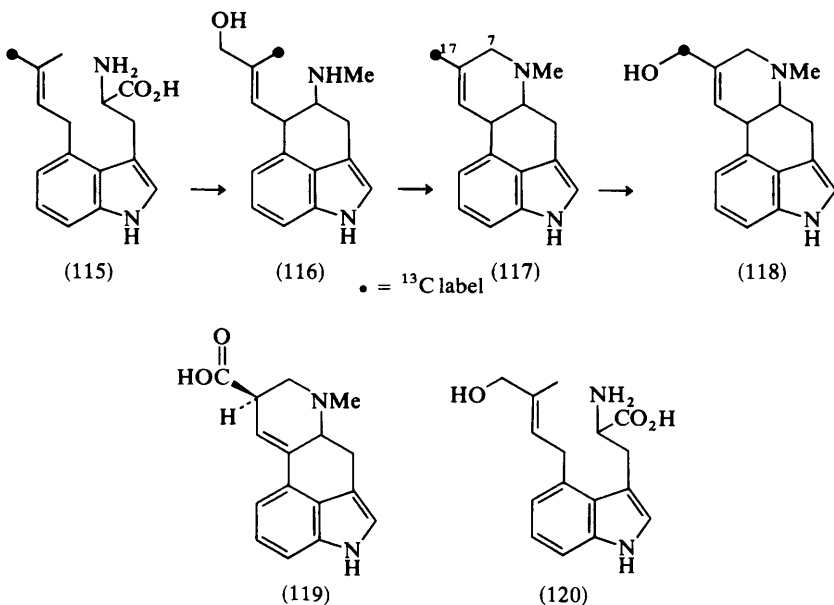


<sup>115</sup> J. K. Allen, K. D. Barrow, A. J. Jones, and P. Hanisch, *J. Chem. Soc., Perkin Trans. 1*, 1978, 152.

<sup>116</sup> C. Fuganti, P. Grasselli, and G. Pedrocchi-Fantoni, *Tetrahedron Lett.*, 1979, 2453.

<sup>117</sup> K. D. Barrow, P. W. Colley, and D. E. Tribe, *J. Chem. Soc., Chem. Commun.*, 1979, 225.

**Ergot Alkaloids.**—The biosynthesis of ergot alkaloids, notably represented by elymoclavine (118), starts with tryptophan. Isoprenylation affords (115), which is converted *via* chanoclavine-I (116) and agroclavine (117) into elymoclavine (118). Each of the ring-closure steps [(115) to (116), and (116) to (117)] involves an enigmatic change of stereochemistry around the side-chain double bond; *cf.* ref. 11. Results of experiments with dimethylallyltryptophan (115), bearing a  $^{13}\text{C}$  label as shown, provide welcome confirmation of this: label appeared at the C-methyl group in (116) and at C-17 in (117), (118), and lysergic acid (119).<sup>118</sup>



Cell-free extracts have been obtained from *Claviceps paspali* cultures which catalyse the formation of (115) and (120) from tryptophan and isopentenyl pyrophosphate. Both compounds were incorporated into lysergic acid amide.<sup>119</sup> Another unidentified compound has been isolated as a product of the incubation, derived from (120) and convertible into lysergic acid amide;<sup>119</sup> *cf.* ref. 9.

The ability of *C. purpurea* to use modified amino-acids for the elaboration of *cyclo*-peptide ergot alkaloids based on lysergic acid has been examined.<sup>120</sup> A varying yield of analogue was observed of 11—66% of total alkaloid formed. The alkaloids studied were, with modified amino-acid in brackets: ergocristine (*p*-chloro- and *p*-fluoro-phenylalanine), ergotamine (*p*-fluorophenylalanine), ergocornine and ergocryptine (L-norvaline, L-norleucine, L- $\alpha$ -aminobutyric acid, 5,5,5-trifluoroleucine, and  $\beta$ -hydroxyleucine).

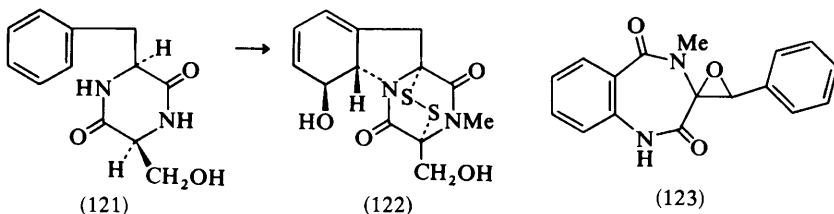
<sup>118</sup> H. Plieninger, E. Meyer, W. Maier, and D. Gröger, *Justus Liebig's Ann. Chem.*, 1978, 813.

<sup>119</sup> R. J. Petroski and W. J. Kelleher, *Lloydia*, 1978, 41, 332.

<sup>120</sup> M. Beacco, M. L. Bianchi, A. Minghetti, and C. Spalla, *Experientia*, 1978, 34, 1291.

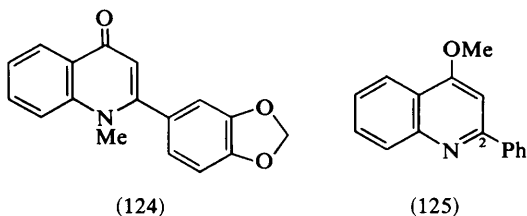
## 5 Miscellaneous

**Gliotoxin.**—*cyclo*-(L-Phenylalanyl-L-seryl) (121) has been observed to be an intact and efficient precursor for gliotoxin (122) in *Trichoderma viride*. This has been confirmed in further experiments with (121) and its three stereoisomers.<sup>121</sup> Only (121) was incorporated at all efficiently (at least forty times better than the others); it was also proved to be utilized intact. Moreover, (121) was formed from labelled phenylalanine in growing cultures. It follows that (121) is either an intermediate in gliotoxin biosynthesis, or is reversibly converted into an intermediate on the pathway. The biosynthesis of gliotoxin has been reviewed.<sup>122</sup>



**Benzodiazepine Alkaloids.**—Benzodiazepine alkaloids, *e.g.* cyclopenin (123), are produced by *Penicillium cyclopium*. Their biosynthesis is pretty well understood.<sup>16</sup> Recently, the production of enzymes involved in the biosynthesis and formation of alkaloid in relation to the development of the organism has been studied.<sup>123</sup> The uptake of one of the precursors, *i.e.* phenylalanine, has also been studied.<sup>124</sup>

**Quinoline Alkaloids.**—Anthranilic acid and a benzoylactic acid derivative, derived from phenylalanine, are precursors for graveoline (124); *cf.* ref. 5. On the other hand, whilst the biosynthesis of (125) no doubt involves anthranilic acid, benzoic acid (carboxyl-labelled material), and not phenylalanine, was a precursor for (125) in *Lunasia amara*; incorporation was specific, with labelling of C-2.<sup>125</sup> The remaining carbons should derive from acetate, and a positive incorporation was recorded. It is clear that further work is required on the biosynthesis of this alkaloid before its origins can be described with certainty.



<sup>121</sup> G. W. Kirby, G. L. Patrick, and D. J. Robins, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1336.

<sup>122</sup> G. W. Kirby, *Pure Appl. Chem.*, 1979, **51**, 705.

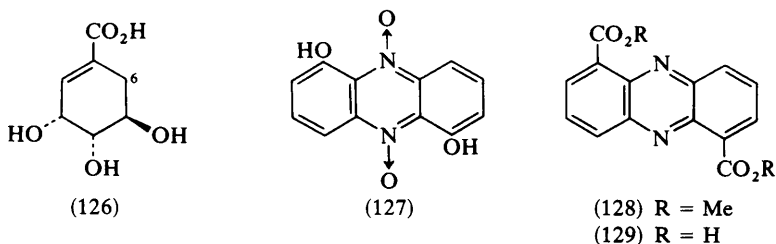
<sup>123</sup> S. Voigt, S. El Kousy, N. Schwelle, L. Nover, and M. Luckner, *Phytochemistry*, 1978, **17**, 1705.

<sup>124</sup> L. Nover, W. Lerbs, W. Müller, and M. Luckner, *Biochim. Biophys. Acta*, 1979, **584**, 270.

<sup>125</sup> A. C. Finlayson and R. H. Prager, *Aust. J. Chem.*, 1978, **31**, 2751.

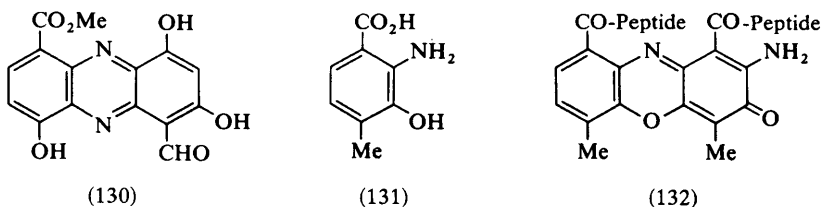
**Phenazines.**—A study using [6- $^{13}\text{C}$ ]shikimic acid [as (126)] has given results<sup>126</sup> which confirm previous ones<sup>54</sup> concerning the orientation of shikimic acid (126) units in the bacterial phenazine iodinin (127).

It has been claimed that dimethyl phenazine-1,6-dicarboxylate (128) is a precursor for 1-carboxyphenazine in *Pseudomonas aureofaciens*; cf. ref. 8. This claim has been disputed: careful checking showed that neither (128) nor the corresponding acid (129) was incorporated into phenazines produced by this organism.<sup>127</sup> This has been supported by the results of other workers,<sup>128</sup> who have found that (128) is metabolically inert in *P. aureofaciens*. Moreover, neither (129) nor (128) was incorporated into phenazines in *P. phenazinium*. On the other hand, efficient incorporations have been recorded of (129), but not of (128), into iodinin (127) and related phenazines in three actinomycetes, i.e. *Streptomyces thioluteus*, *Microbispora amethystogenes*, and *M. parva*.<sup>128</sup>



This latter observation correlates with the observation<sup>127</sup> that (129) is a precursor for lomofungin (130) in *Streptomyces lomodensis*. It seems clear from the combined evidence that phenazine-1,6-dicarboxylic acid (129) is a precursor for all microbial phenazines. Failure to observe incorporation of (129) in *Pseudomonas*, with (by contrast) positive results in actinomycetes, may be attributed to differences in permeability of the cell walls (cf. ref. 127).

**Actinomycin.**—4-Methyl-3-hydroxyanthranilic acid (131) is an important precursor for actinomycin (132); cf. ref. 6. Further support for its role as a biosynthetic intermediate is its accumulation in mutants of *Streptomyces parvulus* that are unable to synthesize (132).<sup>129</sup>



<sup>126</sup> U. Hollstein, D. L. Mock, R. R. Sibbitt, U. Roisch, and F. Lingens, *Tetrahedron Lett.*, 1978, 2987.

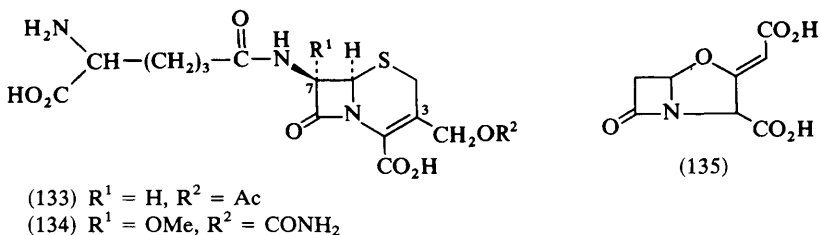
<sup>127</sup> S. P. Gulliford, R. B. Herbert, and F. G. Holliman, *Tetrahedron Lett.*, 1978, 195; R. B. Herbert, in ref. 9, p. 29.

<sup>128</sup> A. J. M. Messenger and J. M. Turner, *Biochem. Soc. Trans.*, 1978, 6, 1326.

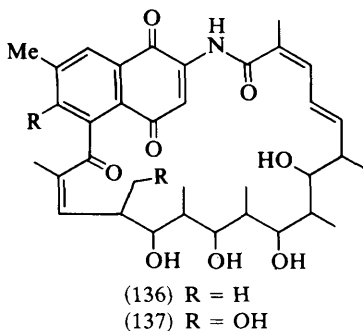
<sup>129</sup> T. Troost and E. Katz, *J. Gen. Microbiol.*, 1979, 111, 121 · see also refs. cited therein.

**$\beta$ -Lactam Antibiotics.**—The oxygen atom attached to the exocyclic methylene at C-3 of cephalosporin C (133) is derived from molecular oxygen, and its introduction is catalysed by a dioxygenase. It has been shown that this oxygen and the one at C-7 in cephamycin C (134) both derive from molecular oxygen.<sup>130</sup>

Investigation of the biosynthesis of clavulanic acid (135), using <sup>13</sup>C-labelled precursors, has shown that glycerol is an intact source for the three  $\beta$ -lactam carbons. Studies with [1-<sup>13</sup>C]-, [2-<sup>13</sup>C]-, and [1,2-<sup>13</sup>C<sub>2</sub>]-acetate indicated that the remaining five carbons probably derive from  $\alpha$ -ketoglutarate.<sup>131</sup>



**Ansamycins.**—Similar patterns of precursor labelling in the rifamycins and streptovaricins led to the suggestion that they are derived from a common precursor, possibly (136); cf. refs. 5—7. This is supported by the isolation of protorifamycin I (137) from a mutant of *Nocardia mediterranei*.<sup>132</sup>



<sup>130</sup> J. O'Sullivan, R. T. Aplin, C. M. Stevens, and E. P. Abraham, *Biochem. J.*, 1979, **179**, 47.

<sup>131</sup> S. W. Elson and R. S. Oliver, *J. Antibiot.*, 1978, **31**, 586.

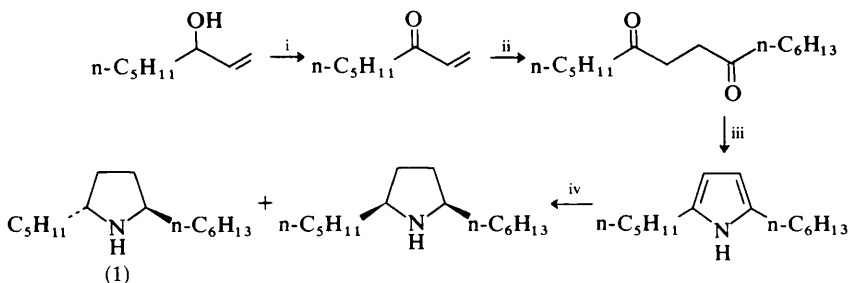
<sup>132</sup> O. Ghisalba, P. Traxler, and J. Nuesch, *J. Antibiot.*, 1978, **31**, 1124.

## Pyrrolidine, Piperidine, and Pyridine Alkaloids

BY A. R. PINDER

### 1 Pyrrolidine Alkaloids

The poison glands of the thief ants *Solenopsis molesta* and *S. texanus* contain *trans*-2-*n*-hexyl-5-*n*-pentylpyrrolidine (1). The structure and stereochemistry of the product were established by application of a stereoselective synthesis of unsymmetrical 2,5-dialkyl-pyrrolidines (Scheme 1). The final product consisted of *cis*- and *trans*-isomers in the ratio about 85:15, the major component being assigned the *cis* configuration by analogy with the behaviour of 2,5-dimethylpyrrole on catalytic hydrogenation. The stereoisomers were separable by preparative g.l.c.; the *trans*-isomer (1) proved to be identical with the product from the fire ants. *trans*-2-*n*-Butyl-5-*n*-pentylpyrrolidine and *trans*-2-*n*-butyl-5-*n*-heptylpyrrolidine, also synthesized by a modification of Scheme 1, were identical with products found in the venom of *S. punctaticeps*.<sup>1</sup>



Reagents: i, pyridinium chlorochromate; ii,  $n\text{-C}_6\text{H}_{13}\text{CHO}$ ,  $\text{Et}_3\text{N}$ , 5-(2'-hydroxyethyl)-4-methyl-3-benzylthiazolium chloride; iii,  $(\text{NH}_4)_2\text{CO}_3$ ; iv,  $\text{Rh}/\text{Al}_2\text{O}_3$ ,  $2\text{H}_2$

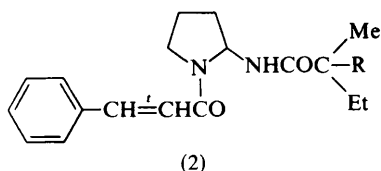
**Scheme 1**

Two amidic pyrrolidine bases, odorine (2;  $\text{R} = \text{H}$ ) and odorol (2;  $\text{R} = \text{OH}$ ), have been isolated from the leaves of *Aglaia odorata* Lour. Their structures have been settled by n.m.r., i.r., and mass spectral analysis. The cinnamoyl residue in each was readily detected by the mass spectral fragmentation and, in the case of odorinol, by acid hydrolysis, which afforded cinnamic and 2-hydroxy-2-methylbutanoic acids.<sup>2</sup>

<sup>1</sup> T. H. Jones, M. S. Blum, and H. M. Fales, *Tetrahedron Lett.*, 1979, 1031.

<sup>2</sup> D. Shiengthong, A. Ungphakorn, D. E. Lewis, and R. A. Massy-Westropp, *Tetrahedron Lett.*, 1979, 2247.





**Sceletium Alkaloids.**—Full details of an earlier briefly reported synthesis of ( $\pm$ )-mesembrine (3) have been published<sup>3</sup> and a new synthesis has been described. The latter is outlined in Scheme 2.<sup>4</sup> A new *Sceletium* alkaloid has been isolated from *S. namaquense*.<sup>5</sup> It has been formulated as (4) on spectral evidence, the assignment of structure being confirmed by direct spectral comparison between the natural base and racemic (4), synthesized earlier.<sup>6</sup> Channaine, another alkaloid of this family, from *S. tortuosum*, has structure (5) on the basis of an X-ray diffraction analysis of its hexahydrate. It may be an artefact arising from the condensation of a pair of *N*-desmethylnesembrenone molecules (6) during isolation.<sup>7</sup>

Several new pyrrolinones have been encountered in marine sources. Malyn-gamide-A, for example, is a chlorine-containing metabolite of the blue-green alga *Lyngbya majuscula* Gomont. Structure (7) has been proposed chiefly on the basis of n.m.r. and mass spectral analysis, aided by some chemical transformations.<sup>8</sup> Seven other compounds, the pukeleimides A, B, C, D, E, F, and G, have also been isolated from the same source, and separated. They are formulated as (8), (9), (10), (11), (12), (13), and (14) as a consequence of spectral and, in the case of C, X-ray diffraction analysis.<sup>9,10</sup>

## 2 Piperidine Alkaloids

A new synthesis of piperine (15) and isochavicine (16) has been reported. It is shown in outline in Scheme 3, the key step being the thermal condensation of a propargylic alcohol with an acetal to yield an allene (steps ii and iii). The mixture was separated by preparative t.l.c.<sup>11</sup>

The (1*Z*,3*E*)- and (1*Z*,3*Z*)-stereoisomers of wisanine have been synthesized *via* Wittig reactions between the phosphonium salt (17) and *cis*-ethyl 3-formylacrylate, one in the absence and one in the presence of lithium iodide. The former conditions led, after hydrolysis, to *cis,trans*-wisanic acid, and the latter to the all-*cis* isomer. The acids were converted respectively into the (1*Z*,3*E*)- (18) and (1*Z*,3*Z*)-wisanines (19) (Scheme 4) by standard procedures.<sup>12</sup>

<sup>3</sup> J. B. P. A. Wijnberg and W. N. Speckamp, *Tetrahedron*, 1978, **34**, 2579.

<sup>4</sup> O. Hoshino, S. Sawaki, N. Shimamura, A. Onodera, and B. Umezawa, *Heterocycles*, 1978, **10**, 61.

<sup>5</sup> P. W. Jeffs and T. M. Capps, *Tetrahedron Lett.*, 1979, 131.

<sup>6</sup> R. V. Stevens, P. M. Lesko, and R. Lapalme, *J. Org. Chem.*, 1975, **40**, 3495.

<sup>7</sup> A. Abu-Donia, P. W. Jeffs, A. T. McPhail, and R. W. Miller, *J. Chem. Soc., Chem. Commun.*, 1978, 1078.

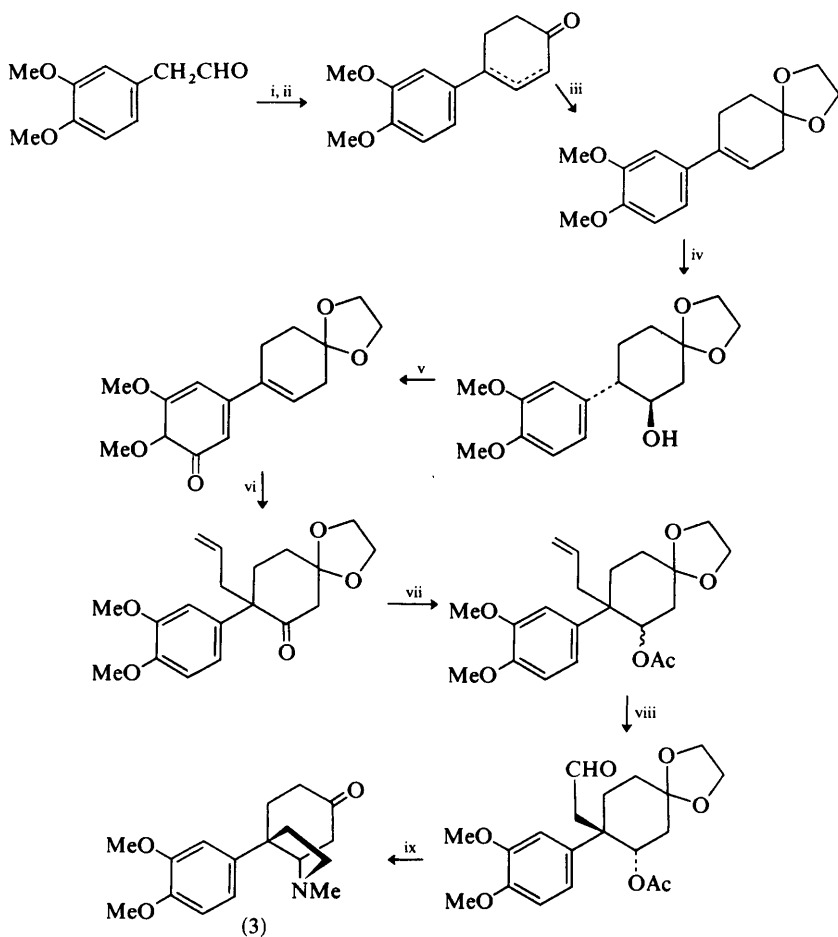
<sup>8</sup> J. H. Cardellina, F.-J. Marner, and R. E. Moore, *J. Am. Chem. Soc.*, 1979, **101**, 240.

<sup>9</sup> C. J. Simmons, F.-J. Marner, J. H. Cardellina, R. E. Moore, and K. Seff, *Tetrahedron Lett.*, 1979, 2003.

<sup>10</sup> J. H. Cardellina and R. E. Moore, *Tetrahedron Lett.*, 1979, 2007.

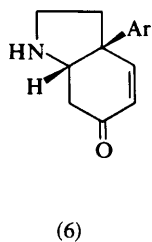
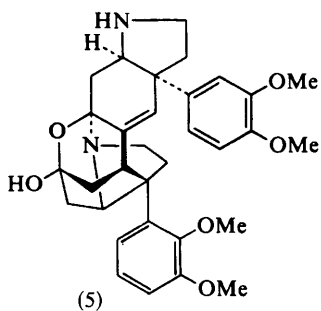
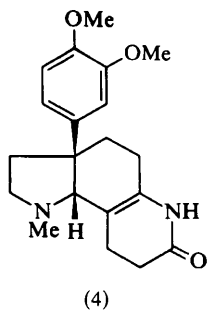
<sup>11</sup> S. Tsuboi and A. Takeda, *Tetrahedron Lett.*, 1979, 1043.

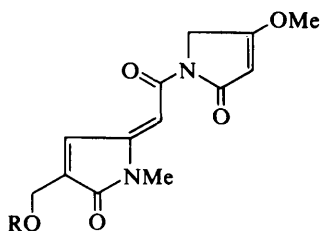
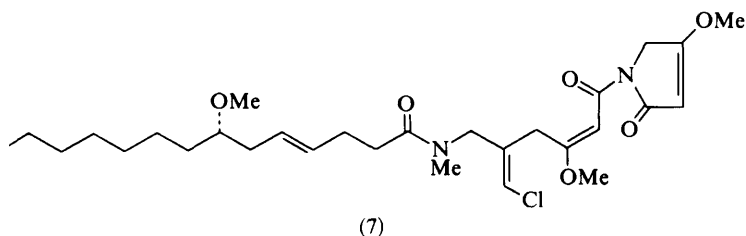
<sup>12</sup> H.-D. Scharf and J. Janus, *Tetrahedron*, 1979, **35**, 385.



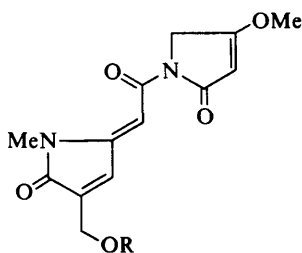
Reagents: i, pyrrolidine; ii, methyl vinyl ketone (MVK); iii,  $(\text{CH}_2\text{OH})_2$ ,  $\text{H}^+$ ; iv, hydroboration-oxidation; v,  $\text{CrO}_3$ , pyridine; vi,  $\text{CH}_2=\text{CHCH}_2\text{Br}$ , base; vii,  $\text{NaBH}_4$ , then  $\text{Ac}_2\text{O}$ , pyridine; viii,  $\text{OsO}_4$ ,  $\text{NaIO}_4$ ; ix,  $\text{MeNH}_2 \cdot \text{HCl}$ ,  $\text{NaBH}_3\text{CN}$ , then  $\text{H}^+$

**Scheme 2**

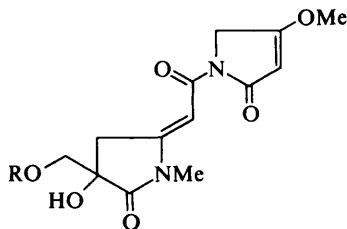




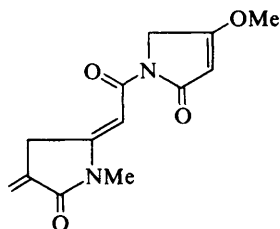
(8) R = H  
(14) R = Me



(9) R = H  
(13) R = Me



(10) R = Me  
(11) R = H



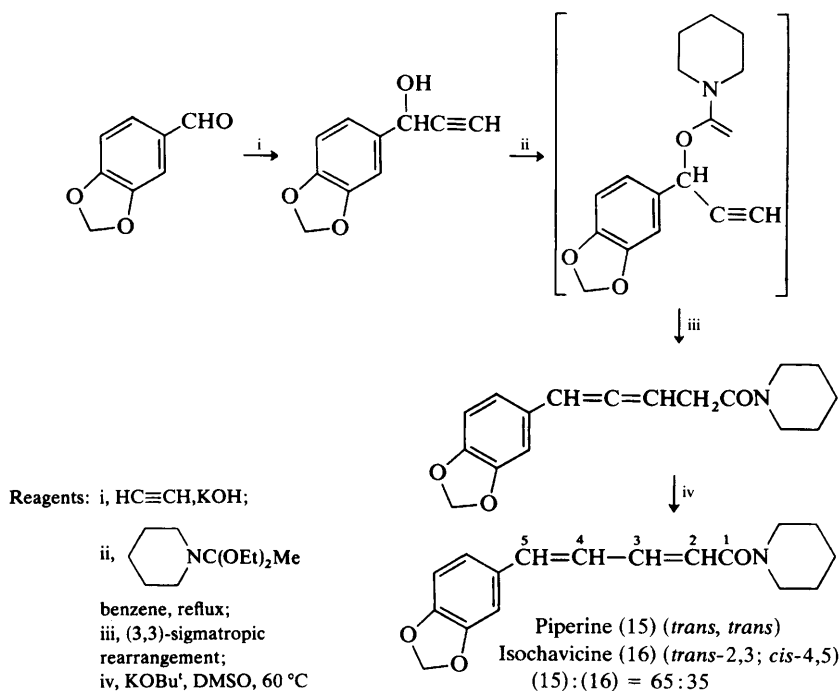
(12)

The nitron (20) (2,3,4,5-tetrahydropyridine 1-oxide) reacts with styrene to furnish a mixture of the two 1,3-dipolar cyclo-adducts (21), methylation of which (with MeI) affords a mixture of stereoisomeric salts, reducible to ( $\pm$ )-sedamine (22) and ( $\pm$ )-allosedamine (23) by lithium aluminium hydride, in ratio of about 1:3.5. A similar reaction between the same nitron and propene leads to an analogous adduct, which on reduction affords ( $\pm$ )-sedridine (24) in quantitative yield, no evidence of the formation of ( $\pm$ )-allosedridine (25) being obtained.<sup>13</sup>

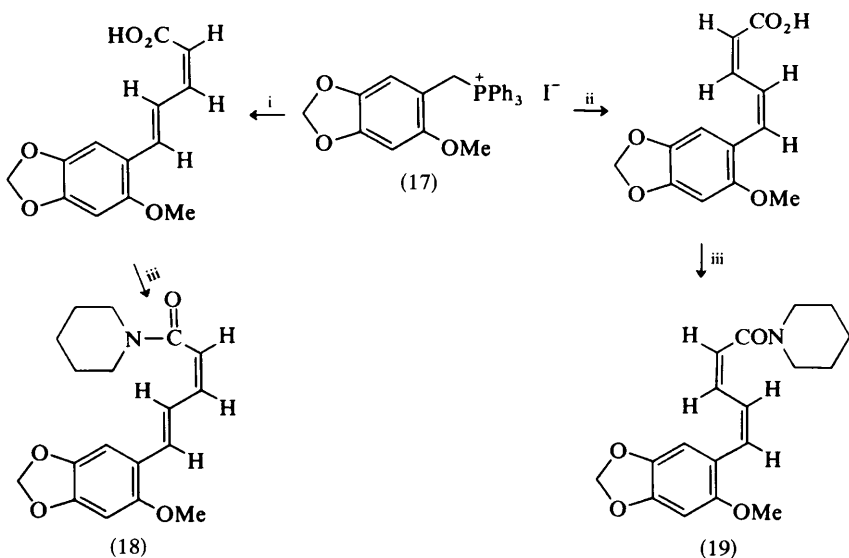
Rohitukine is the principal alkaloid of the leaves and stems of *Amoora rohituka* (syn. *Aphanamixis polystachya*). Structure (26) has been established for the base by X-ray diffraction analysis; it appears to be the first example of structure determination amongst alkaloids of the Meliaceae, and one of a very small family of chromone alkaloids.<sup>14</sup> ( $\pm$ )-7-Desmethyltecmanine (27) has been synthesized stereoselectively by a route which promises to be adaptable to a synthesis of

<sup>13</sup> J. J. Tufariello and S. A. Ali, *Tetrahedron Lett.*, 1978, 4647.

<sup>14</sup> A. D. Harmon, U. Weiss, and J. V. Silverton, *Tetrahedron Lett.*, 1979, 721.

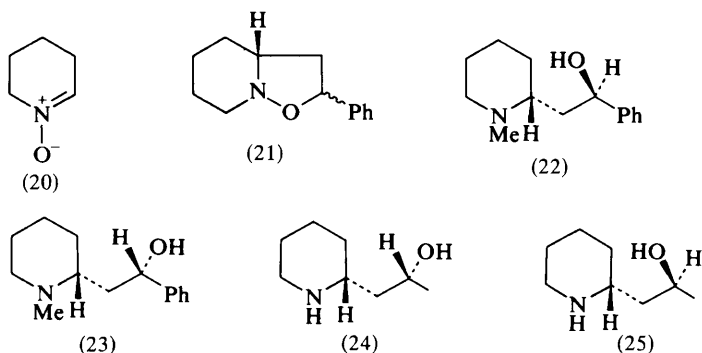


Scheme 3

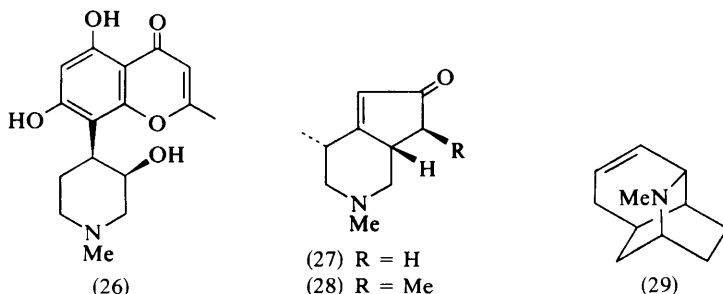


Reagents: i,  $\text{OHCCH}=\text{CHCO}_2\text{Et}$ , BuLi; ii,  $\text{OHCCH}=\text{CHCO}_2\text{Et}$ , BuLi, LiI; iii,  $\text{ClCO}_2\text{Et}$ , piperidine

Scheme 4



( $\pm$ )-tecomanine (28), an alkaloid of *Tecoma stans* Juss.<sup>15</sup> Cannivonine, the simplest alkaloid of a group of several occurring in New Brunswick cranberry leaves (*Vaccinium oxycoccus*), has been formulated as (29).<sup>16,17</sup> However, a synthesis of racemic (29) has been reported, and the spectral properties of the product proved to be different from those reported for the natural base; a re-assignment of the structure of cannivonine is therefore desirable.<sup>18</sup>



A total synthesis of the racemic form of the cyclophane alkaloid lythranthrindine (31) has been described (Scheme 5), starting from the diol (30), synthesized earlier.<sup>19</sup> The total synthesis of ( $\pm$ )-carpaine (32) has been reported preliminarily (Scheme 6); it uses a new reaction between 1-acyl-1,2-dihydropyridines and singlet oxygen, involving the formation of an adduct, which is then cleaved by stannous chloride in the presence of ethyl vinyl ether.<sup>20</sup>

Two new alkaloids of the carpaine group, dehydrocarpaine-I and -II, have been isolated from papaya leaves (*Carica papaya* L.). They have been formulated as (33) and (34) respectively, on spectral evidence and on the basis of their easy hydrogenation to carpaine.<sup>22</sup>

<sup>15</sup> T. Momose, M. Kinoshita, and T. Imanishi, *Heterocycles*, 1979, **12**, 243.

<sup>16</sup> K. Jankowski and I. Jankowski, *Experientia*, 1971, **27**, 1383.

<sup>17</sup> K. Jankowski, *Experientia*, 1973, **29**, 519, 1334; *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, 1973, **21**, 741.

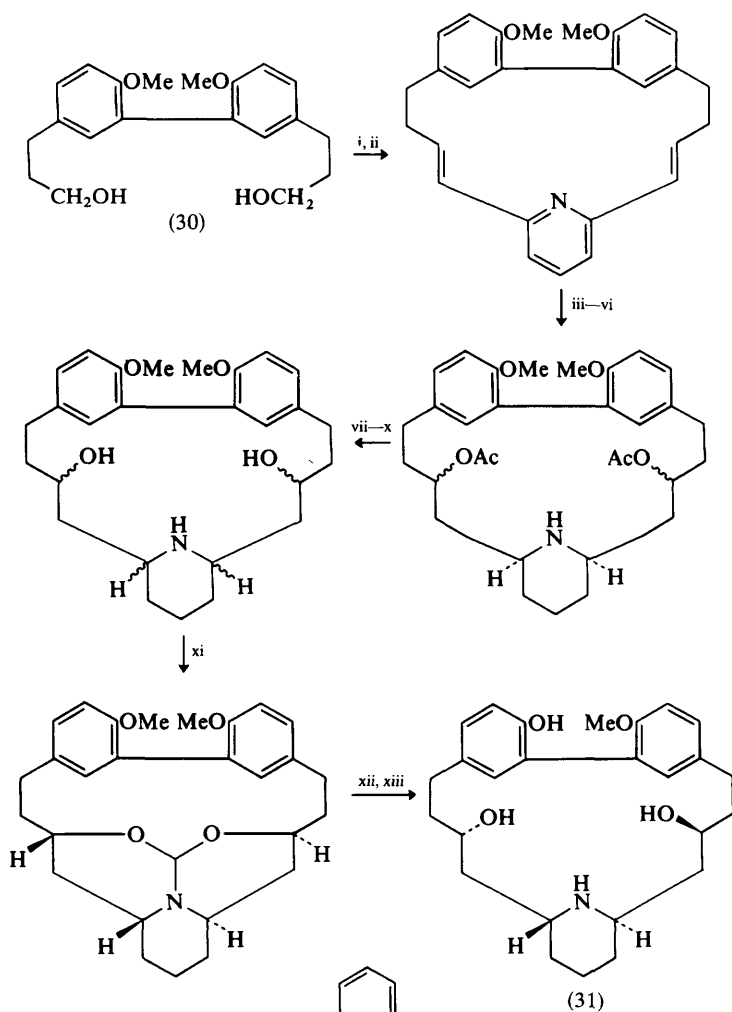
<sup>18</sup> A. P. Kozikowski and R. Schmiesing, *J. Chem. Soc., Chem. Commun.*, 1979, 106.

<sup>19</sup> K. Fuji, K. Ichikawa, and E. Fujita, *Tetrahedron Lett.*, 1979, 361.

<sup>20</sup> M. Natsume and M. Ogawa, *Heterocycles*, 1979, **12**, 159.

<sup>21</sup> N. S. Narasimhan, *Chem. Ind. (London)*, 1956, 1526.

<sup>22</sup> C.-S. Tang, *Phytochemistry*, 1979, **18**, 651.



Reagents: i,  $\text{CrO}_3$ , pyridine; ii,  $\text{Ph}_3\text{P}=\text{CH}-\text{N}(\text{CH}_3)_2-\text{CH}=\text{PPh}_3$ ; iii, *m*-CPBA; iv,  $\text{H}_2$ , Pd/C; v, acetylation; vi,  $\text{H}_2$ ,  $\text{PtO}_2$ -Raney nickel; vii, isoamyl nitrite; viii,  $\text{KO}^t\text{Bu}$ , DMSO,  $90^\circ\text{C}$ ; ix,  $\text{H}_2$ , Ni; x, hydrolysis; xi,  $\text{CH}(\text{OEt})_3$ ,  $\text{H}^+$ ; xii,  $\text{AlCl}_3$ , EtSH, at  $-10^\circ\text{C}$ ; xiii, 20% aq. HCl

**Scheme 5**

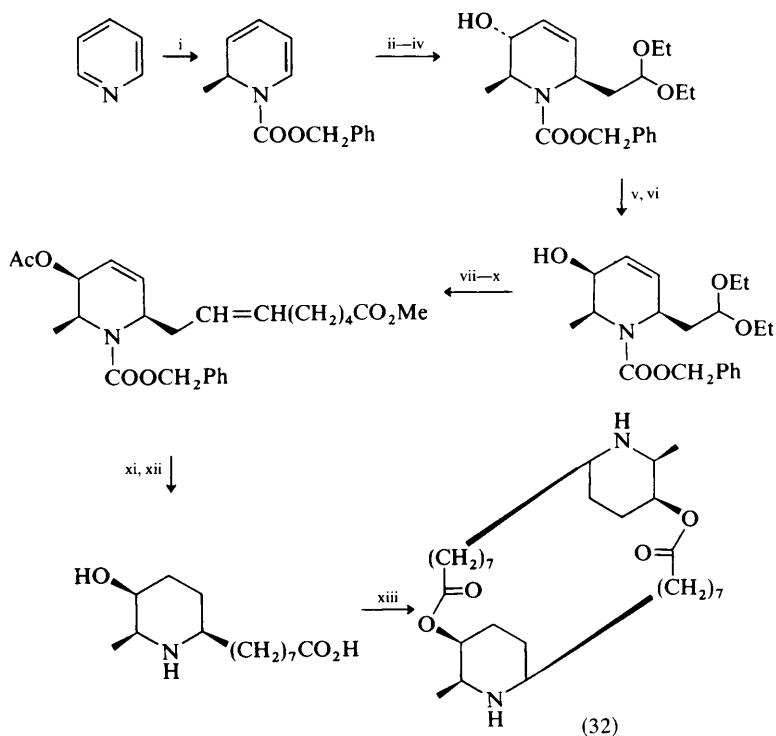
Total stereospecific syntheses of (+)-azimic (35) and (+)-carpamic acids (36), which are the hydroxy-acids in the macrocyclic dilactone structures of azimine and carpaine respectively, have been described, starting from (+)-glucose.<sup>23</sup>

**Decahydroquinoline Alkaloids.**—Full details of two earlier briefly reported total syntheses of (±)-pumiliotoxin-C have been disclosed.<sup>24,25</sup> A third total synthesis

<sup>23</sup> S. Hanessian and R. Frenette, *Tetrahedron Lett.*, 1979, 3391.

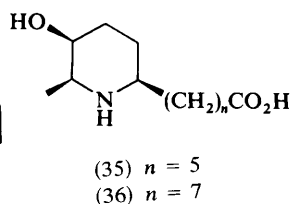
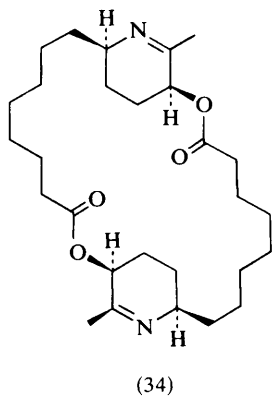
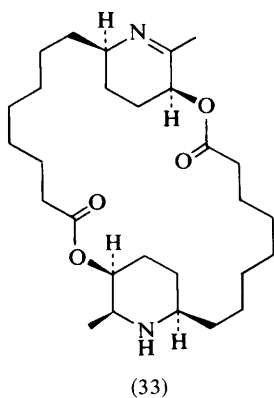
<sup>24</sup> L. E. Overman and P. L. Jessup, *J. Am. Chem. Soc.*, 1978, **100**, 5179.

<sup>25</sup> T. Ibuka, Y. Mori, and Y. Inubushi, *Chem. Pharm. Bull.*, 1978, **26**, 2442.



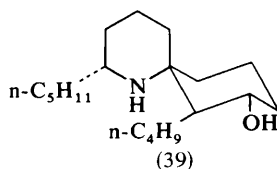
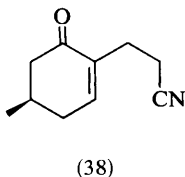
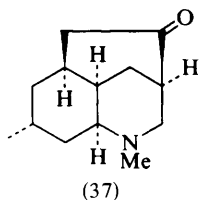
Reagents: i, MeMgBr, then PhCH<sub>2</sub>OCOCl; ii, singlet O<sub>2</sub>; iii,  $\text{CH}_2=\text{CH}(\text{OEt})_2$ , SnCl<sub>2</sub>; iv, EtOH; v, CrO<sub>3</sub>, pyridine; vi, NaBH<sub>4</sub>; vii, H<sup>+</sup>; viii, Ph<sub>3</sub>P=CH(CH<sub>2</sub>)<sub>4</sub>CO<sub>2</sub>Li; ix, CH<sub>2</sub>N<sub>2</sub>; x, Ac<sub>2</sub>O, pyridine; xi, Ba(OH)<sub>2</sub>; xii, cat. H<sub>2</sub>; xiii, ref. 21

Scheme 6



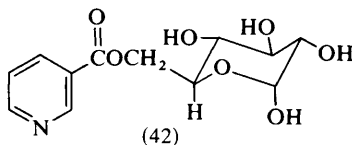
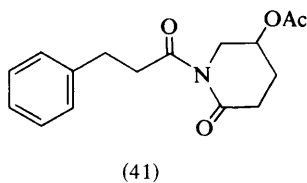
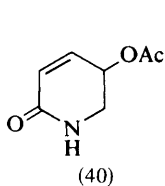
of ( $\pm$ )-luciduline (37) has been described; it uses 2-(2-cyanoethyl)-5-methylcyclohex-2-en-1-one (38), synthesized earlier, as its starting point.<sup>26</sup>

**Spiropiperidine Alkaloids.**—Two more total syntheses of perhydrohistrionicotoxin (39) have been reported.<sup>27,28</sup>



### 3 Pyridine Alkaloids

A new pepper alkaloid, pipermethystine, has been isolated from the leaves of *Piper methysticum* Forst. Mass spectrometric studies, and its conversion into 3-phenylpropanoic acid and the dihydropyridone (40), point to structure (41) for the alkaloid.<sup>29</sup> Buchananine, an alkaloid present in the stems of *Cryptolepis buchanani*, on hydrolysis, affords glucose and nicotinic acid. The base has reducing properties; this observation, and its behaviour towards periodic acid, indicate that the CH<sub>2</sub>OH group of the glucose is involved in the ester linkage. These observations, coupled with spectral evidence, point to structure (42) for the alkaloid, in which, on n.m.r. evidence, the glucose moiety has the  $\alpha$ -configuration.<sup>30</sup>



The root bark of *Schumanniohyton problematicum* contains a new pyridine alkaloid, named schumanniohytine and formulated as the chromone (43), alkaline hydrolysis of which afforded the pyranopyridine (44). Also present are the 2-piperidones (45) and (46), the structures of all three alkaloids being deduced largely on spectral evidence.<sup>31</sup>

Melochinine, an alkaloid occurring in the leaves of *Melochia pyramidata* L., is the first representative of a hitherto unknown group of 4-pyridone bases. Spectroscopic analysis combined with microchemical degradation allows structure (47) to be advanced.<sup>32</sup>

<sup>26</sup> J. Szychowski and D. B. MacLean, *Can. J. Chem.*, 1979, **57**, 1631.

<sup>27</sup> H. E. Schoemaker and W. N. Speckamp, *Tetrahedron Lett.*, 1978, 4841.

<sup>28</sup> D. A. Evans and E. W. Thomas, *Tetrahedron Lett.*, 1979, 411.

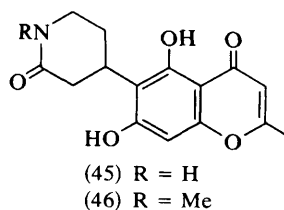
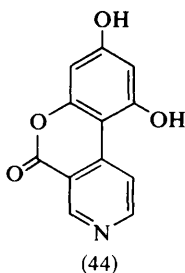
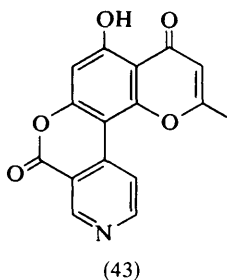
<sup>29</sup> R. M. Smith, *Tetrahedron*, 1979, **35**, 437.

<sup>30</sup> S. K. Dutta, B. N. Sharma, and P. V. Sharma, *Phytochemistry*, 1978, **17**, 2047.

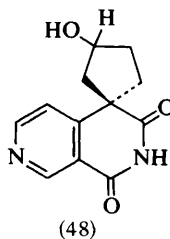
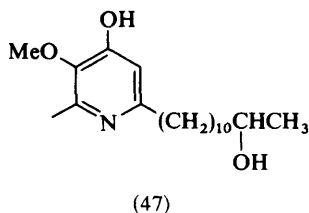
<sup>31</sup> E. Schlittler and U. Spitaler, *Tetrahedron Lett.*, 1978, 2911.

<sup>32</sup> E. Medina and G. Spiteller, *Chem. Ber.*, 1979, **112**, 376.





The elimination-addition pathway proposed for the epoxidation reaction in the synthesis of flavipucine has been challenged on the grounds that this mechanism has not been established unequivocally.<sup>33</sup> Sesbanine is a novel cytotoxic alkaloid occurring in the seeds of *Sesbania drummondii*; its constitution (48) has been settled by spectral study and by X-ray diffraction analysis.<sup>34</sup> Several amino-substituted derivatives of mimosine, (possible inhibitors of the growth of wool) have been synthesized.<sup>35</sup>



Interest in alkaloids of the nicotine group appears to be on the increase. A review has appeared covering tobacco-specific nitrosamines, which may be causative factors in tobacco-related cancers.<sup>36</sup> The solution conformation, and proton, deuterium, carbon-13, and nitrogen-15 n.m.r. spectra of nicotine and its 2- and 4-isomers, have been studied.<sup>37</sup> A new synthesis of nornicotine and nicotine has been described, and a quantitative carbon-13 n.m.r. spectral analysis of nicotine that is labelled at positions 1', 2', and 3' with carbon-13 been presented.<sup>38</sup> The synthesis and mass spectrometry of several structurally related nicotinoids have been reported.<sup>39</sup> Nicotine is dehydrogenated on irradiation in benzene solution in the presence of benzophenone to 1'-methyl-2'-(3-pyridyl)pyrrole.<sup>40</sup> Nornicotine has been synthesized in four steps from 3-bromopyridine and *N*-3-butenyl-phthalimide, using a palladium-catalysed vinylic

<sup>33</sup> J. A. Findlay, *Heterocycles*, 1979, **12**, 389.

<sup>34</sup> R. G. Powell, C. R. Smith, D. Weisleder, D. A. Muthard, and J. Clardy, *J. Am. Chem. Soc.*, 1979, **101**, 2784.

<sup>35</sup> F. H. C. Stewart, *Aust. J. Chem.*, 1978, **31**, 1861.

<sup>36</sup> S. S. Hecht, C. B. Chen, and D. Hoffmann, *Acc. Chem. Res.*, 1979, **12**, 92.

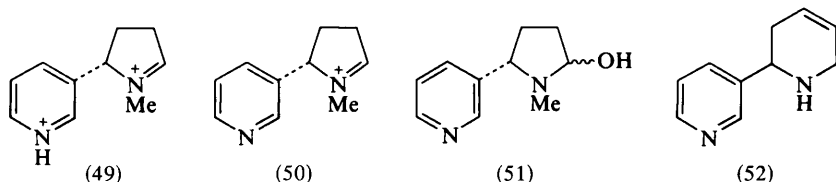
<sup>37</sup> J. F. Whidby, W. B. Edwards, and T. P. Pitner, *J. Org. Chem.*, 1979, **44**, 794.

<sup>38</sup> M. Nakane and C. R. Hutchinson, *J. Org. Chem.*, 1978, **43**, 3922.

<sup>39</sup> D. F. Glenn and W. B. Edwards, *J. Org. Chem.*, 1978, **43**, 2860.

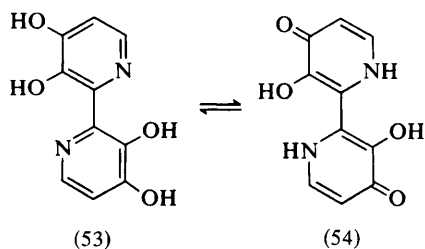
<sup>40</sup> J. Cossy and J.-P. Pete, *Tetrahedron Lett.*, 1978, 4941.

substitution reaction of olefins.<sup>41</sup> The nicotine  $\Delta^{1',5'}$ -iminium ion (49), believed on good evidence to be an intermediate in the metabolism of nicotine in man to cotinine, has been synthesized, and its structure in aqueous solutions of varying pH investigated by n.m.r. spectroscopy. The iminium form (50) is the only structure observed in acidic or neutral solution, and the carbinolamine form (51) the only form in alkaline solution. In weakly basic solution, (50) and (51) are both present.<sup>42</sup> The metabolic oxidation of nicotine by rabbit liver in the presence of cyanide ion yields 5'-cyanonicotine and *N*-cyanomethyl-nornicotine.<sup>43</sup>



When an aqueous solution of baikiain (1,2,3,6-tetrahydropyridine-2-carboxylic acid) is treated with sodium hypochlorite, the alkaloid anatabine (52) is formed, along with pyridine. This observation is consistent with the intermediacy of 2,5-dihydropyridine in the synthetic pathway.<sup>44</sup>

Orelline and orellanine are two toxic alkaloids occurring in the mushroom *Cortinarius orellanus* Fries. Chemical and particularly spectroscopic investigations have revealed that orelline is the tetrahydroxy-2,2'-bipyridyl (53), tautomeric with (54), and orellanine is the corresponding bis-*N*-oxide.<sup>45</sup>



<sup>41</sup> W. C. Frank, Y. C. Kim, and R. F. Heck, *J. Org. Chem.*, 1978, **43**, 2947.

<sup>42</sup> S. Brandänge and L. Lindblom, *Acta Chem. Scand., Ser. B*, 1979, **33**, 187.

<sup>43</sup> T.-L. Nguyen, L. D. Gruenke, and N. Castagnoli, *J. Med. Chem.*, 1979, **22**, 259.

<sup>44</sup> E. Leete, *J. Chem. Soc., Chem. Commun.*, 1978, 1055.

<sup>45</sup> W. Z. Antkowiak and W. P. Gessner, *Tetrahedron Lett.*, 1979, 1931.

# 3

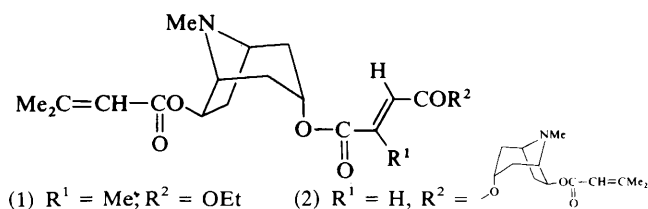
## Tropane Alkaloids

BY G. FODOR & (the late) J. BUTTERICK

### 1 New Alkaloids

Comprehensive reviews have recently appeared on the tropane alkaloids of the Solanaceae<sup>1</sup> and on the biosynthesis and metabolism of the same type of alkaloids.<sup>2</sup> The stereospecific hydroxylation of tropine to 6 $\beta$ -hydroxytropine and the conversion of its tropic acid ester into 6,7-dehydrohyoscyamine and further into scopolamine have been conclusively proven.<sup>2</sup> Hence, the total synthesis of scopolamine<sup>3</sup> from 6-trope-3 $\alpha$ -yl esters is indeed a biomimetic synthesis.

Schizanthins A (1) and B (2) have been isolated<sup>4</sup> from the leaves and stems of *Schizanthus pinnatus*, a very special genus within the family Solanaceae. Thin-layer chromatography led to the separation of seven alkaloids; two of those have now been isolated and subjected to structure determination. The peaks in the i.r. spectrum of schizanthin A at 1720 and 1655 cm<sup>-1</sup> and the u.v. absorption at 221.5 nm can be assigned to an  $\alpha\beta$ -unsaturated carboxylic ester group. Mass spectrometry gave a molecular-ion peak and the fragmentation pattern is congruent with that of a di-acylated 3 $\alpha$ ,6 $\beta$ -tropanediol; e.g., fragments of  $m/z$  92, 94, 95, and 96.



The nature of the acyl residues follows from the proton n.m.r. spectrum. INDOR measurements were used, wherein the methyl signals at  $\delta$  1.83, 1.90, and 2.18 were chosen as monitoring lines. The methyl signal at  $\delta$  1.83 is coupled with the olefinic proton at  $\delta$  6.82, while the two others couple with that at  $\delta$  5.67, indicating exclusively allylic couplings. The former spin-system corresponds to the dicarboxylic acid. The chemical shifts fit mesaconic acid ( $\delta$  6.69 and 5.76, respectively). The second spin-system is congruent with senecioic acid ( $\delta$  1.87,

<sup>1</sup> W. C. Evans, *Linn. Soc. Symp. Ser.*, 1979, **7**, 241.

<sup>2</sup> E. Leete, *J. Med. Plant Res.*, 1979, **2**, 97.

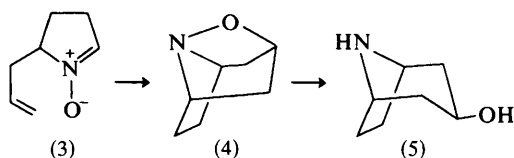
<sup>3</sup> G. Fodor, *et al.*, *J. Chem. Soc.*, 1959, 3461; G. Fodor and A. Romeike, *Ind. Chim. Belge*, 1962, **27**, 555.

2.14, and 5.52), since angelic and tiglic acids would both show vicinal couplings. Chemical evidence, *i.e.* hydrolysis, confirms this view. Schizanthin A gave (+)-(3*R*,6*R*)-tropane-3 $\alpha$ ,6 $\beta$ -diol, mesaconic acid, and senecioic acid. Schizanthin A contains one mole of ethanol as ester while schizanthin B is a 3 $\alpha$ -diester of mesaconic acid.

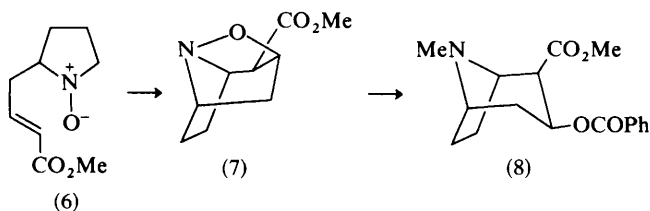
Detailed  $^1\text{H}$  n.m.r. spectra of the alkaloids of *Knightia deplanchei* have been reported.<sup>5</sup>

## 2 Synthesis

The nitrone-based entry into the tropane class of alkaloids has been described in full detail<sup>6</sup> (*cf.* Vol. 9, p. 48). An intramolecular nitrone-induced cycloaddition of the nitrone (3) (itself prepared from 4-nitro-1-butene and acrylic aldehyde) leads to a pseudotropine derivative (4). This, in turn, was reductively cleaved over Pd/C to norpseudotropine (5).



Racemic cocaine (8) was stereospecifically synthesized by cycloaddition of the (*E*) olefinic carboxylic acid nitrone (6) *via* the cyclic hydroxylamine (7). None of the previous approaches to cocaine had the advantage of this stereospecificity since they involved the reduction of an ecgoninone ester, *i.e.* a  $\beta$ -keto-ester, which gave a mixture of diastereoisomers, these being the 2 $\beta$ ,3 $\beta$ -(8), which was



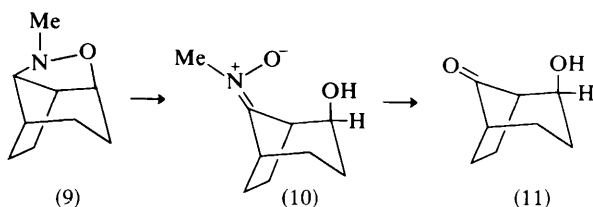
desired, and the 2 $\beta$ ,3 $\alpha$ - and the 2 $\alpha$ ,3 $\beta$ -forms. Unfortunately, the yields from the cyclization of the olefinic nitrone to the cyclic hydroxylamine (isoxazolidine) were far from satisfactory. Therefore, an isoxazolidine (9) was oxidized with peracetic acid to the nitrone (10), and this, in turn, was hydrolysed to the hydroxy-ketone (11).

Similarly, oxazolidine (13) was obtained from  $\Delta^2$ -pyrroline *N*-oxide (12) and methyl but-3-enoate, by cycloaddition (90% yield). *m*-Chloroperbenzoic acid (MCBA) converted the adduct into the ester nitrone (14). The latter, as an adduct

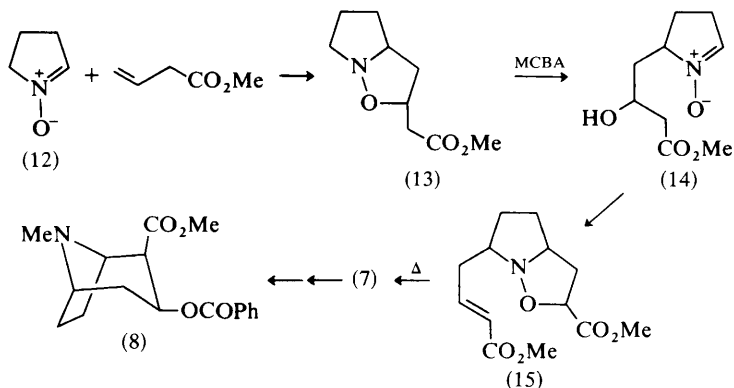
<sup>4</sup> H. Ripperger, *Phytochemistry*, 1979, **18**, 717.

<sup>5</sup> L. Mauri and G. Massiot, *Planta. Med.*, 1978, **34**, 66.

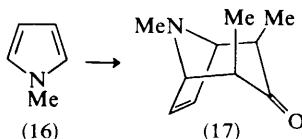
<sup>6</sup> J. J. Tufariello, G. B. Mullen, J. J. Tegeler, E. J. Trybulski, S. C. Wong, and S. A. Ali, *J. Am. Chem. Soc.*, 1979, **101**, 2435.



with methyl acrylate, was dehydrated *via* the mesylate to the blocked nitrone (15), which, as expected, cyclized to the bridged tropane (7) by loss of acrylate. The overall yield, based on methyl acrylate, was 40%. From these the synthesis of (±)-cocaine can be regarded as being accomplished.



A modified Hofmann cyclization<sup>7</sup> of an oxyallyl cation to cocaine analogues was attempted.<sup>8</sup> *N*-Methylpyrrole (16) and 2,4-dibromopentanone gave a fair yield of the cyclo-adduct (17) in the presence of copper and sodium iodide. However, the method did not prove useful for achieving the original aim, *i.e.* a cocaine analogue.



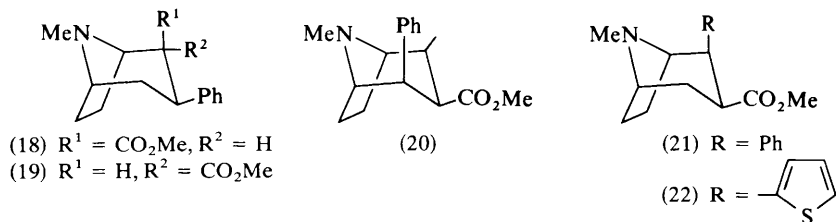
*N*-Alkylated norcocaine derivatives, *e.g.* *N*-allyl-, *N*-dimethylallyl-, *N*-cyclopropylmethyl-, and *N*-(3-butenyl)-norcocaine, were prepared<sup>9</sup> and examined for cocaine-like activity. Cocaine was demethylated with 2,2,2-trichloroethyl chloroformate, followed by reduction in acidic medium, and subsequently *N*-alkylated.

<sup>7</sup> See 'Tropane Alkaloids', in these Reports, Vol. 5, p. 69; Vol. 6, p. 67.

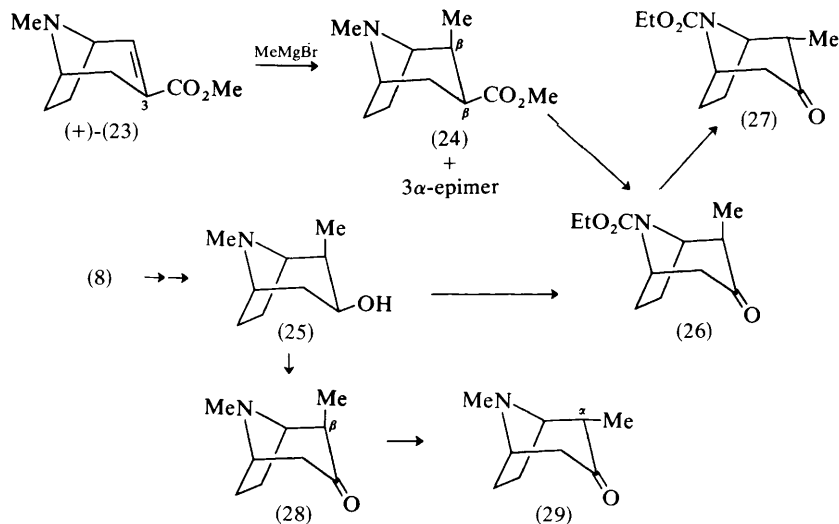
<sup>8</sup> A. P. Cowling and J. Mann, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1564.

<sup>9</sup> E. S. Lazer, N. D. Aggarwal, S. J. Hite, K. A. Nieforth, R. T. Kelleher, R. D. Speakman, C. R. Shuster, and W. Wolverton, *J. Pharm. Sci.*, 1978, **67**, 1656.

*exo,exo*-2-Aryltropane-3-carboxylic esters [(18) and its antipode (19), (20), (21), and (22)] were synthesized<sup>10</sup> by the Grignard reaction from anhydroecgonine esters, as new hypoglycaemic agents that have analgesic activity.



The absolute configuration of (18) was established<sup>11</sup> by analogy with the 2-methyl derivative. Configurational correlation of the 2-methyl derivative gave 2 $\alpha$ -methyl-*N*-ethoxycarbonyl-3-tropane ( $[\alpha]_D^{20} = -26.4^\circ$ ). 2 $\beta$ -Methyl-3-tropanone ( $[\alpha]_D^{20} = -25^\circ$ ) had previously been prepared from cocaine,<sup>12</sup> so its absolute configuration is unequivocal. Since both the 2-methyl and the 2-phenyl derivative were prepared by a Grignard 1,4-addition reaction upon the  $\alpha\beta$ -unsaturated carboxylic ester, *i.e.* 'anhydroecgonine' (23), the authors felt this analogy to be convincing. Scheme 1 shows the way they proceeded [(23)  $\rightarrow$  (24)  $\rightarrow$  (26)  $\rightarrow$  (27), and (8)  $\rightarrow$  (25)  $\rightarrow$  (26)  $\rightarrow$  (27)]. There is some disparity in these optical rotational values, since the authentic<sup>12</sup> 2 $\beta$ -methyl ketone (28) proved to be laevorotatory while the 2 $\alpha$ -methyl ketone (29) was dextrorotary, as its hydrochloride.<sup>12</sup> The oxime of (29) was, however,



**Scheme 1**

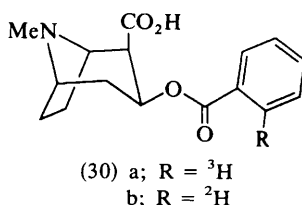
<sup>10</sup> R. L. Clarke, M. L. Heckeler, A. J. Gambino, and S. J. Daum, *J. Med. Chem.*, 1978, **21**, 1243.

<sup>11</sup> R. L. Clarke and M. L. Heckeler, *J. Org. Chem.*, 1978, **24**, 4586.

<sup>12</sup> G. Fodor, O. Kovacs, and I. Weisz, *Helv. Chim. Acta*, 1954, **37**, 892.

strongly laevorotatory ( $[\alpha]_D^{20} = -40.8^\circ$ ). There is a gap between the two publications, since the  $[\alpha]_D^{20}$  value for the oxime of (27) was not reported.\* This optical rotation would be even more conclusive, since the  $[\alpha]_D$  values of the *N*-methyl- and of the *N*-ethoxycarbonylmethyl-2 $\beta$ -methyl-tropanols show no reversal of the sign of optical rotation  $[-58.2^\circ$  (ref. 11) and  $-53.2^\circ$  (ref. 12)].

Despite extensive efforts, solid complexes of metal ions with cocaine were not isolated.<sup>13</sup> For the development of a radioimmunoassay for biotransformed cocaine, a tritium-labelled *O*-benzoylcegonine (30) of high specific activity was



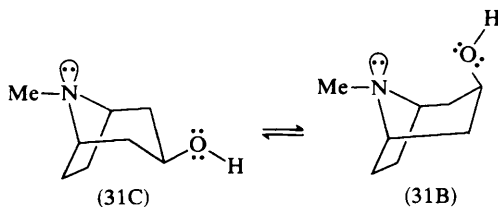
synthesized by  $^3\text{H}$ -hydrogenolysis of 2-iodobenzoylcegonine over Pd on charcoal.<sup>14</sup> Similarly, in a deuterium atmosphere the *O*-[2- $^2\text{H}$ ]benzoylcegonine was obtained.

The Büchi synthesis of betalamic acid dimethyl ester (*cf.* Vol. 9, p. 49) has been described in detail.<sup>15</sup>

The Katritzky reaction of 3-pyridinol has been applied to the synthesis of homotropanes.<sup>16</sup>

### 3 Conformation

The conformation of pseudotropine has been the subject of an extensive  $^1\text{H}$  n.m.r. study<sup>17</sup> by the shift-reagent technique, with  $[\text{Eu}(\text{fod})_3]$ . The change of conformation from the *syn* and *anti* chair form (31C) into the *syn* boat form (31B) upon the action of the shift reagent, when both oxygen and nitrogen may serve as donors, was clearly proven by the good agreement of the calculated *vs.* found values of  $\Delta\delta$ . This was expected, since that conformation is stabilized by chelate formation. The rapid inversion of nitrogen is neglected in our scheme.



\* Note added in proof: Dr. Clarke has informed the Reporter that this gap has been filled.

<sup>13</sup> H. C. Nelson and G. W. Watt, *J. Inorg. Nucl. Chem.*, 1979, **41**, 99.

<sup>14</sup> R. R. Muccino and L. Serico, *J. Labelled Compd. Radiopharm.*, 1979, **14**, 819.

<sup>15</sup> G. Büchi, H. Firi, and R. Shapiro, *J. Org. Chem.*, 1978, **43**, 4765.

<sup>16</sup> A. R. Katritzky, M. Abdallah, S. Bayyuk, A. M. A. Bolcuri, N. Dennis, and G. J. Sabongi, *Pol. Chem. J.*, 1979, **53**, 57.

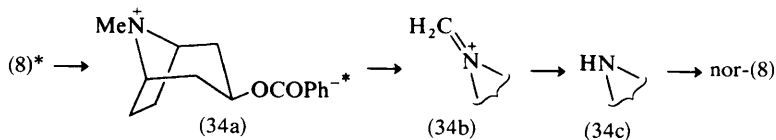
<sup>17</sup> K. Jankowski and J. Israeli, *Bull. Acad. Pol. Sci.*, 1978, **26**, 737.



The analysis<sup>18</sup> of  $^1\text{H}$  n.m.r. spectra of  $3\beta$ -(*N*-propionyl)anilino-*N*-alkyl- and *N*-arylalkyl-nortropenes has shown a preference of the boat form (33) in the  $3\alpha$ -tropanylamines. The compounds were prepared by reductive amination of the corresponding tropanones, followed by von Braun degradation of the tertiary amines with cyanogen bromide, and concluded by *N*-propionylation at N-3. The optimum analgesic properties were achieved with  $3\beta$ -anilino-nortropenes that had *N*-8-benzyl and -phenethyl groups, respectively, probably with the chair form (32) and the bulky group equatorial *vis-à-vis* the piperidine ring.

#### 4 Photochemistry<sup>19</sup>

When irradiated with u.v. light, through a Correx filter, cocaine and its *p*-methoxy and *p*-methyl derivatives, in solution in methanol, produced one mole of formaldehyde besides the norcocaines nor-(8) after a  $\pi$ - $\pi^*$  transition had occurred. However, phenylacetylcegonine methyl ester was *not* *N*-demethylated. The piperidine analogues did not respond to the irradiation either. The mechanism for cocaine is envisaged as being that shown in Scheme 2.



Scheme 2

#### 5 Pharmacology

Most papers referred to in this section are concerned with cocaine. *N*-Demethylation of  $^{14}\text{C}$ -labelled cocaine in isolated hepatocytes was monitored<sup>20</sup> *in vivo* by measuring the exhalation of  $^{14}\text{CO}_2$ . A summary paper on the pharmacology of cocaine has appeared.<sup>21</sup> Furylgyoxylic esters of the tropine type (35) have been synthesized<sup>22</sup> and screened for antiamoebic, antiprotozoal, and antitrichomonal activities.

Inhibitors of the uptake of  $\gamma$ -aminobutyric acid (GABA) have been studied;<sup>23</sup> *e.g.* (1*R*, 2*R*, 5*R*)-nortropene-3-carboxylate, which was prepared for anhydro-

<sup>18</sup> N. Riley and J. R. Bagley, *J. Med. Chem.*, 1979, **22**, 1167.

<sup>19</sup> S. P. Singh, D. Kaufman, and V. I. Stenberg, *J. Heterocycl. Chem.*, 1979, **16**, 625.

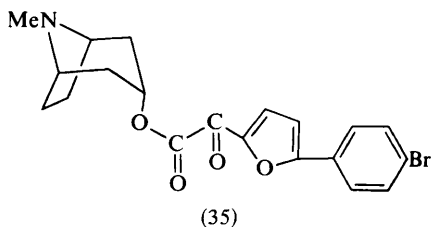
<sup>20</sup> D. J. Stewart, T. Inaba, and W. Kalow, *J. Pharmacol. Exp. Ther.*, 1978, **207**, 171.

<sup>21</sup> P. Kubikowski and W. S. Gomulka, *Zalesnosci Lekowe*, 1978, 113 (*Chem. Abs.* 1979, **90**, 66 293).

<sup>22</sup> A. F. Oleinik, G. A. Modnikova, K. Yu. Novitskii, and N. A. Novitskaya, *Khim. Farm. Zh.*, 1978, **12**, 38.

<sup>23</sup> P. Krogsgaard-Larsen, K. Thyssen, and K. Schaumburg, *Acta Chem. Scand., Sect. B*, 1978, **32**, 327.

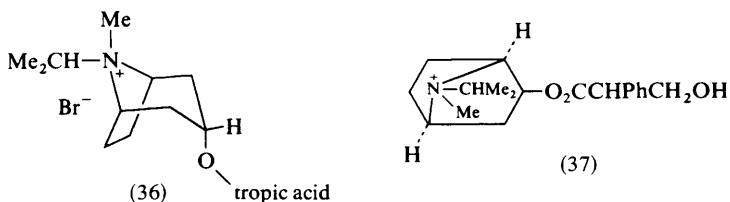




norecgonine. Generalization<sup>24</sup> of norcocaine to the discriminative stimulant properties of cocaine in rats was investigated. Comparative pharmacological studies<sup>25</sup> were conducted in rhesus monkey, *versus Mycobacterium fascicularis*. The behavioural reinforcement produced by cocaine proved to be affected by brain-biogenic amines.<sup>26</sup>

The behavioural effect of self-administered cocaine in squirrel monkeys was investigated by studying the responding that was maintained alternately by cocaine and by the administration of an electric shock.<sup>27</sup> The effects of norcocaine and its derivatives on the schedule-controlled behaviour of pigeons and squirrel monkeys were investigated.<sup>28</sup> Cocaine plasma concentration *vs.* subjective response-time data were obtained and analysed<sup>29</sup> by pharmacokinetic methods. The results corresponded to expectations. Ipratropium bromide (36) [wrong structural formula (37) is shown in the text<sup>30</sup>] proved to be a new bronchodilator.

Scopolamine-induced locomotor activities and rotational behaviour in mice were depressed by catecholamines.<sup>31</sup> The effect of topical scopolamine on the cerebral cortex showed epileptic manifestations in non-anaesthetized cats, and acoustically evoked cortical potentials were decreased.<sup>32</sup>



## 6 Analytical Aspects

A radioimmunoassay for cocaine and benzoylecgonine,<sup>33</sup> using hydroxy-benzoylecgonine and <sup>125</sup>I (thus avoiding false positive results), has been described. A method for mass spectrometric determination of cocaine in urine has

<sup>24</sup> M. L. McKenna, B. T. Ho, and L. F. Englert, *Pharmacol. Biochem. Behav.*, 1979, **10**, 273.

<sup>25</sup> M. C. Wilson, J. A. Bedford, A. H. Kibbe, and J. A. Sam, *Pharmacol. Biochem. Behav.*, 1978, **9**, 141.

<sup>26</sup> J. W. Ross, F. J. Laska, and M. R. Fennessy, *Clin. Exp. Pharmacol. Physiol.*, 1978, **5**, 351.

<sup>27</sup> R. D. Spealman and R. T. Kelleher, *J. Pharmacol. Exp. Ther.*, 1979, **210**, 206.

<sup>28</sup> R. D. Spealman, S. R. Goldberg, R. T. Kelleher, W. H. Morse, D. M. Goldberg, C. G. Hakansson, K. A. Nieforth, and E. S. Lazer, *J. Pharmacol. Exp. Ther.*, 1979, **210**, 196.

<sup>29</sup> M. Mayersohn and D. Perrier, *Res. Commun. Chem. Pathol. Pharmacol.*, 1978, **22**, 465.

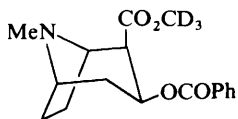
<sup>30</sup> T. Seki and M. Myazaki, *Kyorin Igakukai Zasshi*, 1978, **9**, 91 (*Chem. Abs.*, 1979, **90**, 13 290).

<sup>31</sup> H. Watanabe, K. Watanabe, and K. Hagino, *Jpn. J. Pharmacol.*, 1978, **28**, 465.

<sup>32</sup> F. Senyuva and E. Tan, *Doga*, 1978, **2**, 116 (*Chem. Abs.*, 1979, **90**, 16 283).

<sup>33</sup> J. G. Christenson, U.S. P. 4 102 979 (*Chem. Abs.*, 1979, **90**, 66 873).

been elaborated.<sup>34</sup> Amongst others, the deuteriomethyl ester of benzoylecgonine (38), the *N*-trifluoroacetyl-benzoynorecognine trideuteriomethyl ester (39), and the deuteriomethyl ester of norcocaine (40) have been used as volatile reference compounds. Mapping of cocaine and cinnamoylcocaine was done by MIKES in whole tissues of coca plants.<sup>35</sup> This proved much more sensitive than any other previously known method of analysis.



(38) R = Me

(39) R = COCF<sub>3</sub>

(40) R = H

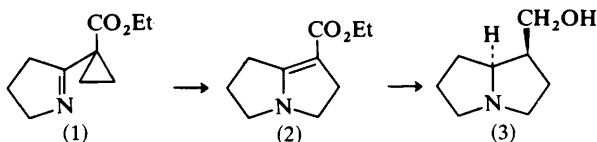
<sup>34</sup> S. P. Jindal, T. Lutz, and P. Westergaard, *Biomed. Mass Spectrom.*, 1978, **5**, 658.

<sup>35</sup> M. Youssefi, R. G. Cooks, and J. L. McLaughlin, *J. Am. Chem. Soc.*, 1979, **101**, 3401.

A comprehensive review on pyrrolizidine chemistry has been published.<sup>1</sup>

### 1 Syntheses of the Necine Bases

Danishefsky<sup>2</sup> has discussed his strategy for the synthesis of necine bases, utilizing the intramolecular opening of activated cyclopropanes (see last year's Reports). Stevens<sup>3</sup> has reviewed some of the synthetic routes available for construction of the necine bases, including his own method which involves the acid-catalysed rearrangement of cyclopropylimines (see these Reports, Vol. 8, Ch. 3). A related approach has been described by Pinnick and Chang.<sup>4</sup> The cyclopropylimine (1) was prepared in nine steps and 42% overall yield. Rearrangement to the unsaturated pyrrolizidine ester (2) took place in 76% yield when the imine (1) was heated at reflux in xylene containing a catalytic amount of ammonium chloride (Scheme 1). The known steps of catalytic hydrogenation



Scheme 1

and reduction with lithium aluminium hydride can be used to synthesize (±)-isoretronecanol (3). The same authors have developed another route to 1-hydroxymethyl-pyrrolizidines;<sup>5</sup> this is outlined in Scheme 2. The lactam (4) was synthesized in 35% yield from pyrrolidone. Complete reduction of the lactam and ester functions of (4) gave (±)-isoretronecanol (3). Selective reduction of the lactam carbonyl of (4) was required, so that (±)-trachelanthamidine (6) could be prepared from the ester (5) by the known steps of epimerization at C-1 and reduction. This selective reduction [(4) → (5)] was achieved with phosphoryl chloride and sodium borohydride in 66% yield.

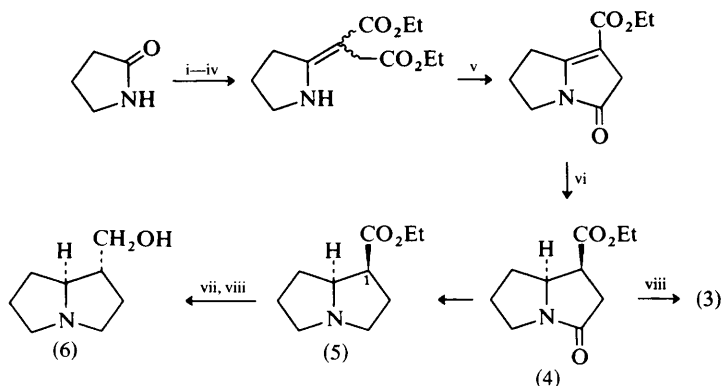
<sup>1</sup> D. J. Robins, *Adv. Heterocycl. Chem.*, 1979, **24**, 247.

<sup>2</sup> S. Danishefsky, *Acc. Chem. Res.*, 1979, **12**, 66.

<sup>3</sup> R. V. Stevens, in 'The Total Synthesis of Natural Products,' ed. J. ApSimon, Wiley-Interscience, New York, 1977, Vol. 3, p. 515.

<sup>4</sup> H. W. Pinnick and Y.-H. Chang, *Tetrahedron Lett.*, 1979, 837.

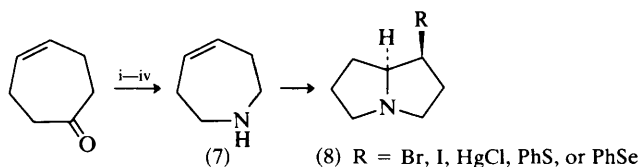
<sup>5</sup> H. W. Pinnick and Y.-H. Chang, *J. Org. Chem.*, 1978, **43**, 4662.



Reagents: i,  $P_2S_5$ ; ii,  $BrCH_2CO_2Et$ ;  $NaHCO_3$ ; iii,  $KOBu^t$ ,  $Ph_3P$ ; iv,  $LiNPr_2$ ,  $BrCH_2CO_2Et$ ; v,  $KH$ ; vi,  $H_2$ , 10%  $Pd/C$ ; vii,  $NaOEt$ ; viii,  $LiAlH_4$ .

**Scheme 2**

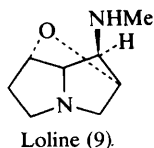
A full paper by Wilson and Sawicki on their transannular route to 1-substituted pyrrolizidines has been published.<sup>6</sup> Transannular electrophilic attack on the amine (7) produced a range of *endo*-1-substituted pyrrolizidines in 63–91% yield (Scheme 3). The stereochemistry of (8;  $R = Br$ ) was confirmed by X-ray crystallography.



Reagents: i,  $NH_2OH \cdot HCl$ ;  $NaHCO_3$ ; ii,  $p\text{-TsCl}$ ,  $py$ ; iii,  $K_2CO_3$ ; iv,  $LiAlH_4$

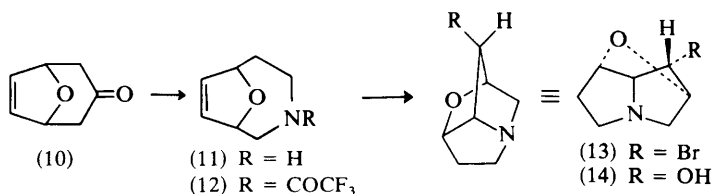
**Scheme 3**

This synthetic strategy has been extended by the same authors to the synthesis of the ring system of the loline alkaloids.<sup>7</sup> Seven simple loline alkaloids [*e.g.* loline (9)] and one dimeric species have been identified (see these Reports, Vol. 8, Ch. 3). The ketone (10) was converted into the amine (11) in analogous fashion to the formation of (7) from cyclohept-4-enone (see Scheme 3). Treatment of the amine (11) with bromine led to transannular cyclization and formation of the 3-aza-9-oxabrendane system (13) in good yield (85%), as shown in Scheme 4. The



<sup>6</sup> S. R. Wilson and R. A. Sawicki, *J. Org. Chem.*, 1979, **44**, 287.

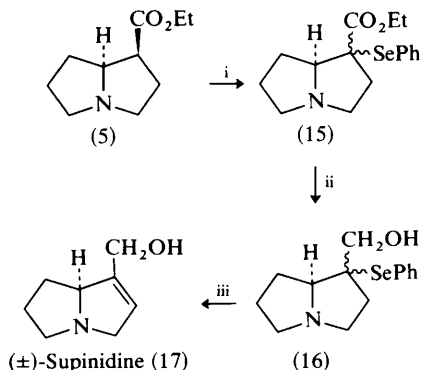
<sup>7</sup> S. R. Wilson and R. A. Sawicki, *Tetrahedron Lett.*, 1978, 2969.



Scheme 4

structure of the bromo-compound (13) was confirmed by X-ray crystallography. Attempts to prepare loline (9) by displacement of the bromine of (13) with methylamine were unsuccessful. A similar route to the related hydroxy-compound (14) has been reported by Glass *et al.*<sup>8</sup> The same amine (11) was prepared and converted into the trifluoroacetamide (12). After formation of the epoxide and removal of the protecting group, transannular displacement of the epoxide by the amine was achieved by heating the amine in ethanol to give the hydroxy-compound (14) in 60% yield. The structure of this compound (14) was also confirmed by X-ray crystallography.

Most of the published syntheses of necine bases have been directed towards fully saturated pyrrolizidine derivatives. Robins and Sakdarat have developed a method for the conversion of saturated pyrrolizidine esters into their 1,2-didehydro-derivatives.<sup>9</sup> Thermal elimination of a phenylseleno-group was used to introduce the unsaturation, and (±)-supinidine (17) was synthesized using this technique. The ester (5) is most conveniently prepared by the two-step stereo-specific route of Pizzorno and Albonico.<sup>10</sup> Phenylselenenylation of the lithium enolate derived from the ester (5) gave the phenylseleno-ester (15), which was reduced to the corresponding alcohol (16) (Scheme 5). *syn*-Elimination of the selenoxide derived from (16) gave (±)-supinidine (17). Each step proceeded in about 60% yield. None of the isomeric 1,8-didehydro-base was detected.



Reagents: i, Pr<sub>2</sub>NH, Bu<sup>n</sup>Li, PhSeCl; ii, LiAlH<sub>4</sub>; iii, H<sub>2</sub>O<sub>2</sub>

Scheme 5

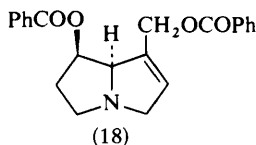
<sup>8</sup> R. S. Glass, D. R. Deardorff, and L. H. Gains, *Tetrahedron Lett.*, 1978, 2965.

<sup>9</sup> D. J. Robins and S. Sakdarat, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1734.

<sup>10</sup> M. T. Pizzorno and S. M. Albonico, *J. Org. Chem.*, 1974, **39**, 731.

## 2 Alkaloids of the Boraginaceae

The flowers of *Caccinia glauca* Savi contain a new alkaloid, retronecine-7,9-dibenzoate (18).<sup>11</sup> The structure was established by spectroscopic data, and by its acid hydrolysis to retronecine and benzoic acid, and confirmed by synthesis from retronecine and benzoyl chloride.



## 3 Alkaloids of the Compositae

The occurrence and distribution of pyrrolizidine alkaloids in members of the tribes Eupatorieae<sup>12a</sup> and Senecioneae<sup>12b</sup> have been reviewed.

Previous investigations on *Petasites japonicus* Maxim. led to the identification of two new alkaloids, petasitenine (20) and neopetasitenine (21) (see these Reports, Vol. 8, Ch. 3). In a further study of this species, Yamada *et al.* have identified senkirkine (19)<sup>13</sup> and two new minor alkaloids, *i.e.* petasinine (23) and petasinoside (24).<sup>14</sup> Hydrolysis of both new alkaloids gave a new necine, petasinecine (22). The mass spectrum of petasinecine was consistent with a 2-hydroxy-1-hydroxymethyl-pyrrolizidine structure. In particular, the peak at  $m/z$  98 that is present in the mass spectrum of (22) is not shown by pyrrolizidine derivatives with hydroxy substituents in ring A.<sup>15</sup> The four possible stereoisomers of 2-hydroxy-1-hydroxymethyl-pyrrolizidine have previously been synthesized as racemates.<sup>16</sup> The diacetate of petasinecine (22) was identical with the diacetate of ( $\pm$ )-2- $\beta$ -hydroxy-1- $\beta$ -hydroxymethyl-8- $\alpha$ -pyrrolizidine. Comparison of the  $^1\text{H}$  n.m.r. spectra of petasinine (23), its acetate derivative, and petasinecine (22) revealed the presence of primary and secondary hydroxy-groups, and indicated that the secondary hydroxy-group is esterified in petasinine. Methanolysis of the triacetate of petasinoside (24) gave petasinecine (22), methyl angelate, and the methyl ester (25), whose structure was established by the synthesis of its triacetate derivative by condensation of L-rhamnose tetra-acetate with methyl *trans*-p-coumarate. The  $\alpha$ -configuration of the glycosidic linkage in petasinoside (24) was deduced from the  $^{13}\text{C}$ - $^1\text{H}$  coupling constant of 174 Hz for the anomeric carbon (a lower value is expected for the  $\beta$ -configuration). Finally, the location of the two esterifying acids in petasinoside was established by conversion of petasinine (23) into the triacetate of petasinoside, using the appropriate acid chloride [derived from the triacetate derivative of (25)].

<sup>11</sup> M. A. Siddiqi, K. A. Suri, O. P. Suri, and C. K. Atal, *Phytochemistry*, 1978, **17**, 2049.

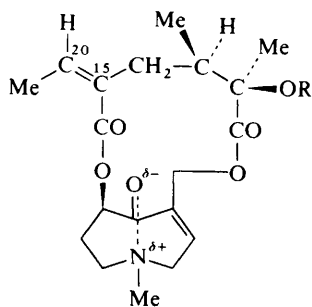
<sup>12</sup> 'The Biology and Chemistry of the Compositae,' ed. V. H. Heywood, J. B. Harborne, and B. L. Turner, Academic Press, London, 1977, (a) X. A. Dominguez, Vol. 1, Ch. 16, p. 487; (b) D. J. Robins, Vol. 2, Ch. 30, p. 831.

<sup>13</sup> K. Yamada, H. Tatematsu, Y. Kyotani, Y. Hirata, M. Haga, and I. Hirono, *Phytochemistry*, 1978, **17**, 1667.

<sup>14</sup> K. Yamada, H. Tatematsu, R. Unno, Y. Hirata, and I. Hirono, *Tetrahedron Lett.*, 1978, 4543.

<sup>15</sup> A. J. Aasen, C. C. J. Culvenor, and L. W. Smith, *J. Org. Chem.*, 1969, **34**, 4137.

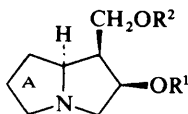
<sup>16</sup> A. J. Aasen and C. C. J. Culvenor, *J. Org. Chem.*, 1969, **34**, 4143.



Senkirkine (19) R = H

Petasitenine (20) R = H;  $\beta$ -epoxide at C-15, C-20

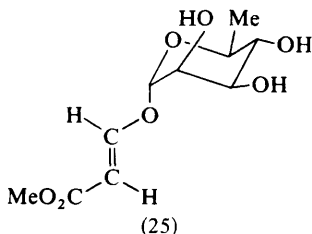
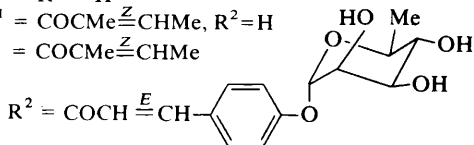
Neopetasitenine (21) R = COMe;  $\beta$ -epoxide at C-15, C-20



Petasinecine (22) R<sup>1</sup> = R<sup>2</sup> = H

Petasinine (23) R<sup>1</sup> = COCMe $\equiv$ CHMe, R<sup>2</sup> = H

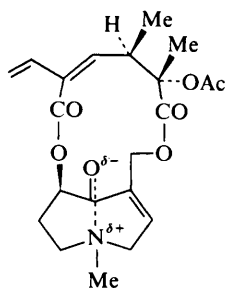
Petasinoside (24) R<sup>1</sup> = COCMe $\equiv$ CHMe



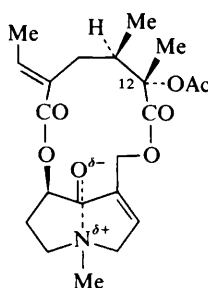
Clivorine (26), ligularine, and an unidentified alkaloid, ligudentine, were previously found in *Ligularia dentata* Hara. (see these Reports, Vol. 3, Ch. 4). Re-investigation of this species by Hikichi *et al.* has yielded clivorine and a new alkaloid, ligularidine (27), which has high mutagenic activity.<sup>17</sup> Alkaline hydrolysis of ligularidine gave otonecine (28) and a lactone which has physical data in agreement with those of the lactone (29) prepared by Edwards and Matsumoto.<sup>18</sup> Confirmation of the structure and absolute configuration of ligularidine was obtained by the conversion of clivorine (26) into ligularidine (27) by partial

<sup>17</sup> M. Hikichi, Y. Asada, and T. Furuya, *Tetrahedron Lett.*, 1979, 1233.

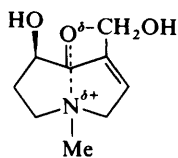
<sup>18</sup> J. D. Edwards and T. Matsumoto, *J. Org. Chem.*, 1967, **32**, 1837.



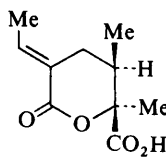
Clivorine (26)



Ligularidine (27)



Otonecine (28)



(29)

hydrogenation, using Raney nickel catalyst. Both alkaloids have the unusual 12*S*-configuration.

More acyl-pyrrole derivatives have been detected in a number of *Senecio* species by Bohlmann and co-workers. Pterophorine (30) has been isolated from *Senecio pubigerus* L.,<sup>19</sup> *S. aucheri* DC., *S. warszewiczii* A. Br. et Bouché,<sup>20</sup> *S. rudbeckiaefolius* Meyer et Walp., *S. colaminus* Cuatr., and *S. pulviniformis* Hieron.<sup>21</sup> The last-mentioned species also yielded a new compound, formulated as the C-7 epimer of pterophorine on the basis of its <sup>1</sup>H n.m.r. spectrum. Senaetnine (31) has also been isolated from *S. longiflorus* and *S. aucheri*.<sup>20</sup> The latter plant contained a new compound, which is believed to be the geometrical isomer of senaetnine (31) from its <sup>1</sup>H n.m.r. spectrum. An isomer (32) of dehydroisosenaetnine (34) was isolated from *S. barbertonicus* Klatt., and a c.d. study of some of these acyl-pyrroles was carried out.<sup>22</sup> The c.d. curves of isosenaetnine (33) and dehydroisosenaetnine (34) were very similar to those of senecionine (35) and seneciphylline (36), respectively. It is therefore assumed that both (33) and (34) possess the same 7β-configuration. The isomer (32) of dehydroisosenaetnine and senaetnine (31) have mirror-image curves compared with that of senecionine (35), suggesting that (31) and (32) have the opposite 7α-configuration.

Senampelines C (37) and D (38) have again been isolated, as a mixture, from *Senecio mikanoides* [Otto ex] Harv.<sup>20</sup> In addition, three new senampelines, i.e. E (39), F (40), and G (41), were also present in this species, in the ratio 2 : 1 : 1. The structures of senampelines E—G were determined by <sup>1</sup>H n.m.r. spectroscopy and by degradation by methoxide to the corresponding aldehyde esters (42).<sup>20</sup>

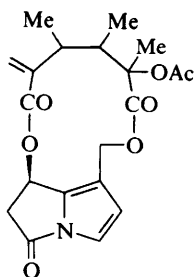
<sup>19</sup> F. Bohlmann, C. Zdero, and A. A. Natsu, *Phytochemistry*, 1978, **17**, 1757.

<sup>20</sup> F. Bohlmann, C. Zdero, D. Berger, A. Suwita, P. Mahanta, and C. Jeffrey, *Phytochemistry*, 1979, **18**, 79.

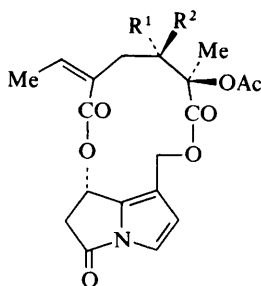
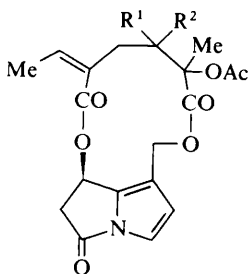
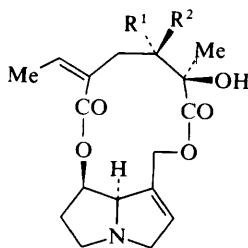
<sup>21</sup> F. Bohlmann and C. Zdero, *Phytochemistry*, 1979, **18**, 125.

<sup>22</sup> F. Bohlmann, C. Zdero, and G. Snatzke, *Chem. Ber.*, 1978, **111**, 3009.





Pterophorine (30)

Senaetnine (31)  $R^1 = H, R^2 = Me$   
(32)  $R^1 R^2 = CH_2$ Isosenaetnine (33)  $R^1 = H, R^2 = Me$   
Dehydroisosenaetnine (34)  $R^1 R^2 = CH_2$ Senecionine (35)  $R^1 = H, R^2 = Me$   
Seneciphylline (36)  $R^1 R^2 = CH_2$ 

Senkirkine (19) and a new alkaloid, procerine, have been obtained from *Senecio procerus* L. var. *procerus* Stoj. Stef. et Kit. by Jovčeva *et al.*<sup>23</sup> The proposed structure (43) for this alkaloid,  $C_{13}H_{18}NO_5$ , m.pt. 238—290 °C(!), was assigned mainly on the basis of the mass spectrum, and there is clearly insufficient evidence to support this structure.

Senecionine (35) has been isolated from *Senecio nemorensis* L. ssp. *fuchsii* Gmelin.<sup>24</sup>

#### 4 Alkaloids of the Eleocarpaceae

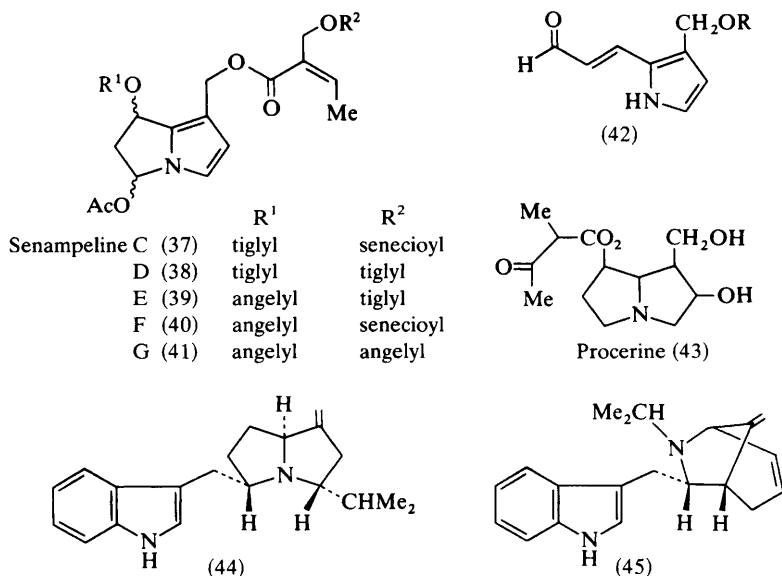
Peduncularine was obtained from *Aristolelia peduncularis* (Labill.) Hook f. by Bick *et al.*<sup>25</sup> who postulated an indole-pyrrolizidine structure (44) for this alkaloid. On the basis of more extensive spectroscopic studies (including  $^{13}C$  n.m.r. spectroscopic data) and degradative work, a revised structure (45) has been proposed by Ros *et al.*<sup>26</sup> which shows that peduncularine belongs to the class of monoterpene indole alkaloids, and has no connection with pyrrolizidine alkaloids.

<sup>23</sup> R. J. Jovčeva, A. Boeva, H. Potěšilová, A. Klásek, and F. Šantavý, *Collect. Czech Chem. Commun.*, 1978, **43**, 2312.

<sup>24</sup> H. Wiedenfeld and E. Röder, *Phytochemistry*, 1979, **18**, 1083.

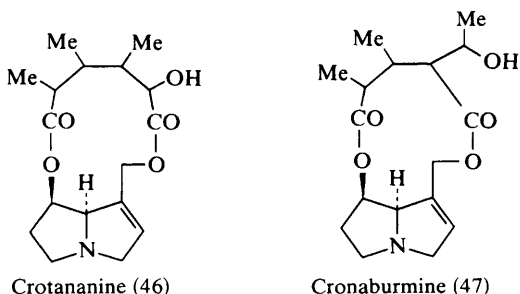
<sup>25</sup> I. R. C. Bick, J. B. Bremner, N. W. Preston, and I. C. Calder, *J. Chem. Soc., Chem. Commun.*, 1971, 1155.

<sup>26</sup> H.-P. Ros, R. Kyburz, N. W. Preston, R. T. Gallagher, I. R. C. Bick, and M. Hesse, *Helv. Chim. Acta*, 1979, **62**, 481.



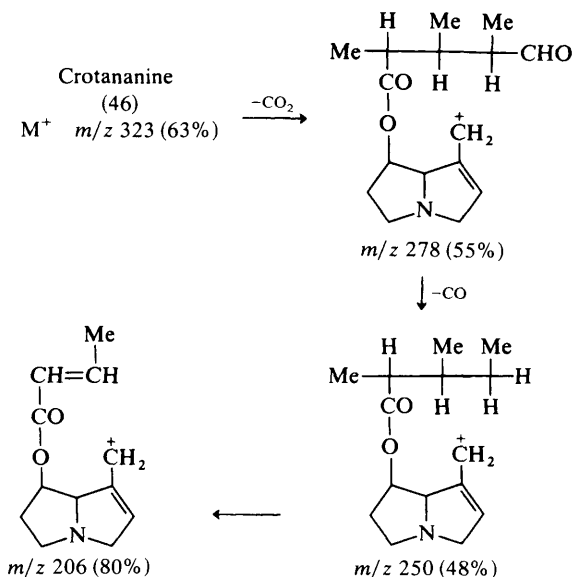
## 5 Alkaloids of the Leguminosae

Investigation of the seeds of *Crotalaria nana* Burm. by Siddiqi *et al.* has established the presence of two new alkaloids, crotananine (46)<sup>27</sup> and cronaburmine (47).<sup>28</sup> In the  $^1\text{H}$  n.m.r. spectrum of crotananine, the difference in chemical shift between the protons attached to C-9 is 0.9 p.p.m. This is considered to be good evidence for a twelve-membered macrocyclic diester ring. Hydrolysis of crotananine (46) with barium hydroxide gave retronecine (51) and a new  $\text{C}_9$  necic acid, crotananic acid. This acid gave a positive ferric chloride test, consistent with the presence of an  $\alpha$ -hydroxy-acid. In the  $^1\text{H}$  n.m.r. spectrum of crotananic acid, all three methyl signals appeared as doublets. In the mass spectrum of crotananine (46), the fragment ion at  $m/z$  278 indicated that the hydroxy-group is at C-12 (Scheme 6), and fragment ions at  $m/z$  250 and 206 were consistent with the



<sup>27</sup> M. A. Siddiqi, K. A. Suri, O. P. Suri, and C. K. Atal, *Phytochemistry*, 1978, **17**, 2143.

<sup>28</sup> M. A. Siddiqi, K. A. Suri, O. P. Suri, and C. K. Atal, *Indian J. Chem., Sect. B*, 1978, **16**, 1132.



Scheme 6

proposed mode of attachment of the necic acid to the base. Acid hydrolysis of cronaburmine (47) gave retronecine and another new  $C_9$  necic acid, isolated as its  $\delta$ -lactone. Proton n.m.r. spectral data for this lactone were consistent with the proposed structure. Major ions in the mass spectrum of cronaburmine (47) at  $m/z$  279 and 207 (cf. Scheme 6) are considered to support the proposed mode of esterification of the acid to retronecine. Unfortunately, due to a misprint in the paper, the difference in chemical shift for the protons attached to C-9 in cronaburmine is not given.

## 6 Alkaloids of the Scrophulariaceae

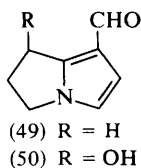
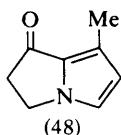
Senecionine (35) has been identified in *Castilleja rhexifolia* Rydb.<sup>29</sup> This is the first report of any alkaloids occurring in the genus *Castilleja* and also the first report of pyrrolizidine alkaloids in the Scrophulariaceae.

## 7 Pyrrolizidine Derivatives in the Lepidoptera

Male *Danaus* butterflies ingest pyrrolizidine alkaloids and convert them into pheromones such as danaidone (48), danaidal (49), and hydroxydanaidal (50), which are released from the abdominal hairpencil organs during courtship behaviour. Boppré *et al.*<sup>30</sup> have observed that for *Danaus chrysippus* males the hairpencils must be dipped into their other scent organs – the wing pockets – before pheromones are produced.

<sup>29</sup> F. R. Stermitz and T. R. Suess, *Phytochemistry*, 1978, **17**, 2142.

<sup>30</sup> M. Boppré, R. L. Petty, D. Schneider, and J. Meinwald, *J. Comp. Physiol., Sect. A*, 1978, **126**, 97.



The Monarch butterfly (*Danaus plexippus*) was found to sequester and store pyrrolizidine alkaloids when fed on homogenized leaves of *Senecio vulgaris*.<sup>31</sup> It is thought that the presence of these alkaloids in the butterfly may contribute towards its defence mechanism, by making it unpalatable to potential predators. Unlike many other danaiids, the Monarch is not dependent on pyrrolizidine alkaloids as precursors of its sex pheromones.

Moths of the families Ctenuchidae and Arctiidae are also attracted to plants containing pyrrolizidine alkaloids.<sup>32</sup> In particular, larvae of *Nyctemera annulata* Boisduval (Arctiidae) (the Magpie moth) ingest pyrrolizidine alkaloids from a variety of *Senecio* species. Benn *et al.*<sup>33</sup> have shown that larvae feeding on *S. spathulatus* A. Rich are able to store pyrrolizidine alkaloids. These alkaloids subsequently appeared in the adult moths and their eggs, and also in a parasite of *N. annulata* larvae.

## 8 General Studies

The *N*-oxides of pyrrolizidine alkaloids are included in a general review of alkaloid *N*-oxides.<sup>34</sup> A method for converting *N*-oxides into their corresponding tertiary bases, using a redox polymer of indigo sulphonate on a highly porous anion-exchanger, has been described.<sup>35</sup> This procedure gives higher yields than reduction by zinc in acid solution. A non-aqueous titration technique has been used for the quantitative determination of the alkaloids present in *Senecio nemorensis* L.<sup>36</sup> A reverse-phase high-performance liquid chromatographic method for separation of pyrrolizidine alkaloids, using a methanol-0.01M-KH<sub>2</sub>PO<sub>4</sub> (pH 6.3) solvent system, has been reported.<sup>37</sup> The identification of necic acids by thin-layer chromatography has been discussed.<sup>38</sup>

The <sup>13</sup>C n.m.r. spectral assignments have been made<sup>39</sup> for a number of pyrrolizidine alkaloids, including retronecine (51), platynecine, heliotrine, supinine, lasiocarpine, crispatine, monocrotaline (54), madurensine, and retrorsine. Some of the assignments reported for retrorsine have been revised. A <sup>1</sup>H n.m.r. spectroscopic method for determination of the amount of pyrrolizidine alkaloids present in the extracts of small samples of a number of *Senecio* species

<sup>31</sup> M. Rothschild and J. A. Edgar, *J. Zool.*, 1978, **186**, 347.

<sup>32</sup> G. J. Goss, *Environ. Entomol.*, 1979, **8**, 487.

<sup>33</sup> M. Benn, J. deGrave, C. Gnanasunderam, and R. Hutchins, *Experientia*, 1979, **35**, 731.

<sup>34</sup> J. D. Phillipson and S. S. Handa, *Lloydia*, 1978, **41**, 385.

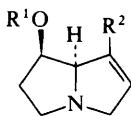
<sup>35</sup> H. J. Huizing and T. M. Malingré, *J. Chromatogr.*, 1979, **173**, 187.

<sup>36</sup> E. Gencheva, *Farmatsiya (Sofia)*, 1978, **28**, 21 (*Chem. Abs.*, 1979, **90**, 127 593).

<sup>37</sup> H. J. Segall, *J. Liq. Chromatogr.*, 1979, **2**, 429.

<sup>38</sup> A. Klásek, M. Ciesla, and S. Dvořáčková, *Acta Univ. Palacki. Olomuc., Fac. Med.*, 1976, **79**, 47 (*Chem. Abs.*, 1978, **89**, 122 653).

<sup>39</sup> N. V. Mody, R. S. Sawhney, and S. W. Pelletier, *J. Nat. Products*, 1979, **42**, 417.

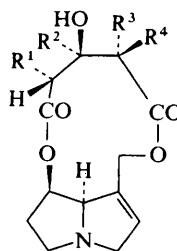


(51)  $R^1 = \text{H}, R^2 = \text{CH}_2\text{OH}$

(52)  $R^1 = \text{COCF}_3 \text{ or } \text{COC}_3\text{F}_7$

$R^2 = \text{CH}_2\text{OCOCF}_3 \text{ or } \text{CH}_2\text{OCOC}_3\text{F}_7$

(53)  $R^1 = \text{COCF}_3 \text{ or } \text{COC}_3\text{F}_7, R^2 = \text{CH}_2^+$



Monocrotaline (54)  $R^1 = R^2 = R^3 = \text{Me}, R^4 = \text{OH}$

Fulvine (55)  $R^1 = R^2 = R^3 = \text{Me}, R^4 = \text{H}$

Axillarine (56)  $R^1 = \text{CHMe}_2, R^2 = \text{H},$   
 $R^3 = \text{CH(OH)Me}, R^4 = \text{OH}$

has been described.<sup>40</sup> The signal for the vinyl proton at C-2 present in retronecine (51), the most common of the necine bases, was measured relative to a known amount of a standard (*p*-dinitrobenzene) added to each sample. Using this technique, the proportions of some individual alkaloids were estimated. Another new analytical method, utilizing electron-capture gas-liquid chromatography, also depends upon the presence of retronecine in many pyrrolizidine alkaloids.<sup>41</sup> A mixture of pyrrolizidine alkaloids from *Senecio jacobaea* was hydrolysed to give retronecine. Derivatization was carried out with a variety of reagents, but the use of fluorinated derivatives (52) made analysis by electron capture more sensitive. The base peak in the mass spectrum is a stabilized allylic cation (53), formed by alkyl-oxygen bond fission of the ion produced by electron impact. The fission of this bond is aided by the electron-withdrawing fluorinated groups on the esters (52). This analytical technique has been applied to the detection of indicine (a C-9 ester of retronecine) and its *N*-oxide in plasma and urine.<sup>42</sup> Derivatization of the free base was carried out with pentafluoropropionic anhydride to facilitate detection by electron-capture g.l.c. Levels of alkaloid of 100 ng ml<sup>-1</sup> (plasma) and 200 ng ml<sup>-1</sup> (urine) were detected in rabbits and one human patient.

The *X*-ray crystal structure of monocrotaline (54) has been determined by Stoeckli-Evans<sup>43</sup> and by Wang.<sup>44</sup> Monocrotaline has an eleven-membered macrocyclic ring, as in fulvine (55) and axillarine (56). The pyrrolizidine nucleus exists in an *exo*-puckered form with a puckering angle of 37° (46° in fulvine, 42° in axillarine).<sup>43</sup> The ester carbonyl groups are *syn*-parallel and are directed below the plane of the eleven-membered ring, as with fulvine and axillarine. Pyrrolizidine alkaloids with twelve-membered rings contain ester carbonyl bonds that are anti-parallel, and the C-9 ester carbonyl bond is directed above the plane of the macro-ring.

<sup>40</sup> R. J. Molyneux, A. E. Johnson, J. N. Roitman, and M. E. Benson, *J. Agric. Food Chem.*, 1979, **27**, 494.

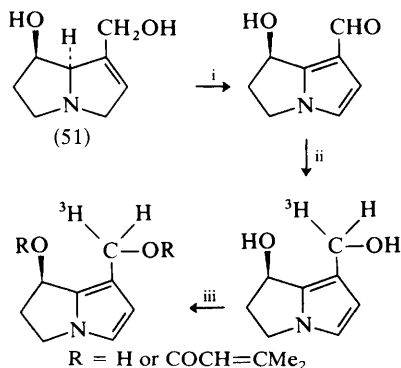
<sup>41</sup> M. Deinzer, P. Thomson, D. Griffin, and E. Dickinson, *Biomed. Mass Spectrom.*, 1978, **5**, 175.

<sup>42</sup> M. M. Ames and G. Powis, *J. Chromatogr.*, 1978, **166**, 519.

<sup>43</sup> H. Stoeckli-Evans, *Acta Crystallogr., Sect. B.*, 1979, **35**, 231.

<sup>44</sup> S.-T. Wang, K'o Hsueh T'ung Pao, 1978, **23**, 670 (*Chem. Abs.*, 1979, **90**, 187 191).

The preparation of tritium-labelled dehydroretronecine esters has been described.<sup>45</sup> A mixture of mono- and di-esters of dehydroretronecine was produced in *ca.* 13% overall yield from retronecine (51) (Scheme 7). The corresponding tritium-labelled diseneciolyretronecine was previously made by these workers.<sup>46</sup>



Reagents: i, Activated  $\text{MnO}_2$ ; ii,  $\text{NaB}^3\text{H}_4$ ; iii,  $\text{Me}_2\text{C}=\text{CHCOCl}$

Scheme 7

## 9 Pharmacological and Biological Studies

Human health problems caused by ingestion of pyrrolizidine alkaloids continue to receive attention. A large outbreak of veno-occlusive disease in Afghanistan was caused by consumption of wheat flour that was heavily contaminated with seeds of *Heliotropium popovii*.<sup>47</sup> The main pyrrolizidine alkaloid present was heliotrine, and the characteristic morphological changes in the liver caused by this disease have now been described.<sup>48</sup> Pyrrolizidine alkaloids have been identified as one of the causes of primary liver cancer in countries of tropical Africa, where the incidence of this cancer is the highest in the world.<sup>49</sup> The occurrence of pyrrolizidine alkaloids in food has been reviewed.<sup>50</sup> Herbal teas made from plants containing pyrrolizidine alkaloids are popular in many countries. Comfrey leaves (*Symphytum* spp.; Boraginaceae) are frequently used. These contain pyrrolizidine alkaloids, and it has been shown that Comfrey roots and leaves cause liver tumours when added to the diet of rats.<sup>51</sup> Pyrrolizidine alkaloids are included in a review of carcinogenic alkaloids of plant origin.<sup>52</sup> Lasiocarpine was shown to cause liver cancer in rats.<sup>53</sup> As observed many times before, rats given extracts of

<sup>45</sup> R. C. Schumaker, M.-T. S. Hsia, J. L. Seymour, and J. R. Allen, *J. Labelled Compd. Radiopharm.*, 1978, **15** (Suppl. Vol.), 227.

<sup>46</sup> I. S. Hsu and J. R. Allen, *J. Labelled Compd.*, 1975, **11**, 71.

<sup>47</sup> O. Mahabbat, R. N. Srivastava, M. S. Younos, G. G. Sediq, A. A. Merzad, and G. N. Aram, *Lancet*, 1976, **2**, 269.

<sup>48</sup> H. D. Tandon, B. N. Tandon, and A. R. Mattocks, *Am. J. Gastroenterol.*, 1978, **70**, 607.

<sup>49</sup> E. A. Bababunmi, *J. Toxicol. Environ. Health*, 1978, **4**, 691.

<sup>50</sup> P. Austwick and A. R. Mattocks, *Chem. Ind. (London)*, 1979, 76.

<sup>51</sup> I. Hirono, H. Mori, and M. Haga, *J. Nat. Cancer Inst.*, 1978, **61**, 865.

<sup>52</sup> I. Hirono, *Gan to Kagaku Ryoho*, 1979, **6**, 91 (*Chem. Abs.*, 1979, **91**, 50 403).

<sup>53</sup> *Gov. Rep. Announce. Index (U.S.)*, 1978, **78**, 216 (*Chem. Abs.*, 1978, **89**, 124 293).

*Senecio vulgaris* L. suffered liver damage.<sup>54</sup> Various aspects of the poisoning of animals by pyrrolizidine alkaloids were discussed at a recent symposium,<sup>55</sup> including the pathology of the disease,<sup>55a</sup> the mechanism of cytotoxic action of the alkaloids,<sup>55b</sup> methods for prevention of pyrrolizidine alkaloid poisoning in animals,<sup>55c</sup> and the transfer of these alkaloids from *Senecio jacobaea* into the milk of lactating cows and goats.<sup>55d</sup>

Pyrrolizidine alkaloids must be metabolized to pyrrole derivatives before they produce pathological changes in animals. Subcutaneous injection or topical application of dehydroretronecine caused a high incidence of skin tumours in mice.<sup>56</sup> Oral administration of this compound or of monocrotaline (54) produced significant pulmonary damage to rats.<sup>57</sup> Pretreatment of rats with monocrotaline gave perfused livers which metabolized less of the biogenic amines such as 5-hydroxytryptamine and noradrenaline than normal perfused lungs.<sup>58</sup> An increased excretion of urinary porphyrins by white rats was observed following intragastrical administration of monocrotaline.<sup>59</sup> Restriction of the diet of rats after monocrotaline intoxication inhibited the progression of pulmonary changes.<sup>60</sup>

It has been suggested that increased levels of  $\gamma$ -glutamyl transpeptidase may be the most specific enzyme indicator for chronic or low-level pyrrolizidine alkaloid toxicosis in cattle and ponies.<sup>61</sup> Oral administration of iodoform (32 mg day<sup>-1</sup>) to sheep which were fed on dried *Heliotropium europaeum* plants led to prolonged survival times.<sup>62</sup> Higher levels of iodoform were hepatotoxic. Indicine *N*-oxide has some antileukaemic activity when given intraperitoneally to mice.<sup>63</sup> However, it produced acute cardiovascular effects on anaesthetized beagle hounds following continuous intravenous infusion.<sup>64</sup>

The seed mortality due to chewing insects is high for the East African population of the shrub *Crotalaria pallida*.<sup>65</sup> Unexpectedly, it was found that plants with higher levels of alkaloid in the seeds experienced greater seed predation.

All 27 bisquaternary derivatives of pyrrolizidine alkaloids tested inhibited nerve muscle transmissions.<sup>66</sup> One of the most active compounds studied was nonamethylene-1,9-bisviridiflorium dibromide (57).

<sup>54</sup> P. Delaveau, S. Ferry, M. Barbagelatta, and C. Casper, *Ann. Pharm. Fr.*, 1979, **37**, 13.

<sup>55</sup> 'Effects of Poisonous Plants on Livestock,' ed. R. F. Keeler, K. R. Van Kampen, and L. F. James, Academic Press, New York, 1978, (a) P. T. Hooper, p. 161; (b) A. R. Mattocks, p. 177; (c) C. C. J. Culvenor, p. 189; (d) J. O. Dickinson and R. R. King, p. 201.

<sup>56</sup> W. D. Johnson, K. A. Robertson, J. G. Pounds, and J. R. Allen, *J. Nat. Cancer Inst.*, 1978, **61**, 85.

<sup>57</sup> R. J. Huxtable, D. Garamitro, and D. Eisenstein, *Mol. Pharmacol.*, 1978, **14**, 1189.

<sup>58</sup> C. N. Gillis, R. J. Huxtable, and R. A. Roth, *Br. J. Pharmacol.*, 1978, **63**, 435.

<sup>59</sup> R. Schoental and S. Gibbard, *Biochem. Soc. Trans.*, 1979, **7**, 127.

<sup>60</sup> Y. Hayashi, M. Kato, and H. Otsuka, *Toxicol. Lett.*, 1979, **3**, 151.

<sup>61</sup> A. M. Craig, C. Meyer, L. D. Koller, and J. A. Schmitz, *Proc. Annu. Meet. Amer. Assoc. Vet. Lab. Diagn.*, 1978, **21**, 161 (*Chem. Abs.*, 1979, **90**, 198 413).

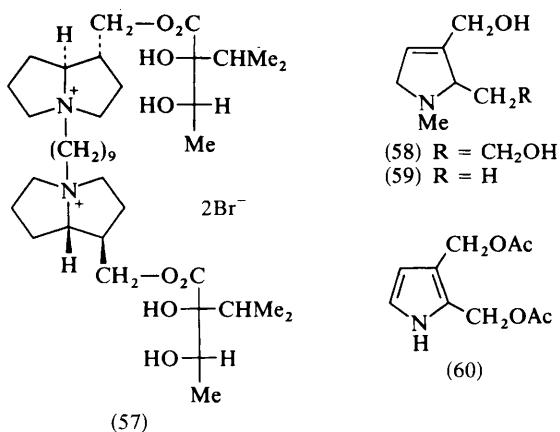
<sup>62</sup> G. W. Lanigan, A. L. Payne, and J. E. Peterson, *Aust. J. Agric. Res.*, 1978, **29**, 1281.

<sup>63</sup> S. Tsukagoshi, *Gan to Kagaku Ryoho*, 1978, **5**, 1081 (*Chem. Abs.*, 1979, **90**, 34 029).

<sup>64</sup> R. L. Hamlin, F. S. Pipers, P. Mihalko, R. M. Folk, and T. Gram, *Gov. Rep. Announce. Index (U.S.)*, 1979, **79**, 88 (*Chem. Abs.*, 1979, **91**, 49 459).

<sup>65</sup> L. R. Moore, *Oecologia (Berlin)*, 1978, **34**, 203.

<sup>66</sup> B. Rustamov and F. S. Sadritinov, *Farmakol. Prir. Veschestv.*, 1978, 77 (*Chem. Abs.*, 1979, **91**, 32 645).



Mattocks has continued his work on the synthesis of cytotoxic pyrrolizidine alkaloid analogues.<sup>67</sup> The esters of synthanecines D (58) and E (59) behave as analogues of the pyrrolizidine alkaloids. They can be dehydrogenated in animals to the corresponding pyrrole derivatives, which are monofunctional alkylating agents. In addition to the hydroxymethyl group on (58) and (59), a second substituent on the 3-pyrroline was required to facilitate metabolism to the pyrrole derivatives. Injection of the tritium-labelled pyrrole (60) into rats caused lung lesions similar to those produced by the pyrrole derivatives of pyrrolizidine alkaloids.<sup>68</sup>

<sup>67</sup> A. R. Mattocks, *J. Chem. Soc., Perkin Trans. 1*, 1978, 896.

<sup>68</sup> A. R. Mattocks, *Toxicol. Lett.*, 1979, **3**, 79.

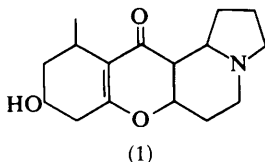


## Indolizidine Alkaloids

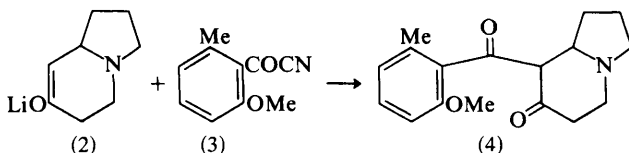
BY J. A. LAMBERTON

1 *Elaeocarpus* Alkaloids

The known alkaloids ( $\pm$ )-elaecarpine and ( $\pm$ )-isoelaecarpine, and a new alkaloid rudrakine,  $C_{16}H_{23}NO_3$ , have been isolated from leaves of *Elaeocarpus ganitrus*. Rudrakine is a minor component, and, mainly from mass spectroscopic data, it has been given structure (1), without any assignment of relative stereochemistry.<sup>1</sup>



A further synthetic route to *Elaeocarpus* alkaloids has been explored.<sup>2</sup> Acylation of the lithium enolate of 7-oxoindolizidine (2) by 2-methoxy-6-methylbenzoyl cyanide (3) gave the diketone (4), which is a key intermediate in a previously reported synthesis<sup>3</sup> of elaecarpine.

2 *Ipomoea* Alkaloids

The previously published structure (5)<sup>4</sup> of the alkaloid ipomine, from *Ipomoea muricata* Jacq., has been questioned. It has now been suggested that the signals from the sugar moiety in the  $^{13}C$  n.m.r. spectrum should be re-assigned, and that ipomine is ipalbidinyl-(6-*O*-*p*-coumaroyl- $\beta$ -D-glucopyranoside) (6), and not the 4-*O*-*p*-coumaroyl- $\beta$ -D-glucopyranoside<sup>5</sup> (5). The formulae (5) and (6) depicted

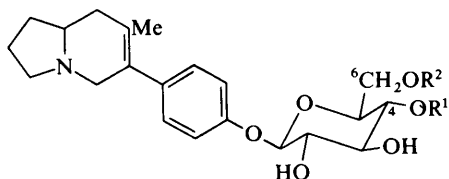
<sup>1</sup> A. B. Ray, L. Chand, and V. B. Pandey, *Phytochemistry*, 1979, **18**, 700.

<sup>2</sup> A. S. Howard, C. A. Meerholz, and J. P. Michael, *Tetrahedron Lett.*, 1979, 1339.

<sup>3</sup> T. Tanaka and I. Iijima, *Tetrahedron*, 1973, **29**, 1285.

<sup>4</sup> A. M. Dawidar, F. Winternitz, and S. R. Johns, *Tetrahedron*, 1977, **33**, 1733.

<sup>5</sup> V. M. Chari, M. Jordan, and H. Wagner, *Planta Med.*, 1978, **34**, 93.

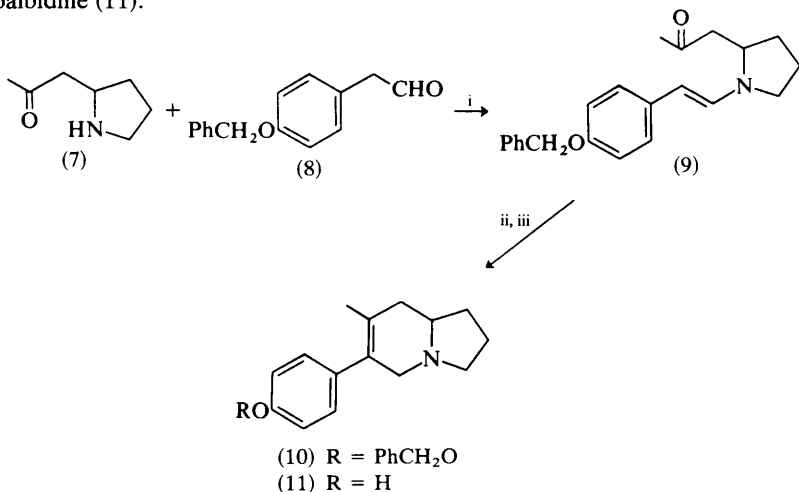


(5)  $R^1 = p\text{-coumaroyl}$ ,  $R^2 = H$

(6)  $R^1 = H$ ,  $R^2 = p\text{-coumaroyl}$

for ipomine have been amended by the Reporter because the ipalbidinyl portion had been drawn incorrectly in both the papers cited.<sup>4,5</sup>

The probable biogenesis of ipalbidine from norhygrine has been used as the basis for a simple and efficient synthesis of that alkaloid.<sup>6</sup> Condensation of norhygrine (7) with 4-benzyloxyphenylacetaldehyde (8) (Scheme 1) gave an enamine (9), which underwent cyclization and dehydration in methanol. Reduction to *O*-benzylipalbidine (10) and subsequent debenzylation afforded ( $\pm$ )-ipalbidine (11).



Reagents: i, benzene, at r.t.; ii, MeOH; iii,  $\text{NaBH}_4$ ,  $\text{Pr}^i\text{OH}$

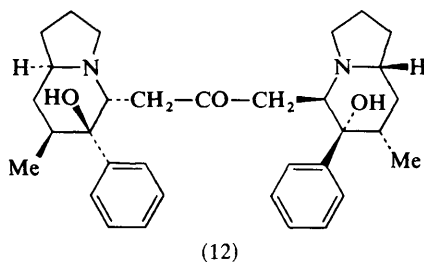
**Scheme 1**

### 3 *Dendrobium* Alkaloids

The  $^{13}\text{C}$  n.m.r. spectrum of the orchid alkaloid dendrocrepine (12) shows that the phenyl groups give rise to six resonances, and the non-equivalence of the two *ortho* and *meta* positions is considered to be caused by steric inhibition of rotation of the phenyl groups.<sup>7</sup> Similar steric inhibition of the free rotation of the phenyl group in 2,3-dimethyl-1-phenylcyclohexanol was demonstrated, and in the spectrum of dendrocrepine the six phenyl resonances were reduced to four at  $+57^\circ\text{C}$ .

<sup>6</sup> S. H. Hedges and R. B. Herbert, *J. Chem. Res. (M)*, 1979, 413.

<sup>7</sup> E. Leete and R. M. Riddle, *Tetrahedron Lett.*, 1978, 5163.



#### 4 Tylophora Alkaloids

The phenanthroindolizidine alkaloid (–)-tylocrebrine has been shown to have the *S* configuration, like (–)-tylophorine, from a study of the o.r.d. and c.d. spectra of these two alkaloids and of the phenanthroquinolizidine alkaloid cryptopleurine.<sup>8</sup>

<sup>8</sup> E. Gellert, R. Rudzats, J. C. Craig, S. K. Roy, and R. W. Woodard, *Aust. J. Chem.*, 1978, **31**, 2095

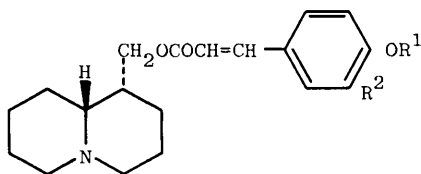
A new review of quinolizidine alkaloids has appeared.<sup>1</sup>

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

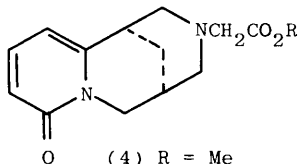
**Occurrence.**—Alkaloid isolation is recorded in Table 1.<sup>2-10</sup> Thirteen new alkaloids have been isolated this year, including four of the matrine group. A further study of the content of quinolizidine alkaloids of *Chamaecytisus* species (*cf.* Vol. 9, p. 69) involved g.l.c. methods.<sup>11</sup>

**Structural and Chemical Studies.**—Three new esters of (–)-lupinine were isolated from young seedlings of *Lupinus luteus*;<sup>5</sup> (–)-(trans-4'-β-D-glucopyranosyloxycinnamoyl)lupinine (1) was identified by enzymatic hydrolysis with β-D-glucosidase and by synthesis from 2,3,4,6-tetra-O-α-D-glucopyranosyl bromide followed by hydrolysis with aqueous ammonia.<sup>5a</sup> The structures of the corresponding 3'-methoxy derivative (2)<sup>5b</sup> and of (–)-(trans-4'-α-L-rhamnosyloxy-3'-methoxycinnamoyl)-lupinine (3)<sup>5c</sup> were established similarly. An X-ray analysis of lupinine was related to infrared data.<sup>12</sup>

A base isolated from *Euchresta japonica* by extraction with methanol was shown by spectroscopic studies and by its synthesis from (–)-cytisine and methyl bromoacetate to be methyl 12-cytisine acetate (4). This compound is apparently an artifact derived from the new alkaloid (5); extraction of the plant with aqueous ethanol gave the latter compound as its zwitterion, and the methyl ester (4) was not detected.<sup>4a</sup>



- (1) R<sup>1</sup> = glucosyl, R<sup>2</sup> = H  
 (2) R<sup>1</sup> = glucosyl, R<sup>2</sup> = OMe  
 (3) R<sup>1</sup> = rhamnosyl, R<sup>2</sup> = OMe



- (4) R = Me  
 (5) R = H

<sup>1</sup> H. C. S. Wood and R. Wigglesworth, "Rodd's Chemistry of Carbon Compounds", Elsevier, Amsterdam, 2nd edn., 1978, 4(H), p. 285.

**Table 1** Isolation of alkaloids of the lupine-cytisine-sparteine-matrine-Ormosia group

Species	Alkaloid (Structure)	Ref.
<i>Anagyris foetida</i>	*Hydroxyanagyrine (8) } Lupanine }	2
<i>Euchresta horsfeldii</i>	Anagyrene *5 $\alpha$ ,9 $\alpha$ -Dihydroxymatrine (18) } N-Formylcytisine } Matrine and its N-oxide } N-Methylcytisine } Sophoranol and its N-oxide }	3
<i>E. japonica</i>	*12-Cytisineacetic acid (5)	4a
	*5,17-Dehydromatrine N-oxide (17)	4b
<i>Lupinus luteus</i>	*Lupanine ester (1)	5a
	*Lupanine ester (2)	5b
	*Lupanine ester (3)	5c
<i>Ormosia costulata</i>	*(-)-Jamine	6a
	*Homodasycarpine	6b
<i>Osyris alba</i>	Anagyrene } Cineverine } N-methylcytisine }	7
<i>Sophora alopecuroides</i>	*13,14-Dehydrosophoridine (16)	8
<i>S. flavescens</i>	*7,8-Dehydrosophoramine (15)	9a
	*13,14-Dehydrosophoridine (16)	9b
	Sophocarpine N-oxide (Sophocarpidine)	9b
<i>S. franchetiana</i>	Anagyrene } Ammodendrine } Baptifoline } Cytisine } N-Formylcytisine } Rhombifoline } *Tsukushinamine (13) }	10

\* New alkaloids

- <sup>2</sup> J. M. Viguero Lobo, J. Fuentes Mota, M. P. Tejero Mateo, and A. Cert Ventual, *An. Quim.*, 1977, **73**, 1366 (*Chem. Abs.*, 1978, **89**, 176 302).
- <sup>3</sup> S. Ohmiya, K. Higashiyama, H. Otomasu, I. Murakoshi, and J. Haginiwa, *Phytochemistry*, 1979, **18**, 645.
- <sup>4</sup> S. Ohmiya, H. Otomasu, J. Haginiwa, and I. Murakoshi, (a) *Phytochemistry*, 1979, **18**, 649; (b) *ibid.*, 1978, **17**, 2021.
- <sup>5</sup> I. Murakoshi, K. Torizuka, J. Haginiwa, S. Ohmiya, and H. Otomasu, (a) *Chem. Pharm. Bull.*, 1979, **27**, 144; (b) *Phytochemistry*, 1979, **18**, 699; (c) *ibid.*, 1978, **17**, 1817.
- <sup>6</sup> (a) J. K. Frank, E. N. Duesler, N. N. Thayer, R. Henendorn, K. L. Rinehart, I. C. Paul, and R. Misra, *Acta Crystallogr., Sect. B.*, 1978, **34**, 2316; (b) A. H. J. Wang, E. N. Duesler, N. N. Thayer, R. Heckendorn, K. L. Rinehart, and I. C. Paul, *ibid.*, p. 2319.
- <sup>7</sup> F. Le Scao-Bogaert, G. Faugeras, and R. R. Paris, *Plant. Med. Phytother.*, 1978, **12**, 315.
- <sup>8</sup> Yu. K. Kushmuradov, S. Kuchkarov, and Kh. A. Aslanov, *Khim. Prir. Soedin.*, 1978, 231 (*Chem. Abs.*, 1978, **89**, 215 627).
- <sup>9</sup> (a) K. Morinaga, A. Ueno, S. Fukushima, M. Namikoshi, Y. Iitaka, and S. Okuda, *Chem. Pharm. Bull.*, 1978, **26**, 2483; (b) A. Ueno, K. Morinaga, S. Fukushima, and S. Okuda, *ibid.*, p. 1832.
- <sup>10</sup> S. Ohmiya, K. Higashiyama, H. Otomasu, J. Haginiwa, and I. Murakoshi, *Chem. Pharm. Bull.*, 1979, **27**, 1055.
- <sup>11</sup> A. Daily, N. Kotsev, L. Ilieva, Kh. Duchevska, and N. Mollov, *Arch. Pharm. (Weinheim, Ger.)*, 1978, **311**, 899 (*Chem. Abs.*, 1979, **90**, 36 314).
- <sup>12</sup> A. Koziol, Z. Kosturkiewica, and H. Podkowinska, *Acta Crystallogr., Sect. B.* 1978, **34**, 3491.

Reductive formylation of angustifoline (6) leads to *N*-methylangustifoline in methanol and to an isomer (7) of the latter in aqueous solution.<sup>13</sup> Derivatives of lupinine,<sup>14</sup> epilupinine,<sup>15</sup> and cytisine<sup>16</sup> have been prepared.

A fresh investigation of the constituents of *Anagyris foetida* resulted in the isolation of a new alkaloid;<sup>2</sup> although the structure has not been fully established, mass spectroscopy indicates that the compound is a hydroxy-anagyrine (8) with a hydroxy-group in ring D.

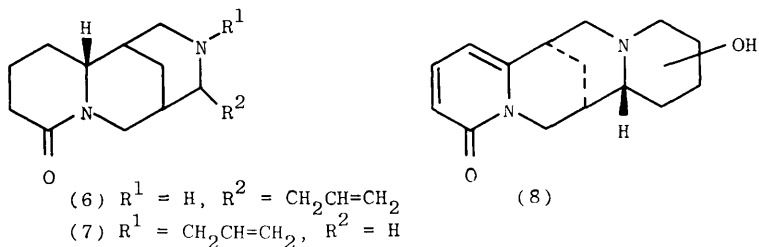
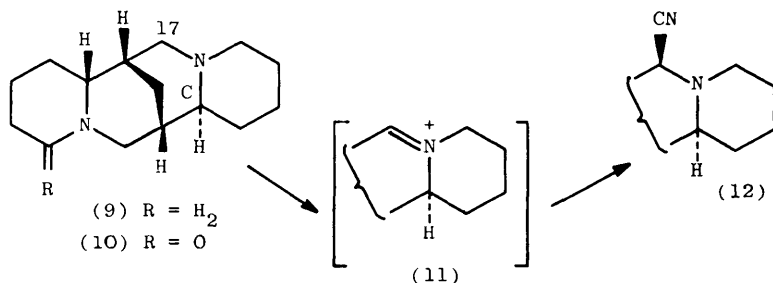


Photo-oxidation of a group of tetracyclic quinolizidine alkaloids in the presence of cyanide ion has been shown to give amino-nitriles or the corresponding primary amides.<sup>17</sup> Sparteine (9) and lupanine (10) were converted into the nitriles (12); it has been proposed that the introduction of a trigonal carbon atom at C-17 in intermediates (11) results in a gain in relative stability of ring C, which is in a boat conformation in (9) and (10). Isosparteine, isolupanine, camoensidine, and tetrahydroleontidine were studied, and in these cases substituents were also inserted at other positions adjacent to the heterocyclic nitrogen atoms.

An X-ray study of the dihydrate of (+)-lupanine hydrochloride, *cf.* (10), showed that ring C was in the boat conformation.<sup>18</sup>



*Sophora franchetiana* contains the most interesting quinolizidine alkaloid of the year, tsukushinamine. The latter is a new type of C<sub>15</sub> tetracyclic alkaloid, and structure (13) was proposed for it on the basis of spectroscopic studies.<sup>10</sup> The i.r. and u.v. spectra indicated that a non-conjugated lactam group was present, and a

<sup>13</sup> M. D. Bratek-Wiewiorowska, *Pol. J. Chem.*, 1979, **53**, 83 (*Chem. Abs.*, 1979, **91**, 57 258).

<sup>14</sup> Sh. M. Gafurova, A. M. Saiitkulov, A. M. Aslanov, A. A. Abdurakhobov, A. I. Ishbaev, and A. M. Maksudov, *Usb. Khim. Zh.*, 1978, 36 (*Chem. Abs.*, 1979, **90**, 23 351).

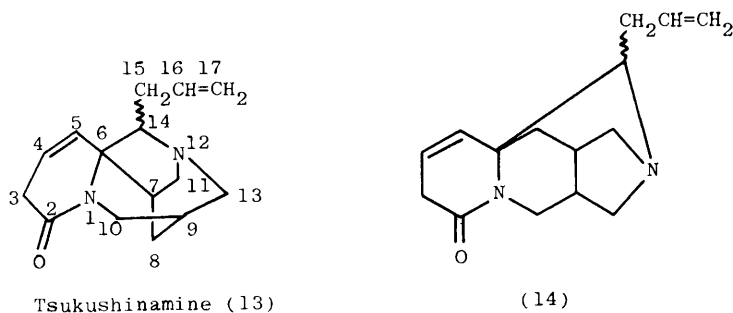
<sup>15</sup> V. U. Rakhmatullina, A. A. Abdurakhobov, and Kh. A. Aslanov, *Zh. Obshch. Khim.*, 1978, **48**, 686 (*Chem. Abs.*, 1978, **89**, 43 868).

<sup>16</sup> I. Primukhamadov and K. S. Tillyaev, *Usb. Khim. Zh.*, 1978, 22 (*Chem. Abs.*, 1979, **90**, 23 350).

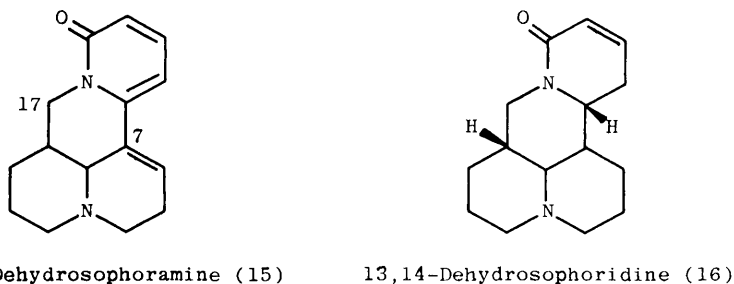
<sup>17</sup> J. Santamaria and F. Khuong-Huu, *Tetrahedron*, 1978, **34**, 1523.

<sup>18</sup> E. Skrzypczak-Jankun and Z. Kaluski, *Acta. Crystallogr., Sect. B*, 1978, **34**, 2651.

major fragmentation in the mass spectrum was attributed to loss of the  $-\text{CH}_2\text{CH}=\text{CH}_2$  group. The  $^{13}\text{C}$  n.m.r. spectrum was completely assigned; a critical observation was that the signal at  $\delta$  70.0 was due to the  $sp^3$  quaternary carbon at C-6, attached to nitrogen. A detailed study of the  $^1\text{H}$  n.m.r. spectrum of the alkaloid, using a shift reagent and correlation with the  $^{13}\text{C}$  n.m.r. spectrum through single-frequency off-resonance decoupling, led to two possible structures (13) and (14). The former is preferred on the basis of n.m.r. data for protons at C-9 and C-10 and from examination of molecular models; configurations at C-7, C-9, and C-14 have not yet been determined.

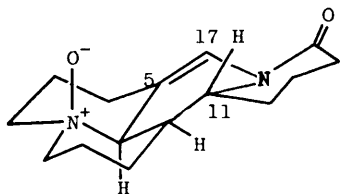
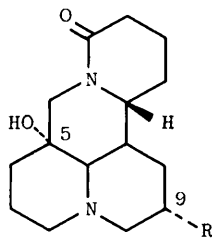


Alkaloids of the matrine group have attracted considerable attention this year. Several alkaloids of this type were obtained previously from the roots of *Sophora flavescens*, and two new alkaloids have now been isolated from the above-ground part of the plant.<sup>9</sup> One of these alkaloids is the fully conjugated pyridone 7,8-dehydrosophoramine (15), since reduction afforded (–)-sophoramine and the  $^1\text{H}$  n.m.r. spectrum indicated the presence of a methylene group at C-17 and a methine proton at C-8.<sup>9a</sup> The structure of the other new alkaloid, 13,14-dehydrosophoridine (16), was established by X-ray analysis of its monohydrate,



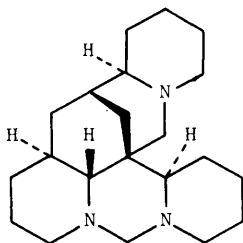
and the absolute configuration was determined by correlation with (+)-matrine and (+)-allomatrine.<sup>9b</sup> 13,14-Dehydrosophoridine has also been obtained from *Sophora alopecuroides*;<sup>8</sup> the corresponding *N*-oxide was isolated earlier from this species (*cf.* Vol. 9, p. 71). New alkaloids have also been isolated from *Euchresta* species. Thus, *E. japonica* contains (+)-5,17-dehydromatrine *N*-oxide (17).<sup>4b</sup> The structure was established by reduction to 5,17-dehydromatrine, which was identical to the compound prepared from sophoranol (19); in the n.m.r. spectrum

of the alkaloid the axial proton at C-11 is deshielded by the N—O bond as in matrine *N*-oxide. The new alkaloid of *E. horsfeldii* is (+)-5,9-dihydroxymatrine (18). The  $^1\text{H}$  and  $^{13}\text{C}$  n.m.r. spectra of the alkaloid are similar to those of sophoranol (19), and the structural problem was mainly concerned with the additional OH group. In the  $^{13}\text{C}$  n.m.r. spectrum, C-9 gave a signal at  $\delta$  62.7, compared to 22.5 for C-9 of sophoranol, and the broad triplet at  $\tau$  5.85 ( $J = 12$ ) in the  $^1\text{H}$  n.m.r. spectrum run in deuteriopyridine showed that the hydroxy-group at C-9 has an equatorial configuration.<sup>3</sup> X-Ray analyses of matrine,<sup>19a</sup> matrine *N*-oxide,<sup>19b</sup> and sophoridine<sup>20</sup> have been published.

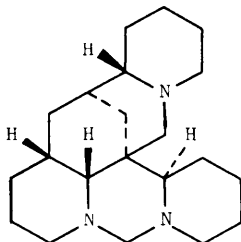
5,17-Dehydromatrine *N*-oxide (17)5 $\alpha$ ,9 $\alpha$ -Dihydroxymatrine (18) R = OH

(19) R = H

The structures of two new hexacyclic alkaloids of *Ormosia costulata* have been determined by X-ray crystallography. One alkaloid is an enantiomer of the optically inactive jamine (20),<sup>6a</sup> and is reported to be identical with a formaldehyde adduct of an alkaloid of *Podopetalum ormondii*;<sup>21</sup> jamine was shown previously to be a constituent of *O. panamensis* and *O. jamaicensis*. A second new optically active alkaloid (21), homodasycarpine, is a stereoisomer of jamine.<sup>6b</sup> Absolute stereochemistry has not been established, and is not implied in structures (20) and (21).



Jamine (20)



Homodasycarpine (21)

<sup>19</sup> B. T. Ibragimov, S. A. Talipov, G. N. Tishchenko, Yu. K. Kushmuradov, and T. F. Aripov, (a) *Kristallografiya*, 1978, **23**, 1189 (*Chem. Abs.*, 1979, **90**, 87 807); (b) *ibid.*, 1979, **24**, 25 (*Chem. Abs.*, 1979, **90**, 204 319).

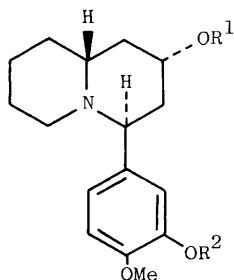
<sup>20</sup> B. T. Ibragimov, S. A. Talipov, Yu. K. Kushmuradov, and T. F. Aripov, *Khim. Pri. Soedin.*, 1978, 538 (*Chem. Abs.*, 1979, **90**, 23 357).

<sup>21</sup> S. McLean and R. Misra, unpublished work.

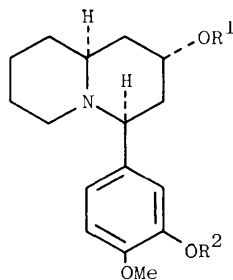
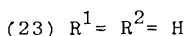


## 2 Alkaloids of the Lythraceae

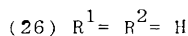
Four new aryl-quinolizidine alkaloids, *i.e.* lasubine-I (22), lasubine-II (25), subcosine-I (24), and subcosine-II (27), have been obtained from *Lagerstroemia subcostata*, and their structures have been established by spectroscopy and by correlation with known compounds.<sup>22</sup> Thus, the *cis*-quinolizidine lasubine-I was prepared by methylation of the known phenol (23), and the *trans*-quinolizidine phenol (26) was similarly converted into lasubine-II. Subcosine-I and subcosine-II were shown to be the corresponding *trans*-3,4-dimethoxycinnamates by their hydrolysis to lasubine-I and lasubine-II, respectively. Extraction of another *Lagerstroemia* species, *L. fauriei*, gave only the known macrocyclic lythraceous alkaloids lythrine, cryogenine, and lythridine.<sup>22</sup>



Lasubine-I (22)  $R^1 = H, R^2 = Me$



Lasubine-II (25)  $R^1 = H, R^2 = Me$

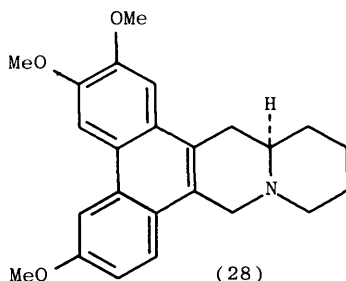


Subcosine-I (24)  $R^1 = \textit{trans}-3,4-dimethoxycinnamoyl,  $R^2 = Me$$

Subcosine-II (27)  $R^1 = \textit{trans}-3,4-dimethoxycinnamoyl,  $R^2 = Me$$

## 3 Cryptopleurine

The *trans*-phenanthroquinolizidine alkaloid cryptopleurine has been shown to have the (*R*) configuration (28) by comparison of o.r.d. and c.d. data with those of the *trans*-phenanthroindolizidine alkaloids of established stereochemistry.<sup>23</sup>

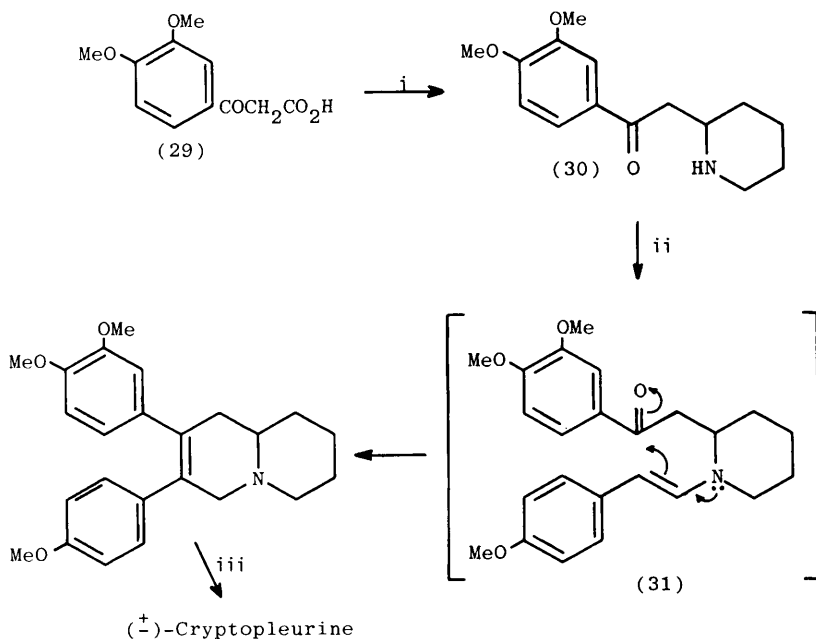


(28)

<sup>22</sup> K. Fuji, T. Yamada, E. Fujita, and H. Murata, *Chem. Pharm. Bull.*, 1978, **26**, 2513.

<sup>23</sup> E. Gellert, R. Rudzats, J. C. Craig, S. K. Roy, and R. W. Woodard, *Aust. J. Chem.*, 1978, **31**, 2095.

A new and efficient synthesis of ( $\pm$ )-cryptopleurine (Scheme 1) has been reported.<sup>24</sup> The piperidylacetophenone (30) was prepared from the benzoylactic acid derivative (29) and  $\Delta^1$ -piperideine, which was generated *in situ* from cadaverine and pea-seedling diamine oxidase. The enamine (31) undergoes cyclization and subsequent dehydration in the presence of a Lewis acid, and biaryl coupling is then effected with thallium trifluoroacetate.



Reagents: i, cadaverine, diamine oxidase, pH 7 (79%); ii,  $p\text{-MeOC}_6\text{H}_4\text{CH}_2\text{CHO}$ ,  $\text{TiCl}_4$ ,  $\text{PhH}$  (29%); iii,  $[(\text{F}_3\text{CCO}_2)_3\text{Tl}]$ ,  $\text{F}_3\text{CCO}_2\text{H}$  (69%)

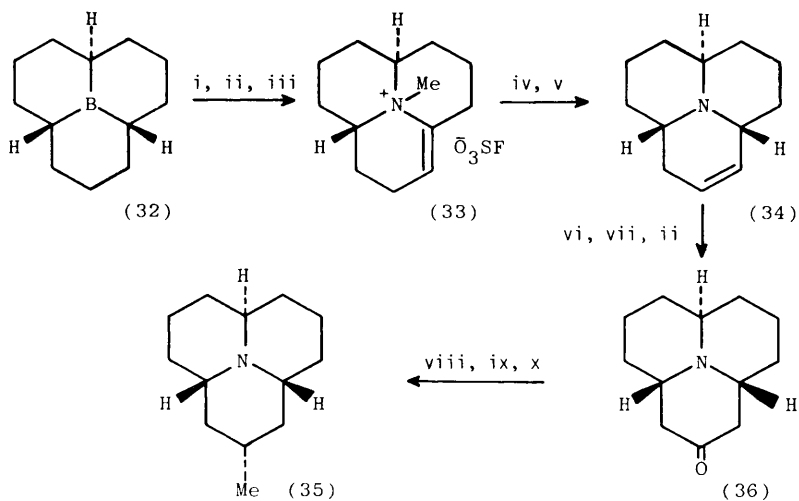
Scheme 1

#### 4 9b-Azaphenylene Alkaloids

Three 2a-methyl-perhydro-9b-azaphenalenenes that constitute defensive substances of ladybird beetles were synthesized recently (*cf.* Vol. 7, p. 79), and an alternative synthesis has now been described<sup>25</sup> (Scheme 2). The perhydrobora-phenalene (32) that was employed earlier to prepare unsubstituted perhydro-azaphenalenenes (*cf.* Vol. 6, p. 101) was converted into the enamine quaternary ammonium salt (33) and thence into the allylamine (34). The allylamine epoxide was used to prepare ketone (36), which provided an efficient route to precoccinellin (35) by means of a Wittig reaction; the same ketone was involved in the earlier synthesis of the alkaloid.

<sup>24</sup> R. B. Herbert, *J. Chem. Soc., Chem. Commun.*, 1978, 794.

<sup>25</sup> R. H. Mueller and M. E. Thompson, *Tetrahedron Lett.*, 1979, 1991.



Reagents: i,  $\text{H}_2\text{O}_2$ , CINHODNP, NaOH; ii,  $\text{CrO}_3$ ,  $\text{H}_2\text{SO}_4$ ; iii,  $\text{MeOSO}_2\text{F}$ ,  $\text{EtOEt}$ ; iv, lithium diisopropylamide, THF; v,  $\text{LiSEt}$ , DMF; vi,  $\text{F}_3\text{CCO}_3\text{H}$ , then  $\text{F}_3\text{CCO}_2\text{H}$ ,  $\text{CH}_2\text{Cl}_2$ ; vii,  $\text{Li}$ ,  $(\text{CH}_2\text{NH}_2)_2$ ; viii,  $\text{PhP}=\text{CH}_2$ ; ix,  $\text{TsOH}$ , xylene, reflux; x,  $\text{H}_2$ ,  $\text{Pd/C}$ ,  $\text{EtOH}$

**Scheme 2**

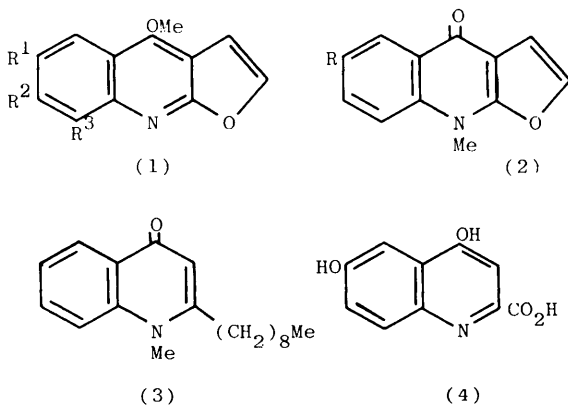
## Quinoline, Quinazoline, and Acridone Alkaloids

BY M. F. GRUNDON

A comprehensive review of quinoline alkaloids related to anthranilic acid covering the period 1966–mid 1976 has been published.<sup>1</sup> A review of the botany, chemistry, and pharmacology of *Choisya ternata* includes an account of the quinoline alkaloids isolated from this rutaceous species.<sup>2</sup>

### 1 Quinoline Alkaloids

New alkaloids and alkaloids of established constitution that have been identified from new sources are listed in Table 1.<sup>3–19,35</sup>



<sup>1</sup> M. F. Grundon in 'The Alkaloids', ed. R. H. F. Manske and R. G. A. Rodrigo, Academic Press, New York, 1979, Vol. XVII, p. 105.

<sup>2</sup> J. C. Chénieux, M. Rideau, and M. Séjourné, *Plant. Med. Phytother.*, 1978, **12**, 327.

<sup>3</sup> L. B. de Silva, V. L. L. de Silva, M. Mahendran, and R. Jennings, *Phytochemistry*, 1979, **18**, 1255.

<sup>4</sup> A. A. L. Gunatilaka, J. S. H. Q. Perera, M. U. S. Sultanbawa, P. M. Brown, and R. H. Thomson, *J. Chem. Res. (S)*, 1979, 61.

<sup>5</sup> M. Rideau, C. Verchère, P. Hibon, J.-C. Chénieux, P. Maupas, and C. Viel, *Phytochemistry*, 1979, **18**, 155.

<sup>6</sup> V. I. Akhmedzhanov, I. A. Bessonova, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 1978, 476 (*Chem. Abs.*, 1978, **89**, 176 371).

<sup>7</sup> P. G. Waterman, I. A. Meshal, J. B. Hall, and M. D. Swaine, *Biochem. Syst. Ecol.*, 1978, **6**, 239.

<sup>8</sup> F. Y. Chou, K. Hostettmann, I. Kubo, K. Nakanishi, and M. Taniguchi, *Heterocycles*, 1977, **7**, 969.

<sup>9</sup> A. Ahond, C. Poupat, and J. Pusset, *Phytochemistry*, 1979, **18**, 1415.

<sup>10</sup> M. Sarker, S. Kundu, and D. P. Chakraborty, *Phytochemistry*, 1978, **17**, 2145.

**Table 1** Isolation of quinoline alkaloids

Species	Alkaloid (Structure)	Ref.
<i>Acronychia pedunculata</i>	Evolitrine ( $1; R^1 = R^3 = H, R^2 = OMe$ ) Kokusaginine ( $1; R^1 = R^2 = OMe, R^3 = H$ )	3
<i>Broussonetia zeylanica</i>	*4-Formyl-8-hydroxyquinoline	4
<i>Choisya ternata</i>	(-)-O-Methylhydroxyluninium cation (23)	5
<i>Dictamnus angustifolius</i>	$\gamma$ -Fagarine ( $1; R^1 = R^2 = H, R^3 = OMe$ ) Isodictamnine ( $2; R = H$ ) Isopteleine ( $2; R = OMe$ ) Preskimmianine (19)	6
<i>Diphasia angolensis</i>	Halfordinine ( $1; R^1 = R^2 = R^3 = OMe$ )	7
<i>Fagara chalybaea</i> <i>F. holstii</i>	N-Methylfindersine (27)	8
<i>Geijera balansae</i>	*(-)-Geibalansine (24) *O-Acetylgeibalansine (25)	9
<i>Glycosmis cyanocarpa</i>	Evolitrine *Glycarpine (10)	10
<i>G. bilocularis</i>	Kokusaginine Skimmianine	35
<i>Haplophyllum latifolium</i>	Glycoperine ( $9; R = H$ )	11
<i>H. perforatum</i>	*Mono- and di-acetylgycoperine	12
<i>H. tuberculatum</i>	Evoxine ( $1; R^1 = H, R^2 = OCH_2CH(OH)-$ $C(OH)Me_2, R^3 = OMe$ ) $\gamma$ -Fagarine Skimmianine ( $1; R^1 = H, R^2 = R^3 = OMe$ )	13
<i>Limonium perezii</i> <i>L. gmelinii</i>	6-Hydroxykynurenic acid (4)	14
<i>Murraya paniculata</i>	Skimmianine	15
<i>Oricia suaveolens</i>	Halfordinine Kokusaginine	16
<i>Pseudomonas aeruginosa</i>	*3-n-Heptyl-3-hydroxy-1,2,3,4-tetrahydro- quinoline-2,4-dione (5) *3-n-Nonyl-3-hydroxy-1,2,3,4-tetrahydro- quinoline-2,4-dione (6)	17
<i>Ptelea trifoliata</i>	*(+)-Isoptelefolonium cation (30) *Pteledimerine (28)	5 18
<i>Xylocarpus granotum</i>	N-Methylfindersine	8
<i>Zanthoxylum bouetense</i>	Skimmianine	19

\* New alkaloids

<sup>11</sup> E. F. Nesmelova, I. A. Bessonova, and S. Yu. Yunusov, *Khim. Pri. Soedin.*, 1978, 758 (*Chem. Abs.*, 1979, **91**, 20 830).

<sup>12</sup> Kh. A. Abdullaeva, I. A. Bessonova, and S. Yu. Yunusov, *Khim. Pri. Soedin.*, 1978, 219 (*Chem. Abs.*, 1978, **89**, 103 710).

<sup>13</sup> A. Al-Shamma, N. A. El-Douri, and J. D. Phillipson, *Phytochemistry*, 1979, **18**, 1417.

<sup>14</sup> J. Mendez, *Planta Med.*, 1978, **34**, 218.

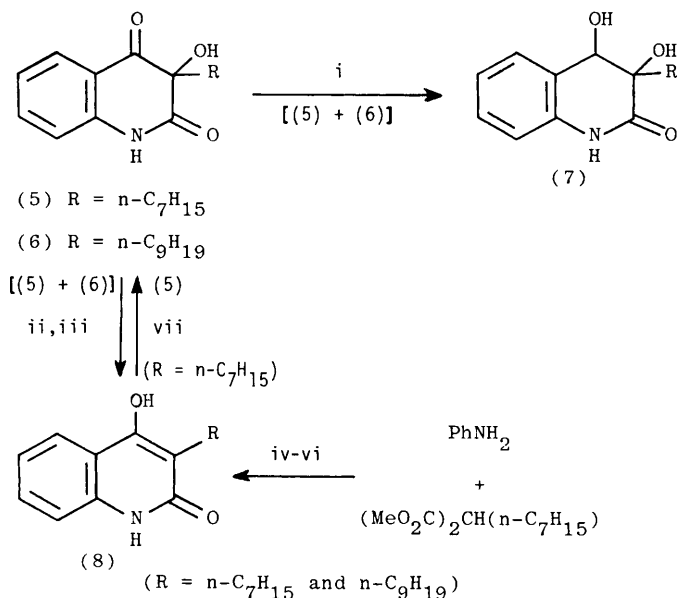
<sup>15</sup> M. T. Fauvel, J. Gleye, C. Moulis, and I. Fouraste, *Plant. Med. Phytother.*, 1978, **12**, 207.

<sup>16</sup> F. Fish, I. A. Meshal, and P. G. Waterman, *Planta Med.*, 1978, **33**, 228.

<sup>17</sup> W. Neuenhaus, H. Budzikiewicz, H. Korth, and G. Pulverer, *Z. Naturforsch., Teil B*, 1979, **34**, 313.

<sup>18</sup> J. Reisch, I. Mester, J. Körösi, and K. Szendrei, *Tetrahedron Lett.*, 1978, 3681.

<sup>19</sup> J. Vaquette, A. Cavé, and P. G. Waterman, *Plant. Med. Phytother.*, 1978, **12**, 235.



Reagents: i, NaBH<sub>4</sub>, EtOH; ii, mesyl chloride, Et<sub>3</sub>N; iii, LiAlH<sub>4</sub>; iv, 175 °C; v, KOH, MeOH; vi, PPA; vii, O<sub>2</sub>, MeOH, u.v.

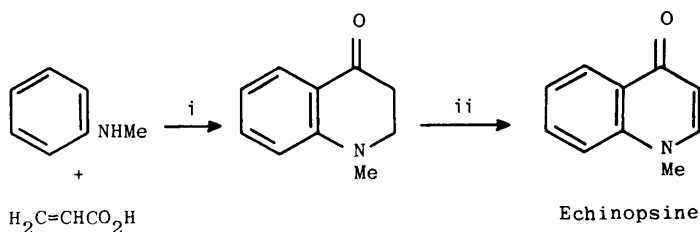
Scheme 1

**Non-hemiterpenoid Quinolines.**—The micro-organism *Pseudomonas aeruginosa* contains a variety of 2-alkyl-4-quinolones,<sup>1</sup> and now two 3-alkyl-3-hydroxy-quinolones (5) and (6) have been obtained from this species.<sup>17</sup> The new metabolites gave molecular-ion peaks in the mass spectra and i.r. ketonic and amidic carbonyl absorptions at 1710 and 1665 cm<sup>-1</sup>, respectively. The structures were established by <sup>1</sup>H and <sup>13</sup>C n.m.r. spectroscopy and by synthesis. In the <sup>1</sup>H n.m.r. spectrum the resonance at  $\tau$  6.84 (OH) was not affected by the addition of deuterium oxide, but the presence of the hydroxy-group was confirmed by conversion of alkaloid (5), with CCl<sub>3</sub>CONCO, into a derivative showing a new N-H signal in the n.m.r. spectrum. The structural problem was completed by reduction of a mixture of alkaloids (5) and (6) to compounds (7), reduction of a mixture of their mesyl derivatives to 4-hydroxy-2-quinolones (8), and by synthesis of alkaloid (5) (Scheme 1). An account of the isolation of the *N*-methyl-4-quinolone (3) from *Ruta graveolens* and the determination of its structure by n.m.r. and mass spectroscopy (cf. Vol. 7, p. 82) has now been published.<sup>20</sup>

A new alkaloid, 4-formyl-8-hydroxyquinoline, was isolated from *Broussonetia zeylanica*;<sup>4</sup> the structure was apparent from spectral studies and by its Wolff-Kishner reduction to 8-hydroxy-4-methylquinoline. 6-Hydroxykynurenic acid was obtained from *Limonium* species;<sup>14</sup> this is the first time that the compound has been isolated from members of the Plumbaginaceae. A new synthesis of echinopsine has been carried out (Scheme 2).<sup>21</sup>

<sup>20</sup> M. F. Grondon and H. M. Okely, *Phytochemistry*, 1979, **18**, 1768.

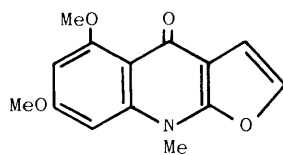
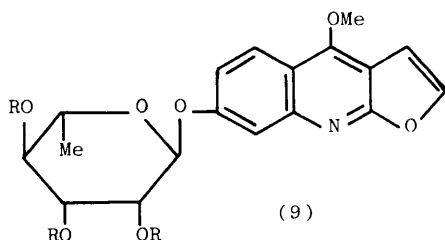
<sup>21</sup> J. R. Merchant and V. Shankaranarayan, *Chem. Ind. (London)*, 1979, 320.



Reagents: i, PPA, 125–130 °C; ii, Pd/C, Ph<sub>2</sub>O or DDQ, PhH

**Scheme 2**

**Furoquinoline Alkaloids.**—Known furoquinoline alkaloids have been obtained for the first time from eleven species of the Rutaceae (see Table 1, refs. 3, 6, 7, 10, 11, 13–16, 19, 35) and include the rare 7-methoxydictamnine (evolitrine; refs. 3 and 10) and 6,7,8-trimethoxydictamnine (halfordinine; refs. 7 and 16). Triacetylglycoperine (9; R = Ac) was recently identified as a constituent of *Haplophyllum perforatum*, and now a mono- and a di-acetylglycoperine are reported to be present in this species.<sup>12</sup>

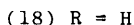
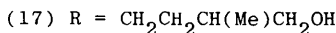
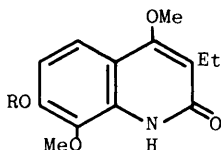
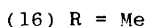
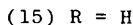
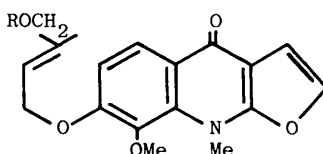
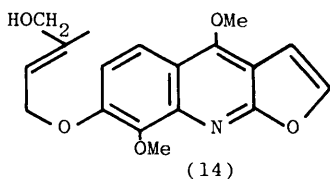
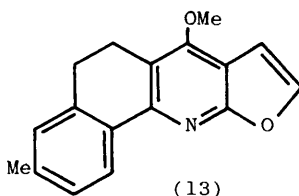
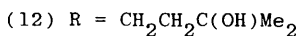
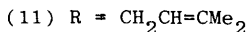
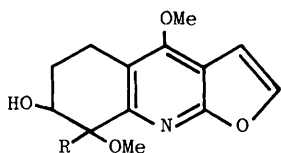


Glycarpine (10)

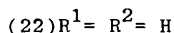
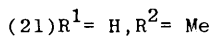
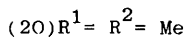
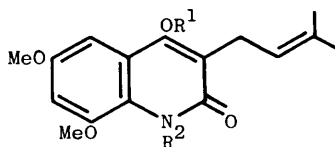
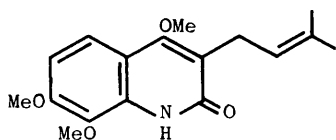
A new furoquinoline alkaloid, glycarpine (10) (5,7-dimethoxyisodictamnine), was obtained from *Glycosmis cyanocarpa*.<sup>10</sup> The structure was established by spectroscopy. The u.v. spectrum of glycarpine was similar to that of other iso-alkaloids, the i.r. absorption at 1620 cm<sup>-1</sup> was characteristic of a 4-quinolone carbonyl group, and the n.m.r. spectrum showed that the compound contained two methoxy-groups, one *N*-methyl substituent, and a furan ring; one-proton singlets at  $\tau$  2.72 and 3.0 (ArH) indicated that there was no proton at C-5, which would be expected to be deshielded by the neighbouring carbonyl group.

The reaction of haplophyllidine (11) or its hydration product, perforine (12), with concentrated sulphuric acid results in dehydration, loss of methanol, and cyclization; the structure (13) of the product was established by spectroscopy and by conversion, with methyl iodide, into the corresponding *N*-methyl-4-quinolone.<sup>22</sup> The reaction of the *Haplophyllum* alkaloid haplatine (14) with methyl iodide also results in formation of an *N*-methyl-quinolone (15), and in this case the methylation of the allylic hydroxy-group gives a second product (16). Reductive cleavage of haplatine furnishes the 3-ethyl-2-quinolones (17) and (18).<sup>11</sup>

<sup>22</sup> I. A. Bessonova, M. R. Yagudaev, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 1978, 597 (*Chem. Abs.*, 1979, **90**, 138 062).



**3-Prenyl-quinolones and Related Tricyclic Alkaloids.**—The 3-prenyl-2-quinolone preskimmianine (19), first obtained from *Dictamnus albus*, has now been recognized as a constituent of *D. angustifolius*.<sup>6</sup> The 3-prenyl-2-quinolone (20), a constituent of the root-bark of *Ptelea trifoliata*, has been synthesized by two research groups, in one case by the reaction of the *N*-methyl-2-quinolone (21) with diazomethane<sup>23</sup> (cf. Vol. 7, p. 84) and in the other by dimethylation of quinolone (22).<sup>24</sup>

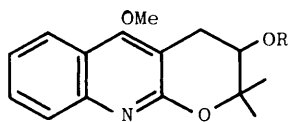
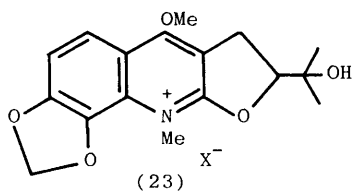


<sup>23</sup> J. L. Gaston and M. F. Grundon, *Tetrahedron Lett.*, 1978, 2629.

<sup>24</sup> P. Venturella, A. Bellino, and M. L. Marino, *Heterocycles*, 1978, **9**, 1433.

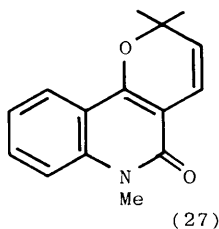
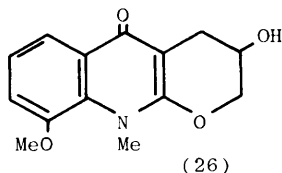


(-)-*O*-Methylhydroxyluninium cation (23), a quinolinium salt of the hydroxyisopropyl-dihydrofuroquinoline group, was previously isolated from *Ptelea trifoliata* and has now been found in *Choisya ternata*.<sup>5</sup> The hydroxydihydropyranoquinolines (-)-geibalansine (24) and its acetate (25) are new alkaloids obtained from *Geijera balansae*,<sup>9</sup> although the racemate (24) was synthesized some time ago.<sup>25</sup> A study of the mechanism of base-catalysed rearrangement of balfouridine (33) into 2-quinolones with angular annelation was previously reported briefly (*cf.* Vol. 1, p. 98). The work has now been fully described,<sup>26</sup> and has been extended to the corresponding rearrangement of isobalfouridine (26). The epoxide mechanism correctly predicts the stereochemistry of each product obtained, and is probably applicable to those rearrangements of isobalfouridine methosulphate, *N*-methylorixidine, and dubinine acetate that are also effected by base.



Geibalansine (24) R = H

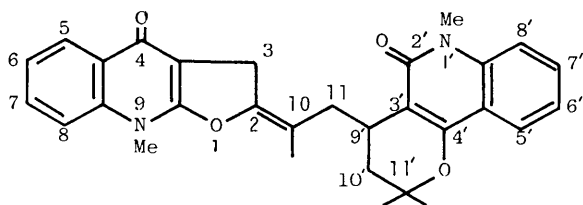
*O*-Acetylgeibalansine (25) R = Ac



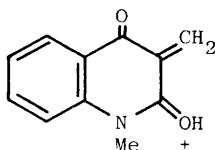
The anti-feedant activity of extracts of *Fagara chalybaea*, *F. holstii*, and *Xylocarpus granatum* has been shown by Nakanishi and his co-workers to be due to the presence of *N*-methylflindersine (27).<sup>8</sup> This alkaloid has been isolated previously from several rutaceous species, including *Ptelea trifoliata*, and it is of particular interest that the latter species has been shown to contain the first 'dimeric' quinoline alkaloid, pteledimerine (28), in which the structural elements of *N*-methylflindersine are apparent.<sup>18</sup> The constitution of pteledimerine was established by spectroscopic methods. Thus, the u.v. and i.r. spectra indicated the presence of 2- and 4-quinolone functions, and in the <sup>1</sup>H n.m.r. spectrum of the alkaloid the deshielded aromatic protons at C-5 and at C-5', the methyl groups at C-1', C-9, C-10, and C-11', the methylene groups at C-3, C-10', and C-11, and the methine proton at C-9' were clearly revealed. A molecular-ion peak was observed in the mass spectrum of pteledimerine, and electron impact also resulted

<sup>25</sup> R. M. Bowman and M. F. Grundon, *J. Chem. Soc. (C)*, 1966, 1504.

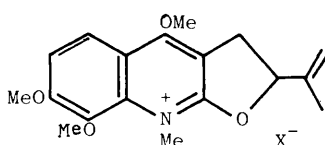
<sup>26</sup> K. J. James and M. F. Grundon, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1467.



Pteleodimerine (28)



(29)



Isoptelefolonium Cation (30)

in cleavage of the 9'-11 bond to give major fragments of  $m/z$  241 [*cf.* *N*-methylfindersine (27)] and 188 (29).

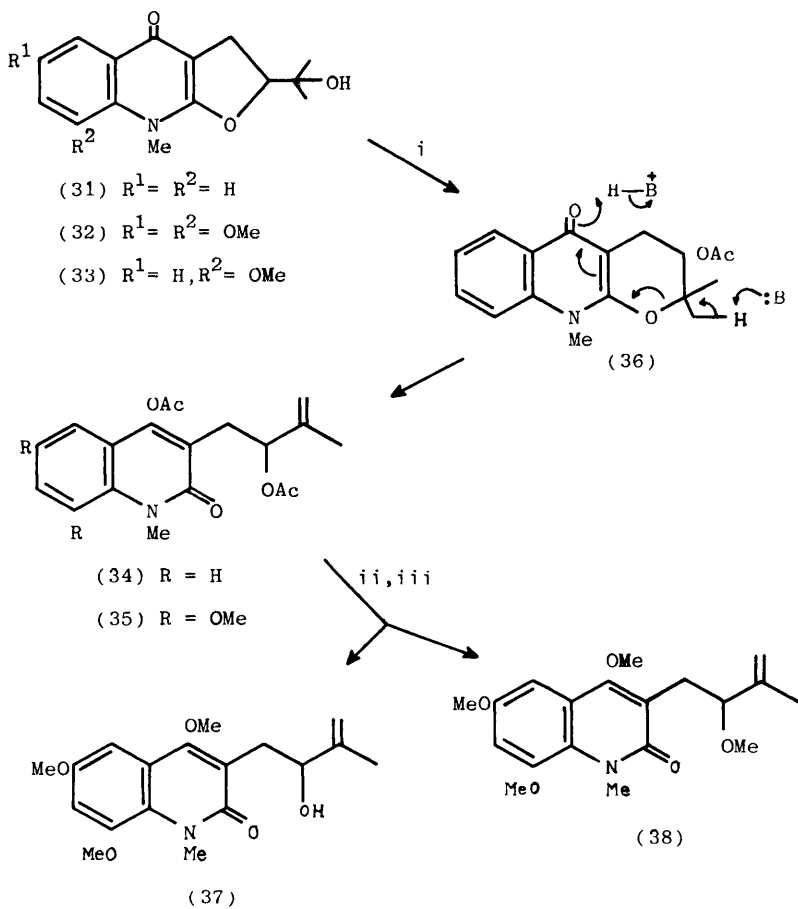
(+)-Isoptelefolonium cation (30) is the tenth hemiterpenoid quinoline alkaloid containing a terminal double bond to be obtained from *Ptelea trifoliata*; the alkaloid was isolated as its perchlorate salt, and the structure was established by spectroscopy.<sup>5</sup> A high-yield synthesis of two members of the group, ptelefoline (37) and ( $\pm$ )-ptelefoline methyl ether (38), has been reported (Scheme 3).<sup>27</sup> The reaction of isoplatydesmine (31) with acetic anhydride in refluxing pyridine results in rearrangement to ribalinine acetate (36) (*cf.* Vol. 9, p. 82), but, when hydrochloric acid is added to the reaction mixture, the only product is the diacetate (34); the latter compound is obtained in the same way from ribalinine acetate, which is probably an intermediate that undergoes elimination-induced ring fission; *cf.* (36). Application of the reaction to the 6,8-dimethoxy-4-quinolone (32), hydrolysis of diacetate (35), and subsequent methylation with diazomethane furnished ptelefoline (37) and ptelefoline methyl ether (38).

## 2 Quinazoline Alkaloids

The alkaloid glycophymine, isolated from *Glycosmis pentaphylla*, was assigned structure (39) on the basis of spectroscopic evidence, its synthesis from phenylacetanilide and ethyl carbamate, and its non-identity with the tautomeric glycosminine (40) that is apparently present in the same species (*cf.* Vol. 9, p. 85). This conclusion has now been disputed;<sup>28</sup> repetition of the above synthesis gave a compound reported to be identical with glycosminine that had been prepared by the reaction of anthranilamide with phenylacetic acid. It thus appears that glycophymine is identical with glycosminine, but it is unfortunate that an authentic sample of glycophymine was not available for comparison. *Glycosmis pentaphylla* is believed to be more correctly named *G. arborea* (Roxb.) DC.

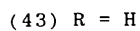
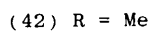
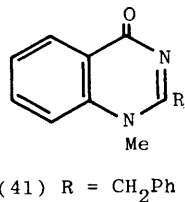
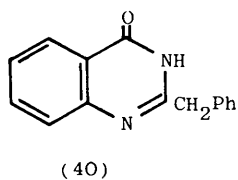
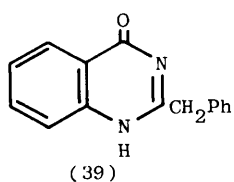
<sup>27</sup> M. F. Grundon, D. M. Harrison, and S. A. Surgenor, *Tetrahedron Lett.*, 1979, 1713.

<sup>28</sup> J. Bhattacharyya and S. C. Pakrashi, *Heterocycles*, 1979, **12**, 929.



Reagents: i,  $\text{Ac}_2\text{O}$ , pyridine, HCl, reflux; ii, aq. NaOH; iii,  $\text{CH}_2\text{N}_2$

Scheme 3



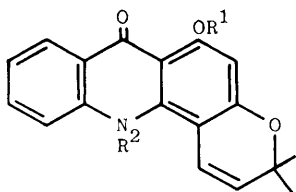
The Kametani synthesis of quinazoline alkaloids (*cf.* Vol. 8, p. 83) has been improved by allowing sulphinamide anhydrides to react with thioamides; arborine (41), glycosminine (40), and glomerine (42) were prepared in this way in good yield.<sup>29</sup> Arborine (41) and glycorine (43) have been synthesized by the reaction of ethylurethane and phosphorus pentoxide with *N*-methyl-phenylacetanilide and with *N*-methylformanilide, respectively.<sup>30</sup>

Arborine (41) and glycorine (43) have been isolated from *Glycosmis bilocularis*,<sup>35</sup> and *Peganum nigellastrum* is a new source of the tricyclic alkaloids *dl*-vasicine (peganine), vasicinone, and desoxyvasicinone.<sup>31</sup>

### 3 Acridone Alkaloids

The <sup>13</sup>C n.m.r. spectra of acridones have been studied by two research groups.<sup>32-34</sup>

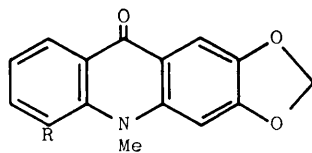
One new acridone alkaloid has been reported this year and known acridone alkaloids have been obtained from several new sources. Thus, des-*N*-methylnoracronycine (45) is the major alkaloid of the roots of *Murraya paniculata*, and noracronycine (44) and des-*N*-methylacronycine (46) have also been isolated.<sup>15</sup> The stem bark of *Oricia suaveolens* contains evoxanthine (47) and teceanone (49);<sup>16</sup> 1,3-dimethoxy-*N*-methylacridone (50) is a minor constituent,<sup>16</sup> and tecleanthine (48) has been tentatively identified.<sup>7</sup> A t.l.c. study of extracts of *Diphasia angolensis* suggested that the latter two alkaloids were also present in this species.<sup>7</sup> Arborinine (51) and the new alkaloid 5-hydroxyarborinine (52) were isolated from the leaves of *Glycosmis bilocularis*.<sup>35</sup> The presence of two phenolic hydroxy-groups in 5-hydroxyarborinine was indicated by the formation of mono- and di-methylation and acetylation products. The <sup>1</sup>H n.m.r. spectrum indicated that the alkaloid contained two methoxy-groups, an *N*-methyl group, and a *peri*-hydroxyl substituent; the shift of all aromatic proton resonances in [<sup>2</sup>H<sub>6</sub>]DMSO-CD<sub>3</sub>SOCD<sub>2</sub>Na showed that the second OH group was in ring A,



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

(45)  $R^1 = R^2 = H$

(46)  $R^1 = OMe, R^2 = H$



(47)  $R = H$

(48)  $R = OMe$

<sup>29</sup> T. Kametani, Chu Van Loc, M. Ihara, and K. Fukumoto, *Heterocycles*, 1978, **9**, 1585.

<sup>30</sup> P. Bhattacharyya, M. Sarker, T. Roychowdhury, and D. P. Chakraborty, *Chem. Ind. (London)*, 1978, 532.

<sup>31</sup> D. Batsuren, M. V. Telezhetskaya, S. Yu. Yunusov, and T. Balden, *Khim. Pri. Soedin.*, 1978, 418 (*Chem. Abs.*, 1978, **89**, 126 170).

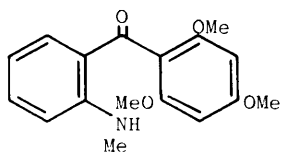
<sup>32</sup> A. Ahond, P. Poupat, and P. Potier, *Tetrahedron*, 1978, **34**, 2385.

<sup>33</sup> I. Mester, D. Bergenthal, Zs. Rózsa, and J. Reisch, *Z. Naturforsch., Teil B*, 1979, **34**, 516.

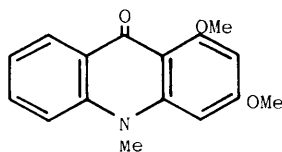
<sup>34</sup> D. Bergenthal, I. Mester, Zs. Rózsa, and J. Reisch, *Phytochemistry*, 1979, **18**, 161.

<sup>35</sup> I. H. Bowen, K. P. W. C. Perera, and J. R. Lewis, *Phytochemistry*, 1978, **17**, 2125.

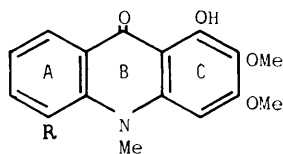
and it was placed at C-5, since the aromatic protons of this ring produced an ABX pattern similar to that in the n.m.r. spectra of tecleanthine (48) and other 5-substituted acridones.



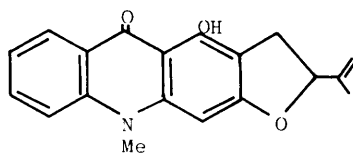
(49)



(50)



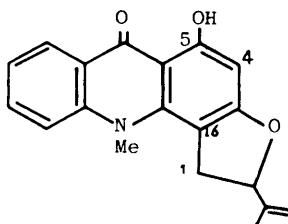
(51) R = H



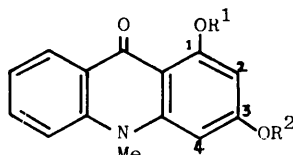
(53)

5-Hydroxyarborinine (52) R = OH

The linear structure (53) was preferred for the *Ruta* alkaloid rutacridone on the basis of n.m.r. shifts induced by trifluoroacetic acid (*cf.* Vol. 8, p. 84), but further spectroscopic studies have now established the angular structure (54) for rutacridone. In the  $^1\text{H}$  n.m.r. spectrum of the alkaloid, chemical shifts for the *N*-methyl group and for the methylene group at C-1 were too close for direct N.O.E. studies to be carried out. In model compounds (55), however, irradiation of the *N*-methyl signal produced 20–30% enhancement of the signal due to the proton attached to C-4; similar treatment of rutacridone produced no effect, thus excluding structure (53).<sup>36</sup> The correspondence in chemical shifts in the  $^{13}\text{C}$  n.m.r. spectrum of rutacridone to those of similar angular dihydrofuroacridones, especially for C-1, C-4, and C-16, provides further support for structure (54).<sup>34</sup>



(54)



(55)

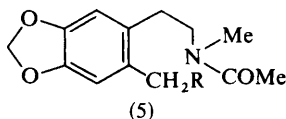
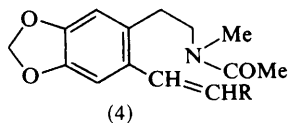
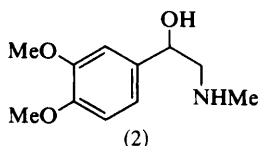
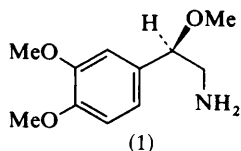
<sup>36</sup> J. Reisch, Zs. Rózsa, and I. Mester, *Z. Naturforsch., Teil B*, 1978, **33**, 957.

## $\beta$ -Phenylethylamines and the Isoquinoline Alkaloids

BY K. W. BENTLEY

### 1 $\beta$ -Phenylethylamines

The absolute configuration of (-)-calipamine (1) has been determined by circular dichroism studies.<sup>1</sup> Mescaline and 3,4-dimethoxyphenylethylamine have been isolated from the cactus *Opuntia spinosior*.<sup>2</sup> The metabolism of mescaline to 3,4,5-trimethoxybenzoic acid in humans has been recorded and the isolation of this metabolite from urine studied.<sup>3</sup> The behavioural effects of mescaline have been further studied<sup>4</sup> and the psycho-activity of normacromerine (2) has been compared with those of mescaline, of psilocin, and of amphetamine.<sup>5</sup>  $\beta$ -(4-Hydroxy-3-methoxyphenyl)ethylamine has been isolated from the Mexican cactus *Pachycereus pecten-aboriginum*.<sup>6</sup> *N*-Acetylhydrastinine (3) has been condensed with substances containing reactive methylene groups to give the olefins (4; R = NO<sub>2</sub>, CO<sub>2</sub>Et, CO<sub>2</sub>H, or COMe) and has been converted also into the amides (5; R = H, OH, Cl, Br, or CN).<sup>7</sup>



<sup>1</sup> R. W. Woodard, J. C. Craig, and J. G. Bruhn, *Acta Chem. Scand., Ser. B*, 1978, **32**, 619.

<sup>2</sup> J. H. Pardanani, B. N. Meyer, J. L. McLaughlin, W. H. Earle, and R. G. Enghard, *Lloydia*, 1978, **41**, 286.

<sup>3</sup> L. Demisch, P. Kaczmarczyk, and N. Seiler, *Drug Metab. Dispos.*, 1978, **6**, 507.

<sup>4</sup> R. J. Sbordone, J. A. Wingard, M. L. Elliott, and J. Jervey, *Pharmacol. Biochem. Behav.*, 1978, **8**, 543.

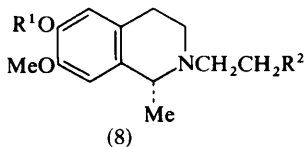
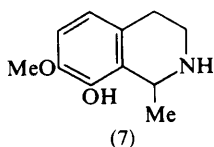
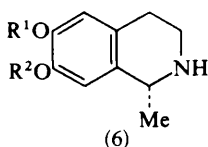
<sup>5</sup> W. M. Bourne, W. J. Keller, and J. F. Bonfiglio, *Life Sci.*, 1978, **23**, 1175.

<sup>6</sup> J. Strombom and J. G. Bruhn, *Acta Pharm. Suec.*, 1978, **15**, 127.

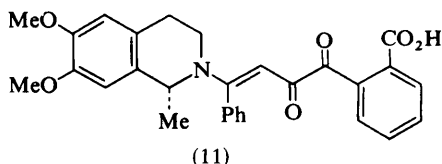
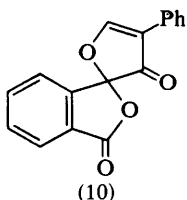
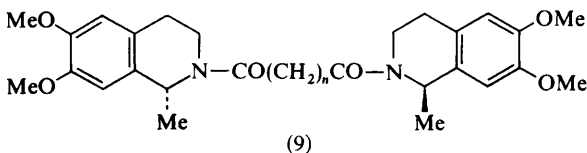
<sup>7</sup> M. D. Rozwadowska, *Pol. J. Chem.*, 1978, **52**, 823.

## 2 Simple Isoquinoline Alkaloids

The Mexican cactus *Pachycereus pecten-aboriginum* has been shown to contain salsoline (6;  $R^1 = H$ ,  $R^2 = Me$ ) and the new bases isosalsoline (6;  $R^1 = Me$ ,  $R^2 = H$ ), the isomeric arizonine (7) (which has the same orientation of oxygen substituents as is found in tepenine), and heliamine, which is 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline.<sup>6</sup> Salsoline (6;  $R^1 = H$ ,  $R^2 = Me$ ) and salsolidine (6;  $R^1 = R^2 = Me$ ), on treatment with ethylene oxide, afford the  $\beta$ -hydroxyethyl compounds (8;  $R^1 = H$ ,  $R^2 = OH$ ) and (8;  $R^1 = Me$ ,  $R^2 = OH$ ),<sup>7</sup> and these have been converted into a series of esters by reaction with acid chlorides.<sup>8</sup> The  $\beta$ -chloroethyl compound (8;  $R^1 = H$ ,  $R^2 = Cl$ ) has been shown to decrease



protein synthesis *in vitro*.<sup>9</sup> The  $^{13}C$  n.m.r. spectra of salsolidine and of 1,2,3,4-tetrahydroisoquinoline have been studied in detail.<sup>10</sup> Salsolidine has been converted into a series of diamides of structure (9) by reaction with acid chlorides of dibasic acids.<sup>11</sup> The alkaloid has also been shown to react with fluorescanine (10) to give the unsaturated  $\alpha$ -diketone (11), which has strong absorption at long wavelengths and is useful for chiroptical studies.<sup>12</sup> Both (+)- and (-)-salsolidine have been synthesized from the resolved optical isomers of the dihydroisoquinolinium salt (12), which was reduced with sodium borohydride to the (+)- and (-)-bases (13); these were then subjected to hydrogenolysis.<sup>13</sup> The effect of salsolinol (6;  $R^1 = R^2 = H$ ) on tyrosine hydroxylase has been studied.<sup>14</sup>



<sup>8</sup> Yu. R. Khakimov, A. A. Abduvakhobov, A. A. Sadykov, and Kh. A. Aslanov, *Dokl. Akad. Nauk Uzb. SSR*, 1977, 50.

<sup>9</sup> O. Kh. Saitmuratova, D. Tursunova, and V. B. Leont'ev, *Uzb. Biol. Zh.*, 1978, 55.

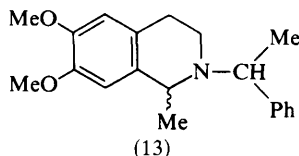
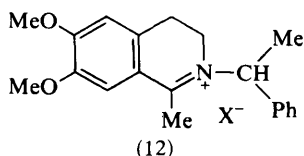
<sup>10</sup> S. P. Singh, S. S. Parmar, V. I. Stenberg, and S. A. Farnum, *J. Heterocycl. Chem.*, 1978, **15**, 541.

<sup>11</sup> V. Rakhmatullina, A. A. Abduvakhobov, and Kh. A. Aslanov, *Zh. Obshch. Khim.*, 1978, **48**, 689.

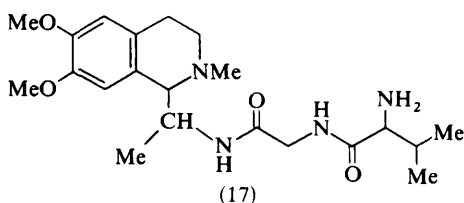
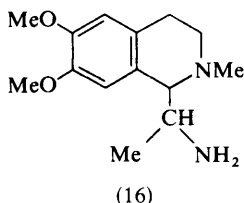
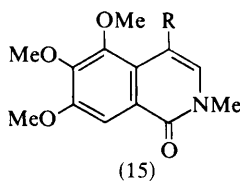
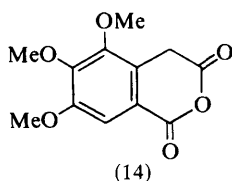
<sup>12</sup> V. Toome, B. Wegrzynski, and J. Dell, *Heterocycles*, 1977, **7**, 787.

<sup>13</sup> T. Kametani, Jpn. Kokai Tokkyo Koho 78 90 272 (*Chem. Abs.*, 1979, **90**, 23 363).

<sup>14</sup> M. A. Collins and C. D. Weiner, *Alcohol Aldehyde Metab. Syst.*, 1977, **3**, 511.



Thalactamine (15; R = H) and its 6,7-dimethoxy-analogue have been synthesized from the appropriately substituted homophthalic anhydride, *e.g.* (14); this, with phosphorus oxychloride and dimethylformamide, gives the acid (15; R = CO<sub>2</sub>H), which can be decarboxylated.<sup>15</sup> The peptide alkaloid amphi-bine (17) has been synthesized by the condensation of the primary amine (16) with *N*-benzyloxycarbonyl-L-valylglycine, followed by removal of the *N*-benzyloxy-carbonyl group.<sup>16</sup>



Further examination of *Triphiphyllum peltatum* has shown that *O*-methyl-triphiophylline and its 1,2-dehydro-analogue are accompanied by iso-triphiophylline (18), *N*-methyltriphiophylline (19), and *O*-methyltetra-dehydrotriphiophylline (20).<sup>17</sup> The structure of hamatine (21) and its absolute stereochemistry have been determined,<sup>18</sup> and an X-ray crystallographic study of ancistrocladine has confirmed the structure previously deduced (see Volume 7, p. 106).<sup>19</sup>

### 3 Benzylisoquinolines

Two new benzylisoquinoline alkaloids have been reported. Ledecorine, found in *Corydalis ledebouriana*, has been assigned the structure (22) on the basis of spectroscopic studies,<sup>20</sup> and it appears to be the first alkaloid of this group to be

<sup>15</sup> V. H. Belgaonkar and R. S. Usgaonkar, *J. Heterocycl. Chem.*, 1978, **15**, 257.

<sup>16</sup> J. Koyama, Y. Suzuta, K. Kuriyama, H. Yajima, K. Koyama, and H. Irie, *Heterocycles*, 1978, **9**, 443.

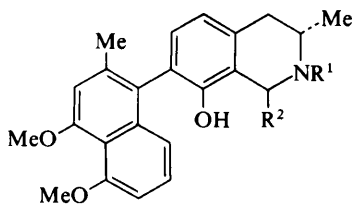
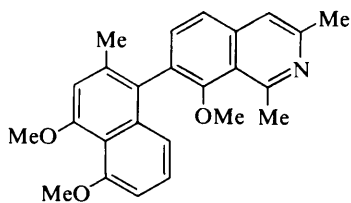
<sup>17</sup> M. Lavault and J. Bruneton, *C.R. Hebd. Seances Acad. Sci., Ser. C*, 1978, **287**, 129.

<sup>18</sup> P. Parsatharathy, H. K. Desai, and M. T. Saindane, *Indian J. Chem., Sect. B*, 1977, **15**, 871.

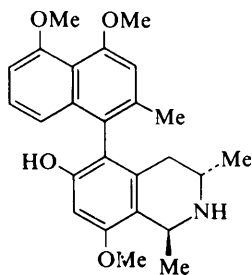
<sup>19</sup> J. S. Chen, *Diss. Abs. Int. B*, 1978, **38**, 4028.

<sup>20</sup> I. S. Israilov, M. S. Yunusov, and S. Yu. Yunusov, *Khim. Pri. Soedin.*, 1978, 537.

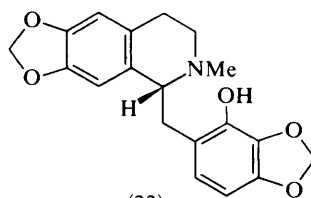


(18)  $R^1 = H$ ,  $R^2 = \alpha\text{-Me}$ (19)  $R^1 = \text{Me}$ ,  $R^2 = \beta\text{-Me}$ 

(20)



(21)

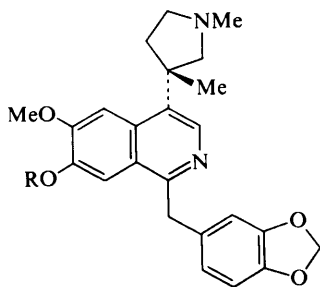


(22)

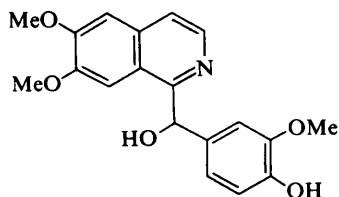
discovered that has a third oxygen function in the benzyl group. Arenine, isolated from *Papaver arenarium*, has been identified as the 4-substituted base (23;  $R = H$ ) by spectroscopic studies and by its methylation to macrostomine by diazomethane.<sup>21</sup>

The quaternary alkaloid tembetarine has been isolated from *Zanthoxylum bouetense*.<sup>22</sup>

The selective demethylation of papaverinol by 90% sulphuric acid or 89% phosphoric acid has been shown to give the phenol (24)<sup>23,24</sup> rather than the 3'-hydroxy-4'-methoxy-compound previously reported, and this has been confirmed by the synthesis of the phenol from *O*-benzylvanillin.<sup>24</sup>



(23)



(24)

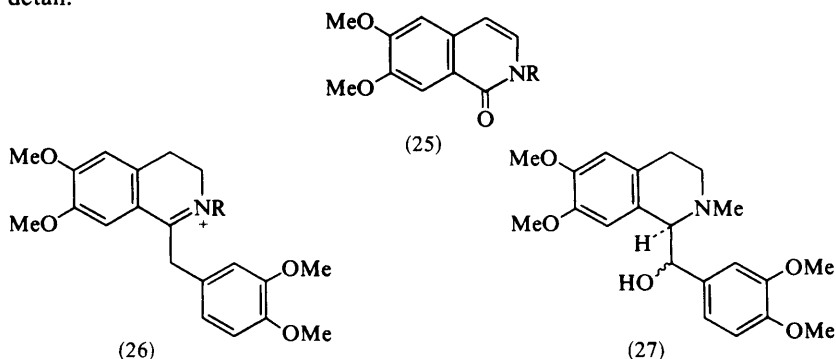
<sup>21</sup> I. A. Israilov, M. A. Manushakyan, and M. S. Yunusov, *Khim. Prir. Soedin.*, 1978, 417.

<sup>22</sup> J. Vaquette, A. Cave, and P. G. Waterman, *Plant. Med. Phytother.*, 1978, **12**, 235.

<sup>23</sup> L. Castedo, J. M. Saa, R. Suau, and C. Villaverde, *Heterocycles*, 1978, **9**, 659.

<sup>24</sup> S. Ruchirawat, S. Suparlucknarce, and N. Pratsipan, *Heterocycles*, 1978, **9**, 859.

A patent for the preparation of quaternary salts of papaverine from C<sub>5</sub>, C<sub>6</sub>, and C<sub>8</sub> halides been published.<sup>25</sup> *N*-Alkyl-papaverinium salts have been found to undergo oxidation by oxygen either photolytically or in the presence of cuprous chloride, to give the isoquinolones (25).<sup>26</sup> The corresponding dihydro-papaverinium salts (26), with oxygen and cuprous chloride, do not suffer fission, and oxidation of the *N*-methyl compound (26; R = Me) in this way, followed by reduction of the product with sodium borohydride, affords  $\alpha$ - and  $\beta$ -hydroxy-laudanosines (27).<sup>26</sup> The <sup>13</sup>C n.m.r. spectrum of laudanosine has been studied in detail.<sup>10</sup>



A method for the extraction of papaverine from aqueous solution by toluene and organic acids has been described,<sup>27</sup> as have methods for the determination of the alkaloid in blood by gas chromatography.<sup>28,29</sup> The metabolism of papaverine has been studied,<sup>30</sup> as have its effects on the release of renin *in vivo* and *in vitro*,<sup>31–33</sup> on responses to isoprenaline,<sup>34</sup> on sodium excretion,<sup>35</sup> on calcium uptake by mitochondrial fractions from rat uterine muscle,<sup>36</sup> on the treatment of neuroblastoma,<sup>37</sup> on recovery from injury of the spinal cord,<sup>38</sup> on post-ischaemic arrhythmias,<sup>39</sup> on rabbit atrial chromotropic response,<sup>40</sup> on the noradrenalin- and calcium-evoked contraction of rabbit aorta and mesenteric arteries,<sup>41</sup> on isolated coronary arteries,<sup>42</sup> on autonomic heart contractions in the frog,<sup>43</sup> on cyclic AMP

<sup>25</sup> S. Tanaka and K. Ueda, Jpn. Kokai Tokkyo Koho 78 130 676 (*Chem. Abs.*, 1979, **90**, 138 074).

<sup>26</sup> S. Ruchirawat, *Symp. Heterocycl. [Pap.]*, 1977, 226.

<sup>27</sup> V. V. Egorov and G. L. Starobinets, *Vestsi Akad. Navuk B. SSR, Ser. Khim. Navuk*, 1978, 128.

<sup>28</sup> V. Bellia, J. Jacob, and H. T. Smith, *J. Chromatogr.*, 1978, **161**, 231.

<sup>29</sup> E. Zuccato, F. Marcucci, and E. Mussini, *J. Pharmacol. Methods*, 1978, **1**, 9.

<sup>30</sup> M. G. Bogaert and F. M. Belpaire, *Verh. K. Vlaam. Acad. Geneesk. Belg.*, 1977, **39**, 65.

<sup>31</sup> K. Gaal, J. Siklos, T. Mozes, and G. Fejes Toth, *Kiserl. Orvostud.*, 1978, **30**, 159.

<sup>32</sup> K. Gaal, J. Siklos, T. Mozes, and G. Fejes Toth, *Acta Physiol. Acad. Sci. Hung.*, 1978, **51**, 305.

<sup>33</sup> H. J. Lyons and P. E. Churchill, *Proc. Soc. Exp. Biol. Med.*, 1979, **160**, 237.

<sup>34</sup> D. Reinhardt, P. Freynik, and H. J. Scheumann, *Arch. Int. Pharmacodyn. Ther.*, 1977, **229**, 67.

<sup>35</sup> E. H. Blaine, *Proc. Soc. Exp. Biol. Med.*, 1978, **158**, 250.

<sup>36</sup> K. Sakai, I. Takayanagi, M. Uchida, and K. Takagi, *Eur. J. Pharmacol.*, 1978, **50**, 131.

<sup>37</sup> Z. Wajzman, P. Williams, and G. P. Murphy, *Oncology*, 1978, **35**, 1.

<sup>38</sup> A. S. Rivlin and C. H. Tator, *J. Neurosurg.*, 1979, **50**, 349.

<sup>39</sup> P. Lacroix, P. Linee, and J. B. LePolles, *C.R. Soc. Biol.*, 1977, **171**, 1075.

<sup>40</sup> M. J. Hughes, *Res. Commun. Chem. Pathol. Pharmacol.*, 1978, **21**, 251.

<sup>41</sup> A. Broekaert and T. Godfraind, *Eur. J. Pharmacol.*, 1979, **53**, 281.

<sup>42</sup> S. B. Shishkin and A. G. Baranov, *Krovoobrashchenie*, 1978, **11**, 3.

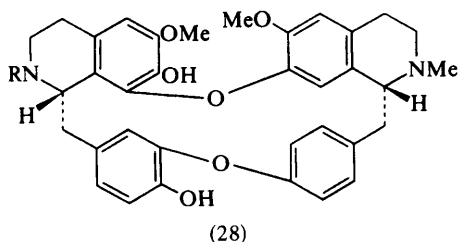
<sup>43</sup> J. Slavicek and M. Stojan, *Sb. Lek.*, 1978, **80**, 129.

phosphodiesterase levels in the guinea pig,<sup>44</sup> on cyclic nucleotide phosphodiesterase and cyclic AMP levels in psoriatic dermatitis,<sup>45</sup> on smooth muscle of guinea-pig taenia coli,<sup>46,47</sup> and on tissue oxygen levels in cat brain;<sup>48</sup> the haemodynamics of the alkaloid have also been studied.<sup>49</sup> Papaveroline has been shown to produce a dose-related inhibition of the aggregation of platelets that is caused by thrombin or ADP *in vitro*,<sup>50</sup> and the effects of tetrahydropapaveroline (norlaudanoline) on the cardiovascular system and skeletal muscle of the anaesthetized cat have been studied.<sup>51</sup> The determination of papaveroline (norlaudanoline) on the cardiovascular system and skeletal muscle of the anaesthetized cat have been studied.<sup>51</sup> The determination of papaveroline tetraethyl ether in body fluids by h.p.l.c. has been described.<sup>52</sup>

(-)-*N*-Methylcoclaurine has been isolated from *Thalictrum dioicum*<sup>53</sup> and (S)-reticuline from *T. minus*.<sup>54</sup>

#### 4 Bisbenzylisoquinolines

A review of bisbenzylisoquinoline alkaloids has been published.<sup>55</sup> Several new bases of this sub-group have been isolated and identified during the period under review. Two bases that are related to peinamine have been isolated from *Abuta grisebachii* Triana et Planchon, together with peinamine itself, namely 7-*O*-desmethylpeinamine (28; R = H) and *N*-methyl-7-*O*-desmethylpeinamine (28;



R = Me), the structures being determined by spectroscopic methods and by the interrelationship of the three alkaloids by *O*- and *N*-methylations.<sup>56</sup> Also isolated from the same plant were two alkaloids having the alternative diphenyl ether linkage between the isoquinoline units, namely macolidine (29) and macoline, which is the mono-*N*-methyl quaternary salt of macolidine at the nitrogen atom

<sup>44</sup> M. Kimura, I. Waki, and I. Kimura, *J. Pharmacobio.-Dyn.*, 1978, **1**, 145.

<sup>45</sup> L. J. Rusin, E. A. Duell, and J. J. Voorhees; *J. Invest. Dermatol.*, 1978, **71**, 154.

<sup>46</sup> A. A. Galkin, D. A. Sarkisyan, E. N. Timin, and B. I. Khodorov, *Byull. Eksp. Biol. Med.*, 1978, **85**, 177.

<sup>47</sup> A. A. Galkin and E. N. Timin, *Byull. Eksp. Biol. Med.*, 1978, **86**, 447.

<sup>48</sup> R. Nikolov and E. Leninger-Follert, *Naunyn-Schmiedbergs Arch. Pharmacol.*, 1978, **305**, 149.

<sup>49</sup> J. L. Montastruc, J. Cotonat, and M. Andrieu, *Arch. Pharmacol. Toxicol.*, 1978, **4**, 90.

<sup>50</sup> A. Imperatore and M. Sasso, *Rass. Int. Clin. Ter.*, 1978, **58**, 587.

<sup>51</sup> M. W. Nott and G. A. Head, *Clin. Exp. Pharmacol. Physiol.*, 1978, **5**, 313.

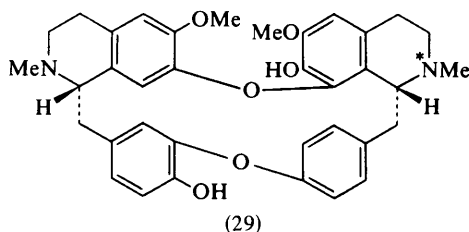
<sup>52</sup> E. Renier, K. Kjeldsen, and M. Pays, *Feuill. Biol.*, 1979, **106**, 111.

<sup>53</sup> M. Shamma and A. S. Rothenberg, *Lloydia*, 1978, **41**, 169.

<sup>54</sup> W.-T. Liao, J. L. Beal, W.-N. Wu, and R. W. Doskotch, *Lloydia*, 1978, **41**, 257.

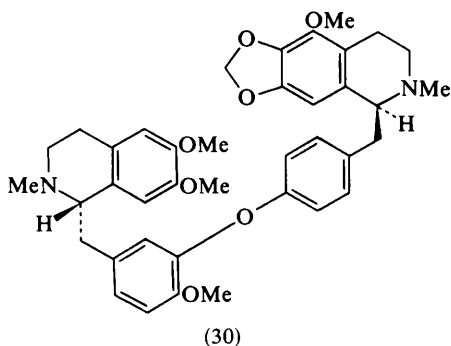
<sup>55</sup> K. P. Guha, B. Mukherjee, and R. Mukherjee, *J. Nat. Prod.*, 1979, **42**, 1.

<sup>56</sup> C. Galeffi, P. Scarpetti, and G. B. Marini-Bettolo, *Farmaco, Ed. Sci.*, 1977, **32**, 853.

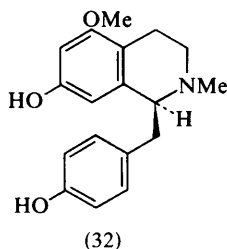
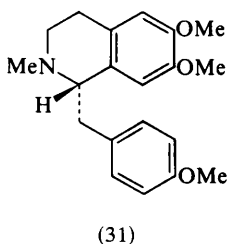


marked with an asterisk.<sup>56</sup> Macoline has also been isolated from the sample of curare of unknown origin, from the upper Orinoco region, that was the original source of peinamine.<sup>57</sup>

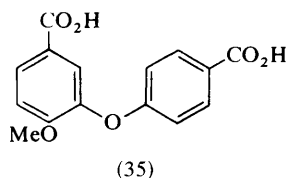
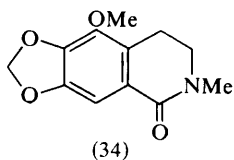
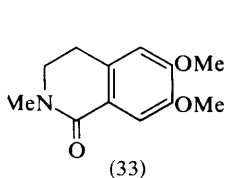
An investigation of the alkaloids of *Thalictrum minus* (race B) has resulted in the isolation of two new bases, together with thalfine and thalfinine, thalrugosaminine, thalidasine, obaberine, and the degraded aporphine thaliglucunone.<sup>54</sup> The new alkaloids thalirabine and thaliracebine have marked antihypertensive activity. Thaliracebine has the structure (30), as deduced from its cleavage by



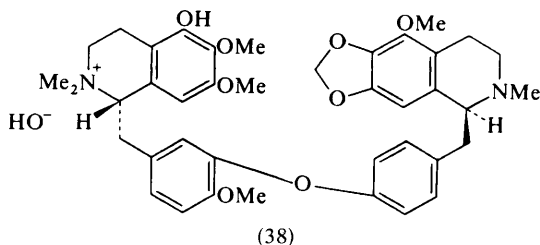
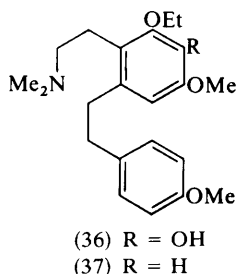
sodium and liquid ammonia to produce the benzylisoquinolines (*S*)-*O*-methyl-armepavine (31) and (32) and its oxidation to the isoquinolones (33) and (34) and the dicarboxylic acid (35).<sup>54</sup>



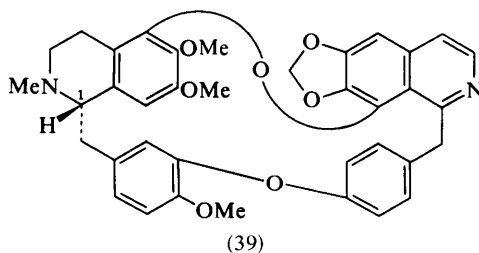
<sup>57</sup> C. Galeffi and G. B. Marini-Bettolo, *Atti Accad. Naz. Lincei, Cl. Sci. Fis., Mat. Nat., Rend.*, 1977, **62**, 825.



Thalirabine is a monoquaternary salt of a hydroxylated thaliracebine, and its *O*-methyl ether is identical with thalistryline. It gives a positive test with Gibbs' reagent and its *O*-ethyl ether suffers fission with sodium and liquid ammonia to give the phenolic bases (32) and (36), together with the non-phenolic base (37), the last two being products of Emde reduction of the quaternary salt. On this evidence, thalirabine was assigned the structure (38).<sup>54</sup>



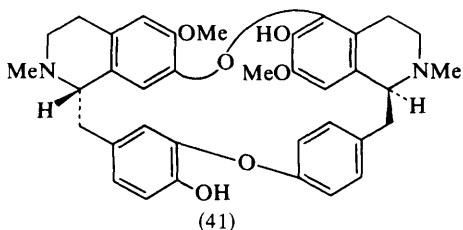
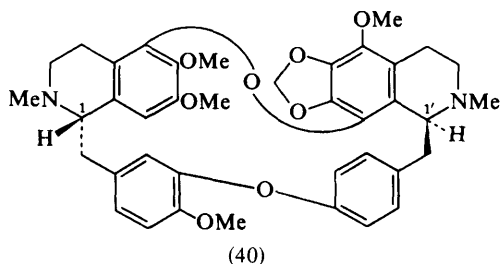
Thalfine and thalfinine have previously been isolated from *T. foetidum* L. and the former has been detected in *T. minus* (race B). Thalfine (39) is reduced by zinc and hydrochloric acid to secondary bases that give thalfinine and epithalfinine (epimeric at the new asymmetric centre) on *N*-methylation. Reductive cleavage of thalfinine with sodium and liquid ammonia affords (*S*)-*O*-methylarmepavine (31), thus determining the stereochemistry at C-1 in both thalfinine and thalfine.



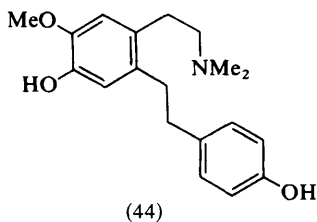
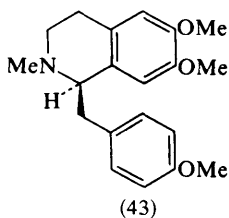
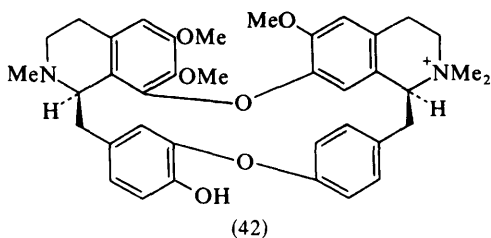
The phenolic product of this cleavage was not isolated, so that the stereochemistry at C-1' in thalfinine could not be determined, but it was concluded that, since the alkaloid occurs alongside thalirabine, it is most probably the (*S,S*)-form (40).<sup>54</sup>

The new base thalbadenzine (41) has been isolated from *Thalictrum sultanabadense*, Stapf., the structure being assigned on spectroscopic evidence.<sup>58</sup>

<sup>58</sup> S. Abdizhabbarova, S. Kh. Maekh, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 1978, 139.



A new quaternary alkaloid, 2'-*N*-methylberbamine (42), has been obtained from *Berberis oblongata*. The structure was determined on the basis of spectroscopic studies and the Hofmann degradation of the *O*-methyl ether, followed by reductive fission to (*R*)-*O*-methyarmepavine (43) and the coclaurine derivative (44).<sup>59</sup>

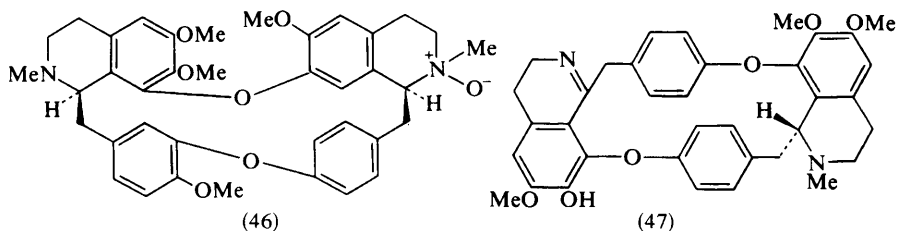
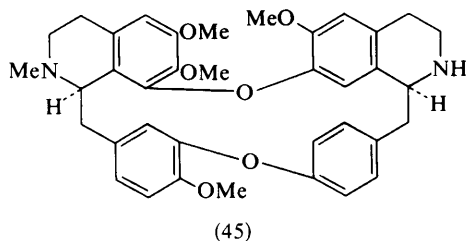


An investigation of *Limnapiopsis loangensis* has revealed the presence of thirteen alkaloids, including the bisbenzylisoquinolines thalrugosine, thalrugosamine, cycleanine, and berbamine, and two new bases of this group, *i.e.* 2'-norisotetrandrine (45) and isotetrandrine 2'-*N*-oxide (46).<sup>60</sup>

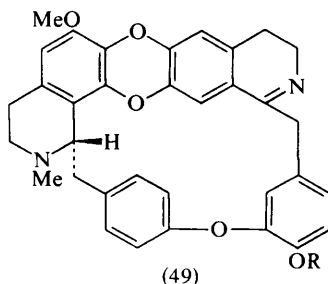
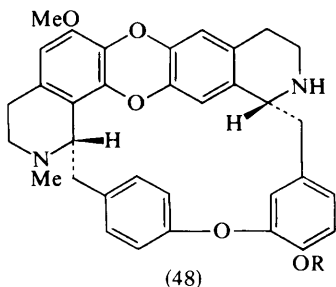
<sup>59</sup> A. Karimov, M. V. Telezhenetskaya, K. L. Lutfullin, and S. Yu. Yunusov, *Khim. Priro. Soedin.*, 1978, 227.

<sup>60</sup> A. Cavé, M. Leboeuf, R. Hocquimiller, A. Bouquet, and A. Fornet, *Planta Med.*, 1979, **35**, 31.

*Sciadotenia toxifera* Krukhoff and A. C. Smith has been shown to contain isochondodendrine and a new base sciadoferine (47), which is 1,2-dehydro-*N*-desmethylnorcycleanine.<sup>61</sup>



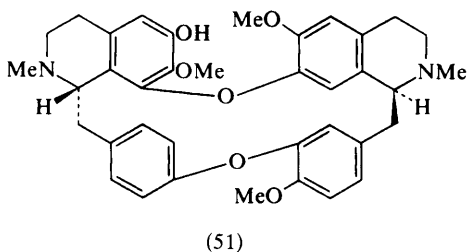
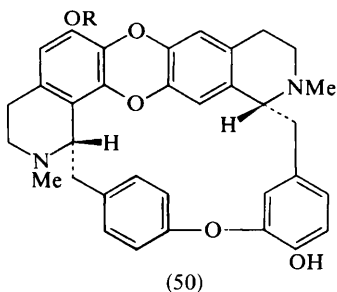
Five new tris-diphenyl ethers of this group, with the same orientation of substituents as found in trilobine and the rare alkaloid telobine, have been isolated from *Daphnandra* species. *D. apatela* yields telobine (48; R = Me) and 1,2-dehydrotelobine (49; R = Me), and apateline (48; R = H) and 1,2-dehydroapateline (49; R = H). The structures were determined on spectroscopic evidence and by the identity of telobine with *O*-methylapateline and the reduction of the 1,2-dehydro-compounds to the parent secondary bases.<sup>62</sup> *D. johnsonii* contains the ditertiary bases *N*-methylapateline (50; R = Me) and *N*-methylnorapateline (50; R=H), identified by their relationship to apateline,<sup>63</sup> and also repandine, repandine, *O*-methylrepandine, nortenuipine, and a new base, johnsonine (51), identified by spectroscopic studies and the identity of its *O*-methyl ether with *O*-methylrepandine.<sup>63</sup>



<sup>61</sup> C. Galeffi, R. La Bua, I. Messana, R. Zapata Alcazar, and G. B. Marini-Bettolo, *Gazz. Chim. Ital.*, 1978, **108**, 97.

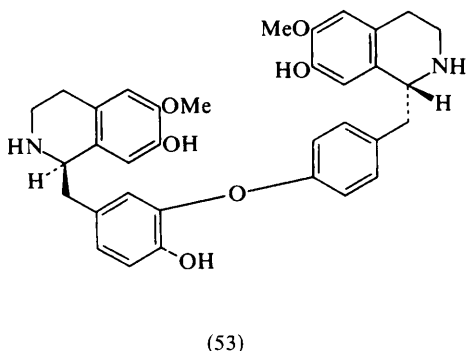
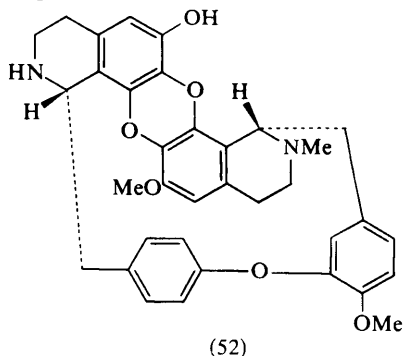
<sup>62</sup> I. R. C. Bick and S. Sotheeswaran, *Aust. J. Chem.*, 1978, **31**, 2077.

<sup>63</sup> I. R. C. Bick and H. M. Leow, *Aust. J. Chem.*, 1978, **31**, 2539.



A new base of menisarine type, *i.e.* gillettine, has been isolated from *Triclisia gillettii*. It is a phenolic secondary and tertiary base and has been assigned the structure (52) on the basis of spectroscopic data and *O*- and *N*-methylations.<sup>64</sup>

The structure of the alkaloid lindholdamine (53), from *Lindera oldhamii*, has been determined by cleavage of the *OOO*-trimethyl ether by sodium and liquid ammonia to produce (*R*)-*O*-methyl-*N*-norarmepavine and (*R*)-*N*-norarmepavine.<sup>65</sup>



Benzylisoquinoline-aporphine dimers have been isolated from *Thalictrum dioicum* (pennsylvamine),<sup>53</sup> *T. revolutum* (thalirevoline, thalirevolutine, thalilutine, and thalilutidine),<sup>66</sup> and *T. minus* (thaliadamine).<sup>67</sup>

The discrepancy in the physical properties of samples of *OO*-dimethyl-tubocurine (54; R = Me) that were prepared by *N*-demethylation of the corresponding quaternary salt *OO*-dimethylchondrocurarine chloride by sodium thiophenoxide<sup>68</sup> and by ethanolamine,<sup>69</sup> respectively, has been explained following a re-investigation of these reactions.<sup>70</sup> It has been shown that sodium thiophenoxide effects predominant *N*-demethylation and that the ditertiary base

<sup>64</sup> D. Dwuma-Badu, J. S. K. Ayin, A. N. Tackie, P. D. Owusu, J. E. Knapp, D. J. Slatkin, and P. L. Schiff, *Heterocycles*, 1978, **9**, 995.

<sup>65</sup> S.-T. Lu and I.-S. Chen, *J. Chin. Chem. Soc. (Taipei)*, 1977, **24**, 187.

<sup>66</sup> W.-N. Wu, J. L. Beal, and R. W. Dосkotch, *Tetrahedron*, 1977, **33**, 2919.

<sup>67</sup> W.-T. Liao, J. L. Beal, W.-N. Wu, and R. W. Dосkotch, *Lloydia*, 1978, **41**, 271.

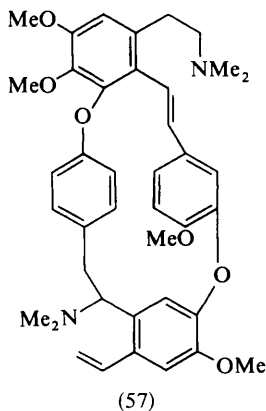
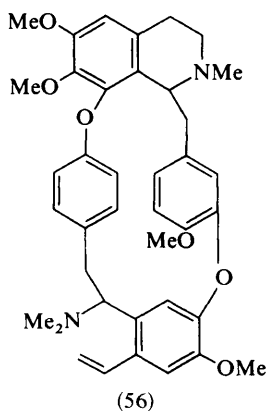
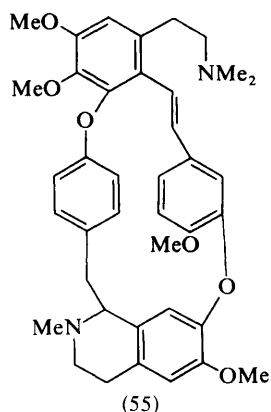
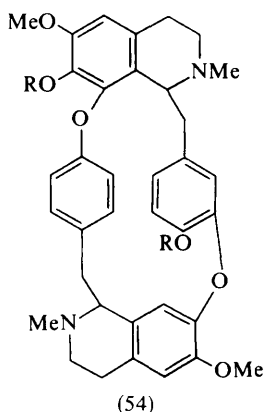
<sup>68</sup> M. Shamma, N. C. Deno, and J. F. Remar, *Tetrahedron Lett.*, 1966, 1375.

<sup>69</sup> I. G. Marshall, J. B. Murray, G. A. Smail, and J. B. Stenlake, *J. Pharm. Pharmacol.*, 1967, **19**, 535.

<sup>70</sup> J. A. Naghaway and T.-O. Soine, *J. Pharm. Sci.*, 1978, **67**, 1204.



(54; R = Me) prepared in this way has the structure claimed. This was confirmed by *N*-demethylation of the monoquaternary salt (+)-tubocurarine with the same reagent to produce (+)-tubocurine (54; R = H) and methylation of this with diazomethane, to give the dimethyl ether (54; R = Me), identical with the product of demethylation of *OO*-dimethylchondrocurarine chloride. Ethanolamine, however, effects predominant Hofmann degradation, and this reagent converts *OO*-dimethylchondrocurarine salts into *OO*-dimethyl-tubocurine methine (55), isomethine (56), and dimethine (57), together with only small amounts of *OO*-dimethyltubocurine.<sup>70</sup>



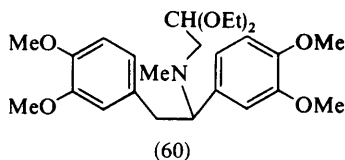
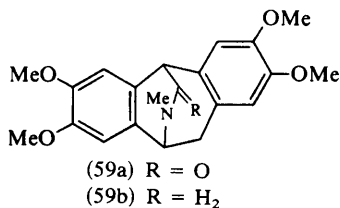
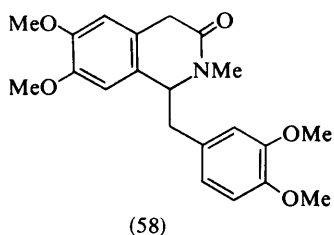
Attempts to methylate (+)-tubocurarine chloride to its dimethyl ether with diazomethane have shown that this reagent, even when alkali-free, can effect Hofmann degradation, the product being a mixture of the methine (55) and the dimethine (57). Similar degradations have been observed with diazomethane and isotubocurarine, the benzyloisoquinoline laudanidine methiodide, and the simple tetrahydroisoquinoline carnegine methiodide.<sup>71</sup>

<sup>71</sup> J. A. Naghaway and T.-O. Soine, *J. Pharm. Sci.*, 1978, **67**, 473.

Reports of the following pharmacological and physiological studies of (+)-tubocurarine chloride have been published: pharmacokinetics in hypothermia of the cat,<sup>72</sup> pharmacodynamics,<sup>73</sup> effect on respiration<sup>74</sup> and on the heart,<sup>75</sup> actions at the motor end-plate,<sup>76</sup> interaction with suxamethonium in hyperkalaemia,<sup>77</sup> effect on hepatic transport,<sup>78</sup> action on smooth muscle of guinea-pig taenia coli,<sup>79</sup> vagolytic action,<sup>80</sup> and neuromuscular blocking action and autonomic blockade.<sup>81</sup> The neuromuscular and clinical effects of metocurine [(+)-tubocurarine methyl ether] have been studied.<sup>81,82</sup> The protective effect of cepharanthine on the suppression of haemopoiesis by anti-tumour agents has been examined.<sup>83</sup>

### 5 Pavines and Isopavines

Syntheses of *O*-methylthalisopavine (59b) have been recorded. In one of these the construction of the carbon-nitrogen skeleton was effected by oxidative cyclization of the lactam (58) to the lactam (59a) by vanadium oxyfluoride in acetonitrile, in 40% yield. Reduction of (59a) by diborane in tetrahydrofuran gave the tertiary amine (59b).<sup>84</sup> An alternative synthesis involved the cyclization, with sulphuric acid, of the acetal (60), prepared from deoxyveratrin.<sup>84</sup>



<sup>72</sup> J. Ham, R. D. Miller, L. Z. Benet, R. S. Matteo, and L. L. Roderick, *Anaesthesiology*, 1978, **49**, 324.

<sup>73</sup> L. B. Sheiner, D. R. Stanski, S. Vozeh, R. D. Miller, and J. Ham, *Clin. Pharmacol. Ther.*, 1979, **25**, 358.

<sup>74</sup> N. A. Saunders, J. R. A. Rigg, L. D. Pengelly, and E.-J. M. Campbell, *J. Appl. Physiol.*, 1978, **44**, 589.

<sup>75</sup> P. A. O'Sullivan, T. A. Matyas, and M. G. King, *Pharmacol. Biochem. Behav.*, 1978, **8**, 357.

<sup>76</sup> B. Katz and R. Miledi, *Proc. R. Soc. London, Ser. B*, 1978, **203**, 119.

<sup>77</sup> C. J. Castenada, D. M. Palomo, and D. A. Almazan, *Rev. Esp. Anesthesiol. Reanim.*, 1978, **25**, 329.

<sup>78</sup> R. J. Vonk, E. Scholtens, G. T. P. Keulemans, and D. K. F. Meijer, *Naunyn-Schmiedeberg Arch. Pharmacol.*, 1978, **302**, 1.

<sup>79</sup> G. Gianni, *Boll. Soc. Ital. Biol. Sper.*, 1977, **53**, 2020.

<sup>80</sup> S. L. Son and D. R. Waud, *Anaesthesiology*, 1978, **48**, 191.

<sup>81</sup> J. J. Savarese, *Anaesthesiology*, 1979, **50**, 40.

<sup>82</sup> N. G. Goudsouzian, L. M. P. Liu, and J. J. Savarese, *Anaesthesiology*, 1978, **49**, 266.

<sup>83</sup> M. Mori, S. Nakamoto, Y. Arashina, and S. Seno, *Gan to Kagaku Ryoho*, 1979, **6**, 175.

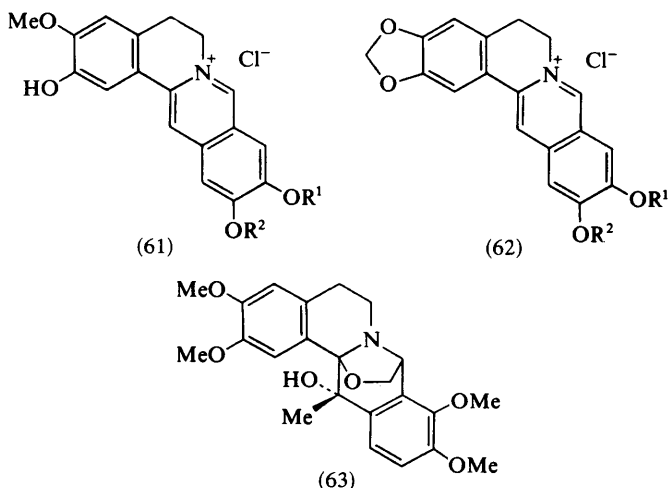
<sup>84</sup> I. W. Elliott, *J. Org. Chem.*, 1979, **44**, 1162.

## 6 Berberines

Berberine, coptisine, and  $\beta$ -stylopine methohydroxide have been isolated from *Papaver rhoeas* L.,<sup>85</sup> berberine, berberubine, isocorypalmine, and thalifendine from *Thalictrum dioicum*,<sup>53</sup> berberine from *T. sachalinense*,<sup>86</sup> corydaline from *Corydalis marschalliana*,<sup>87</sup> scoulerine, ophiocarpine, isocorypalmine, and cheilanthifoline from *C. vaginans*, *C. gigantea*, and *C. marschalliana*,<sup>87</sup> and ophiocarpine, stylopine, cheilanthifoline, isocorypalmine, and the chlorides of berberine, coptisine, and dehydrocheilanthifoline from *C. ophiocarpa*.<sup>88</sup> The alkaloids of *C. ophiocarpa* were separated by droplet counter-current chromatography.<sup>88</sup>

Four new alkaloids of the quaternary berberine type, but with the coreximine orientation of oxygen substituents, have been found in *Isopyrum thalictroides*. The structures of these 'pseudoberberines' were determined as (61;  $R^1 = R^2 = \text{Me}$ ), (61;  $R^1R^2 = \text{CH}_2$ ), (62;  $R^1 = R^2 = \text{Me}$ ), and (62;  $R^1R^2 = \text{CH}_2$ ) by spectroscopic methods and by their reduction with sodium borohydride to tetrahydropseudoberberines and comparison of the  $^{13}\text{C}$  n.m.r. spectra of these compounds with those of five synthetic tetrahydropseudoberberines. It was concluded that bases of the berberine and pseudoberberine group (and their tetrahydro-derivatives) can be distinguished by the  $^{13}\text{C}$  chemical shift of C-8.<sup>89</sup>

A new alkaloid, solidaline, representing a modified protoberberine, has been isolated from *Corydalis solida*. It has been assigned the structure (63) on the basis of spectroscopic studies.<sup>90</sup> The structures assigned to aequaline and schefferine,



<sup>85</sup> J. Slavik, *Collect. Czech. Chem. Commun.*, 1978, **43**, 316.

<sup>86</sup> D. Umarova, S. Kh. Maekh, S. Yu. Yunusov, N. M. Zaitseva, S. Volkova, and P. G. Gorovoi, *Khim. Pri. Soedin.*, 1978, 594.

<sup>87</sup> N. N. Margvelashvili, O. N. Tolkachev, N. P. Prisyazhuyuk, and A. T. Kir'yanova, *Khim. Pri. Soedin.*, 1978, 592.

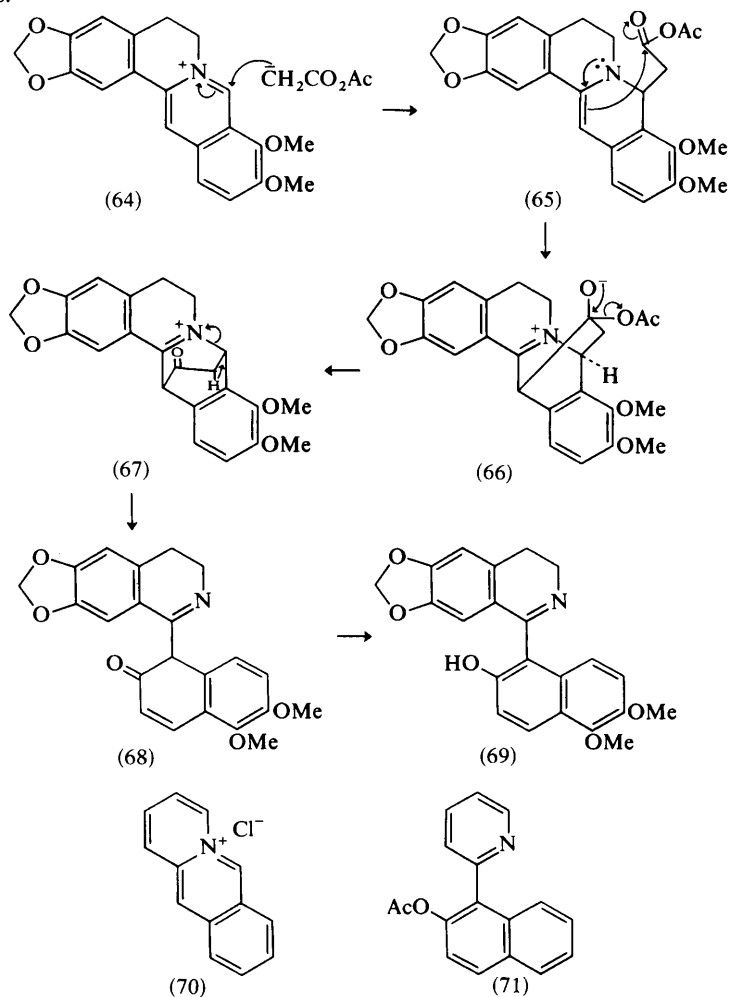
<sup>88</sup> C. Tani, N. Nagakura, and C. Kuriyama, *Yakugaku Zasshi*, 1978, **98**, 1658.

<sup>89</sup> C. Moulis, E. Stanislas, and J. C. Rossi, *Org. Magn. Reson.*, 1978, **11**, 398.

<sup>90</sup> R. H. F. Manske, R. Rodrigo, H. L. Holland, D. W. Hughes, D. B. MacLean, and J. K. Saunders, *Can. J. Chem.*, 1978, **56**, 383.

shown to be identical with discretamine and (-)-corydalmine respectively (see Vol. 9), have been confirmed.<sup>91</sup>

Berberine chloride has been shown to be degraded, by heating with sodium acetate and acetic anhydride at 115 °C for 48 hours, to the acetyl ester of the dihydroquinolyl- $\beta$ -naphthol (69). The process has been formulated as involving initial nucleophilic attack of the isoquinolinium salt by the anhydride anion (64) to give the anhydride (65), from which a plausible pathway, (65)  $\rightarrow$  (69), can easily be constructed to the naphthol. The reaction was shown to be a general one by the conversion of the quaternary salt (70) into the naphthyl ester (71) and of *N*-methylisoquinolinium salts into 2-acetoxynaphthalene under the same conditions.<sup>92</sup>

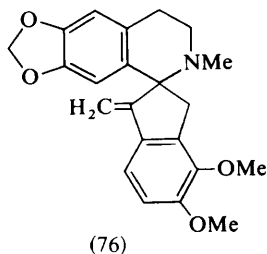
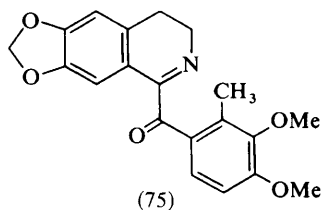
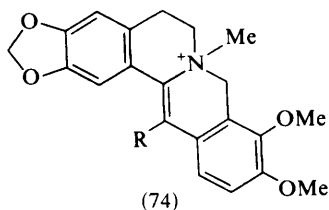
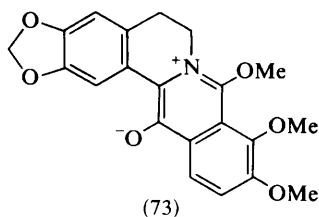
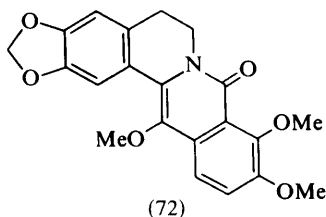


<sup>91</sup> B. R. Pai, H. Suguna, and S. Rajeswari, *Indian J. Chem., Sect. B*, 1978, **16**, 646.

<sup>92</sup> M. Shamma, J. L. Moniot, L. A. Smeltz, W. A. Shores, and L. Toeke, *Tetrahedron*, 1977, **33**, 2907.

A patent that covers the oxidation of berberines to oxybisberberines with potassium ferricyanide, and the conversion of these into 13-methoxyoxyberberines, *e.g.* (72), has been reported.<sup>93</sup> Conditions for the conversion of the oxybisberberines into the 8-methoxyoxyberberine betaine (73) have previously been reported (Vol. 8, p. 105).

The behaviour of quaternary dihydroberberinium salts on photolysis in the presence of air has been studied. Such enamine salts as are unsubstituted at C-13, *e.g.* (74; R = H), are converted into 1-benzoyldihydroisoquinolines (75), whereas those bearing a methyl group at C-13, *e.g.* (74; R = Me), are converted into spiro-indeneisoquinolines (76).<sup>94</sup>



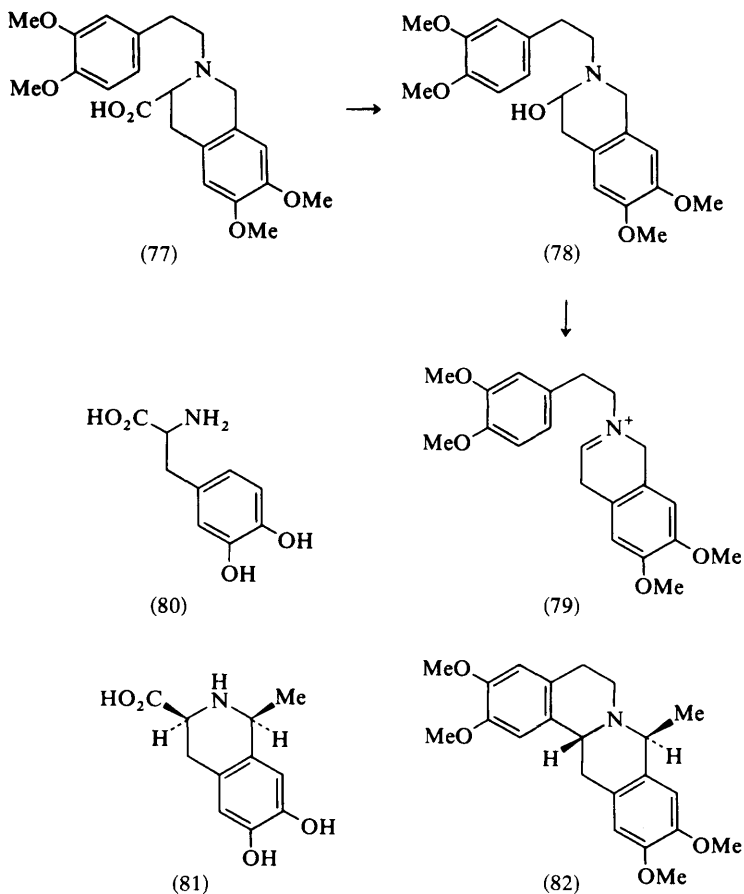
A general synthesis of protoberberines has been achieved from amino-acids of the type (77) by regiospecific decarbonylation, using phosphorus oxychloride, to iminium salts of the type (79), followed by acid cyclization.<sup>95</sup> This method of preparation of the iminium salts has certain advantages over other routes. Amino-acids with the orientation of substituents shown in (77) are relatively easy to obtain from dihydroxyphenylalanine (80), but the more common orientation of substituents found in the protoberberines necessitates more lengthy methods of synthesis, which have been developed.<sup>95</sup> This synthetic route has been further

<sup>93</sup> M. Shamma and J. L. Moniot, U.S. P. 4 087 426 (*Chem. Abs.*, 1978, **89**, 129 774).

<sup>94</sup> T.-T. Wu, J. L. Moniot, and M. Shamma, *Tetrahedron Lett.*, 1978, 3419.

<sup>95</sup> R. T. Dean and H. Rapoport, *J. Org. Chem.*, 1978, **43**, 2115.

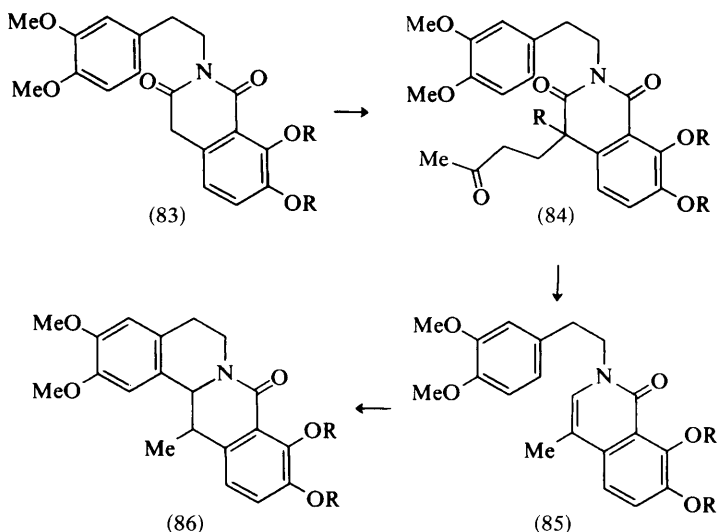
developed, using C-methylated amino-acids, to prepare both 8- and 13-methylprotoberberines, *O*-methylcorytenchirine (82), for example, being prepared from the amino-acid (81).<sup>96</sup> Special conditions were found to be necessary for the *O*- and *N*-alkylation of (81) in order to avoid unwanted reactions and racemization.<sup>96</sup>



Details of an alternative synthesis of 13-methylprotoberberines have been published. The starting point is an *N*-phenethyl-homophthalimide of the type (83), and monomethylation is achieved by its Michael addition to methyl vinyl ketone to give the ketone (84; R = H), followed by methylation of this to the intermediate (84; R = M). Conversion of this into the ethylene ketal, followed by reduction with sodium borohydride and heating with toluene-*p*-sulphonic acid, results in the unsaturated lactam (85), and cyclization of this compound yields the lactam (86), which can be reduced to the 13-methyl-tetrahydroberberine.<sup>97</sup>

<sup>96</sup> R. T. Dean and H. Rapoport, *J. Org. Chem.*, 1978, **43**, 4183.

<sup>97</sup> H. Iida, M. Narimiya, N. Katoh, H. Ina, and T. Kikuchi, *Heterocycles*, 1978, **9**, 727.



Syntheses of ( $\pm$ )-canadine, ( $\pm$ )-thalictricavine, ( $\pm$ )-corydaline, and berlambine have been achieved from dimethoxyhomophthalic anhydride (88). The anhydride reacts with hydrastinine (87;  $R^1R^2 = CH_2$ ) and its dimethoxy-analogue (87;  $R^1 = R^2 = Me$ ) to give the lactam acids (89;  $R^1R^2 = CH_2$ ) and (89;  $R^1 = R^2 = Me$ ) the methyl esters of which, on reduction with lithium aluminium hydride, yield the alcohols (90;  $R^1R^2 = CH_2$ ,  $R^3 = CH_2OH$ ) and (90;  $R^1 = R^2 = Me$ ,  $R^3 = CH_2OH$ ). The conversion of these alcohols into their methanesulphonyl esters, followed by reduction with sodium borohydride, then affords ( $\pm$ )-thalictricavine (90;  $R^1R^2 = CH_2$ ,  $R^3 = Me$ )<sup>98</sup> and ( $\pm$ )-corydaline (90;  $R^1 = R^2 = R^3 = Me$ ).<sup>99</sup> Oxidation of the lactam acid (89;  $R^1R^2 = CH_2$ ) with lead tetra-acetate and copper(II) acetate in acetic acid and dimethylformamide gives the unsaturated lactam berlambine (91), which can be reduced by lithium aluminium hydride in the presence of aluminium chloride to ( $\pm$ )-canadine (90;  $R^1R^2 = CH_2$ ,  $R^3 = H$ ).<sup>98</sup>

A patent that covers the synthesis of 13-hydroxy-protoberberines by conventional Mannich cyclization of benzylisoquinolines with formaldehyde has been published.<sup>100</sup>

A general synthesis of 8-oxo-protoberberines, e.g. (93), and their analogues has been developed, using the photolysis of *N*-benzoyl-1-methylene-tetrahydroisoquinolines (92). In this way, lactams of structures (94)–(97) have been prepared.<sup>101</sup>

Patents for the preparation and use of quaternary salts of tetrahydroberberines<sup>102</sup> and of esters of protoberberines of general structure (98), where  $R^1$

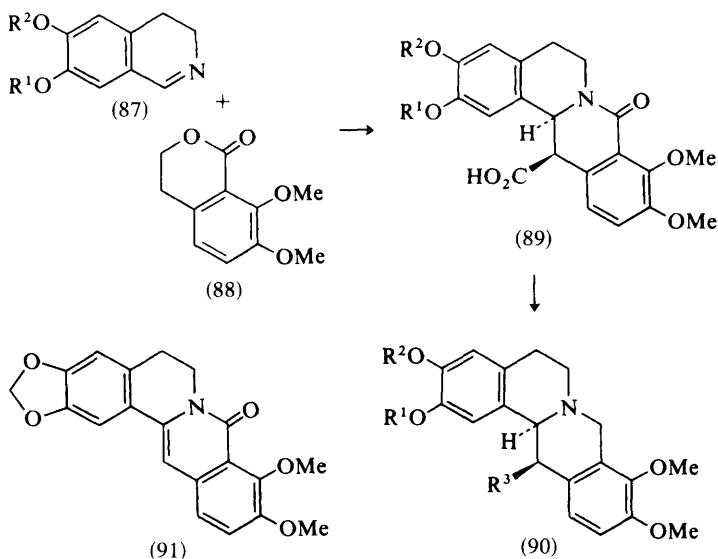
<sup>98</sup> M. Cushman and F. W. Dekow, *J. Org. Chem.*, 1979, **44**, 407.

<sup>99</sup> M. Cushman and F. W. Dekow, *Tetrahedron*, 1978, **34**, 1435.

<sup>100</sup> T. Kametani, Jpn. Kokai 78 15 400 (*Chem. Abs.*, 1978, **89**, 43 902).

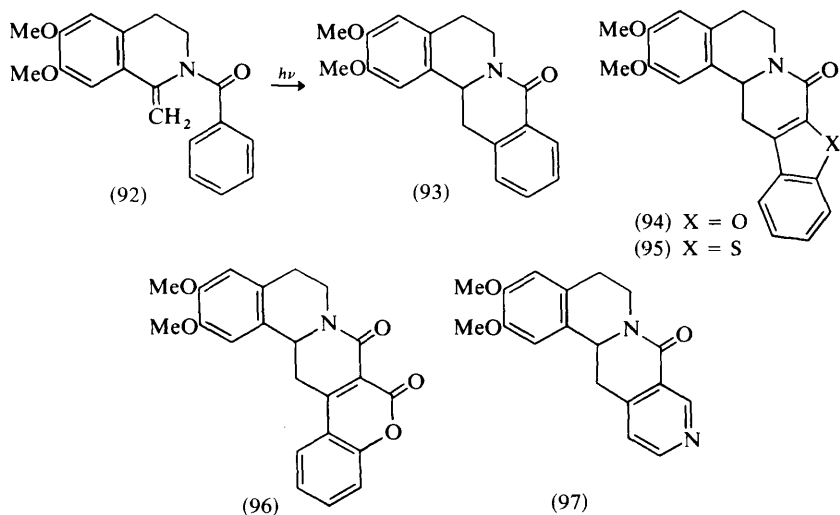
<sup>101</sup> G. R. Lenz, *J. Heterocycl. Chem.*, 1979, **16**, 433.

<sup>102</sup> S. Tanaka and K. Ueda, Jpn. Kokai 78 130 676 (*Chem. Abs.*, 1979, **90**, 138 074).



and R<sup>2</sup> are H or alkoxy and the benzoyl group may be substituted in the 3-, 4-, and 5-positions,<sup>103</sup> have been published.

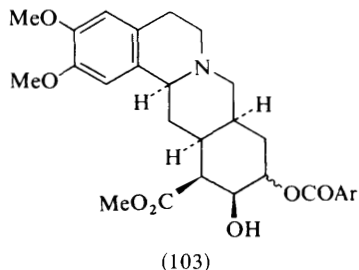
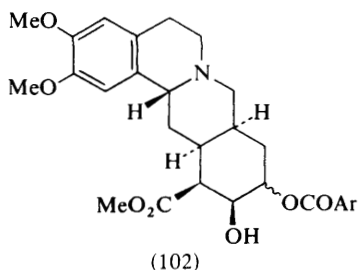
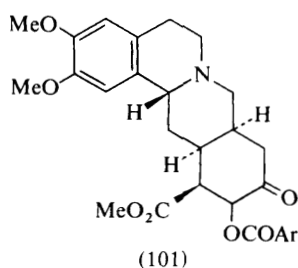
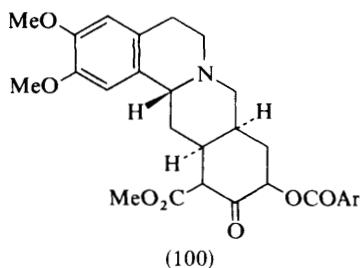
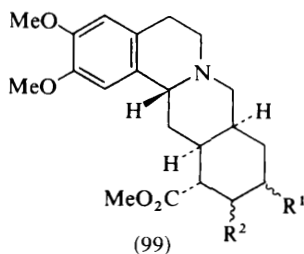
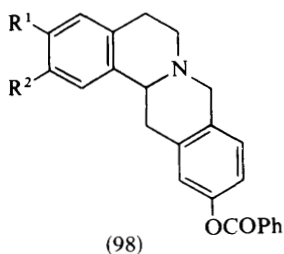
Following the synthesis of despyrroloreserpine (see Volume 9), a synthesis of 10,11-dimethoxy(despyrrolo)raunesine has been achieved.<sup>104</sup> The two bases (100) and (101) of the epialloberban series have been reduced with sodium borohydride to the bases (99; R<sup>1</sup> =  $\alpha$ -OH, R<sup>2</sup> =  $\alpha$ -OTMB), (99; R<sup>1</sup> =  $\alpha$ -OH,



<sup>103</sup> T. Kameya, Jpn. Kokai 78 44 479 (*Chem. Abs.*, 1979, **90**, 187 198).

<sup>104</sup> I. Toth, L. Szabo, M. Kajtar-Peredi, E. Baitz-Gacs, L. Radics, and C. Szantay, *Tetrahedron*, 1978, **34**, 2113.





$R^2 = \beta$ -OTMB), (99;  $R^1 = \alpha$ -OTMB,  $R^2 = \alpha$ -OH), (99;  $R^1 = \alpha$ -OTMB,  $R^2 = \beta$ -OH), (99;  $R^1 = \beta$ -OH,  $R^2 = \beta$ -OTMB), and (99;  $R^1 = \beta$ -OTMB,  $R^2 = \beta$ -OH), acyl migration being observed during reduction (TMB=3,4,5-trimethoxybenzoyl). In addition, bases of the epialloberban series (102;  $\alpha$ - and  $\beta$ -OTMB) were prepared from the corresponding alloberbans (103) by oxidation with mercuric acetate and acetic acid at 100 °C followed by reduction with zinc and hydrochloric acid.<sup>104</sup>

The differences in the  $^1\text{H}$  n.m.r. chemical shifts of protons at C-13 and C-8 and of  $\text{CH}_3$  at C-13 in *cis*- and *trans*-fused 13-methyltetrahydroberberines have been the subject of detailed study.<sup>105</sup>

Analytical studies of alkaloids of this group that have recently been reported include the quantitative analysis of berberine in urine by chemical ionization mass spectrometry<sup>106</sup> and by a field-desorption selected-ion-monitoring system,<sup>107</sup> and

<sup>105</sup> B. R. Pai, K. Nagajaran, H. Suguna, and S. Natarajan, *Heterocycles*, 1978, **9**, 1287.

<sup>106</sup> H. Miyazaki, E. Shirai, M. Ishibashi, K. Niizima, and Y. Kamura, *J. Chromatogr.*, 1978, **152**, 79.

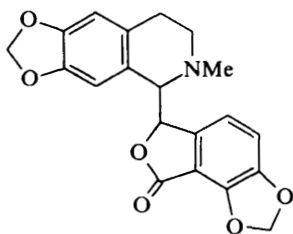
<sup>107</sup> H. Miyazaki, E. Shirai, M. Ishibashi, K. Hosoi, S. Shibata, and M. Iwanaga, *Biomed. Mass Spectrom.*, 1978, **5**, 559.

a fluorimetric assay for the biological half-life of coralyne sulpho-acetate in dogs and monkeys.<sup>108</sup>

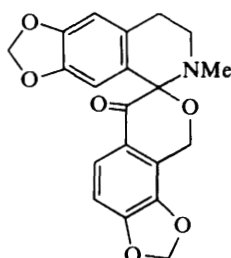
The hypotensive and other pharmacological actions of berberine have been studied.<sup>109</sup>

## 7 Secoberberines

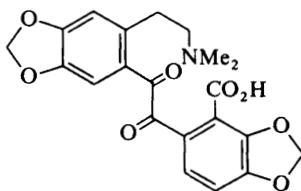
A synthesis of hypecorinine (105) has been achieved by the reduction of dehydrobicuculline (104) with lithium aluminium hydride.<sup>110</sup> N-Methylation of (104), followed by treatment of the quaternary salt with Triton B in ethanol, followed then by treatment with hydrochloric acid, afforded bicucullinine (106).<sup>110</sup> Syntheses of tetramethoxy-analogues of hypecorine (108;  $R^1 = R^2 = H$ ) and hypecorinine (108;  $R^1R^2 = O$ ) have been accomplished by the action of alkali on the iminium salts (107;  $R^1 = R^2 = H$ ) and (107;  $R^1R^2 = O$ ).<sup>111</sup>



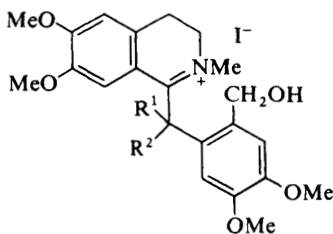
(104)



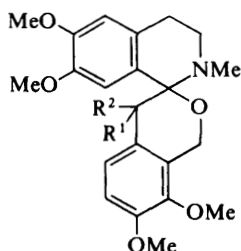
(105)



(106)



(107)



(108)

<sup>108</sup> J. M. Finkel and D. L. Hill, *J. Pharm. Sci.*, 1978, **67**, 1331.

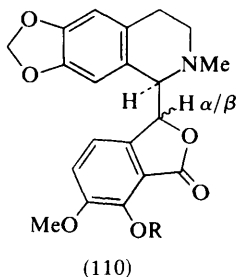
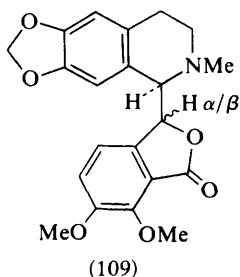
<sup>109</sup> M. Sabir, M. H. Akhter, and N. K. Bhide, *Indian J. Physiol. Pharmacol.*, 1978, **22**, 9.

<sup>110</sup> B. C. Nalliah and D. B. MacLean, *Can. J. Chem.*, 1978, **56**, 1378.

<sup>111</sup> V. Simanek, V. Preininger, F. Grambal, and L. Dolejs, *Heterocycles*, 1978, **9**, 1233.

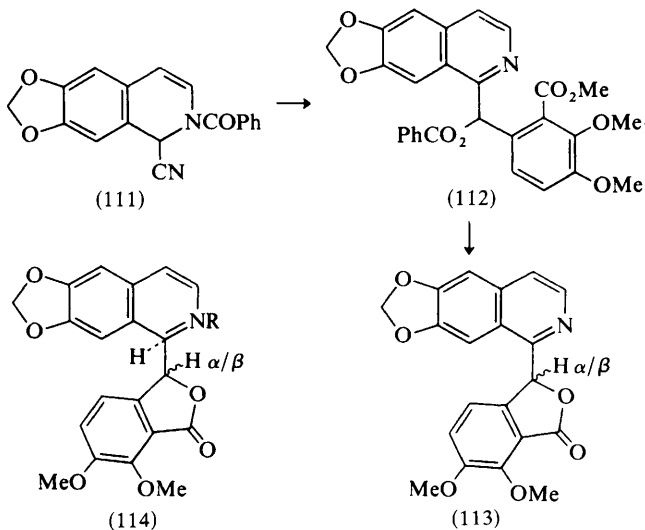
### 8 Phthalide-isoquinolines

Adlumine and adlumidine have been isolated from *Corydalis gigantea*, *C. remota*, *C. rosea*, and *C. vaginans*.<sup>87</sup> Both  $\alpha$ - and  $\beta$ -narcotine (109) have been shown to undergo alkoxy-exchange reactions on heating with EtOH, Bu<sup>n</sup>OH, Bu<sup>t</sup>OH, and Et<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>OH in the presence of the corresponding alkoxide, with equilibration between the  $\alpha$ - and  $\beta$ -forms; the  $\alpha$ -form predominates, and the products have the composition (110).<sup>112</sup>



The electrolysis of narcotine in a diaphragmless cell with graphite anode and pre-polarized nickel cathode has been shown to give yields of 80% opianic acid and 55% cotarnine. Addition of potassium chloride prevents cathodic reduction of the narcotine.<sup>113</sup>

A route for the synthesis of phthalide-isoquinoline alkaloids from Reissert compounds has been reported. The Reissert compound (111) reacts with methyl opianate in the presence of sodium hydride to give the isoquinoline (112), hydrolysis of which yields dehydrohydrastine (113); this can be reduced in



<sup>112</sup> H. Schmidhammer and W. Kloetzer, *Arch. Pharm. (Weinheim, Ger.)*, 1978, **311**, 664.

<sup>113</sup> N. A. Prikhod'ko, M. Zh. Zhurinov, and M. Ya. Fioshin, *Elektrokhimiya*, 1978, **14**, 1253.

ethanolic perchloric acid to  $\alpha$ - and  $\beta$ -norhydrastines (114; R = H), and these can be *N*-methylated to ( $\pm$ )- $\alpha$ - and ( $\pm$ )- $\beta$ -hydrastines (114; R = Me).<sup>114</sup>

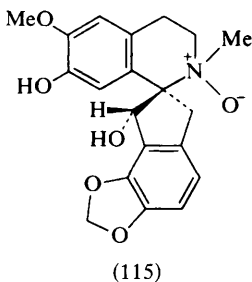
A patent that covers the equilibration of narcotine and hydrastine to the  $\alpha$ - and  $\beta$ -forms, with racemization, by ultraviolet light has been published.<sup>115</sup> The circular dichroism of the phthalide-isoquinoline alkaloids has been studied and correlations have been made between the stability of the  $\alpha$ - and  $\beta$ -forms and the intensity of the Cotton effect.<sup>116</sup> The effects of solvents on the parameters of the n.m.r. spectra of  $\alpha$ - and  $\beta$ -hydrastines, adlumine, and corlumine have been studied.<sup>117</sup>

## 9 Protopines

Protopine and allocryptopine have been isolated from *Papaver rhoeas*,<sup>85</sup> and protopine from *Corydalis cava*,<sup>118</sup> *C. gigantea*, *C. marschalliana*, *C. remota*, *C. rosea*, and *C. vaginans*.<sup>87</sup> The effect of protopine on induced cardiac arrhythmias has been studied.<sup>119</sup>

## 10 Spirobenzylisoquinolines

Ochotensine has been isolated from *Corydalis solida*,<sup>90</sup> and raddeamine, raddeanamine, raddeanidine, and raddeanone from *C. ochotensis*.<sup>120</sup> Fumaritine *N*-oxide (115) has been obtained from *Fumaria kralikii* Jord., the structure being determined by n.m.r. spectroscopy and confirmed by reduction of the *N*-oxide to fumaritine.<sup>121</sup>



## 11 Rhoeadines

Rhoeadine and isorhoeadine have been isolated from *Papaver rhoeas* L., as have smaller amounts of rhoeadine, isorhoeadine, rhoeagenine, and papaver-rubines A, C, D, and E;<sup>85</sup> rhoeadine has been obtained from *P. tauricola*.<sup>122</sup> The LD<sub>50</sub> of rhoeadine has been determined, and five metabolites arising from its *O*-

<sup>114</sup> P. Kerekes, G. Horvath, G. Gaal, and R. Bogner, *Acta Chim. Acad. Sci. Hung.*, 1978, **97**, 353.

<sup>115</sup> T. Kametani, Jpn. Kokai 78 15 399 (*Chem. Abs.*, 1979, **90**, 39 098).

<sup>116</sup> G. P. Moiseeva, I. A. Israilov, M. S. Yunusov, and S. Yu. Yunusov, *Khim. Pri. Soedin.*, 1978, 103.

<sup>117</sup> K. L. Seitanidi, M. R. Yagudaev, I. A. Israilov, and M. S. Yunusov, *Khim. Pri. Soedin.*, 1978, 465.

<sup>118</sup> G. Verzar-Petri and P. T. Minh Hoang, *Sci. Pharm.*, 1978, **46**, 169.

<sup>119</sup> V. N. Burtsev, E. N. Dormidontov, and V. A. Salayev, *Kardiologiya*, 1978, **18**, 76.

<sup>120</sup> T. Kametani, Jpn. Kokai 78 53 668 (*Chem. Abs.*, 1978, **89**, 160 388).

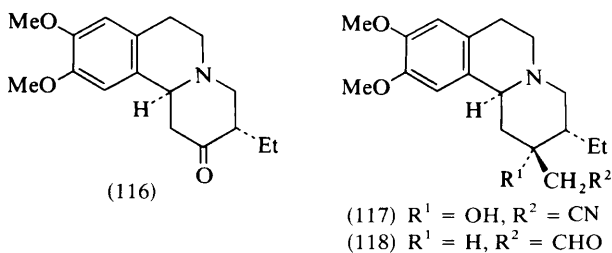
<sup>121</sup> H. G. Kiraykov, D. W. Hughes, B. C. Nalliah, and D. B. MacLean, *Can. J. Chem.*, 1979, **57**, 53.

<sup>122</sup> J. D. Phillipson and G. Sariyar, *J. Pharm. Pharmacol.*, 1978, **30**, 84P.

and *N*-demethylation and *C*-hydroxylation have been isolated from animal studies.<sup>123</sup>

## 12 Emetine and Related Bases

New routes to bases of the emetine type have been developed. In one, ( $\pm$ )-protoemetine (118) has been prepared by the reduction of the  $\beta$ -hydroxy-nitrile (117) with lithium di-isobutylaluminium hydride, (117) being obtained from the known ketone (116) by a Reformatsky-type reaction.<sup>124</sup>



A more novel route to protoemetinol (126) starts from norcamphor (119), which is converted (by Baeyer–Villiger oxidation) into the lactone (120), *C*-ethylation of which, followed by heating with homoveratrylamine, yields the amide (122), with the correct stereochemistry for the generation of protoemetinol. Oxidation of the secondary alcohol, reaction of the resulting ketone with pyrrolidine and toluene-*p*-sulphonic acid, and treatment of the resulting enamine with propane-1,3-dithiol ditoluene-*p*-sulphonate gives the dithioketal (123); this, with potassium hydroxide, is converted into the acid (124). Treatment of (124) with acid liberates the aldehyde from the thioketal, and this function then reacts with the homoveratryl system to form the protoemetine skeleton (125) with both  $\alpha$  and  $\beta$  disposition of the hydrogen atom in the isoquinoline ring. Reduction of the  $\alpha$ -compound with lithium aluminium hydride affords protoemetinol (126) (Scheme 1).<sup>125,126</sup> The  $\beta$ -form of (125) can be epimerized to the  $\alpha$ -form by acetylation, dehydrogenation, reduction, and deacetylation.<sup>125</sup>

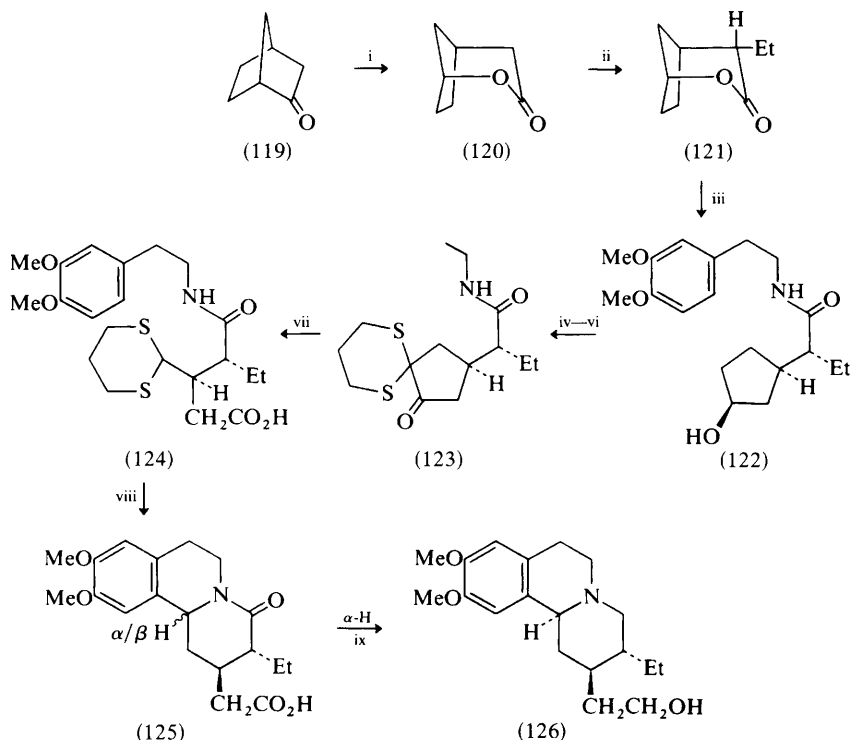
Another imaginative approach (Scheme 2) started with the protoberberine system (127). Reduction of the trimethoxy-compound (127;  $R = \text{Me}$ ) with lithium and liquid ammonia gave the enol ether (128), and conditions could not be found for the selective reduction of only the monomethoxylated aromatic ring. However, the reduction of the benzyl ether (127;  $R = \text{CH}_2\text{Ph}$ ), followed by methylation of the product, gave the enol ether (129), which could be hydrolysed to the  $\alpha\beta$ -unsaturated ketone (130). This ketone was also found to be obtainable in good yield from the enol ether (128) by selective aromatization by *N*-chlorosuccinimide in methylene chloride, hydrolysis (presumably by water in the

<sup>123</sup> D. Walterova, K. Hatle, A. Nemeekova, and B. Vecerek, *Cesk. Farm.*, 1979, **27**, 314.

<sup>124</sup> C. Szantay, L. Toke, and G. Blasko, *Acta Chim. Acad. Sci. Hung.*, 1978, **95**, 81.

<sup>125</sup> S. Takano, S. Hatakeyama, and K. Ogasawara, *Tetrahedron Lett.*, 1978, 2519.

<sup>126</sup> S. Takano, S. Hatakeyama, M. Takahashi, Y. Takahashi, H. Iwata, K. Shishido, and K. Ogasawara, *Tennen Yuki Kagobutsu Toronkai Koen Yoshidu 21st.*, 1978, 50.



Reagents: *i*,  $m\text{-ClC}_6\text{H}_4\text{CO}_2\text{H}$ ; *ii*, NaH, EtBr; *iii*, homoveratrylamine; *iv*, Jones reagent; *v*, pyrrolidine,  $p\text{-MeC}_6\text{H}_4\text{SO}_3\text{H}$ ; *vi*,  $\text{TosS}(\text{CH}_2)_3\text{STos}$ ; *vii*, KOH; *viii*,  $\text{H}^+$ ,  $\text{H}_2\text{O}$ ; *ix*,  $\text{LiAlH}_4$

**Scheme 1**

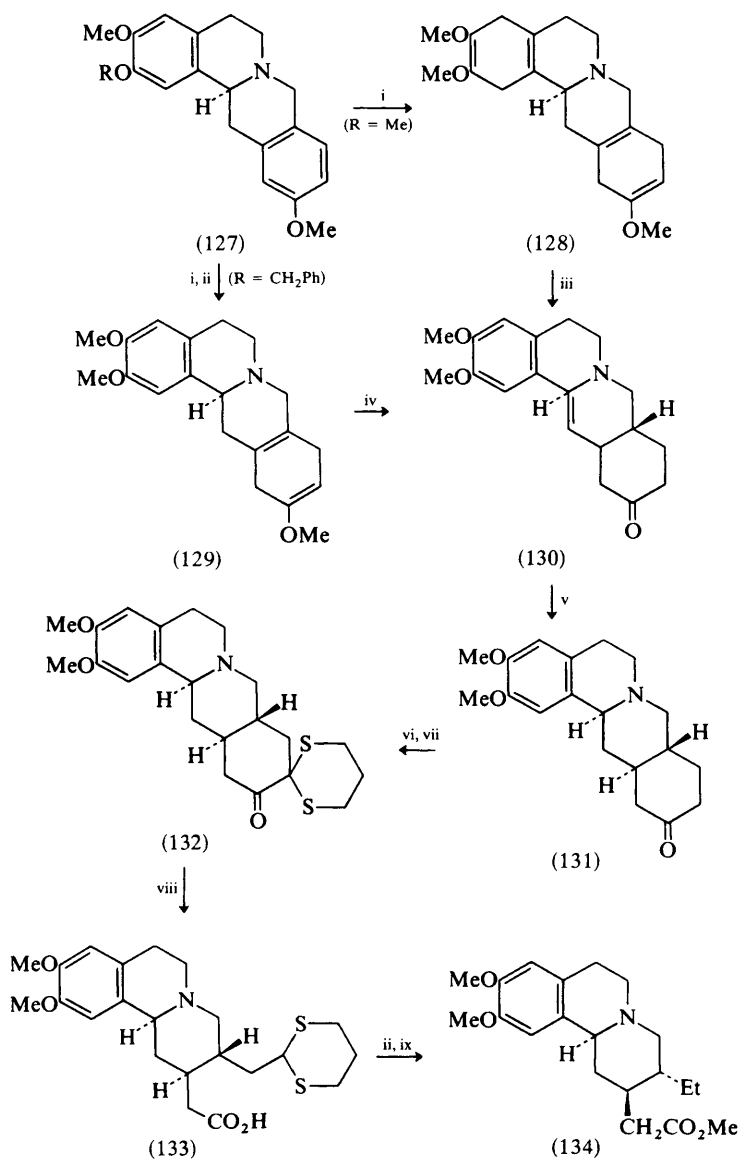
solvent) accompanying the aromatization. Reduction of the double bond of (130) proceeded stereospecifically to give the ketone (131), which was converted, through the enamine, into the dithioketal (132) together with a small amount of the isomer resulting from reaction on the other side of the carbonyl group. Treatment of the ketal (132) with potassium hydroxide gave the acid (133), desulphurization of which afforded the ester (134); this was converted into (±)-emetine by the known three-step process.<sup>127</sup> Reduction of the 13-cyano-derivatives of (127; R = Me) and (127; R =  $\text{CH}_2\text{Ph}$ ) with lithium and liquid ammonia furnished (128) and (129), respectively.<sup>127</sup>

Dehydroemetine (136) has been synthesized by Pictet–Spengler synthesis from dehydropseudoemetine (135; R = CHO) and by Bischler–Napieralsky synthesis from the corresponding acid (135; R =  $\text{CO}_2\text{H}$ ) and homoveratrylamine.<sup>128</sup> The tetra-ethoxy analogue of emetine has also been prepared, by the conventional Bischler–Napieralsky route, using appropriately substituted intermediates.<sup>129</sup>

<sup>127</sup> S. Takano, M. Sasaki, H. Kanno, K. Shishido, and K. Ogasawara, *J. Org. Chem.*, 1978, **43**, 4169.

<sup>128</sup> G. Szantay and J. Rohaly, *Acta Chim. Acad. Sci. Hung.*, 1978, **96**, 55.

<sup>129</sup> J. Rohaly and G. Szantay, *Acta Chim. Acad. Sci. Hung.*, 1978, **96**, 45.

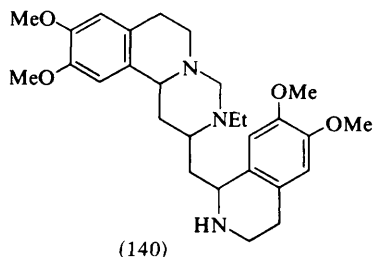
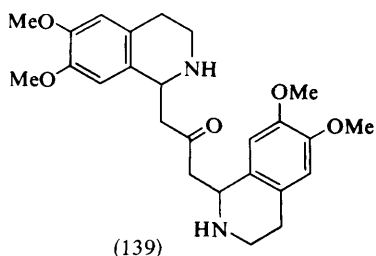
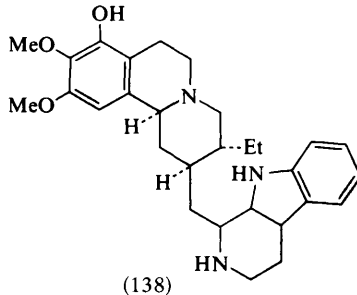
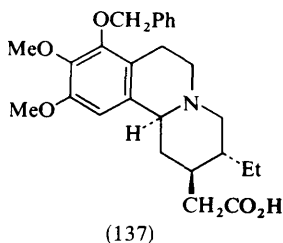
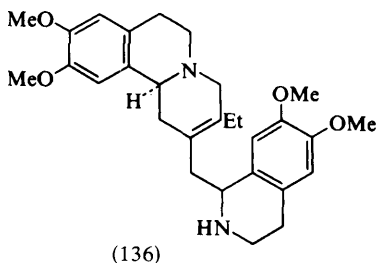
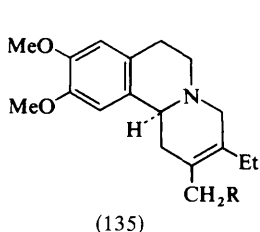


Reagents: i, Li,  $\text{NH}_3$ ; ii,  $\text{CH}_2\text{N}_2$ ; iii, *N*-chlorosuccinimide,  $\text{CH}_2\text{Cl}_2$ ; iv,  $\text{H}^+$ ,  $\text{H}_2\text{O}$ ; v,  $\text{H}_2$ , Pd/C, MeOH; vi, Pyrrolidine, *p*- $\text{MeC}_6\text{H}_4\text{SO}_3\text{H}$ ; vii,  $\text{TosS}(\text{CH}_3)_3\text{Tos}$ ; viii, KOH; ix, W-2 Raney nickel, MeOH

Scheme 2

Alangimarckine (138) has been synthesized from the acid (137) and tryptamine by the Bischler–Napieralsky route, with debenzoylation as the final step.<sup>130</sup>

<sup>130</sup> T. Fujii, H. Kogen, and M. Ohba, *Tetrahedron Lett.*, 1978, 3111.



3-Aza-emetine (140) has been synthesized by the reductive aminoethylation of 1,3-bis-(1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolyl)acetone (139) followed by cyclization with formaldehyde.<sup>131</sup>

The effect of emetine on the synthesis of protein and DNA in leukaemic cells has been studied,<sup>132</sup> as has its effect on ultrastructural changes in muscles<sup>133</sup> and its cytotoxic effect in rat kidney.<sup>134</sup> A bioassay for possible carcinogenicity of emetine has been developed.<sup>135</sup>

### 13 Morphine Alkaloids

Pallidine has been isolated from *Thalictrum dioicum*;<sup>53</sup> bound morphine and codeine in the polysaccharide fraction from *Papaver somniferum* capsule has been

<sup>131</sup> J. Gilbert, C. Gansser, C. Viel, R. Cavier, E. Chenu, and M. Hayat, *Farmaco, Ed. Sci.*, 1978, **33**, 237.

<sup>132</sup> M. P. Chitnis and R. K. Johnson, *J. Natl. Cancer Inst.*, 1978, **60**, 1049.

<sup>133</sup> L. Bindoff and M. J. Cullen, *J. Neurol. Sci.*, 1978, **39**, 1.

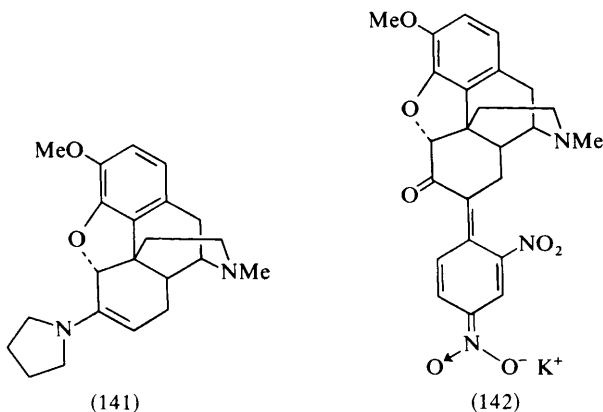
<sup>134</sup> B. R. Jones and G. A. Ofori, *Cytobios*, 1977, **19**, 109.

<sup>135</sup> National Cancer Institute, *Gov. Rep. Announce Index (U.S.)*, 1978, **78**, 124.



Improved preparations of (+)-codeine and (+)-morphine have been reported. *N*-Ethoxycarbonyl-(+)-norcodeine, obtained from (-)-sinomenine, can be reduced by lithium aluminium hydride to (+)-codeine, which yields (+)-morphine on *O*-demethylation.<sup>138</sup>

Stereoselective reduction of 6-keto-compounds in the morphine, codeine, and morphinan series to 6- $\alpha$ - and 6- $\beta$ -hydroxy-compounds by formamidine-sulphinic acid has been reported.<sup>139</sup> Dihydrocodeinone pyrrolidine enamine (141) has been shown to react with 2,4-dinitrofluorobenzene in the presence of potassium hydroxide to give the *aci*-nitro-salt (142), accessible also directly from dihydrocodeinone and *m*-dinitrobenzene in alkali.<sup>140</sup>



6-*O*-Methanesulphonyl-dihydrocodeine has been shown to react with tetrabutylammonium fluoride, lithium chloride, and lithium bromide, with inversion at C-6, to give the related 6-halogeno-dihydrocodides, but when the ester is heated with sodium iodide in dimethylformamide the product is  $\Delta^5$ -deoxycodine (deoxycodine-C) (143).<sup>143</sup> Reductive amination of naltrexone with 2,2'-dihydroxydiethylamine and sodium cyanoborohydride yields the 6-amino-compound (144; R = OH),<sup>144</sup> which can be converted by carbon tetrachloride and tri-

<sup>136</sup> J. K. Wold, *Phytochemistry*, 1978, **17**, 832.

<sup>137</sup> M. Ikram, *Pak. J. For.*, 1978, **28**, 1.

<sup>138</sup> K. C. Rice, I. Iijima, and A. Brossi, *Symp. Heterocycl. [Pap.]*, 1977, 49.

<sup>139</sup> N. Chatterjee and C. E. Inturissi, U.S. P. 4 089 855 (*Chem. Abs.*, 1978, **89**, 147 121).

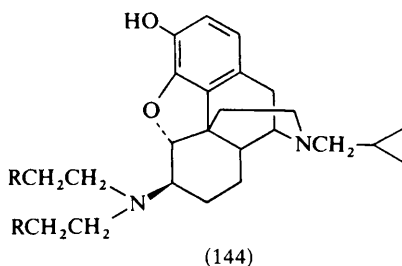
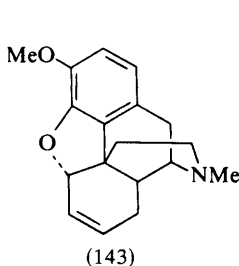
<sup>140</sup> K. A. Kovar and F. Schielein, *Arch. Pharm. (Weinheim, Ger.)*, 1978, **311**, 73.

<sup>141</sup> E. L. Grew and H. A. S. Payne, Ger. Offen. 2 736 260 (*Chem. Abs.*, 1978, **89**, 584).

<sup>142</sup> M. Matsui and Y. Saionji, *Daüchi Yakka Daigaku Kenkyu Nempo*, 1978, **9**, 11.

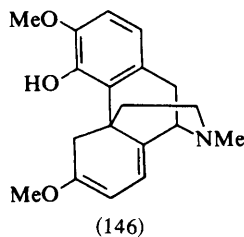
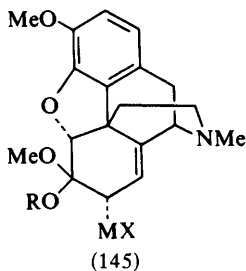
<sup>143</sup> G. Somogyi, S. Makleit, and R. Bogнар, *Acta Chim. Acad. Sci. Hung.*, 1978, **97**, 339.

<sup>144</sup> P. S. Portoghesi, D. L. Larson, J. B. Jiang, A. E. Takemori, and T. P. Caruso, *J. Med. Chem.*, 1978, **21**, 598.



phenylphosphine into the dichloro-compound (144;  $R = Cl$ ), which is a potent alkylating agent of opioid receptors, with ultra-long narcotic antagonist activity.<sup>145</sup>

Patent details have been published,<sup>146</sup> covering the preparation of neopinone from thebaine by a route previously reported (Volume 8, p. 113). Mercuric acetate reacts with thebaine in methanol to give 7-hydroxymercurineopinone dimethyl ketal (145;  $R = Me$ ,  $M = Hg$ ,  $X = OH$ ), which can be converted into neopinone by treatment with acetic acid. The patent also covers the preparation of other compounds of general structure (145), where  $R = alkyl$ ,  $M = Hg$ ,  $Pd$ , or  $Pt$ , and  $X = OAc$ ,  $OCOPh$ ,  $Br$ , or  $Cl$ . Conditions for the reduction of thebaine to  $\beta$ -dihydrothebaine (146) in good yield by potassium and liquid ammonia have



been described.<sup>147</sup> Thebaine has been shown to react with dinitrogen tetroxide in dry ethyl acetate and dry tetrahydrofuran to give a 23% yield of  $14\beta$ -nitrocodeinone (147) and 7% of 8-nitrothebaine (148). It is suggested that the reaction proceeds *via* the addition product 8,14-dinitrodihydrothebaine (149).<sup>148</sup> Patents covering the preparation of the derivatives of  $14\beta$ -aminocodeinone of general structure (150) from  $14\beta$ -nitrocodeinone dimethyl ketal have been published.<sup>149,150</sup>

<sup>145</sup> P. S. Portoghese, D. L. Larson, J. B. Jiang, T. P. Caruso, and A. E. Takemori, *J. Med. Chem.*, 1979, **22**, 168.

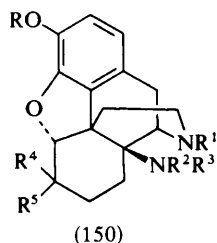
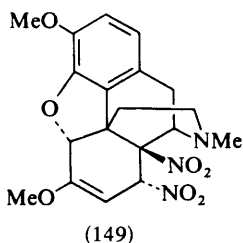
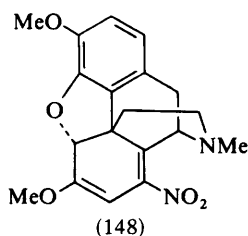
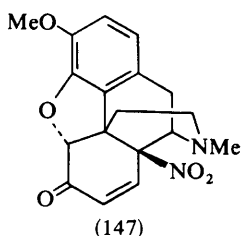
<sup>146</sup> H. Rapoport and R. Barber, U.S. P. 4 110 329 (*Chem. Abs.*, 1979, **90**, 138 071).

<sup>147</sup> R. K. Razdan, D. E. Porlock, H. C. Dalzell, and C. Malmberg, *J. Org. Chem.*, 1978, **43**, 3604.

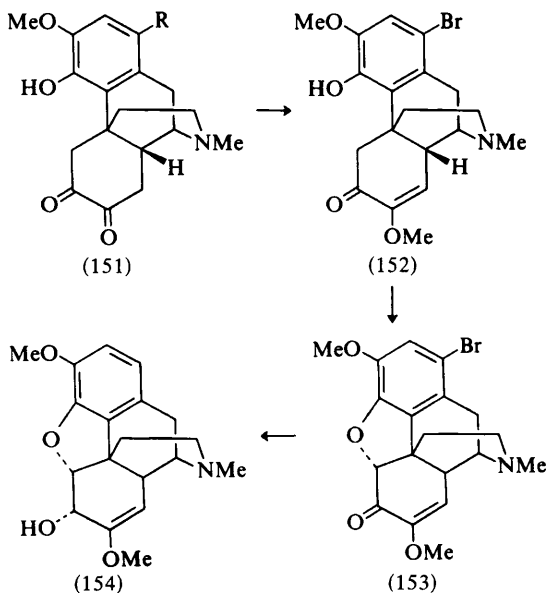
<sup>148</sup> S. Archer and P. Osei-Gyimah, *J. Heterocycl. Chem.*, 1979, **16**, 389.

<sup>149</sup> R. J. Kobylecki, I. G. Guest, J. W. Lewis, and G. W. Kirkby, Ger. Offen. 2 812 581 (*Chem. Abs.*, 1979, **90**, 39 100).

<sup>150</sup> R. J. Kobylecki, I. G. Guest, and J. W. Lewis, Ger. Offen. 2 812 580 (*Chem. Abs.*, 1979, **90**, 87 709).



7-Methoxycodeine (154) has been prepared from 1-bromo-( $-$ )-sinomeninone (151;  $R = \text{Br}$ ) *via* 1-bromo-( $+$ )-sinomenine (152), which on bromination and cyclization with alkali yields 1-bromo-7-methoxycodeinone (153); this, on reduction with lithium aluminium hydride, yields (154). This derivative of codeine is an orally active analgesic, in spite of the fact that it is unstable to acids, which convert it into the inactive ( $-$ )-sinomeninone (151;  $R = \text{H}$ ).<sup>151</sup>

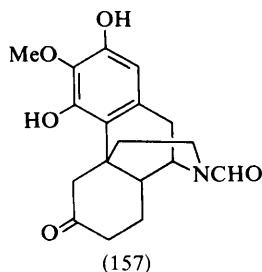
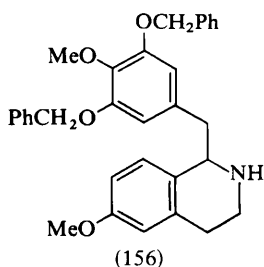
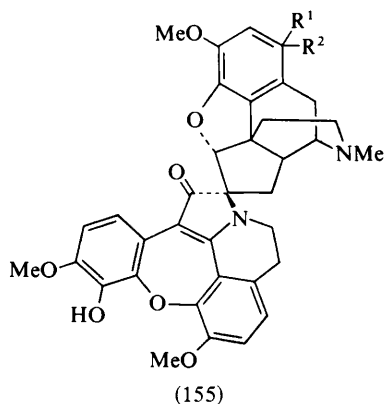


<sup>151</sup> I. Iijima, J. Minamikawa, K. C. Rice, and A. E. Jacobson, *J. Med. Chem.*, 1978, **21**, 1320.

A patent has been published that covers the rearrangement of ethers of morphine and *N*-alkyl-normorphines to the corresponding derivatives of apomorphine and *N*-alkyl-norapomorphines by phosphoric acid at 125–140 °C.<sup>152</sup> 10-Oxomorphine has been isolated as an oxidation production from solutions of morphine hydrochloride,<sup>153</sup> and morphine has been shown to be converted into morphine *N*-oxide and normorphine by guinea-pig liver microsomal preparations, which convert codeine, under similar conditions, into codeine *N*-oxide, norcodeine, morphine, and normorphine.<sup>154</sup>

The <sup>13</sup>C n.m.r. spectra of cancentreine (155; R<sup>1</sup> = R<sup>2</sup> = H) and a new alkaloid, 10-oxocancentreine (155; R<sup>1</sup>R<sup>2</sup> = O), have been studied and the structure of 10-oxocancentreine has been assigned, following a comparison of its n.m.r., i.r., u.v., and mass spectra with the spectra of codeine, codeinone, 10-oxocodeinone, cularine, and 9,10-dihydrocancentreine methine *O*-methyl ether.<sup>155</sup>

A new synthesis of *N*-formylnordihydrothebainone, and hence a formal synthesis of codeine and morphine, has been reported. The (+)-(*R*)-isomer of the tetrahydroisoquinoline (156) was subjected to Birch reduction, *N*-formylation, and cyclization (with scission of the benzyl ether groups) to give *N*-formyl-2-hydroxynordihydrothebainone (157). Selective conversion of this into the 2-(1-



<sup>152</sup> R. R. Lorenz, E. D. Parady, and W. H. Thielking, Ger. Offen. 2 758 954 (*Chem. Abs.*, 1978, **89**, 163 834).

<sup>153</sup> B. Proska, Z. Voticky, L. Molnar, J. Putek, and M. Stefek, *Pharmazie*, 1978, **33**, 609.

<sup>154</sup> J. D. Phillipson, S. W. El-Dabbas, and J. W. Gorrod, *Biol. Oxid. Nitrogen Proc. Int. Symp. 2nd.*, 1977, 125.

<sup>155</sup> H. L. Holland, D. W. Hughes, D. B. MacLean, and R. G. A. Rodrigo, *Can. J. Chem.*, 1978, **56**, 2467.

phenyltetrazol-5-yl)oxy-compound, followed by hydrogenolysis, effected the removal of the 2-hydroxy-group.<sup>156</sup>

Analytical methods for the determination of morphine alkaloids have been described as follows: underivatized morphine at the nanogram level, using low-activity packed columns,<sup>157</sup> morphine by combined enzyme immunological-t.l.c. methods,<sup>158</sup> morphine in urine<sup>159,160</sup> and in adulterated opium<sup>161</sup> by t.l.c. methods, simultaneous determination of morphine and codeine in blood by the use of selective ion monitoring and deuteriated internal standards,<sup>162</sup> and of morphine and codeine in plasma,<sup>163</sup> identification and determination of morphine in biological fluids,<sup>164-166</sup> interference by formaldehyde in the determination of morphine in urine,<sup>167</sup> determination of heroin by t.l.c.<sup>168</sup> and by g.c.,<sup>169</sup> and of 3-acetylmorphine by g.c.,<sup>170</sup> extraction of heroin and its metabolites from hydrolysing body fluids,<sup>171</sup> analytical methods for the study of illicit heroin,<sup>172</sup> determination of codeine by m.s.-chromatography<sup>173</sup> and by t.l.c.,<sup>174</sup> the simultaneous determination of dihydromorphinone and dihydrocodeinone and their 6 $\alpha$ - and 6 $\beta$ -hydroxy metabolites<sup>175</sup> and of 14-hydroxymorphinone, 14-hydroxycodeinone, and their metabolites<sup>176</sup> in urine, estimation of 14-hydroxydihydrocodeinone in human plasma by g.l.c.,<sup>177</sup> quantitative extraction from and estimation of thebaine in *Papaver bracteatum*,<sup>178</sup> g.c.-m.s. determination of etorphine with stable-isotope-labelled internal standard,<sup>179</sup> and the determination of *N*-cyclopropylmethyl-14-hydroxydihydronormorphine (nalbuphine) by electron capture.<sup>180</sup> The recovery of morphine from biological samples<sup>181</sup> and the hydrolysis of morphine 3-glucuronide<sup>182</sup> have been studied.

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- <sup>159</sup> J. Lopez, J. E. Buttery, and G. F. De Witt, *Mod. Med. Asia*, 1978, **14**, 7.
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- <sup>170</sup> J. M. Moore and M. Klein, *J. Chromatogr.*, 1978, **154**, 76.
- <sup>171</sup> E. R. Garrett and T. Gurkan, *J. Pharm. Sci.*, 1979, **68**, 26.
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- <sup>174</sup> T. Borkowski and A. Dluzniewska, *Z. Zagadnien Krym.*, 1977, **12**, 57.
- <sup>175</sup> E. J. Cone and W. D. Darwin, *Biomed. Mass Spectrom.*, 1978, **5**, 291.
- <sup>176</sup> R. C. Baselt and C. B. Stewart, *J. Anal. Toxicol.*, 1978, **2**, 107.
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Pharmacological and related studies of the alkaloids of this group include the following. Investigations concerning morphine: inhibition of interferon synthesis,<sup>183</sup> effects on brain chromatin and nuclear synthesis,<sup>184</sup> on dopaminergic systems,<sup>185</sup> on tryptophan and 5-hydroxy-indoles in the CNS,<sup>186</sup> on the release of oxytocin,<sup>187</sup> bradykinin,<sup>188</sup> prolactin,<sup>189-193</sup> growth hormone,<sup>193</sup> dopamine,<sup>194</sup> and luteinizing-hormone-releasing hormone (LHRH),<sup>195</sup> on axonal transport in neurones,<sup>196</sup> on reproductive physiology<sup>197</sup> and the long-term development of progeny,<sup>198</sup> on erythrocyte ultrastructure and blood viscosity,<sup>199</sup> on the location and binding of calcium in brain,<sup>200,201</sup> on adenylyl cyclase<sup>202,203</sup> and cAMP levels in brain,<sup>204,205</sup> on the incorporation of lysine into neurones<sup>206</sup> and of serine into phospholipids,<sup>207</sup> on acetylcholine turnover<sup>208</sup> and release,<sup>209</sup> on human lung-cell cultures,<sup>210</sup> on the primary humoral immune response,<sup>211</sup> on histamine concentration and histidine decarboxylase activity in brain,<sup>212</sup> on intestinal transit,<sup>213</sup> on  $\gamma$ -aminobutyric acid and taurine concentrations<sup>214-216</sup> and L-glutamate decarboxylase activity<sup>214</sup> in brain, on temperature<sup>217</sup> and thermoregulatory responses,<sup>218</sup> on detection of shock,<sup>219</sup> on thalamic and

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<sup>227</sup> M. Ilcheva and R. Ovcharov, *Izv.-Durzh. Inst. Kontrol Lek. Sredstva*, 1978, **11**, 111.  
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<sup>231</sup> G. T. Maughan, J. H. Johnson, and J. A. Rosenerans, *Brain Res.*, 1978, **155**, 413.  
<sup>232</sup> H. N. Bhargava, *Pharmacol. Biochem. Behav.*, 1978, **9**, 167.  
<sup>233</sup> D. Adam-Carriere, Z. Merali, and R. Stretch, *Can. J. Physiol. Pharmacol.*, 1978, **56**, 707.  
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<sup>235</sup> G. A. Young, G. F. Steinfeld, N. Khazan, and E. M. Glaser, *Pharmacol. Biochem. Behav.*, 1978, **9**, 559.  
<sup>236</sup> R. A. Levitt, D. J. Stilwell, and T. M. Evans, *Pharmacol. Biochem. Behav.*, 1978, **9**, 567.  
<sup>237</sup> R. Stretch and J. R. Sanchez-Ramos, *Can. J. Physiol. Pharmacol.*, 1979, **57**, 98.  
<sup>238</sup> J. T. Huang, *Res. Commun. Psychol. Psychiatr. Behav.*, 1979, **4**, 31.  
<sup>239</sup> C. Gros, B. Malfroy, J. P. Swerts, F. Day, and J. C. Schwartz, *Eur. J. Pharmacol.*, 1978, **51**, 317.  
<sup>240</sup> J. Marquez-Montes, J. J. Goiti, O. L. J. Castillo, E. De Teresa, F. Avello, and M. De Artaza, *Arch. Inst. Cardiol. Mex.*, 1977, **47**, 714.  
<sup>241</sup> H. J. Haigler, *Eur. J. Pharmacol.*, 1978, **51**, 361.  
<sup>242</sup> D. Bensemana and A. L. Gascon, *Can. J. Physiol. Pharmacol.*, 1978, **56**, 721.  
<sup>243</sup> A. Jackubovic, E. G. McGreer, and P. L. McGreer, *Experientia*, 1978, **34**, 1617.  
<sup>244</sup> M. E. Davis, T. Akera, and T. M. Brody, *Life Sci.*, 1978, **23**, 2675.  
<sup>245</sup> B. B. Fredholm and L. Vernet, *Acta Physiol. Scand.*, 1978, **104**, 502.  
<sup>246</sup> J. G. Clement, *Arch. Int. Pharmacodyn. Ther.*, 1978, **236**, 60.  
<sup>247</sup> B. E. Dahlstrom, L. K. Paalzow, G. Segre, and A. J. Agren, *J. Pharmacokinet. Biopharm.*, 1978, **6**, 41.  
<sup>248</sup> D. R. Stanski, D. J. Greenblatt, and E. Lowenstein, *Clin. Pharm. Ther.*, 1978, **24**, 52.  
<sup>249</sup> E. R. Garrett and T. Gurkan, *J. Pharm. Sci.*, 1978, **67**, 1512.  
<sup>250</sup> A. R. Gintzler and H. Tamir, *Brain Res.*, 1978, **49**, 519.  
<sup>251</sup> M. Lujan, T.-T. Chau-Pham, M. D. Aceto, and W. L. Dewey, *Life Sci.*, 1978, **23**, 1431.  
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<sup>253</sup> M. C. Nowicky, J. R. Walters, and R. H. Roth, *J. Neural Transm.*, 1978, **42**, 99.

methadone and (–)- $\alpha$ -methadol,<sup>254</sup> studies of the physical dependence potential of morphine<sup>255</sup> and the blocking of the development of physical dependence in mice by prolyl-leucyl-glycinamide and by cycloleucylglycine,<sup>256</sup> and reviews on the mechanism of action of morphine<sup>257–259</sup> and its effects on the synthesis of specific antibodies.<sup>260</sup>

Studies relating to derivatives of morphine include the pharmacokinetics of tritiated codeine after oral and rectal administration,<sup>261</sup> the effect of heroin on spontaneous activity in rats,<sup>262</sup> and on pituitary and testicular function;<sup>263</sup> the binding of dihydromorphine to mouse brain;<sup>264</sup> the metabolism of normorphine in dogs,<sup>265</sup> of codeine in rats,<sup>266</sup> and of dihydrocodeinone in humans, rats, dogs, rabbits, and guinea pigs;<sup>267</sup> the pharmacology,<sup>268</sup> analgesic properties,<sup>269</sup> and anaesthetic<sup>270,271</sup> and immobilizing actions<sup>272,273</sup> of etorphine; the pharmacology,<sup>274,275</sup> and abuse potential<sup>275</sup> of buprenorphine; the pharmacology of thebaine;<sup>276</sup> the correlation of the analgesic activities of esters of 14-hydroxy-codeinone with partition coefficients;<sup>277</sup> the antitussive properties of 6-azido-ethylmorphine;<sup>278</sup> the physical dependence properties of the isomers of N-s-butylmorphine;<sup>279</sup> the morphine-antagonist properties of naloxone,<sup>280–290</sup> its

<sup>254</sup> S. Chiba, E. J. Moreton, and N. Khazan, *Jpn. J. Pharmacol.*, 1978, **28**, 498.

<sup>255</sup> T. Murano, H. Senda, H. Yamamoto, and I. Yano, *Jpn. J. Pharmacol.*, 1978, **28**, 403.

<sup>256</sup> R. Walter, R. F. Ritzmann, H. N. Bhargava, N. Hemendra, and L. B. Flexner, *Proc. Natl. Acad. Sci. USA*, 1979, **76**, 518.

<sup>257</sup> J. M. Besson, D. Le Bars, and J. L. Oliveras, *Ann. Anaesthesiol. Fr.*, 1978, **19**, 343.

<sup>258</sup> H. H. Loh and R. J. Hitzemann, *Proc. Eur. Soc. Neurochem.*, 1978, **1**, 404.

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<sup>260</sup> I. E. Kovalev, *Khim.-Farm. Zh.*, 1978, **12**, 3.

<sup>261</sup> N. De Vera, E. Rodriguez Farre, and F. G. Valdecasas, *Arch. Farmacol. Toxicol.*, 1978, **4**, 113.

<sup>262</sup> V. Filibeck and C. Castellano, *Boll. Soc. Ital. Biol. Sper.*, 1978, **54**, 79.

<sup>263</sup> C. Wang, V. Chan, and R. T. T. Yeung, *Clin. Endocrinol.*, 1978, **9**, 455.

<sup>264</sup> T.-T. Chau-Pham, G. King, and W. L. Dewey, *Life Sci.*, 1978, **23**, 1293.

<sup>265</sup> S. Y. Yeh, R. L. McQuinn, and H. A. Krebs, *J. Pharm. Sci.*, 1978, **67**, 878.

<sup>266</sup> J. D. Phillipson, S. W. El-Dabbas, and J. W. Gorrod, *Eur. J. Drug Metab. Pharmacokinet.*, 1978, **3**, 117.

<sup>267</sup> E. J. Cone, W. D. Darwin, C. W. Gorodetsky, and T. Tan, *Drug Metab. Dispos.*, 1978, **6**, 488.

<sup>268</sup> R. L. MacDonald and P. G. Nelson, *Science*, 1978, **199**, 1949.

<sup>269</sup> F. Miranda, G. Candelaesi, and R. Samanin, *Psychopharmacology*, 1978, **58**, 105.

<sup>270</sup> T. D. Williams and F. H. Kocher, *J. Am. Vet. Med. Assoc.*, 1978, **173**, 1127.

<sup>271</sup> J. A. Bogan, G. MacKenzie, and D. H. Snow, *Vet. Record*, 1978, **103**, 471.

<sup>272</sup> R. A. Magonigle, E. H. Stauber, and H. W. Vaughn, *J. Wildl. Dis.*, 1977, **13**, 258.

<sup>273</sup> T. A. McKean, M. Stock, and B. Magonigle, *J. Wildl. Manage.*, 1978, **42**, 176.

<sup>274</sup> R. C. Heel, R. N. Brogden, T. M. Speight, and G. S. Avery, *Drugs*, 1979, **17**, 81.

<sup>275</sup> D. R. Jasinski, J. S. Pevnick, and J. D. Griffith, *Arch. Gen. Psychiatry*, 1978, **35**, 501.

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<sup>277</sup> E. J. Lien, G. L. Tong, D. B. Srulovitch, and C. Dias, *NIDA Res. Mongr.*, 1978, **22**, 186.

<sup>278</sup> J. Knoll, L. G. Harsing, and T. Friedemann, *Acta Physiol. Acad. Sci. Hung.*, 1977, **50**, 341.

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<sup>280</sup> R. J. Bodnar, D. D. Kelly, A. Spiaggi, C. Ehrenberg, and M. Glusman, *Pharmacol. Biochem. Behav.*, 1978, **8**, 667.

<sup>281</sup> M. A. Nalda and M. R. Flores, *Rev. Esp. Anesthesiol. Reanim.*, 1978, **25**, 1.

<sup>282</sup> R. H. Peters and R. A. Hughes, *Pharmacol. Biochem. Behav.*, 1978, **9**, 153.

<sup>283</sup> J. Lagowska, B. Calvino, and Y. Ben-Ari, *Neurosci Lett.*, 1978, **8**, 241.

<sup>284</sup> J. Kugler, P. Hug, A. Doenicke, R. Spatz, and W. Zimmermann, *Arzneim.-Forsch.*, 1978, **28**, 1532.

<sup>285</sup> V. K. Khanna and B. J. Pleuvry, *Br. J. Anaesth.*, 1978, **50**, 905.

<sup>286</sup> N. H. Dodman and A. E. Waterman, *Vet. Record*, 1978, **103**, 334.

<sup>287</sup> K. L. McGilliard and A. E. Takemori, *J. Pharmacol. Exp. Ther.*, 1978, **207**, 494.

<sup>288</sup> R. E. Wilcox and R. A. Levitt, *Pharmacol. Biochem. Behav.*, 1978, **9**, 425.

<sup>289</sup> K. L. McGilliard and A. E. Takemori, *J. Pharmacol. Exp. Ther.*, 1978, **207**, 884.

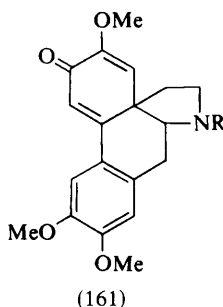
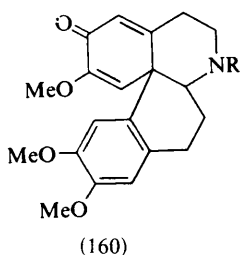
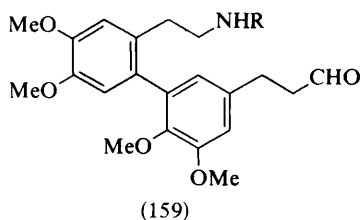
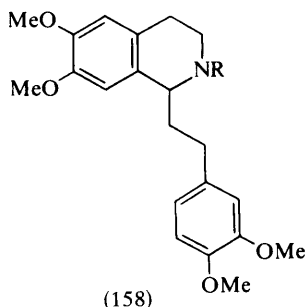
<sup>290</sup> A. Horita and M. A. Carino, *Life Sci.*, 1978, **23**, 1681.



effects on behaviour,<sup>291</sup> in anaesthesia,<sup>292-296</sup> on leucocytic pyrogen,<sup>297</sup> on respiration in Man,<sup>298</sup> and on opiate-binding sites in brain,<sup>299</sup> and its pharmacokinetics;<sup>300</sup> the metabolism of naltrexone<sup>301</sup> and the identification of metabolites of naltrexone,<sup>301,302</sup> the mutagenic effects<sup>303</sup> and morphine-antagonist properties<sup>304</sup> of naltrexone and its effect on the development of physical dependence on morphine<sup>305</sup> and on plasma corticosteroid levels.<sup>306</sup>

#### 14 Phenylethylisoquinolines

Anodic and chemical oxidative coupling of homolaudanosine (158; R = Me) yields homoglaucine, but oxidation of *N*-acyl-nor-analogues, e.g. (158; R = COF<sub>3</sub>), by vanadium oxyfluoride in trifluoroacetic acid and anhydride affords a



<sup>291</sup> A. Bertolini, S. Genedani, and M. Castelli, *Experientia*, 1978, **34**, 771.

<sup>292</sup> M. H. Harper, P. M. Winter, B. H. Johnson, and E. I. Eger, *Anaesthesiology*, 1978, **49**, 3.

<sup>293</sup> R. S. Smith, M. Wilson, and K. W. Miller, *Anaesthesiology*, 1978, **49**, 6.

<sup>294</sup> P. B. Bennett, *Anaesthesiology*, 1978, **49**, 9.

<sup>295</sup> P. Hug, W. Zimmermann, M. Laub, and A. Doenicke, *Anaesthetist*, 1978, **27**, 280.

<sup>296</sup> J. M. Desmonts, G. Bohm, and E. Conderc, *Anaesthesiology*, 1978, **49**, 1.

<sup>297</sup> W. G. Clark and N. F. Harris, *Eur. J. Pharmacol.*, 1978, **49**, 301.

<sup>298</sup> C. Dauthier, F. Boureau, J. C. Willer, and H. Cauthier, *Ann. Anaesthesiol. Fr.*, 1978, **19**, 155.

<sup>299</sup> R. A. Lahti and R. J. Collins, *Eur. J. Pharmacol.*, 1978, **51**, 185.

<sup>300</sup> N. L. Pace, R. G. Parrish, M. M. Liebermann, K. C. Wong, and R. A. Blatnick, *J. Pharmacol. Exp. Ther.*, 1979, **208**, 254.

<sup>301</sup> E. J. Cone, C. W. Gorodetsky, W. D. Darwin, F. I. Carroll, G. A. Brine, and C. D. Welch, *Res. Commun. Chem. Pathol. Pharmacol.*, 1978, **20**, 413.

<sup>302</sup> G. A. Brine, D. R. Brine, C. D. Welch, V. C. Bondeson, and F. I. Carroll, *Res. Commun. Chem. Pathol. Pharmacol.*, 1978, **22**, 455.

<sup>303</sup> S. Zimmering, *Mutat. Res.*, 1979, **66**, 129.

<sup>304</sup> J. B. Smith, *Neurosci. Lett.*, 1978, **8**, 265.

<sup>305</sup> M. N. Bhargava, *Eur. J. Pharmacol.*, 1978, **50**, 193.

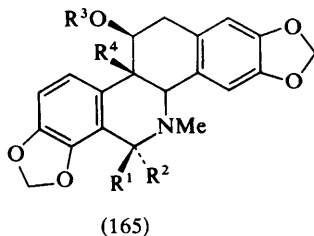
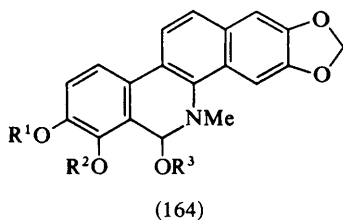
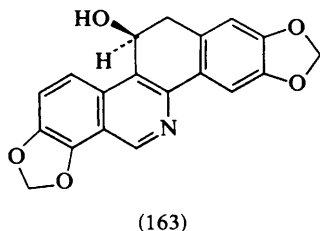
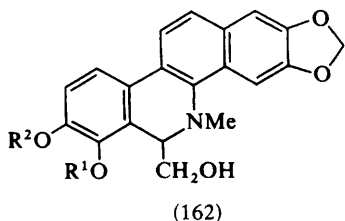
<sup>306</sup> A. L. Misra, R. B. Pontani, and N. L. Vadlamani, *Res. Commun. Chem. Pathol. Pharmacol.*, 1978, **20**, 43.

mixture of the homo-aporphine (2%), the diphenyl (159) (5%), and an equilibrium mixture of the homoproerythradienones (160) (5%) and (161) (64%); this is in marked contrast to the oxidation of non-phenolic benzylisoquinolines by the same reagent, which yields morphinandienones.<sup>307</sup>

### 15 Benzophenanthridines

Sanguinarine has been isolated from *Corydalis ophiocarpa*,<sup>88</sup> and from *C. gigantea*, *C. marshalliana*, *C. remota*, *C. rosea*, and *C. vaginans*;<sup>87</sup> sanguinarine, norsanguinarine, chelerythrine, norchelerythrine, bocconoline (162;  $R^1 = R^2 = \text{Me}$ ), and its methylenedioxy-analogue (162;  $R^1R^2 = \text{CH}_2$ ), which is a new base, from *Chelidonium major*;<sup>308</sup> chelerythrine and nitidine from *Zanthoxylum bouetense*;<sup>309</sup> chelidonine from *Symphoricarpos albus*;<sup>310</sup> norsanguinarine, oxy-sanguinarine, and a new base luguine (163) from *Glaucium flavum* Cr. var. *vestitum*;<sup>311</sup> and sanguinarine, chelerythrine, and the carbinolamine ethers (164;  $R^1 = R^2 = R^3 = \text{Me}$ ), (164;  $R^1 = R^2 = \text{Me}$ ,  $R^3 = \text{Et}$ ) and (164;  $R^1R^2 = \text{CH}_2$ ,  $R^3 = \text{Me}$ ) and (164;  $R^1R^2 = \text{CH}$ ,  $R^3 = \text{Et}$ ) from *Hunnemannia fumariaefolia*.<sup>312</sup>

Studies of i.r. and of  $^1\text{H}$  and  $^{13}\text{C}$  n.m.r. spectra of the bases (165), where  $R^3 = \text{H}$  and Ac,  $R^4 = \text{H}$  and Me, in the two series  $R^1 = \text{H}$ ;  $R^2 = \text{H}$ , Me,  $\text{CH}=\text{CH}_2$ ,  $\text{CH}_2\text{COMe}$ ,  $\text{CH}_2\text{OH}$ , and  $\text{CH}_2\text{OAc}$  and that with the alternative stereochemistry of  $R^1$  and  $R^2$  have resulted in the assignment of configurations to the two series.<sup>313</sup>



<sup>307</sup> S. M. Kupchan, O. P. Dhingra, C. K. Kim, and V. Kameswaran, *J. Org. Chem.*, 1978, **43**, 2521.

<sup>308</sup> H. Itokawa, A. Ikuta, N. Tsutsui, and I. Ishiguro, *Phytochemistry*, 1978, **17**, 839.

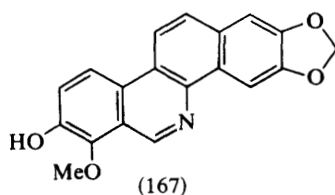
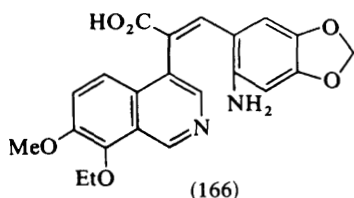
<sup>309</sup> J. Vaquette, A. Cave, and P. G. Waterman, *Plant Med. Phytother.*, 1978, **12**, 235.

<sup>310</sup> M. Szafer, Z. Kowalewski, and J. D. Phillipson, *Phytochemistry*, 1978, **17**, 1446.

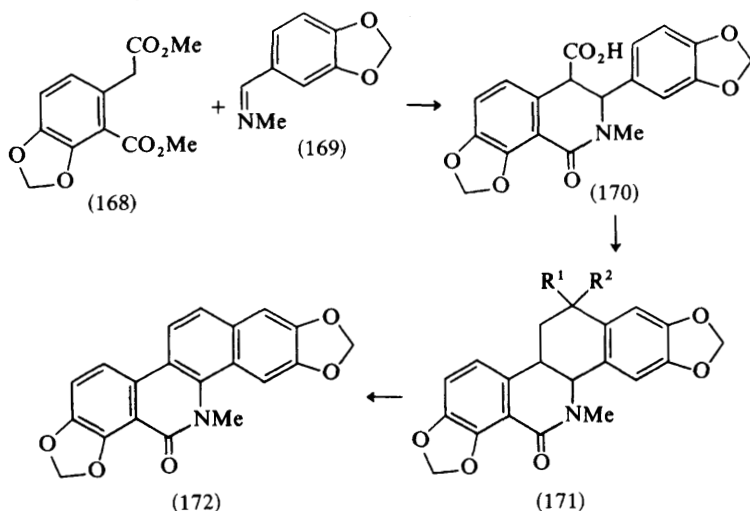
<sup>311</sup> L. Castedo, D. Dominguez, J. M. Saa, and R. Suau, *Tetrahedron Lett.*, 1978, 2923.

<sup>312</sup> L. A. Mitscher, Y. N. Park, D. Clark, G. W. Clark, P. D. Hammesfahr, W. Wu, and J. L. Beal, *Lloydia*, 1978, **41**, 145.

<sup>313</sup> N. Takao, K. Iwasa, M. Kamigauchi, and M. Sugiura, *Chem. Pharm. Bull.*, 1978, **26**, 1880.



Pschorr ring-closure of the diazonium salt from the amino-acid (166) is accompanied by decarboxylation, and gives a base that is isomeric with *O*-ethyldecarine, indicating that decarine has the structure (167).<sup>314</sup> Oxy-sanguinarine (172) has been synthesized by condensation of the diester (168) with the imine (169), hydrolysis of the product to the lactam-acid (170), followed by Arndt-Eistert conversion into the homologous acid, cyclization of which gave the ketone (171;  $R^1R^2 = O$ ). Reduction of this ketone to the secondary alcohol (171;  $R^1 = H$ ,  $R^2 = OH$ ), followed by dehydration and aerial oxidation, afforded oxysanguinarine (172).<sup>315</sup>



A synthesis of chelirubine (174;  $R^1R^2 = CH_2$ ) has been achieved by the photolysis of the enamide (173),<sup>316</sup> and a synthesis of the related sanguilutine (181) by the process shown in Scheme 3; an analogous process, starting from 2-methoxy-4,5-methylenedioxybenzaldehyde, afforded sanguirubine (174;  $R^1 = R^2 = Me$ ).<sup>317</sup>

Photolysis of the amide (182) has been shown to give tetrahydro-oxochelerythrine (183) together with two dimers of (182), of structures (184) and (185).<sup>318</sup> In

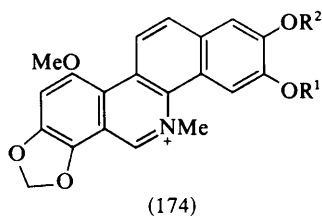
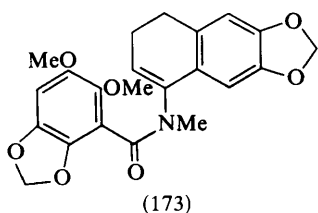
<sup>314</sup> H. Ishii, T. Ishikawa, and Y. Ichikawa, *Chem. Pharm. Bull.*, 1978, **26**, 514.

<sup>315</sup> M. Shamma and H. Tomlinson, *J. Org. Chem.*, 1978, **43**, 2852.

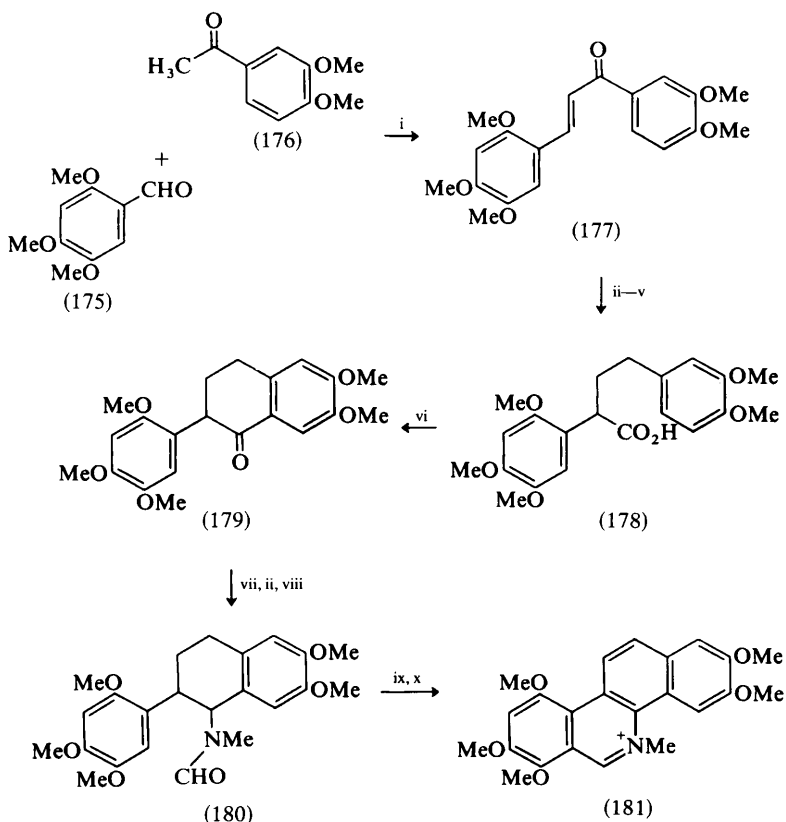
<sup>316</sup> H. Ishii, E. Ueda, K. Nakajima, T. Ishida, T. Ishikawa, K. Harada, I. Ninomiya, T. Naito, and T. Kiguchi, *Chem. Pharm. Bull.*, 1978, **26**, 864.

<sup>317</sup> H. Ishii, T. Watanabe, and T. Ishikawa, *Chem. Pharm. Bull.*, 1978, **26**, 3252.

<sup>318</sup> M. Onda and Y. Yamaguchi, *Heterocycles*, 1978, **9**, 449.



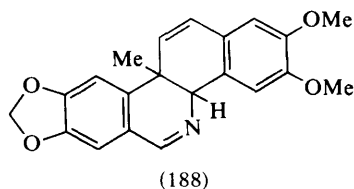
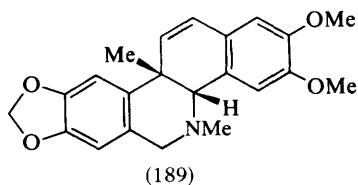
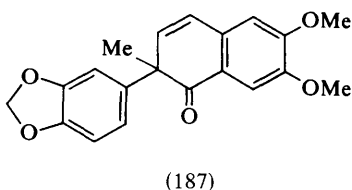
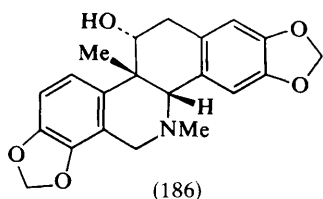
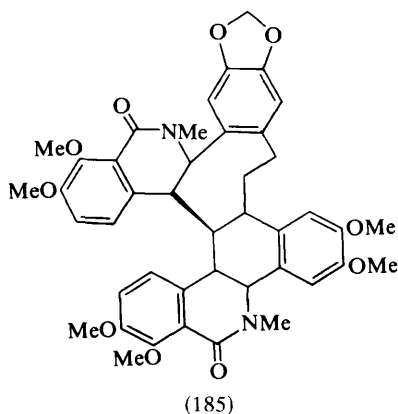
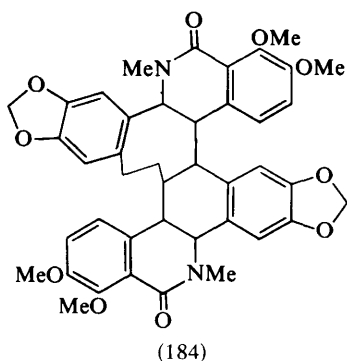
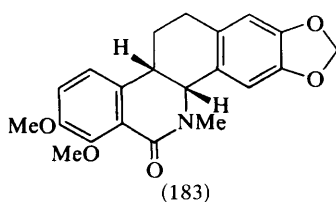
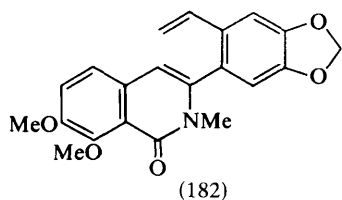
an approach to the synthesis of analogues of corynoline (186), the enone (187) was subjected to Leukart reaction and Bischler–Napieralsky ring-closure to give *cis*- and *trans*-forms of the base (188), the *cis*-form of which was converted into the *N*-methyl compound (189).<sup>319</sup>



Reagents: i, Base; ii, H<sub>2</sub>, Pd; ii, KCN; iv, H<sub>2</sub>, Pt; v, H<sup>+</sup>, H<sub>2</sub>O; vi, PCl<sub>5</sub>, SnCl<sub>4</sub>; vii, MeNH<sub>2</sub>; viii, HCO<sub>2</sub>Et; ix, Pd/C; x, POCl<sub>3</sub>

**Scheme 3**

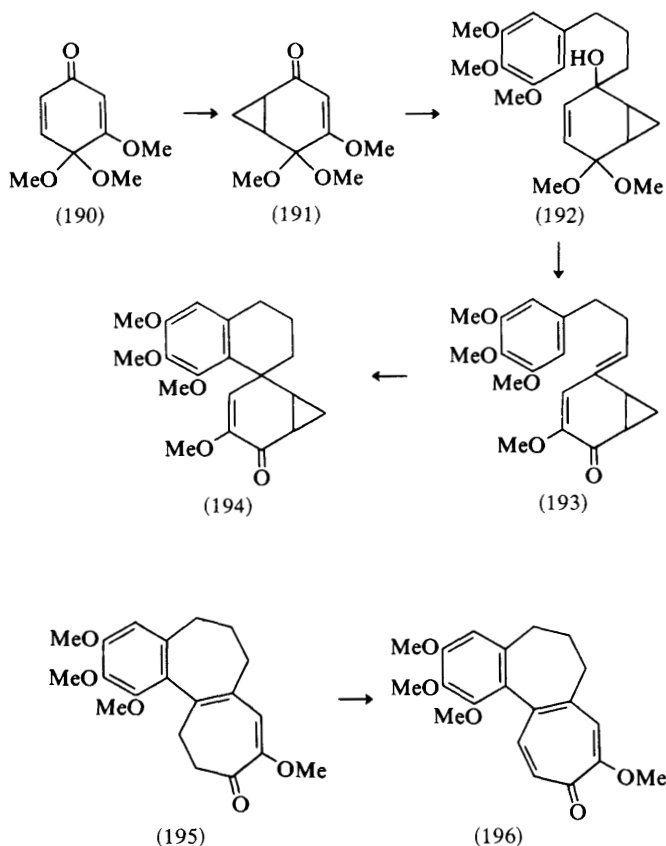
<sup>319</sup> M. Onda, Y. Harigaya, and J. Horie, *Chem. Pharm. Bull.*, 1978, **26**, 3330.



## 16 Colchicine

Colchicine, *N*-formyl-desacetylcolchicine, and  $\gamma$ -lumicolchicine have been isolated from *Merendera caueasia*.<sup>320</sup> A new synthesis of desacetamido-isocolchicine (196), and hence a formal synthesis of colchicine, has been achieved in good yield. The methoxyquinone ketal (190) reacts with dimethyloxosulphonium methylide to give the enone (191) (93%), and this, with 3-(3,4,5-trimethoxyphenyl)propylmagnesium bromide, gives the alcohol (192) (90%). Treatment of this alcohol

<sup>320</sup> A. Ulubelen and M. Tanker, *Planta Med.*, 1978, **34**, 216.



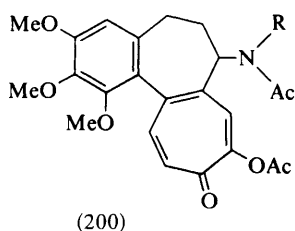
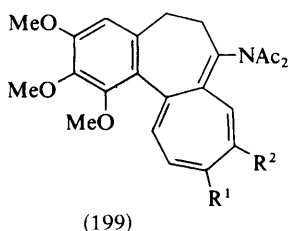
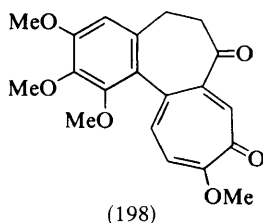
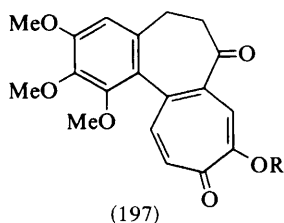
with anhydrous trifluoroacetic acid gives dihydrodesacetamido-isocolchicine (195) (73%), which can be oxidized to desacetamido-isocolchicine (196) in 72% yield. Treatment of (192) with trifluoroacetic acid for limited periods has shown that the route to (195) proceeds *via* the dienone (193) and the spiro-compound (194).<sup>321</sup>

The hydrolysis of (–)-*N*-benzylidenedesacetylcolchicine in 7.5% potassium hydroxide in methanol gives 7-oxodesacetamidocolchicine (197; R = H), which can be methylated by diazomethane to 7-oxodesacetamidocolchicine (198) and 7-oxodesacetamido-isocolchicine (197; R = Me), whereas hydrolysis with >10% potassium hydroxide yields (±)-*N*-desacetylcolchicine.<sup>322</sup> Isocolchicine and thiocolchicine, when boiled with acetic anhydride, are converted into the *N*-diacetyl compounds (199; R<sup>1</sup> = OAc, R<sup>2</sup> = OMe) and (199; R<sup>1</sup> = SMe, R<sup>2</sup> = OAc) respectively; under the same conditions, colchicine yields (200; R = H) and (200; R = Ac).<sup>323</sup>

<sup>321</sup> D. A. Evans, D. J. Hart, and P. M. Koelsch, *J. Am. Chem. Soc.*, 1978, **100**, 4593.

<sup>322</sup> M. A. Iorio, A. Brossi, and J. V. Silverton, *Helv. Chim. Acta*, 1978, **61**, 1213.

<sup>323</sup> A. Blade-Font, *Afinidad*, 1978, **35**, 239.



The  $^{13}\text{C}$  n.m.r. spectrum<sup>324</sup> and emission spectrum<sup>325</sup> of colchicine have been studied. The mode of action of colchicine in familial Mediterranean fever,<sup>326</sup> the kinetics and mechanism of its binding to tubulin,<sup>327</sup> its binding to human and bovine serum albumin and human plasma,<sup>328</sup> its effects on atherogenesis,<sup>329</sup> on morphogenic processes in amphibian embryonic cells,<sup>330</sup> on intestinal transport and ATPase activity,<sup>331</sup> on glucose-induced secretion of insulin and glucose tolerance,<sup>332</sup> on the growth and morphology of *Trypanosoma cruzi*,<sup>333</sup> on the absorption of drugs from the intestine,<sup>334</sup> on the survival of mammalian cells when exposed to frost-thaw damage,<sup>335</sup> on intra-ocular pressure,<sup>336</sup> on the ultrastructure of lactating mammary gland,<sup>337</sup> and on guinea-pig intrinsic factor- $\text{B}_{12}$  receptor<sup>338</sup> have been studied. *N*-Desacetyl-*N*-glycosyl-alkylthio-colchicines have been tested as anti-leukaemic agents.<sup>339</sup>

<sup>324</sup> S. P. Singh, S. S. Parmar, V. I. Stenberg, and S. A. Farnum, *Spectrosc. Lett.*, 1977, **10**, 1001.

<sup>325</sup> R. Croteau and R. M. Le Blanc, *Photochem. Photobiol.*, 1978, **28**, 33.

<sup>326</sup> J. Y. Leullier, *Vie Med.*, 1978, **59**, 1567.

<sup>327</sup> D. L. Garland, *Biochemistry*, 1978, **17**, 4266.

<sup>328</sup> Z. Truavska, M. Kuchar, V. Rejholec, and K. Truavsky, *Pharmacology*, 1979, **18**, 123.

<sup>329</sup> D. M. Kramsch and C. T. Chan, *Circ. Res.*, 1978, **42**, 562.

<sup>330</sup> L. E. Martynova and L. V. Belousov, *Ontogenez*, 1978, **9**, 382.

<sup>331</sup> D. Rachmilewitz, R. Fogel, and F. Karmeli, *Gut*, 1978, **19**, 759.

<sup>332</sup> J. H. Shah and N. Wongsurawat, *Diabetes*, 1978, **27**, 925.

<sup>333</sup> F. S. Astolfi, E. R. Pereira de Almeida, and E. S. Gander, *Acta Trop.*, 1978, **35**, 229.

<sup>334</sup> V. M. K. Venho and A. Koimuniemi, *Acta Pharmacol. Toxicol.*, 1978, **43**, 251.

<sup>335</sup> P. Law, J. R. Lepock, J. E. Thompson, and J. Kruuv, *Cryobiology*, 1978, **15**, 675.

<sup>336</sup> P. Bhattacharjee and K. E. Eakins, *Exp. Eye Res.*, 1978, **27**, 649.

<sup>337</sup> V. M. Knudson, B. H. Steinberger, and S. Patton, *Cell Tissue Res.*, 1978, **195**, 169.

<sup>338</sup> E. G. Stopa, R. O'Brien, and M. Katz, *Gastroenterology*, 1979, **76**, 309.

<sup>339</sup> G. T. Shiau, K. K. De, and R. E. Harmon, *J. Pharm. Sci.*, 1978, **67**, 394.

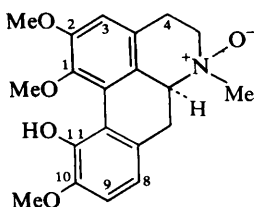
# 9

## Aporphinoid Alkaloids

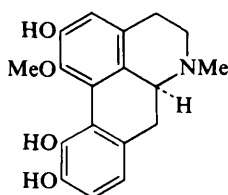
BY M. SHAMMA

### 1 Aporphines

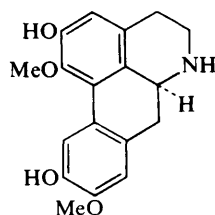
The year under review has witnessed a particularly bountiful harvest of new aporphine alkaloids. These, with their botanical sources, are given below.



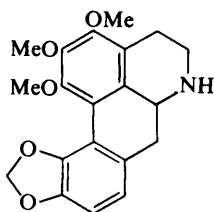
(+)-Isocorydine *N*-oxide<sup>1</sup>  
*Berberis integerrima* Bge.  
(Berberidaceae)



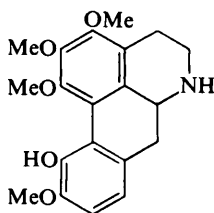
(+)-Glaufine<sup>2</sup>  
*Glaucium fimbriigerum*  
(Papaveraceae)



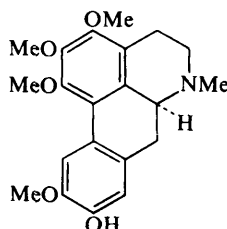
(+)-Laetanine<sup>4</sup>  
*Litsea laeta* Benth. & Hook. f.  
(Lauraceae)



Polygospermine<sup>3</sup>  
both from *Polyalthia oligosperma* (Danguy) Diels  
(Annonaceae)



Noroconovine<sup>3</sup>



(+)-Thalisopypnine<sup>5</sup>  
*Thalictrum isopyroides* C. A. Mey.  
(Ranunculaceae)

<sup>1</sup> A. Karimov, M. V. Telezhenetskaya, K. L. Lutfullin, and S. Yu. Yunusov, *Khim. Pri. Soedin.*, 1978, 419 [*Chem. Nat. Compd. (Engl. Transl.)* 1978, **14**, 360].

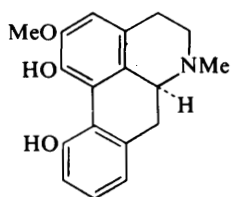
<sup>2</sup> S. U. Karimova, I. A. Israilov, M. S. Yunusov, and S. Yu. Yunusov, *Khim. Pri. Soedin.*, 1978, 814 [*Chem. Nat. Compd. (Engl. Transl.)*, 1978, **14**, 699].

<sup>3</sup> H. Guinaudeau, A. Ramahatra, M. Leboeuf, and A. Cavé, *Plant. Med. Phytother.*, 1978, **12**, 166 (*Chem. Abs.*, 1979, **90**, 118 062).

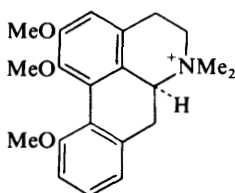
<sup>4</sup> N. Borthakur and R. C. Rastogi, *Phytochemistry*, 1979, **18**, 910.

<sup>5</sup> S. Abduzhabbarova, S. Kh. Maekh, S. Yu. Yunusov, M. R. Yagudaev, and D. Kurbakov, *Khim. Pri. Soedin.*, 1978, 472 [*Chem. Nat. Compd. (Engl. Transl.)* 1978, **14**, 400].

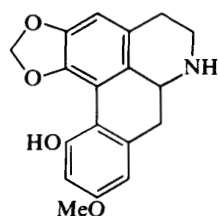




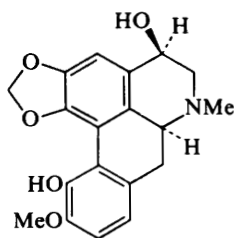
(+)-Isothebaidine<sup>6</sup>  
*Papaver orientale* L.  
(Papaveraceae)



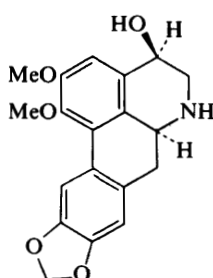
(+)-Zanthoxyphylline<sup>7</sup>  
*Zanthoxylum oxyphyllum* Edgew.  
(Rutaceae)



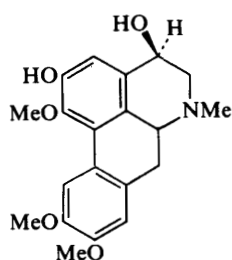
Calycinine<sup>8</sup>  
*Duguetia calycina* Benoist  
(Annonaceae)



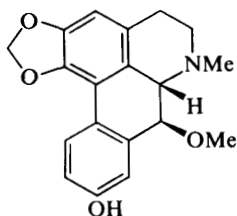
(+)-4-Hydroxybulbocapnine<sup>9</sup>  
*Glaucium vitellinum*  
Boiss. & Buhse  
(Papaveraceae)



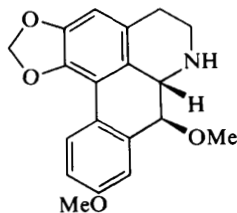
(+)-4-Hydroxynornantenine<sup>10a</sup>  
*Laurelia philippiana* Looser  
(Atherospermataceae)



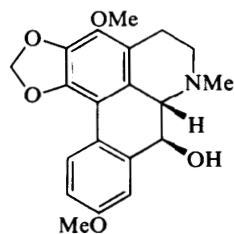
(+)-Srilankine<sup>11</sup>  
*Alseodaphne semicarpifolia* Nees  
(Lauraceae)



(+)-Polysuavine<sup>12</sup>



(+)-Noroliverine<sup>12</sup>



(+)-Polyalthine<sup>12</sup>

all three from *Polyalthia* sp. (Annonaceae)

<sup>6</sup> I. A. Israilov, O. N. Denisenko, M. S. Yunusov, D. A. Muraveva, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 1978, 474 [*Chem. Nat. Compd. (Engl. Transl.)*, 1978, **14**, 402].

<sup>7</sup> K. P. Tiwari and M. Masood, *Phytochemistry*, 1978, **17**, 1068.

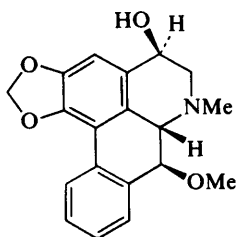
<sup>8</sup> F. Roblot, R. Hocquemiller, H. Jacquemin, and A. Cavé, *Plant. Med. Phytother.*, 1978, **12**, 259 (*Chem. Abs.*, 1979, **91**, 2517).

<sup>9</sup> A. Shafiee, A. Ghanbarpour, I. Lalezari, and S. Lajevardi, *J. Nat. Prod.*, 1979, **42**, 174.

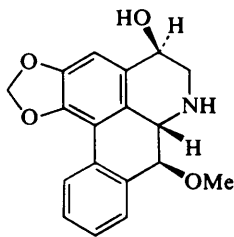
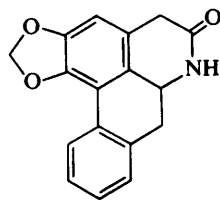
<sup>10</sup> (a) A. Urzúa and B. K. Cassels, *Tetrahedron Lett.*, 1978, 2649; (b) W. H. Watson, unpublished results cited in ref. 10a.

<sup>11</sup> W. D. Smolnycki, J. L. Moniot, D. M. Hindenlang, G. A. Miana, and M. Shamma, *Tetrahedron Lett.*, 1978, 4617.

<sup>12</sup> A. Cavé, H. Guinaudeau, M. Leboeuf, A. Ramahatra, and J. Razafindrazaka, *Planta Medica*, 1978, **33**, 243.

(+) -Pachystaudine<sup>13</sup>

both from *Pachypodanthium* sp.  
(Annonaceae)

(+) -Norpachystaudine<sup>13</sup>Fuseine<sup>14</sup>

*Fusea longifolia* (Aubl.) Safford  
(Annonaceae)

Of particular interest is calycine, which possesses a *meta* substitution pattern in ring D,<sup>8</sup> and fuseine, which is the first simple lactam known in the aporphine series.<sup>14</sup> A complete *X*-ray analysis was carried out on the *N,O*-diacetyl derivative of 4-hydroxynornantenine to confirm its stereochemistry and absolute configuration.<sup>10b</sup> The stereochemical assignments for all 4-hydroxylated aporphines are, therefore, predicated upon this *X*-ray study.

Known aporphines that have been re-isolated from natural sources are shown in Table 1.<sup>1-3,6-9,15-23</sup>

**Table 1** Aporphines that have recently been re-isolated, and their natural sources

Alkaloid	Source	Ref.
Isoboldine	<i>Berberis integerrima</i>	1
	<i>Delphinium dictyocarpum</i>	15
Thaliporphine	<i>Croton draconoides</i>	16
Thaliporphine <i>N</i> -oxide	<i>Berberis integerrima</i>	1
Magnoflorine	<i>Stephania japonica</i>	17
	var. <i>australis</i>	
<i>N</i> -Methyl-lindcarpine	<i>Glaucium fimbriigerum</i>	2
	<i>G. vitellinum</i>	9
Anonaine	<i>Polyalthia emarginata</i>	3
Isothebaine	<i>Papaver orientale</i>	6
Bracteoline	<i>Papaver orientale</i>	6

<sup>13</sup> F. Bévalot, M. Leboeuf, and A. Cavé, *Plant. Med. Phytother.*, 1977, **11**, 315.

<sup>14</sup> R. Braz Filho, S. J. Gabriel, C. M. R. Gomes, O. R. Gottlieb, M. das G. A. Bichara, and J. G. S. Maia, *Phytochemistry*, 1976, **15**, 1187.

<sup>15</sup> B. T. Salimov, N. D. Abdullaev, M. S. Yunusov, and S. Yu. Yunusov, *Khim. Priro. Soedin.*, 1977, 235 [*Chem. Nat. Compd. (Engl. Transl.)*, 1978, **14**, 194].

<sup>16</sup> R. Marini-Bettolo and M. L. Scarpati, *Phytochemistry*, 1979, **18**, 520.

<sup>17</sup> M. Matsui, M. Uchida, I. Usuki, Y. Saionji, H. Murata, and Y. Watanabe, *Phytochemistry*, 1979, **18**, 1087.

<sup>18</sup> V. A. Chelombitko, V. A. Mnatsakanyan, and L. V. Salnikova, *Khim. Priro. Soedin.*, 1978, 270 [*Chem. Nat. Compd. (Engl. Transl.)*, 1978, **14**, 228].

<sup>19</sup> N. N. Margvelashvili, O. N. Tolkachev, N. P. Prisyazhnyuk, and A. T. Kiryanova, *Khim. Priro. Soedin.*, 1978, 592 [*Chem. Nat. Compd. (Engl. Transl.)*, 1978, **14**, 509].

<sup>20</sup> G. Verzar-Petri and P. T. Ming Hoang, *Sci. Pharm.*, 1978, **46**, 169.

<sup>21</sup> Pol, P. 82 864 (*Chem. Abs.*, 1979, **90**, 43 798).

<sup>22</sup> M. A. Manushakyan and V. A. Mnatsakanyan, *Khim. Priro. Soedin.*, 1977, 713 [*Chem. Nat. Compd. (Engl. Transl.)*, 1977, **13**, 599].

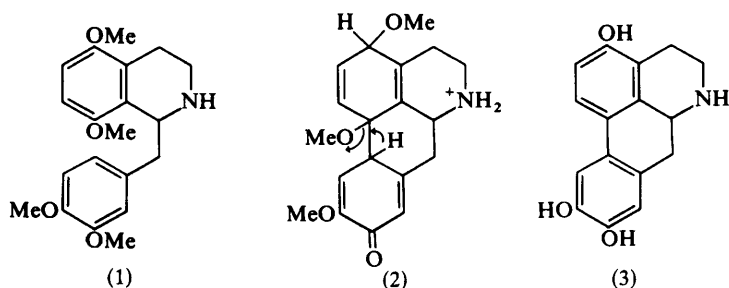
<sup>23</sup> I. Khokhar, *Pak. J. Sci. Res.*, 1978, **30**, 81.

Table 1—continued

Alkaloid	Source	Ref.
Corydine	<i>Zanthoxylum oxyphyllum</i>	7
	<i>Glaucium vitellinum</i>	9
Isocorydine	<i>Glaucium vitellinum</i>	9
	<i>Papaver lisae</i>	18
Puterine	<i>Duguetia calycina</i>	8
O-Methylpukateine	<i>Duguetia calycina</i>	8
Obovanine	<i>Duguetia calycina</i>	8
Dicentrine	<i>Glaucium vitellinum</i>	9
Bulbocapnine	<i>Glaucium vitellinum</i>	9
	<i>Corydalis vaginans</i>	19
	<i>C. marschalliana</i>	19
	<i>C. cava</i>	20
Glaucine	<i>Glaucium vitellinum</i>	9
	<i>Croton draconoides</i>	16
	<i>Glaucium flavum</i>	21
Neolitsine	<i>Glaucium vitellinum</i>	9
N-Methyl-laurotetanine	<i>Glaucium vitellinum</i>	9
	<i>Delphinium dictyocarpum</i>	15
Dehydrodicentrine	<i>Glaucium vitellinum</i>	9
(+)-Remrefidine	<i>Papaver fugax</i>	22
Nornuciferine	<i>Zizyphus sativa</i>	23
Asimilobine	<i>Zizyphus sativa</i>	23

The different approaches to the synthesis of aporphines have been summarized.<sup>24</sup> A useful review on the photochemistry of enamides has appeared, detailing conditions under which aporphines may be obtained.<sup>25</sup>

Attempted demethylation of the benzylisoquinoline (1) in concentrated hydrobromic acid at 140 °C gave rise to 3,9,10-trihydroxynoraporphine (3) through the probable intermediacy of the quinone methide (2).<sup>26</sup>

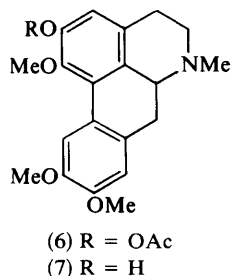
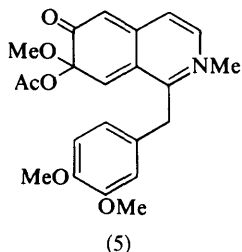
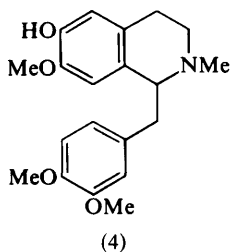


<sup>24</sup> B. Umezawa and O. Hoshino, *Yuki Gosei Kagaku Kyokaishi*, 1978, **36**, 858 (*Chem. Abs.* 1979, **90**, 168 802).

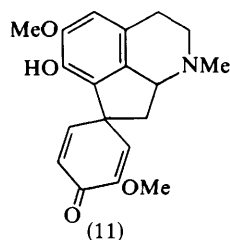
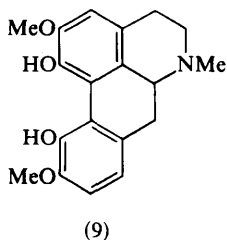
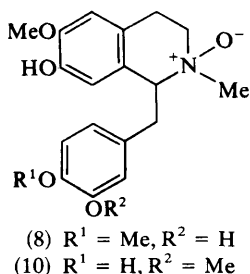
<sup>25</sup> G. R. Lenz, *Synthesis*, 1978, 489.

<sup>26</sup> F. C. Copp, A. R. Elphick, and K. W. Franzmann, *J. Chem. Soc., Chem. Commun.*, 1979, 507.

Oxidation of the benzyloisoquinoline (4) with lead tetra-acetate in methylene chloride led to a diastereomeric mixture of *o*-quinol acetates (5), whose treatment with acetic anhydride in concentrated sulphuric acid provided *O*-acetyl-predicentrine (6). Basic hydrolysis then afforded predicentrine (7). Iso-domesticine, which corresponds to 1-methoxy-2-hydroxy-9,10-methylene-dioxyaporphine, was synthesized by a parallel route.<sup>27</sup>



The reaction of reticuline *N*-oxide (8) with cuprous chloride in methanol in the absence of oxygen afforded a 61% yield of corytuberine (9), while orientalene *N*-oxide (10) supplied a 5% yield of orientalnone (11). It is assumed that cuprous chloride is oxidized by the *N*-oxides to an active cupric species which lends itself to *ortho-ortho* phenolic oxidative coupling.<sup>28</sup>



A full paper has appeared on the oxidation of monophenolic benzyloisoquinolines with VOF<sub>3</sub> and TFA in TFAA. The aporphines (12), (13), and (14) were thus obtained in 70–80% yields from the benzyloisoquinolines (15), (16), and (17), respectively. Aporphine (13) corresponds to thaliporphine, while (14) is bracteoline.<sup>29</sup>

The Bischler–Napieralski–Pschorr or the Reissert–Pschorr cyclizations have allowed the preparation of the aporphines (18)–(20).<sup>30</sup>

Photolysis of tetrahydrobenzyloisoquinolines brominated at C-2' was utilized in the preparation of cryptodrine (norneolitsine) (21)<sup>31</sup> and of 1,9-dihydroxy-2-

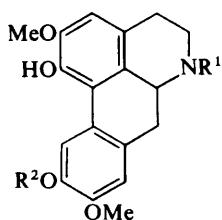
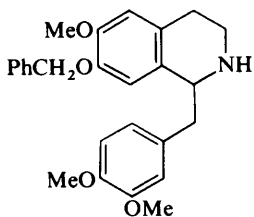
<sup>27</sup> O. Hoshino, M. Ohtani, and B. Umezawa, *Chem. Pharm. Bull.*, 1978, **26**, 3920.

<sup>28</sup> T. Kametani and M. Ihara, *Heterocycles*, 1979, **12**, 893.

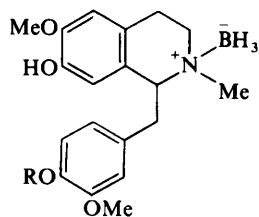
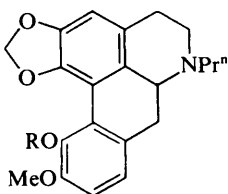
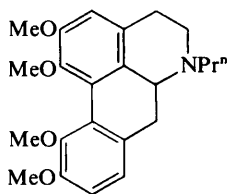
<sup>29</sup> S. M. Kupchan, O. P. Dhingra, and C.-K. Kim, *J. Org. Chem.*, 1978, **43**, 4076.

<sup>30</sup> D. R. Elmaleh, F. E. Granchelli, and J. L. Neumeyer, *J. Heterocycl. Chem.*, 1979, **16**, 87.

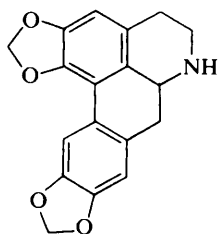
<sup>31</sup> B. R. Pai, S. Natarajan, H. Suguna, and G. Manikumar, *Indian J. Chem., Sect. B*, 1977, **15**, 1042.

(12)  $R^1 = \text{COCF}_3$ ,  $R^2 = \text{Me}$ (13)  $R^1 = R^2 = \text{Me}$ (14)  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ 

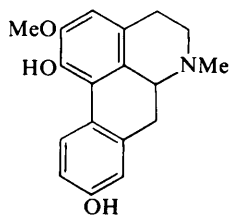
(15)

(16)  $R = \text{Me}$ (17)  $R = \text{CH}_2\text{Ph}$ (18)  $R = \text{Me}$ (19)  $R = \text{H}$ 

(20)



(21)



(22)

methoxyaporphine (22), whose *O*-methylation supplied 1-hydroxy-2,9-dimethoxyaporphine.<sup>32</sup>

Attempted photocyclization of a series of 4-oxazolin-2-ones did not lead to aporphines.<sup>33</sup>

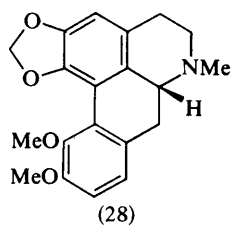
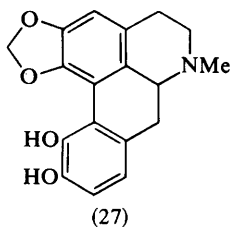
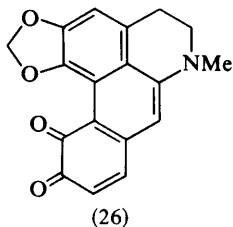
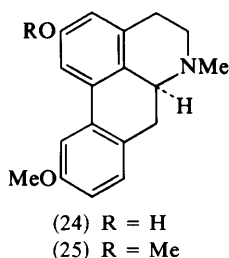
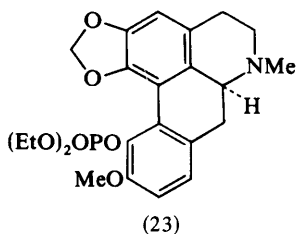
Since boldine and, to a lesser extent, bulbocapnine are the only two generally available naturally occurring aporphines, a useful series of chemical transformations has been worked out that leads from them to a variety of other aporphines. Thus reduction of the phosphate ester (23) of bulbocapnine with sodium in liquid ammonia resulted in the formation of 2-hydroxy-10-methoxyaporphine (24), whose *O*-methylation generated (25).<sup>34</sup>

Also, oxidation of (+)-bulbocapnine with mercuric chloride afforded the known quinone (26); this was reduced to the catechol (27). This racemate was resolved as its diacetate derivative, using (+)-tartaric acid. The resulting (−)-

<sup>32</sup> B. R. Pai, H. Suguna, S. Rajeswari, and G. Manikumar, *Indian J. Chem., Sect. B*, 1978, **16**, 421.

<sup>33</sup> I. Ninomiya, I. Furutani, O. Yamamoto, T. Kiguchi, and T. Naito, *Heterocycles*, 1978, **9**, 853.

<sup>34</sup> K. C. Rice and A. Brossi, *Synth. Commun.*, 1978, **8**, 391.

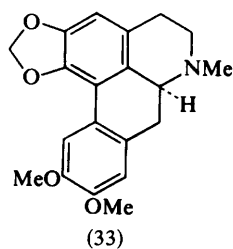
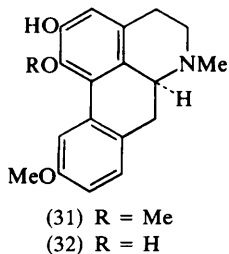
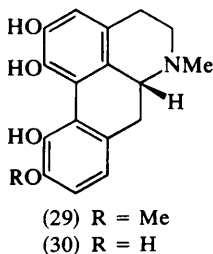


bulbocapnine obtained after hydrolysis was *O*-methylated to the known (–)-bulbocapnine methyl ether (28).<sup>35</sup>

Alternatively, treatment of a mixture of bulbocapnine *N*-oxides with acetic anhydride at 0 °C led to dehydrobulbocapnine, which could be reduced with zinc and acid to racemic bulbocapnine. Resolution using the tartrate salt provided (–)-bulbocapnine. The methylenedioxy and the methoxyl groups were sequentially cleaved, by treatment with boron trichloride, to produce the triphenol (29); cleavage with boron tribromide gave rise to the hydrobromide of tetraphenol (30) in good yield.<sup>35</sup>

Furthermore, boron trichloride can selectively *O*-demethylate a methoxyl group adjacent to a phenolic function to afford the corresponding catechol. In this fashion, the mono-*O*-methyl derivative of boldine, *i.e.* (31), was converted into the unstable catechol (32), whose methylenation using methylene chloride in DMSO containing sodium hydroxide provided dicentrine (33).<sup>36</sup>

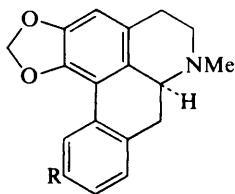
A methoxyl group within a molecule that also includes a methylenedioxy function can be cleaved selectively, using trimethylsilyl iodide in hot dichloro-



<sup>35</sup> M. Gerecke, R. Borer, and A. Brossi, *Helv. Chim. Acta*, 1979, **62**, 1543.

<sup>36</sup> J. P. O'Brien and S. Teitel, *Heterocycles*, 1978, **11**, 347.

benzene, in the presence of DABCO. ( + )-Laureline (34) thus supplied ( + )-mecambroline (35), whose deoxygenation by the Musliner–Gates procedure gave rise to partially racemized ( + )-roemerine (36).<sup>37</sup>



(34) R = Me

(35) R = OH

(36) R = H

The selective *N*-acylation -*O*-trimethylsilylation of a series of nor-aporphines related to apomorphine has been achieved.<sup>38</sup>

New data on the <sup>13</sup>C n.m.r. spectra of aporphines have appeared,<sup>39,40</sup> and the spectra of several aporphinoids have been summarized.<sup>41</sup>

Compounds (27) and (28) have shown dopaminergic activity in rats, but to a lower extent than ( - )-apomorphine.<sup>35</sup> Glaucine shows definite anti-tussive activity,<sup>42</sup> and its tetrahydroxy-derivative exhibits anti-thrombic action.<sup>43</sup>

## 2 Dimeric Aporphinoids

A very useful complete listing of all proaporphine- and aporphine-benzylisoquinoline dimers, as well as aporphine-pavine dimers, together with their physical constants, has appeared.<sup>44</sup>

The known proaporphine-benzylisoquinoline pakistanamine has been found to be the main alkaloid in the seeds of *Berberis julianae* (Berberidaceae).<sup>45</sup>

A review has appeared dealing with the microbial transformations of natural anti-tumour agents, including thalicarpine.<sup>46</sup>

## 3 Oxoaporphines

Splendidine (37), a new oxoaporphine, has been obtained from *Abuta rufescens* Aublet (= *A. splendida*) (Menispermaceae). Following its structural elucidation, its total synthesis was achieved *via* a Reissert–Pschorr sequence.<sup>47</sup>

The known phenolic oxoaporphine subessiline, found in a *Guatteria* species (Annonaceae), has been established to possess structure (39) instead of the

<sup>37</sup> J. Minamikawa and A. Brossi, *Can. J. Chem.*, 1979, **57**, 1720.

<sup>38</sup> J. V. Evans and P. Vouros, *Anal. Biochem.*, 1978, **90**, 389.

<sup>39</sup> A. J. Marsaioli, F. de A. M. Reis, A. F. Magalhães, and E. A. Rúveda, *Phytochemistry*, 1979, **18**, 165.

<sup>40</sup> J. C. Trewella, Ph.D. Thesis, Department of Chemistry, The Pennsylvania State University, 1979.

<sup>41</sup> M. Shamma and D. M. Hindenlang, 'C-13 NMR Shift Assignments of Amines and Alkaloids', Plenum Press, N.Y., 1979.

<sup>42</sup> Ger. Offen. 2 717 062 (*Chem. Abs.* 1979, **90**, 43 806).

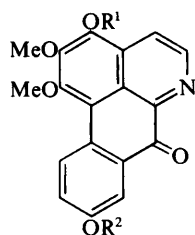
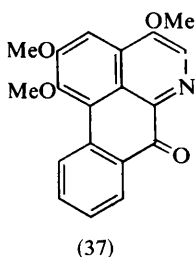
<sup>43</sup> Ger. Offen. 2 717 001 (*Chem. Abs.* 1979, **90**, 43 807).

<sup>44</sup> H. Guinaudeau, M. Leboeuf, and A. Cavé, *J. Nat. Prod.*, 1979, **42**, 133.

<sup>45</sup> D. Košťálová, B. Brázdovičová, and J. Tomko, *Chem. Zvesti*, 1978, **32**, 706.

<sup>46</sup> J. P. Rosazza, *Lloydia*, 1978, **41**, 297.

<sup>47</sup> J. W. Skiles, J. M. Saá, and M. P. Cava, *Can. J. Chem.*, 1979, **57**, 1642.



previously postulated (38) through total synthesis, again by the Reissert–Pschorr sequence.<sup>48</sup>

Known oxoaporphines re-isolated from natural sources include those shown in Table 2.

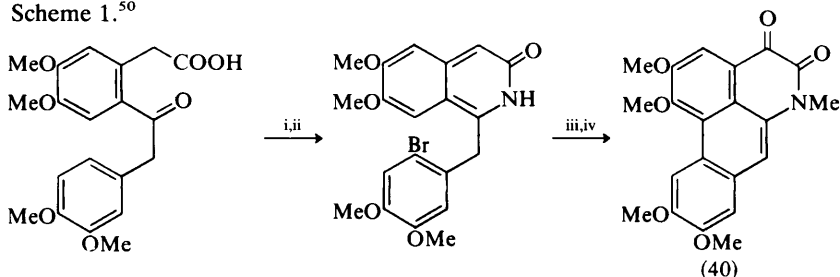
**Table 2** Some known oxoaporphines recently re-isolated

Alkaloid	Source	Ref.
Lysicamine	<i>Abuta rufescens</i>	47
Homomoschatoline	<i>Abuta rufescens</i>	47
Imenine	<i>Abuta rufescens</i>	47
Liriodenine	<i>Polyalthia emarginata</i>	3
	<i>Siparuna guianensis</i>	14
Lanuginosine	<i>Polyalthia emarginata</i>	3
Cassamedine	<i>Siparuna guianensis</i>	14
Dicentrinone	<i>Glaucium vitellinum</i>	9
Oxoputerine	<i>Duguetia calycina</i>	8

2,3,9-Trimethoxyoxoaporphine and the 1,2,9- and 1,2,10-isomers have been synthesized by a Bischler–Napieralski–Pschorr sequence.<sup>49</sup>

#### 4 4,5-Dioxoaporphines

A total synthesis of pontevedrine (40) has been achieved, and is outlined in Scheme 1.<sup>50</sup>



Reagents: i, Br<sub>2</sub>, HOAc; ii, NH<sub>4</sub>OH, HOAc; iii, hν, O<sub>2</sub>, NaOH, MeOH; iv, NaH, DMF, methyl fluorosulphonate

**Scheme 1**

Alternatively, pontevedrine has been prepared by direct photo-oxidation of glaucine or of dehydroglaucine.<sup>51</sup>

<sup>48</sup> J. W. Skiles and M. P. Cava, *J. Org. Chem.*, 1979, **44**, 409.

<sup>49</sup> J. Kunitomo, Y. Murakami, and M. Sugisakon, *Yakugaku Zasshi*, 1979, **99**, 102.

<sup>50</sup> L. Castedo, R. Estévez, J. M. Saá, and R. Suau, *Tetrahedron Lett.*, 1978, 2179.

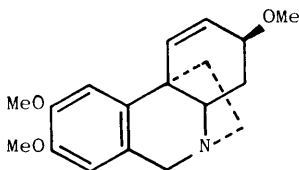
<sup>51</sup> L. Castedo, J. Fumega, R. Riguera, J. Saá, and R. Suau, *An. Quim.* 1978, **74**, 164.



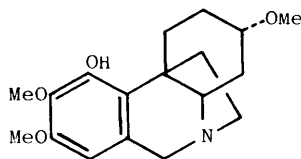
## 1 Isolation and Structural Studies

The bulbs of *Hippeastrum ananuca* have been shown to contain lycorine, homolycorine, and the rare alkaloid maritidine (1).<sup>1</sup> Lycorine has also been isolated for the first time from the rhizomes of *Curculigo orchoides*<sup>2</sup> and from the leaves of *Ungernia tadshicorum*;<sup>3</sup> maritidine is a constituent of *Zephyranthes robusta* and of *Z. sulphurea*,<sup>4</sup> and an X-ray crystallographic study of the alkaloid has been carried out.<sup>5</sup> Two new alkaloids, hippeastidine (2) and 17-*epi*-homolycorine (3), were obtained from *Hippeastrum ananuca* and their structures were established by X-ray analysis.<sup>1,6</sup>

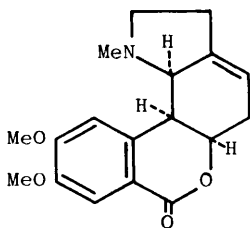
*Crinum ornatum* and *C. natans* were previously reported to be devoid of alkaloids, but a re-investigation has shown that the bulbs contain small amounts.



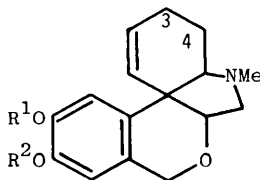
(1)



Hippeastidine (2)



Epihomolycorine (3)



(4)

<sup>1</sup> P. Pacheco, M. Silva, W. Steglich, and W. H. Watson, *Rev. Latinoam. Quim.*, 1978, **9**, 28 (*Chem. Abs.*, 1978, **89**, 103 746).

<sup>2</sup> R. V. K. Rao, N. Ali, and M. N. Reddy, *Indian J. Pharm. Sci.*, 1978, **40**, 104.

<sup>3</sup> T. Sadikov and T. T. Shakirov, *Khim. Prir. Soedin.*, 1978, 818 (*Chem. Abs.*, 1979, **90**, 200 284).

<sup>4</sup> R. V. K. Rao and J. V. L. N. S. Rao, *Curr. Sci.*, 1979, **48**, 110.

<sup>5</sup> V. Zabel, W. H. Watson, P. Pacheco, and M. Silva, *Cryst. Struct. Commun.*, 1979, **8**, 371.

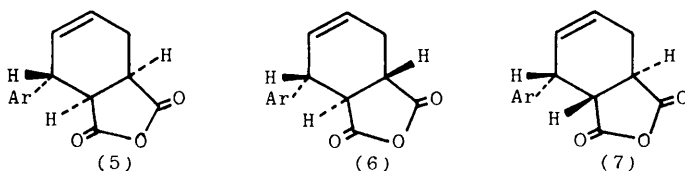
<sup>6</sup> E. M. Gopalakrishna, W. H. Watson, M. Silva, and P. Pacheco, *Cryst. Struct. Commun.*, 1978, **7**, 41.

Application of field desorption mass spectroscopy to the alkaloid mixtures and g.l.c.-m.s. analysis of the trimethylsilylated extracts showed that *C. ornatum* contains at least seven alkaloids, and at least eight alkaloids are present in *C. natans*; lycorine is the major alkaloid of both species. Chromatography of the alkaloid fractions resulted in the isolation of three new alkaloids (ornamine, ornazamine, and ornazidine) from *C. ornatum* and the new alkaloid crinitine from *C. natans*. Ornazidine ( $C_{16}H_{19}NO_3$ ) contains two phenolic OH groups and one *N*-methyl group; a phenolic OH, an *N*-methyl, and an *O*-acetyl group is present in ornazamine ( $C_{18}H_{21}NO_4$ ), and ornamine ( $C_{18}H_{21}NO_3$ ) has one *N*-methyl and two ArOMe groups. Structures (4) have been suggested for these alkaloids, with ornamine possessing an additional double bond, possibly at the 3,4-position. Crinitine,  $C_{18}H_{21}NO_5$ , contains a methylenedioxy-group. An extension of this preliminary investigation will be awaited with interest.<sup>7</sup>

The search for new sources of galanthamine continues, and *Galanthus nivalis*,<sup>8</sup> *G. woronowi*,<sup>9</sup> *Eucharis subedenata*,<sup>8</sup> *Leucojum aestivum*,<sup>9</sup> and *Vallota speciosa*<sup>8</sup> have been investigated this year.

## 2 Synthesis

A full account of Irie's synthesis of the alkaloids clivonine and clividine has appeared<sup>10</sup> (cf. Vol. 5, p. 174) and the conversion of the intermediate anhydrides (5), (6), and (7) into  $\alpha$ -,  $\beta$ -, and  $\delta$ -lycoranes, respectively, is described.<sup>11</sup> The



conversion, which is illustrated for  $\alpha$ -lycorane (9) (Scheme 1), involved the isocyanate (8) derived from anhydride (5) and then formation of a five-membered lactam ring. Another intermediate (10) in the clivonine-clividine synthesis has been employed for the synthesis of lycorine (12) and zephyranthine (14) (Scheme 2). Successive cyclization reactions gave the pentacyclic compound (11), which by epoxidation and application of the Sharpless diphenyl selenide procedure was converted into the allylic alcohol (12). Repetition of the selenide reaction then led to lycorine. Zephyranthine (14) was formed from the olefin (11) by hydroxylation and then reduction of the diacetate of the major stereoisomer.<sup>12</sup>

<sup>7</sup> O. S. Onyiriuka and A. H. Jackson, *Isr. J. Chem.*, 1978, **17**, 185.

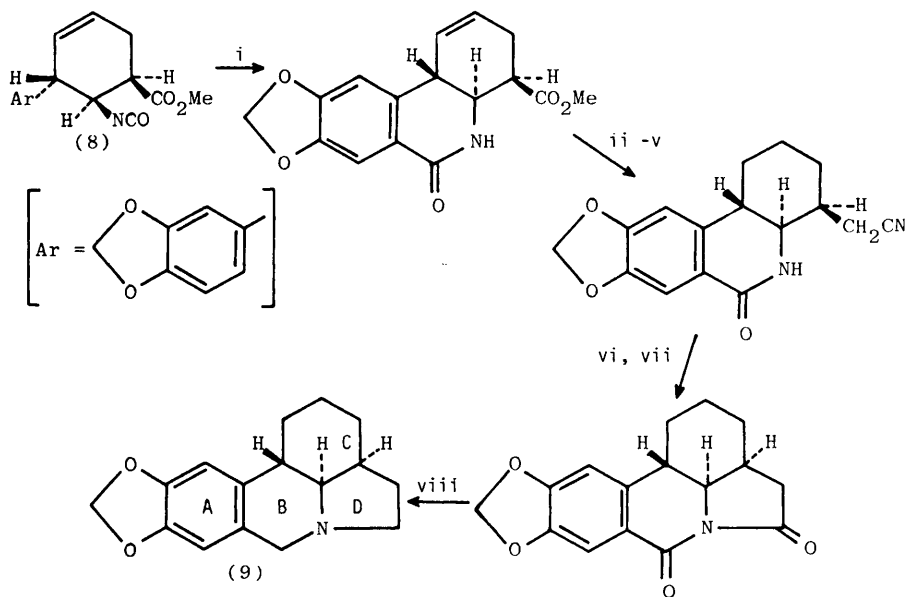
<sup>8</sup> G. M. Gorbunova, A. V. Patudin, and V. D. Gorbunov, *Khim. Pri. Soedin.*, 1978, 420 (*Chem. Abs.*, 1978, **89**, 126 172).

<sup>9</sup> L. S. Kovtun, A. V. Patudin, G. M. Gorbunova, V. D. Gorbunov, V. A. Stikhin, S. D. Gogitidze, and A. Kh. Nakaidze, *Farm. Zh. (Kiev)*, 1978, 59 (*Chem. Abs.*, 1979, **90**, 200 291).

<sup>10</sup> H. Tanaka, H. Irie, S. Baba, S. Uyeo, A. Kuno, and Y. Ishiguro, *J. Chem. Soc., Perkin Trans. 1*, 1979, 535.

<sup>11</sup> H. Tanaka, Y. Nagai, H. Irie, S. Uyeo, and A. Kuno, *J. Chem. Soc., Perkin Trans. 1*, 1979, 874.

<sup>12</sup> Y. Tsuda, T. Sano, J. Taga, K. Isobe, J. Toda, S. Takagi, M. Yamaki, M. Murata, H. Irie, and H. Tanaka, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1358.



Reagents: i, SnCl<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>; ii, Pt, H<sub>2</sub>, AcOH; iii, LiAlH<sub>4</sub>, THF, at -78 °C, then NaBH<sub>4</sub>; iv, TsCl, pyridine; v, KCN, DMSO; vi, conc. HCl, AcOH, 100 °C; vii, Ac<sub>2</sub>O, 100 °C; viii, LiAlH<sub>4</sub>, THF, reflux

**Scheme 1**

A modification of the enaminone synthesis of  $\gamma$ -lycorane (*cf.* Vol. 7, p. 173) gives compound (16), which is readily oxidized to the lycorane intermediate (17) or is reduced to a mixture of  $\alpha$ -dihydrocaranone (18) and 1-*epi*- $\gamma$ -dihydrocaranine (19) (Scheme 3).<sup>13a</sup> Irradiation of the bromo-derivative (15) or the corresponding iodo-compound gives the dicarbonyl compound (17) directly.<sup>13b</sup>

An interesting new approach to the synthesis of the galanthamine system involving intramolecular Diels–Alder reaction of a  $\Delta^2$ -pyrroline dienophile has been reported by Stork<sup>14</sup> (Scheme 4). Cyclization of (20) gave a mixture of amides (21) and (22) in the ratio of 0.84 : 1 (n.m.r.), from which the diacetate (23) related to diacetyldihydrolycorine lactam was prepared; it is disappointing that the ‘natural’ stereoisomer (21) is formed in lesser amount in the ring-closure reaction.

The conversion of acetyl-lycorine (13) into the alkaloid ungminorine (25) (Scheme 5) has been reported, although in an inaccessible journal.<sup>15</sup>

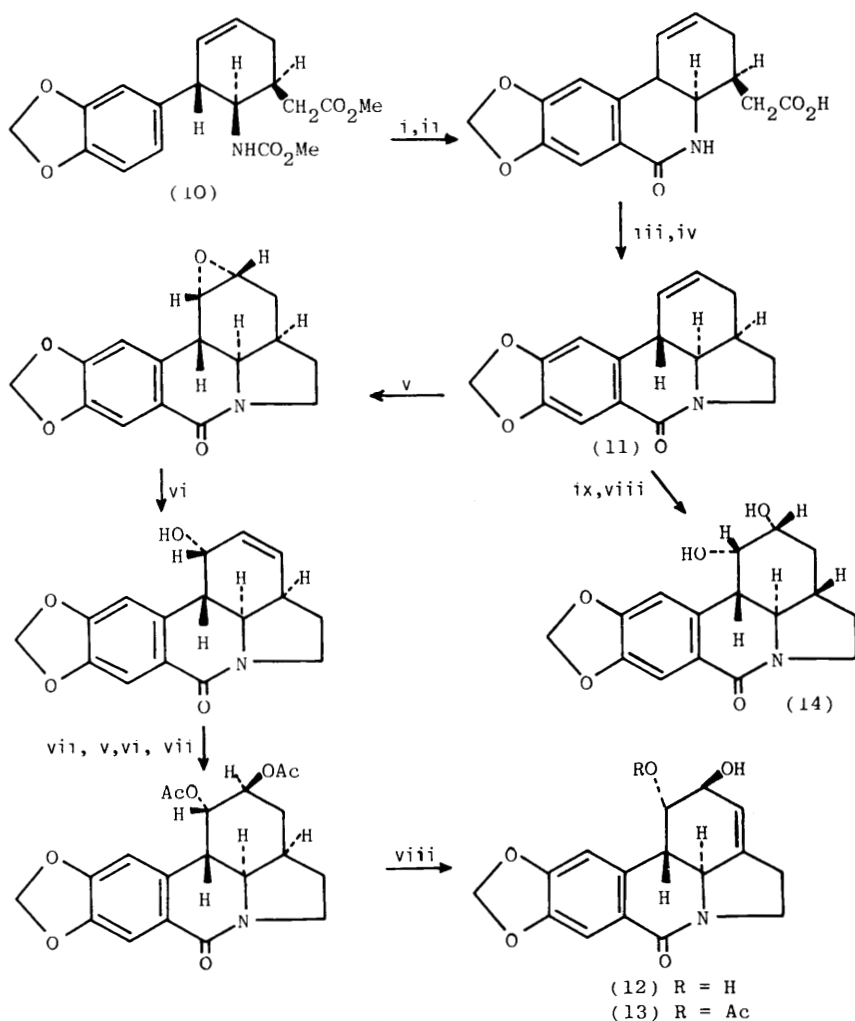
The key intermediate (26) in the synthesis of crinine alkaloids (*cf.* Vol. 8, p. 138) has now been applied by Tsuda and co-workers to the synthesis of ( $\pm$ )-dihydrolycoricidines (Scheme 6).<sup>16</sup> The reaction of the urethane acid (27) with *N*-bromosuccinimide gave the bromo-lactone (28), which was converted into the

<sup>13</sup> H. Iida, Y. Yuasa, and C. Kibayashi, (a) *J. Org. Chem.*, 1979, **44**, 1074; (b) *ibid.*, p. 1236.

<sup>14</sup> D. J. Morgans and G. Stork, *Tetrahedron Lett.*, 1979, 1959.

<sup>15</sup> J. Toda, T. Sano, Y. Tsuda, and Y. Itatani, *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu*, 21st., 1978, 58 (*Chem. Abs.*, 1979, **90**, 187 190).

<sup>16</sup> K. Isobe, J. Taga, and Y. Tsuda, *Heterocycles*, 1978, **9**, 625.



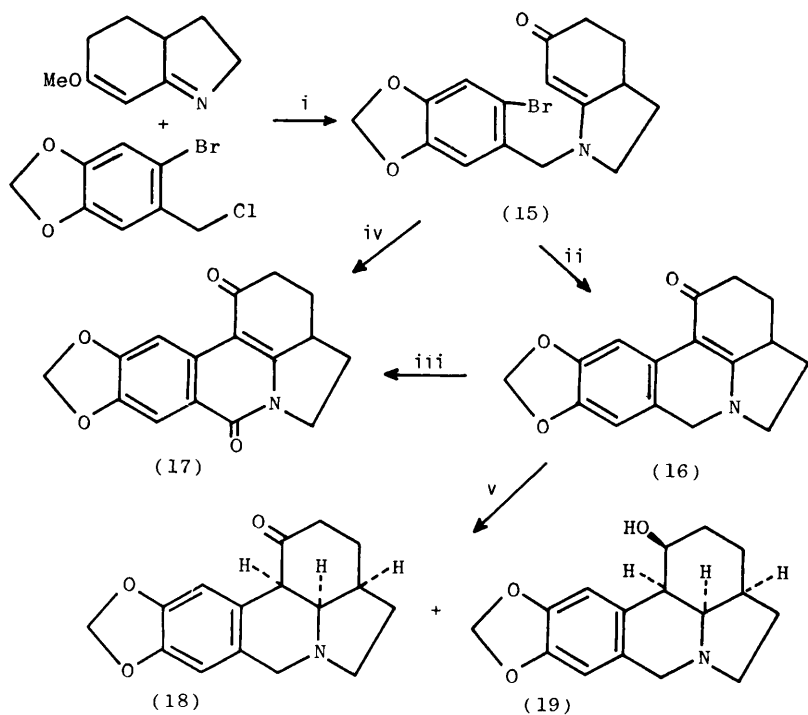
Reagents: i,  $\text{POCl}_3$ , reflux, then  $\text{SnCl}_4$ ; ii,  $\text{HCl}$ ,  $\text{AcOH}$ ; iii,  $\text{Ac}_2\text{O}$ ; iv,  $\text{LiAlH}_4$ , ether; v,  $m\text{-ClC}_6\text{H}_4\text{CO}_2\text{H}$ ; vi,  $\text{Ph}_2\text{Se}_2$ ,  $\text{NaBH}_4$ , then  $\text{NaIO}_4$ ; vii,  $\text{Ac}_2\text{O}$ , pyridine; viii,  $\text{LiAlH}_4$ , THF, reflux; ix,  $\text{OsO}_4$ , pyridine, then  $\text{Ac}_2\text{O}$ , pyridine

**Scheme 2**

diacetoxy-derivative (29). Hydrolysis of the lactone function and photolytic decarboxylation followed by acetylation gave a 1:1 mixture of *cis*- and *trans*-dihydrolycoricidine triacetates (30), which were separated and then hydrolysed with ammonia in methanol to *cis*- and *trans*-(±)-dihydrolycoricidines (31).

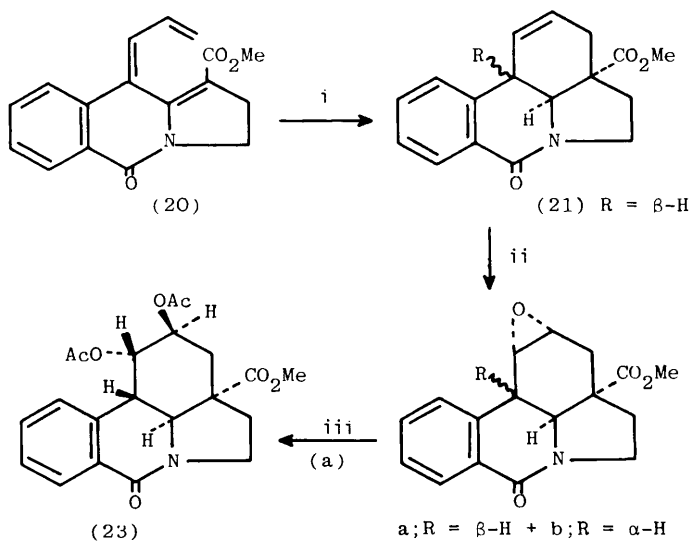
A full account of the asymmetric synthesis of galanthamine from L-tyrosine (*cf.* Vol. 9, p. 140) is now available.<sup>17</sup>

<sup>17</sup> K. Shimizu, K. Tomioka, S. Yamada, and K. Koga, *Chem. Pharm. Bull.*, 1978, **26**, 3765.



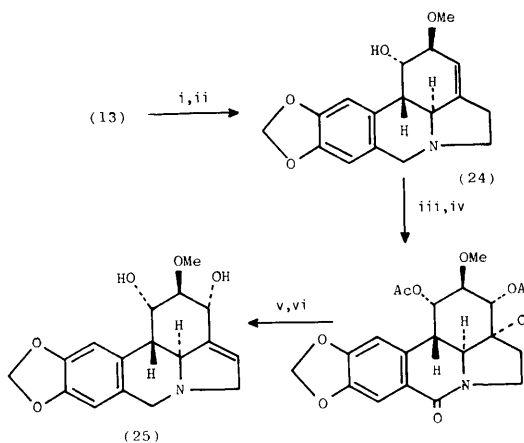
Reagents: i, PhMe, reflux; ii, lithium diethylamide; iii, O<sub>2</sub>, KOH, aq. EtOH; iv, *hν*; v, LiAlH<sub>4</sub>, THF

**Scheme 3**



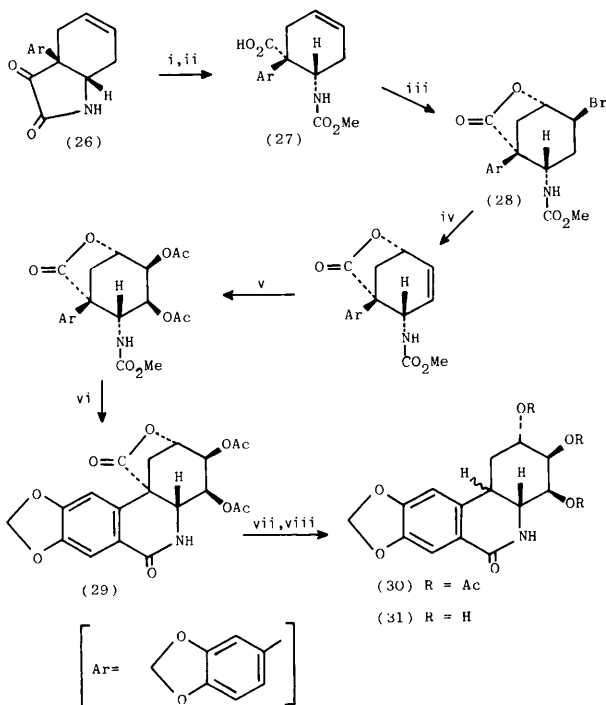
Reagents: i, C<sub>6</sub>H<sub>4</sub>-o-Cl<sub>2</sub>, reflux; ii, *m*-ClC<sub>6</sub>H<sub>4</sub>CO<sub>3</sub>H, CH<sub>2</sub>Cl<sub>2</sub>; iii, THF, H<sub>2</sub>O, catalytic HClO<sub>4</sub>, 60 °C, then Ac<sub>2</sub>O, pyridine

**Scheme 4**



Reagents: i,  $\text{POCl}_3$ ,  $\text{HCl}$ ; ii,  $\text{K}_2\text{CO}_3$ ,  $\text{MeOH}$ , then epoxide  $\rightarrow$  (24); iii,  $\text{KMnO}_4$ ; iv, acetylation; v, dehydration; vi, reduction

**Scheme 5**



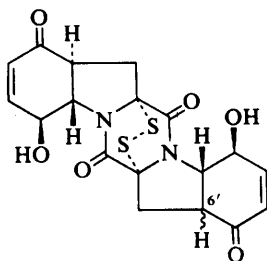
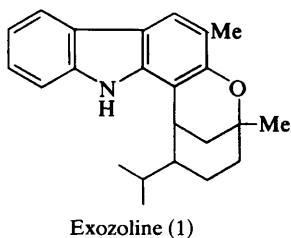
Reagents: i,  $\text{ClCO}_2\text{Me}$ ,  $\text{KOH}$ ,  $\text{MeCN}$ , then 10%  $\text{KOH}$  in  $\text{MeOH}$ ; ii,  $\text{H}_2\text{O}_2$ ,  $\text{NaOH}$ ; iii,  $\text{NBS}$ ,  $\text{CH}_2\text{Cl}_2$ ; iv, 1,5-diazabicyclo[5.4.0]undec-5-ene,  $\text{PhMe}$ ,  $100^\circ\text{C}$ ; v,  $\text{OsO}_4$ , then acetylation; vi, modified Bischler-Napieralski reaction; vii, 0.1M- $\text{NaOH}$ , then  $h\nu$ ; viii,  $\text{Ac}_2\text{O}$ , pyridine

**Scheme 6**

## 1 Simple Alkaloids

**Non-tryptamines.**—The stem bark of *Murraya exotica* L. [*M. paniculata* (L.) Jack.] contains mahanimbine and murrayazoline,<sup>1</sup> and the leaves contain a new carbazole alkaloid, exozoline (1), which proves to be dihydrocyclo-mahanimbine;<sup>2</sup> it is of some interest that this plant has been examined on several previous occasions, but this is the first report of the presence of alkaloids in any of the tissues.

The overall structure (2a) deduced<sup>3a</sup> for epicorazine A has been confirmed,<sup>4</sup> and stereochemical detail has been added, by X-ray diffraction measurements. Its isomer, epicorazine B, which also occurs<sup>5a</sup> in *Epicoccum nigrum*, is simply<sup>5b</sup> the C-6' epimer (2b). The absolute configuration of epicorazine A follows from the



close similarity of its c.d. spectrum with those of gliotoxin and acetylaranotin;<sup>4a</sup> the absolute configuration of epicorazine B is similarly based on a comparison of its c.d. spectrum with that of epicorazine A.<sup>5b</sup>

<sup>1</sup> P. Bhattacharyya, S. Roy, A. Biswas, L. Bhattacharyya, and D. P. Chakraborty, *J. Indian Chem. Soc.*, 1978, **55**, 308.

<sup>2</sup> N. Ganguly and A. Sarkar, *Phytochemistry*, 1978, **17**, 1816.

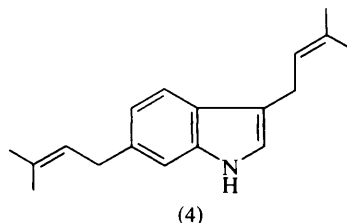
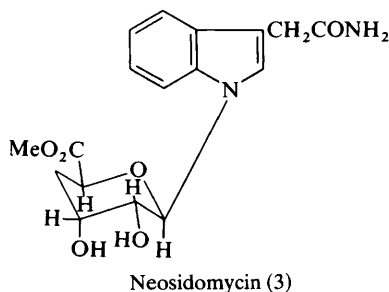
<sup>3</sup> J. E. Saxton, in 'The Alkaloids', ed. M. F. Grondon (Specialist Periodical Reports), The Chemical Society, London, 1978, Vol. 8; (a) p. 152; (b) p. 155; (c) p. 177; (d) p. 178; (e) p. 184; (f) p. 188; (g) p. 189; (h) p. 191; (i) p. 203; (j) p. 204.

<sup>4</sup> (a) G. Deffieux, M. A. Baute, R. Baute, and M. J. Filleau, *J. Antibiot.*, 1978, **31**, 1102; (b) G. Deffieux, M. Gadret, and J. M. Leger, *Acta Crystallogr., Sect. B*, 1977, **33**, 1474.

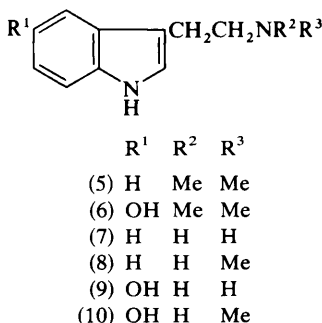
<sup>5</sup> (a) M. A. Baute, G. Deffieux, R. Baute, and A. Neveu, *J. Antibiot.*, 1978, **31**, 1099; (b) G. Deffieux, M. J. Filleau, and R. Baute, *ibid.* p. 1106.

The first naturally occurring indole *N*-glycoside has been encountered in neosidomycin, an antibiotic constituent of *Streptomyces hygroscopicus*;<sup>6a</sup> its structure (3) is also unique in that it is the only natural product known so far to contain methyl 4-deoxy-*ribo*-hexopyranuronate as the sugar component. However, the configuration (D or L) of this sugar unit is at present unknown.

3,6-Bis( $\gamma,\gamma$ -dimethylallyl)indole (4), a new indole derivative from natural sources, occurs in the stem bark of *Uvaria elliptica* Engl. et Diels (family Annonaceae).<sup>6b</sup>



**Non-isoprenoid Tryptamines.**—*NN*-Dimethyltryptamine (5), bufotenine (6), and bufotenine *N*-oxide have been found in the roots and stems of *Desmodium caudatum* DC.<sup>7</sup> *NN*-Dimethyltryptamine and bufotenine have also been isolated, together with four other simple tryptamine derivatives (7)–(10), from a red-violet octocoral, *Paramuricea chamaeleon*, collected in the Bay of Naples.<sup>8</sup>



The pod walls of *Erythrina arborescens* Roxb. contain a number of alkaloids of the *Erythrina* group, together with hypaphorine and a new base, erysodino-phorine, which has the structure (11), since it can be hydrolysed to hypaphorine and erysodine.<sup>9</sup>

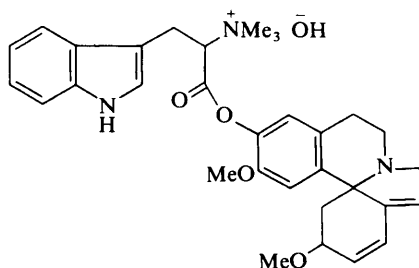
<sup>6</sup> (a) R. Furuta, S. Naruto, A. Tamura, and K. Yokogawa, *Tetrahedron Lett.*, 1979, 1701; (b) H. Achenbach and B. Raffelsberger, *ibid.*, p. 2571.

<sup>7</sup> A. Ueno, Y. Ikeya, S. Fukushima, T. Noro, K. Morinaga, and H. Kuwano, *Chem. Pharm. Bull.*, 1978, **26**, 2411.

<sup>8</sup> G. Cimino and S. De Stefano, *Comp. Biochem. Physiol., Sect. C*, 1978, **61**, 361.

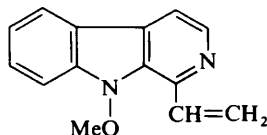
<sup>9</sup> K. P. Tiwari and M. Masood, *Phytochemistry*, 1979, **18**, 704.





Erysodinophorine (11)

Three alkaloids occur in *Picrasma excelsa* (Swartz) Planchon, in association with bitter principles of the quassin group.<sup>10</sup> Two of these were identified as canthin-6-one and 5-hydroxy-6-methoxycanthin-6-one; the third is new, and was shown to be *N*-methoxy-1-vinyl- $\beta$ -carboline (12). The presence of an *N*-methoxy-group in indole alkaloids is rare, the only other examples known at present being gelsedine and 1,5-dimethoxygramine.



(12)

Details of Speckamp's synthesis<sup>11a</sup> of deoxyeseroline (13) have now been published,<sup>12</sup> and its extension to the preparation of ( $\pm$ )-eserethole (14) has also been reported. This latter synthesis, which also constitutes a new formal route to physostigmine (15), involved a modification to the original approach, in which the nitro-group was introduced at a much later stage (Scheme 1).

Physostigmine (15) reacts reversibly with sodium bisulphite to give a product which probably has the constitution (16), according to the <sup>13</sup>C n.m.r. and optical rotation evidence.<sup>13</sup> This result is of some interest, since bisulphite is often added as an antioxidant to ophthalmic preparations containing physostigmine.

Two new sporidesmins have been isolated from the biologically active polar constituents of *Pithomyces chartarum*.<sup>14</sup> Of these, sporidesmin J is des-*N*<sup>6</sup>-methylsporidesmin (17), since acetylation followed by methylation gives diacetylsporidesmin. The second metabolite, sporidesmin H, was not obtained pure but appears, from its mass spectrum, to have the molecular formula C<sub>18</sub>H<sub>20</sub>ClN<sub>3</sub>O<sub>4</sub>S<sub>2</sub>. The presence of two *ortho*-coupled aromatic protons (n.m.r. spectrum) is unique in the sporidesmin series, as is the loss of HCl, in addition to the customary loss of H<sub>2</sub>S<sub>2</sub>, in the mass spectrometer. These data, together with

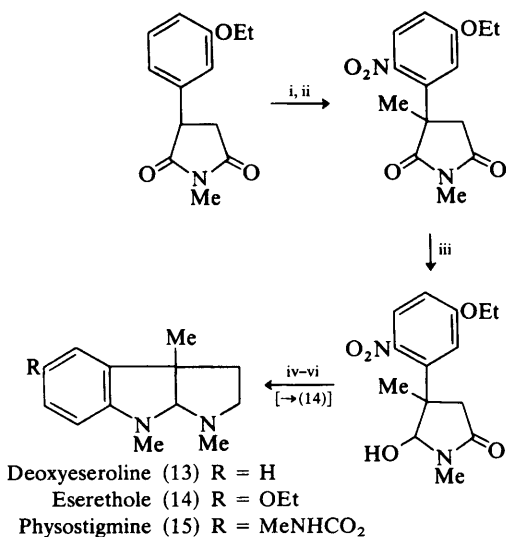
<sup>10</sup> H. Wagner and T. Nestler, *Tetrahedron Lett.*, 1978, 2777.

<sup>11</sup> J. E. Saxton, in 'The Alkaloids', ed. M. F. Grondon (Specialist Periodical Reports), The Chemical Society, London, 1977, Vol. 7; (a) pp. 186-7; (b) p. 184; (c) p. 188; (d) p. 220.

<sup>12</sup> J. B. P. A. Wijnberg and W. N. Speckamp, *Tetrahedron*, 1978, **34**, 2399.

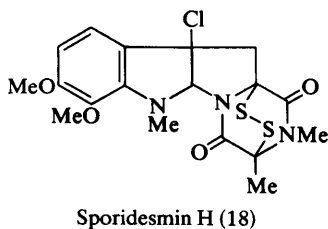
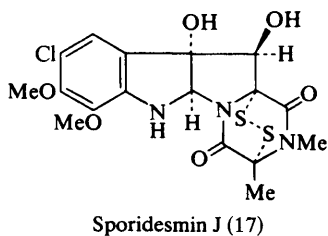
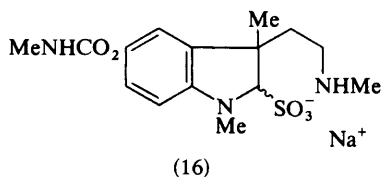
<sup>13</sup> A. Hussain, H. Wahnner, and J. Triplett, *J. Pharm. Sci.*, 1978, **67**, 742.

<sup>14</sup> R. Rahman, S. Safe, and A. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1476.



Reagents: i, AcOH, Fuming HNO<sub>3</sub>; ii, K<sub>2</sub>CO<sub>3</sub>, MeI, DMF; iii, NaBH<sub>4</sub>, HCl, EtOH, THF, at 0 °C, for 4 h; iv, H<sub>2</sub>, Pd/C; v, AcOCHO, CHCl<sub>3</sub>, at 0 °C, for 3 h; vi, LiAlH<sub>4</sub>, Et<sub>2</sub>O

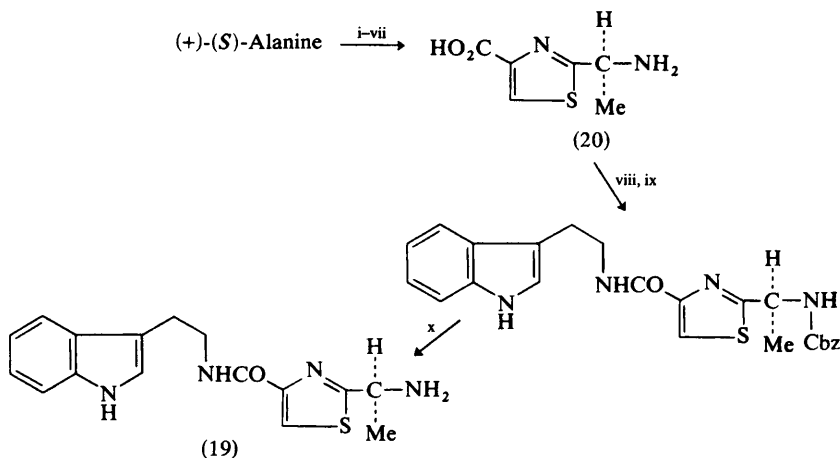
**Scheme 1**



comparison of the n.m.r. spectra of sporidesmin H and appropriate model compounds, lead to the proposal that sporidesmin H has the structure (18).

The structure of the un-named alkaloid (19) obtained<sup>15</sup> from a *Thermoactinomyces* strain has been confirmed by a simple synthesis from tryptamine and the thiazole amino-acid (20), prepared from (+)-(*S*)-alanine (Scheme 2).<sup>15</sup>

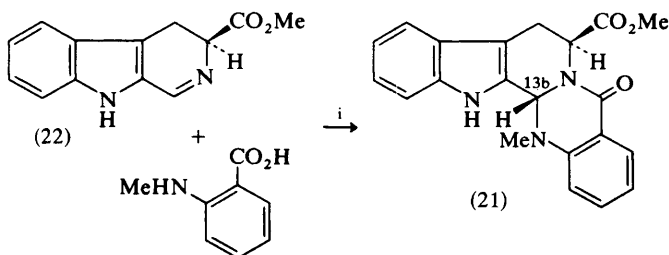
<sup>15</sup> M. Onda and Y. Konda, *Chem. Pharm. Bull.*, 1978, **26**, 2167.



Reagents: i,  $\text{PhCOCl}$ ; ii,  $\text{CH}_2\text{N}_2$ ; iii,  $\text{MeOH}$ ,  $\text{NH}_3$ , at  $100\text{--}110^\circ\text{C}$  for 7 h; iv,  $\text{POCl}_3$ ,  $\text{py}$ ; v,  $\text{H}_2\text{S}$ ,  $\text{MeOH}$ , triethanolamine; vi,  $\text{BrCH}_2\text{COCO}_2\text{Et}$ ,  $\text{EtOH}$ , boil for 2 h; vii,  $\text{HCl}$ ,  $\text{H}_2\text{O}$ , heat for 4 h; viii,  $\text{ClCO}_2\text{CH}_2\text{Ph}$ ,  $\text{C}_6\text{H}_5\text{Me}$ ,  $2\text{M-NaOH}$ , at  $5^\circ\text{C}$  for 30 min; ix, tryptamine,  $\text{MeCN}$ ,  $\text{DCC}$ ,  $\text{CH}_2\text{Cl}_2$ , at  $0\text{--}5^\circ\text{C}$ ; x, 10%  $\text{Pd/C}$ ,  $\text{H}_2$ ,  $\text{MeOH}$ ,  $\text{BF}_3\cdot\text{Et}_2\text{O}$ , at  $40^\circ\text{C}$  for 4 h.

Scheme 2

The tryptophan-derived alkaloid (21) has been isolated from *Evodia rutaecarpa* (Juss.) Benth. et Hook.;<sup>16</sup> this is the first alkaloid containing the tryptophan carboxy-group to be found in this genus. The structure of (21) was confirmed by synthesis from the optically active dihydro- $\beta$ -carboline derivative (22) and *N*-methylantranilic acid (Scheme 3); apparently none of the 13b-epimer of (21) was obtained. The alkaloid (21) appears to contain an axial ester group (n.m.r. spectrum), the equatorial epimer presumably being destabilized by interaction of the ester group with the ring D carbonyl group. The absolute configuration at C-13b is not known, since the o.r.d./c.d. spectra of the tetrahydro- $\beta$ -carboline system are perturbed unpredictably by the anthranilic acid chromophore.

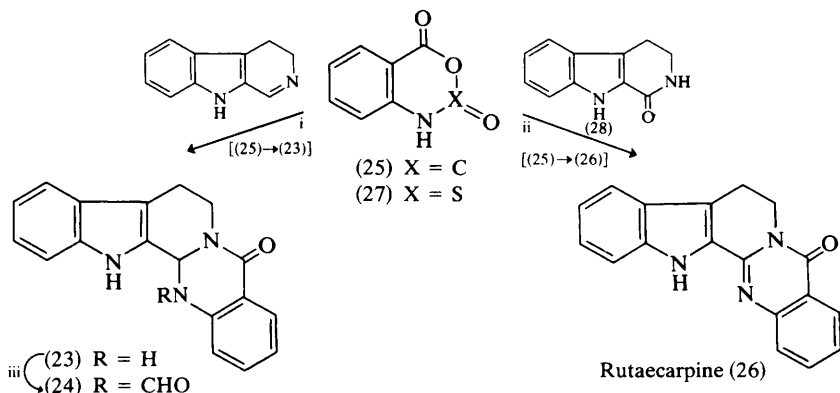


Reagents: i,  $\text{PPh}_3$ ,  $\text{CBr}_4$ ,  $\text{THF}$ ,  $\text{py}$ .

Scheme 3

<sup>16</sup> B. Danieli, G. Lesma, and G. Palmisano, *Experientia*, 1979, **35**, 156.

The ripe fruits of *E. rutaecarpa* contain<sup>17</sup> two new alkaloids, *i.e.* dihydro-rutaecarpine (23) and its 14-formyl derivative (24), in addition to evodiamine and rutaecarpine. The racemic forms of the new bases, (23) and (24), were readily synthesized by condensation of 3,4-dihydro- $\beta$ -carboline with isatoic anhydride (25)  $\rightarrow$  ( $\pm$ )-(23)], followed by formylation (Scheme 4).



Reagents: i, PhH, py, at 60 °C for 30 min; ii, 190–200 °C for 2 h; iii, HCO<sub>2</sub>Ac

**Scheme 4**

The synthesis of rutaecarpine (26) itself from the sulphur analogue (27) of isatoic anhydride and 3,4-dihydro- $\beta$ -carboline is reported to proceed in 80% yield;<sup>3b,11c</sup> however, the corresponding condensation with isatoic anhydride (25) is unsatisfactory, presumably owing to the instability of 3,4-dihydro- $\beta$ -carboline at the high temperature used. This may be circumvented by condensation of (25) with the more stable 1-oxo-1,2,3,4-tetrahydro- $\beta$ -carboline (28), which affords rutaecarpine directly, a spontaneous dehydrogenation step obviously not being required in this reaction.<sup>18</sup>

Yet another efficient synthesis of evodiamine and rutaecarpine has been reported.<sup>19</sup> This latest one involves the oxidative cyclization of the tetracyclic amide (29) by means of mercuric acetate, which gave ( $\pm$ )-evodiamine (30) in 92% yield (Scheme 5). Oxidation of evodiamine with active manganese dioxide then completed the synthesis of rutaecarpine (26).

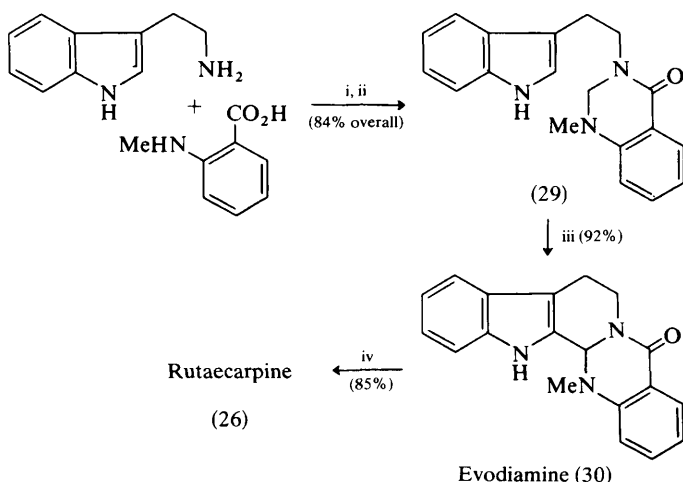
The chemical behaviour of euxylophorines A and B has been discussed.<sup>20</sup> Both show the expected regioselectivity towards nucleophilic reagents. Euxylophorine A (31) exists in aqueous solvents as an equilibrium mixture of the orange-red anhydronium base form (31) and the yellow tetracyclic form (32); this interconversion clearly involves nucleophilic attack at C-13b. The tetracyclic form (32), obtained by crystallization from wet benzene, reverts to the pentacyclic form (31) when heated, alone or in anhydrous benzene.

<sup>17</sup> T. Kamikado, S. Murakoshi, and S. Tamura, *Agric. Biol. Chem.*, 1978, **42**, 1515.

<sup>18</sup> T. Kametani, T. Ohsawa, M. Ihara, and K. Fukumoto, *Chem. Pharm. Bull.*, 1978, **26**, 1922.

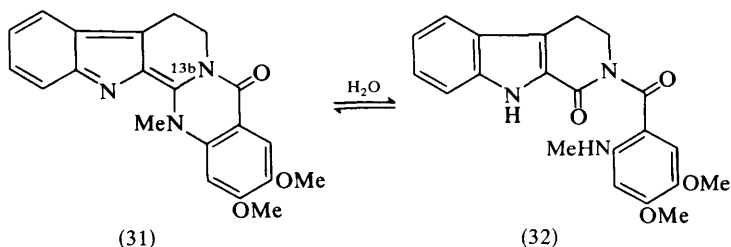
<sup>19</sup> B. Danieli and G. Palmisano, *Heterocycles*, 1978, **9**, 803.

<sup>20</sup> B. Danieli, G. Lesma, and G. Palmisano, *Heterocycles*, 1979, **12**, 353.



Reagents: i, PPh<sub>3</sub>, CBr<sub>4</sub>, PhMe, heat for 5 h; ii, CH<sub>2</sub>O, H<sub>2</sub>O, HCl, MeOH, heat for 3 h; iii, Hg(OAc)<sub>2</sub>, AcOH, H<sub>2</sub>O, at r.t. for 24 h; iv, active MnO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, at r.t. for 3 h

**Scheme 5**

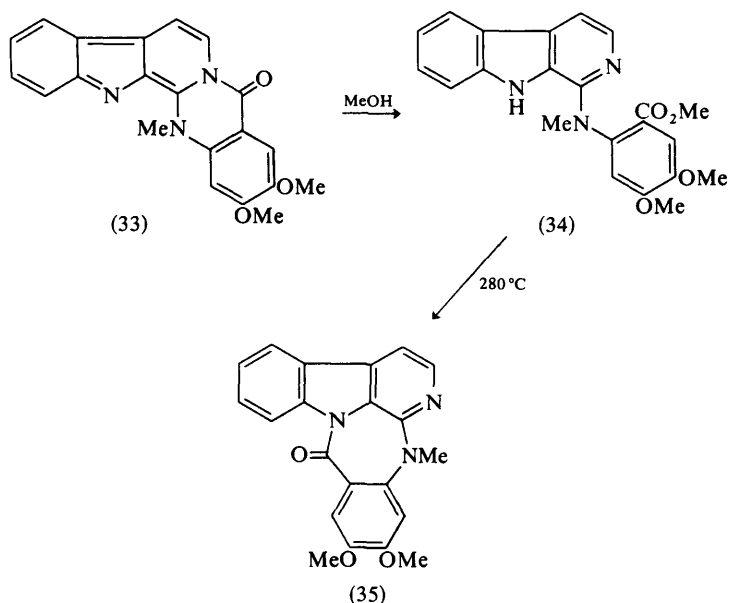


In contrast, the orange base euxylophorine B (33) is stable in acetonitrile solution, but in methanol suffers nucleophilic attack at C-5 with formation of the colourless  $\beta$ -carboline derivative (34). Treatment of (34) with trifluoroacetic acid results in slow conversion into the trifluoroacetate of euxylophorine B; on the other hand, thermolysis of (34) does not regenerate (33), but gives instead the benzodiazepine derivative (35).

## 2 Isoprenoid Tryptamine and Tryptophan Alkaloids

**Mould Metabolites.**—Alkaloid Z (now renamed roquefortine D), a minor metabolite of *Penicillium roqueforti*,<sup>21a</sup> proves to be simply dihydroroquefortine C (36), and may be prepared, together with a diastereoisomer, by the reduction of roquefortine C ( $\equiv$  roquefortine) by means of zinc and acetic acid.<sup>21b</sup>

<sup>21</sup> (a) S. Ohmomo, T. Utagawa, and M. Abe, *Agric. Biol. Chem.*, 1977, **41**, 2097; (b) S. Ohmomo, K. Oguma, T. Ohashi, and M. Abe, *ibid.*, 1979, **42**, 2387.



Roquefortine itself (37) has the (*E*) configuration about the 3,12 double-bond,<sup>22</sup> since in its geometrical isomer, obtained by photoisomerization of roquefortine, the hydrogen attached to C-12 gives a signal at lower field in the n.m.r. spectrum than the corresponding proton in roquefortine, as a result of deshielding by the oxo-group at C-4. When heated in dilute methanolic hydrochloric acid, roquefortine loses the angular isopentenyl group, with production of the indole derivative (38).<sup>22</sup>

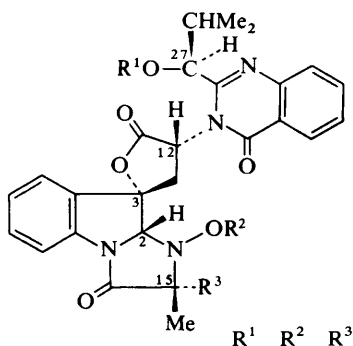
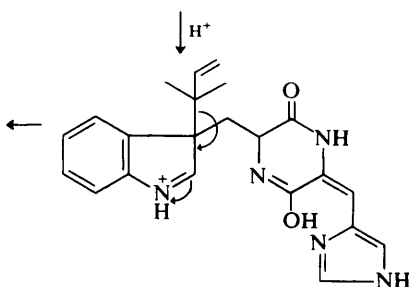
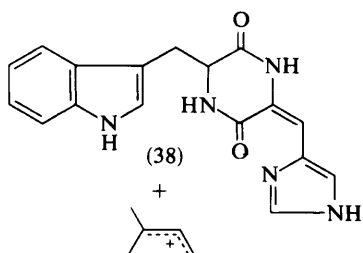
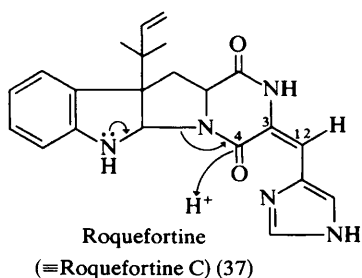
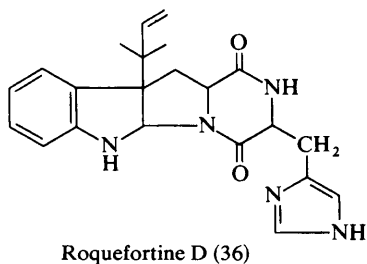
The structure and relative stereochemistry of tryptoquivaline (39) were established earlier by the X-ray method,<sup>23a</sup> and the absolute configuration at C-15 in tryptoquivaline D (40) was determined by degradation to L-(+)-alanine.<sup>23b</sup> However, this latter result gave no information concerning the absolute configuration of tryptoquivaline, in which C-15 is achiral, or of the other asymmetric centres in tryptoquivaline D. The issue has recently been resolved by determination of the relative configuration of nortryptoquivaline (41) by a single-crystal X-ray diffraction determination. Since C-15 is derived from L-(+)-alanine, by reason of previous correlation with tryptoquivaline D, the complete absolute stereochemistry of nortryptoquivaline is as shown in (41). It should be noted that the correct absolute configuration at positions 2, 3, 12, and 27 is opposite to that depicted in the earlier literature.<sup>24</sup>

Neoechinulin A (42) can be prepared by dehydrogenation of the diastereoisomeric 8,9-dihydro-derivatives by means of DDQ in trichloroethanol or

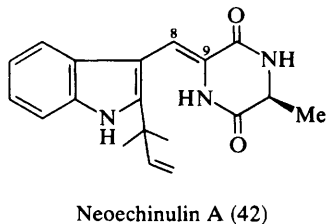
<sup>22</sup> P. M. Scott, J. Polonsky, and M. A. Merrien, *J. Agric. Food Chem.*, 1979, **27**, 201.

<sup>23</sup> (a) J. Clardy, J. P. Springer, G. Büchi, K. Matsuo, and R. Wightman, *J. Am. Chem. Soc.*, 1975, **97**, 663; (b) M. Yamazaki, H. Fujimoto, and E. Okuyama, *Chem. Pharm. Bull.*, 1977, **25**, 2554.

<sup>24</sup> J. P. Springer, *Tetrahedron Lett.*, 1979, 339.



Tryptoquvaline (39)	Ac	H	Me
Tryptoquvaline D (40)	H	Ac	H
Nortryptoquvaline (41)	Ac	H	H

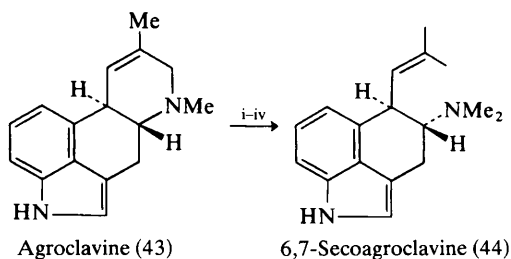


dioxan.<sup>25</sup> This reaction, followed by hydroxylation of the double bond so formed, has been utilized in the synthesis of a model diol related to fumitremorgin B.<sup>25</sup>

**Ergot Alkaloids.**—Agroclavine (43) and elymoclavine are the two principal alkaloids of *Claviceps purpurea* strain AA-218. Of the five minor constituents recently isolated, two were further investigated, and were shown to be setoclavine and a new alkaloid, 6,7-seco-agroclavine (44), whose structure was confirmed by partial synthesis from agroclavine (Scheme 6).<sup>26a</sup>

<sup>25</sup> Y. Oikawa, T. Yoshioka, and O. Yonemitsu, *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* 21st, 1978, 22 (*Chem. Abs.*, 1979, **90**, 152 436).

<sup>26</sup> (a) D. C. Horwell and J. P. Verge, *Phytochemistry*, 1979, **18**, 519; (b) J. K. Porter, C. W. Bacon, and J. D. Robbins, *J. Agric. Food Chem.*, 1979, **27**, 595.



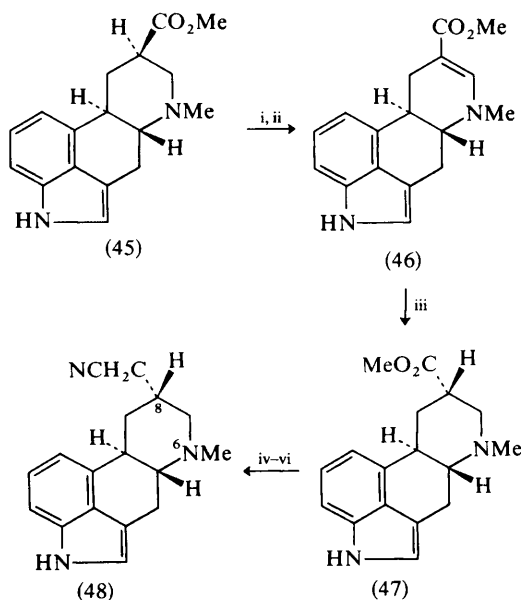
Reagents: i, MeI; ii, Na, NH<sub>3</sub>; iii (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>; iv, EtO<sub>2</sub>CN=NCO<sub>2</sub>Et

**Scheme 6**

Ergosine, ergosinine, and chanoclavine-I have been shown to occur in *Epichloe typhina*.<sup>26b</sup>

Further examples of the use of h.p.l.c. in the analysis of complex mixtures of ergot alkaloids have been described.<sup>27</sup>

A new two-stage epimerization of methyl dihydrolysergate (45) at position 8 has been reported<sup>28</sup> which proceeds *via* the enamine ester (46), prepared by a Polonovski reaction on the *N*-oxide of (45) (Scheme 7). The product (47) was



Reagents: i, *m*-CPBA; ii, Ac<sub>2</sub>O, TFA; iii, H<sub>2</sub>, PtO<sub>2</sub>, AcOH, DMF; iv, LiAlH<sub>4</sub>; v, MeSO<sub>2</sub>Cl; vi, KCN

**Scheme 7**

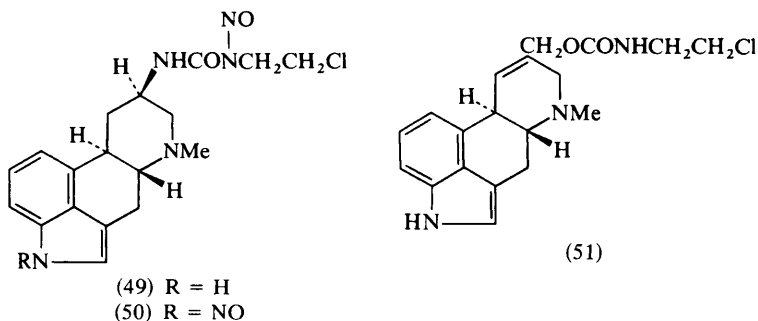
<sup>27</sup> A. Yoshida, S. Yamazaki, and T. Sakai, *J. Chromatogr.*, 1979, **170**, 399.

<sup>28</sup> P. L. Stütz, P. A. Stadler, J. M. Vigouret, and A. Jaton, *J. Med. Chem.*, 1978, **21**, 754.



used as an intermediate in the synthesis of various ergoline derivatives, including 8-cyanomethyl-6-methylergoline (48), which has potential as a central dopaminergic agent. A series of 8-cyanomethyl-ergolines, epimeric with (48) at position 8, and carrying various substituents on the basic nitrogen atom, have been prepared by a Czech group<sup>29</sup> for evaluation as prolactin inhibitors.

Other ergoline derivatives of potential pharmacological value that have been reported include the nitroso-compounds (49) and (50), which show some activity against L 1210 leukaemia in mice, and the elymoclavine-derived urethane (51),



which is an effective prolactin inhibitor.<sup>30</sup> Other workers have prepared *ind.-N*-nitroso- and/or *N*<sup>6</sup>-nitroso-derivatives of substituted ergolines, also as possible prolactin inhibitors.<sup>31</sup>

**Monoterpenoid Alkaloids.**—A review<sup>32</sup> which covers the whole area of alkaloid *N*-oxides naturally contains substantial sections devoted to the occurrence, chemical transformations, and applications in synthesis of the *N*-oxides of monoterpenoid indole alkaloids.

**Peduncularine.** Although not overtly derived from tryptamine and a monoterpenene unit, peduncularine is included here because it seems highly probable that it is so derived, by a process that at present has no parallel in the indole alkaloid area. The earlier structure for peduncularine, on which doubt has already been cast,<sup>33</sup> has now been shown<sup>34</sup> to be invalid, the correct structure being (52). In accordance with (52), the base peak in the mass spectrum (and the only fragment peak at low potential) at *m/z* 162 is due to the ion (53), which arises by fission of the doubly activated 6,10-bond. The characteristic indole fragment (54) is not accompanied by its homologue, which argues against methylene substitution at the indole  $\alpha$ -position, and against an unsubstituted ethanamine chain. The other features of the structure were deduced from analysis of the <sup>1</sup>H and <sup>13</sup>C n.m.r.

<sup>29</sup> A. Černý, J. Křepelka, and M. Semonský, *Collect. Czech. Chem. Commun.*, 1979, **44**, 946.

<sup>30</sup> A. M. Crider, C. K. L. Lu, H. G. Floss, J. M. Cassidy, and J. A. Clemens, *J. Med. Chem.*, 1979, **22**, 32.

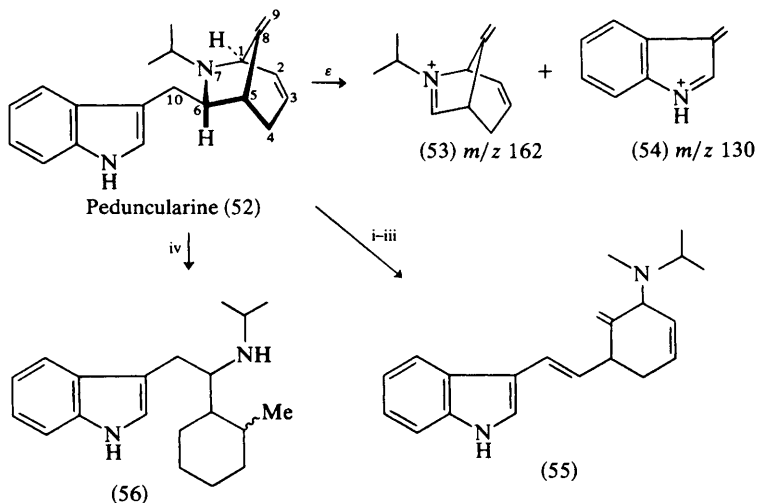
<sup>31</sup> J. Křepelka and M. Semonský, *Collect. Czech. Chem. Commun.*, 1978, **43**, 1723.

<sup>32</sup> J. D. Phillipson and S. S. Handa, *Lloydia*, 1978, **41**, 385.

<sup>33</sup> J. A. Joule, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1973, Vol. 3, p. 193.

<sup>34</sup> H. P. Ros, R. Kyburz, N. W. Preston, R. T. Gallagher, I. R. C. Bick, and M. Hesse, *Helv. Chim. Acta*, 1979, **62**, 481.

spectra, and by chemical degradation. This included the Hofmann degradation (Scheme 7a), which gave the conjugated derivative (55) of 3-vinylindole, and hydrogenation, which gave the base (56) by predictable hydrogenolysis of the doubly activated 1,7-bond, followed by hydrogenation.<sup>34</sup>



Reagents: i, MeI; ii,  $F^-$ , Amberlite IRA-400 resin; iii, pyrolysis at 175 °C; iv,  $H_2$ , Pt

**Scheme 7a**

**Corynantheine–Heteroyohimbine–Yohimbine Group, and Related Oxindoles.** A comprehensive review<sup>35a</sup> of the alkaloids of *Uncaria* species provides a valuable summary of the considerable number of investigations reported on the alkaloid content and the chemotaxonomy of *Uncaria*, and it also includes Ridsdale's revision of the genus, which has resulted in the recognition of 34 species—a considerable reduction and simplification when compared with the 120 recorded in the Kew Index.

The major alkaloids of *Alstonia venenata* R.Br. belong to the yohimbine and aspidospermine groups, and are also the subject of a comprehensive review.<sup>35b</sup>

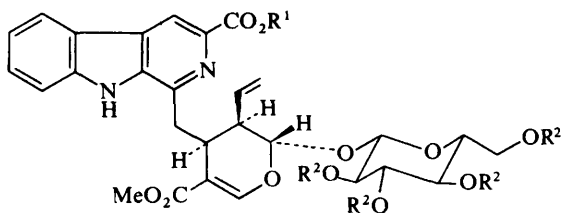
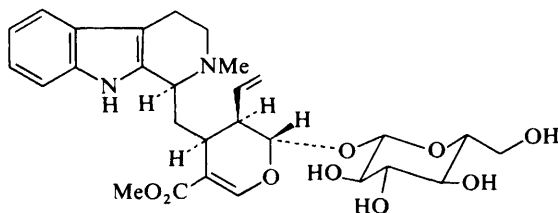
New alkaloids in this group include two  $\beta$ -glucosides. Desoxycordifoline (57) is a constituent of the heartwood of *Adina rubescens*, and was identified by conversion into the known methyl desoxycordifoline tetra-acetate (58).<sup>36</sup> The closely related tetrahydro- $\beta$ -carboline derivative dolichantoside (59), which is simply  $N_b$ -methylstrictosidine, occurs in the roots of *Strychnos gossweileri* Exell., from Zaïre.<sup>37,38a</sup> Four other alkaloids isolated<sup>38a</sup> from this source include strychnochrome and strychnoxanthine (two alkaloids of unknown structure),

<sup>35</sup> (a) J. D. Phillipson, S. R. Hemingway, and C. E. Ridsdale, *Lloydia*, 1978, **41**, 503; (b) A. Chatterjee, S. Mukhopadhyay, and A. B. Ray, *J. Sci. Ind. Res.*, 1978, **37**, 187.

<sup>36</sup> R. T. Brown and B. F. M. Warambwa, *Phytochemistry*, 1978, **17**, 1686.

<sup>37</sup> C. Coune and L. Angenot, *Planta Med.*, 1978, **34**, 53.

<sup>38</sup> (a) C. Coune, *Plant. Med. Phytother.*, 1978, **12**, 106; (b) C. A. Coune and L. J. G. Angenot, *Phytochemistry*, 1978, **17**, 1447; (c) M. Urrea, A. Ahond, H. Jacquemin, S. K. Kan, C. Poupat, P. Potier, and M. M. Janot, *C.R. Hebd. Seances Acad. Sci. Ser. C*, 1978, **287**, 63.

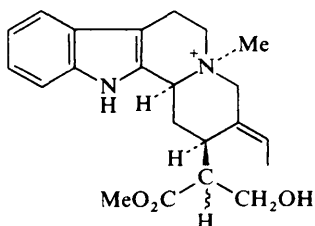
Desoxycordifoline (57)  $R^1 = R^2 = H$ Methyl desoxycordifoline tetra-acetate (58)  $R^1 = Me, R^2 = Ac$ 

Dolichantoside (59)

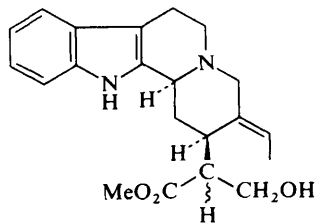
alstonine, and a new quaternary alkaloid, diploceline (60a), which is the double-bond isomer of  $N_b$ -methylsitsirikine.<sup>38b</sup> This last alkaloid exists as a pair of C-16 epimers, which are readily interconverted, even on chromatography on silica gel. The absolute configuration at C-15 was assumed, that at C-3 follows from the c.d. spectrum (positive Cotton effect), and the *cis* C/D ring junction is inferred from the absence of Bohlmann bands in the i.r. spectrum.

The tertiary base  $\Delta^{19,20}$ -(-)-isositsirikine (60b), corresponding to diploceline (60a), is one of twenty-five alkaloids isolated from the seeds of *Aspidosperma album* (Vahl) R. Ben.<sup>38c</sup> Two others are (+)-sitsirikine and 16-*epi*-sitsirikine.

The non-polar alkaloid fractions of *Strychnos dale* de Wild. and *S. elaeocarpa* Gilg. ex Leeuwenberg contain the same five, closely related, alkaloids, of which akagerine (60c) may be regarded as the parent base.<sup>39a</sup> The other four are 17-*O*-methylakagerine (60d), kribine (60e), which is the internal hemi-acetal of

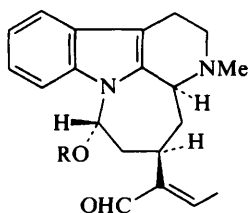


Diploceline (60a)

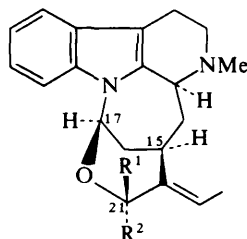


(60b)

<sup>39</sup> (a) W. Rolfsen, L. Bohlin, S. K. Yeboah, M. Geevaratne, and R. Verpoorte, *Planta Med.*, 1978, **34**, 264 (*Chem. Abs.*, 1979, **90**, 109 841); (b) L. Angenot, C. Coune, and M. Tits, *J. Pharm. Belg.*, 1978, **33**, 284.



Akagerine (60c) R = H  
 O-Methylakagerine (60d) R = Me



	R <sup>1</sup>	R <sup>2</sup>
Kribine (60e)	$\begin{cases} \text{H} \\ \text{OH} \end{cases}$	$\begin{cases} \text{OH} \\ \text{H} \end{cases}$
21-O-Methylkribine (60f)	OMe	H
epi-21-O-Methylkribine (60g)	H	OMe

17-*epi*-akagerine, and the two epimeric 21-*O*-methyl ethers [(60f) and (60g)] of kribine. As expected from these formulations, kribine, which is a mixture of two epimers, affords the ethers (60f) and (60g) on methylation (MeOH-HCl), and is transformed into akagerine (60c) by treatment with acid (acetone-HCl-H<sub>2</sub>O). In view of the ease of these interconversions, and the fact that methanol and acid were used in the extraction procedure, it may well be that the methyl ethers (60d), (60f), and (60g) are artefacts.

The major alkaloid of the allegedly toxic fruits of *S. usambarensis* has been identified as desmethoxycarbonyl-dihydrogambirtannine.<sup>39b</sup>

Yet another labile intermediate in the biosynthesis of the heteroyohimbine alkaloids has been isolated<sup>40</sup> in 20,21-didehydroheteroyohimbine (61); this was obtained from *Guettarda eximia* as an inseparable mixture of epimers at C-16 and/or C-17, together with cathenamine (62). The configurations at positions 3, 15, and 19 follow from the conversion of (61) into 19-*epi*-ajmalicine (63) by reduction (NaBH<sub>4</sub>) and dehydration (TsOH). However, treatment of (61) with chloroform and silica gel (as used in preparative t.l.c.) gave cathenamine (62) almost quantitatively, presumably *via* the ring-E-*seco*-derivative (64), which can be equilibrated at C-19 by reversible proton loss from C-18 to give the corresponding dienamine. A mechanism is thus available for the preferential formation of the (19*S*) configuration, as observed in cathenamine (62).<sup>40</sup>

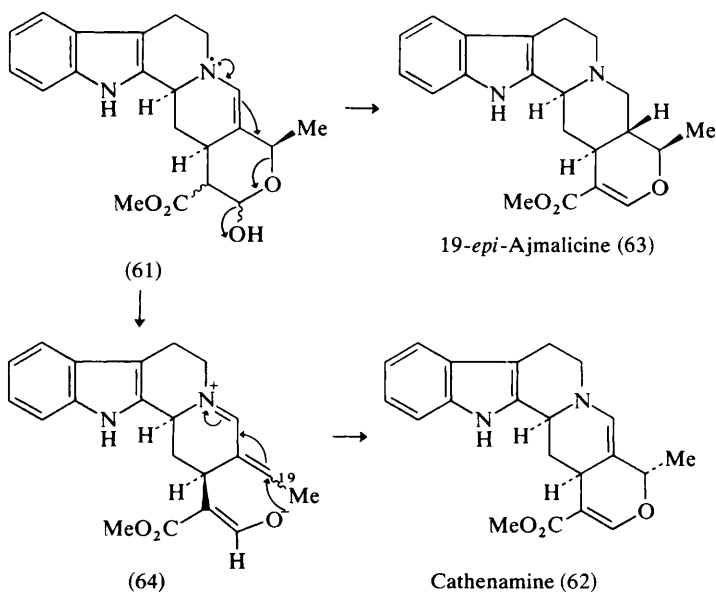
*Catharanthus ovalis* Mgf. contains a wide variety of indole alkaloids, of which 24 have recently been isolated from the aerial parts.<sup>41a</sup> These include serpentine, alstonine, and 16-*epi*-pleiocarpamine; this last base had not been encountered previously in the genus *Catharanthus*. Pleiocarpamine has been found in the trunk and root bark of *Hunteria congolana* Pichon, and 2,7-dihydropleiocarpamine in the root bark.<sup>41b</sup> The N<sub>b</sub>-oxide of 16-*epi*-pleiocarpamine occurs in the leaves of *Vinca minor*,<sup>42</sup> and isoreserpine in *Vinca herbacea*.<sup>43</sup>

<sup>40</sup> C. Kan-Fan and H. P. Husson, *J. Chem. Soc., Chem. Commun.*, 1978, 618.

<sup>41</sup> (a) N. Langlois, L. Diatta, and R. Z. Andriamialisoa, *Phytochemistry*, 1979, **18**, 467; (b) L. Le Men-Olivier, *Plant. Med. Phytother.*, 1978, **12**, 173.

<sup>42</sup> Z. Votický, L. Dolejš, and E. Grossmann, *Collect. Czech. Chem. Commun.*, 1979, **44**, 123.

<sup>43</sup> E. Z. Dzshakely, *Khim. Pri. Soedin.*, 1978, 420.



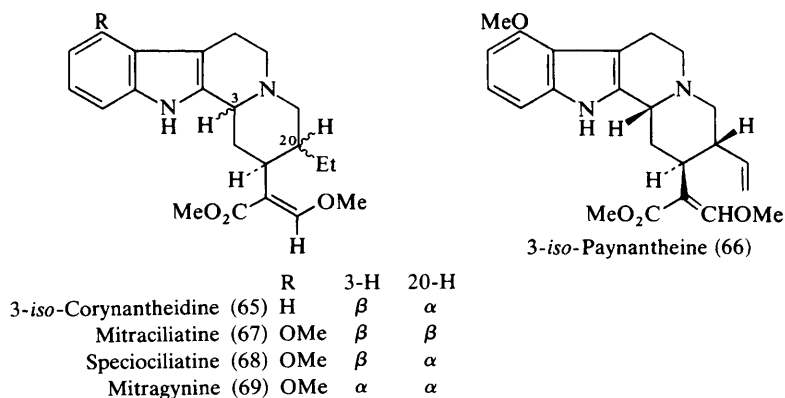
The constituents of the roots and leaves of *Rauwolfia cumminsii* having been studied, Court and his collaborators have now examined the stem bark, from which 24 alkaloids were isolated.<sup>44</sup> The alkaloids belonging to this group were corynantheol, ajmalicine, aricine, 10,11-dimethoxyajmalicine, serpentine, 19-*epi*-serpentine, ajmalicinine, and an incompletely identified base (CMS 11), which is tentatively regarded as the tertiary base (60b?) related to (60a), although no proposals could be made regarding the stereochemistry. A similar study<sup>45</sup> of the stem bark of *R. vomitoria* yielded 22 alkaloids, which included from this group 10-methoxygeissoschizol, 10-hydroxygeissoschizol, reserpiline, isoreserpiline, 19,20-didehydroreserpiline, isoreserpiline pseudoindoxyl, carapanaubine, isocarapanaubine, and rauvoxine.

The alkaloid content of immature plants of *Mitragyna speciosa* Korth., grown from seeds derived from a single mature specimen, has been carefully investigated.<sup>46</sup> A total of 23 alkaloids was isolated from one or more of the tissues: leaves, stem bark, and root bark. Some variation in exact alkaloid content was observed among the plants, in spite of the fact that the seeds germinated and the plants were harvested and extracted at the same time. Aside from the alkaloids known to occur in older plants, several additional ones were detected, a point of interest being that there seemed to be a distinct preference for alkaloids of the 3 $\beta$ -H series. Thus, 3-*iso*-corynantheidine (65), 3-*iso*-paynantheine (66), and mitraciliatine (67), none of which had previously been observed to occur in *M. speciosa*, were shown to be present, and speciociliatine (68) was more abundant than in older plants. In contrast, mitragynine (69), the major alkaloid of the leaves

<sup>44</sup> M. M. Iwu and W. E. Court, *Phytochemistry*, 1978, **17**, 1651.

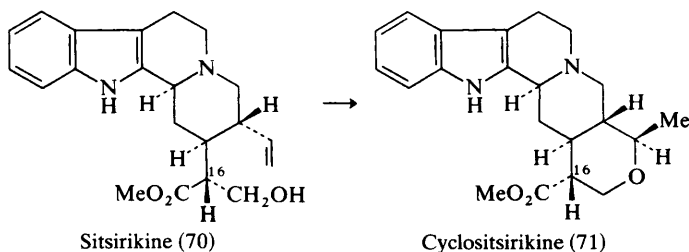
<sup>45</sup> N. N. Sabri and W. E. Court, *Phytochemistry*, 1978, **17**, 2023.

<sup>46</sup> E. J. Shellard, P. J. Houghton, and M. Resha, *Planta Med.*, 1978, **34**, 253.



of mature plants, was present in trace amounts only. 3-iso-Ajmalicine and akuammigine were also detected, but each one was observed in only one of the three groups of plants examined. The oxindole alkaloids rhynchociline, ciliaphylline, and mitragynine oxindoles A and B<sup>47</sup> were also found for the first time in *M. speciosa*. An unexpected observation was the occurrence of mitrajavine and javaphylline in some of the plants; this may have been due to cross-pollination with a specimen of *Mitragyna javanica* that was apparently growing close to the specimen from which the *M. speciosa* seeds were obtained. On the basis of these results and the pattern of alkaloid distribution in older plants, a possible sequence of biosynthesis of the alkaloids was discussed.<sup>46</sup>

The absolute configuration at positions 3, 15, and 20 in sitsirikine (70) was earlier established by correlation with corynantheine, and only the configuration at C-16 remained uncertain. This has now been elucidated<sup>48</sup> by hydration of the 18,19 double-bond by means of mercuric acetate and sodium borohydride, followed by formation of a cyclic ether. The product, cyclositsirikine, in which the configuration at C-3 has remained unchanged (c.d. spectrum), has the stereochemistry shown in (71), since the proton at C-16 appears in the 300 MHz n.m.r. spectrum as a triplet of doublets which shows two large, diaxial couplings and one small, axial-equatorial, coupling. In contrast, the 16-epimer, prepared from 16-iso-sitsirikine, exhibits in its n.m.r. spectrum a complex signal owing to H-16

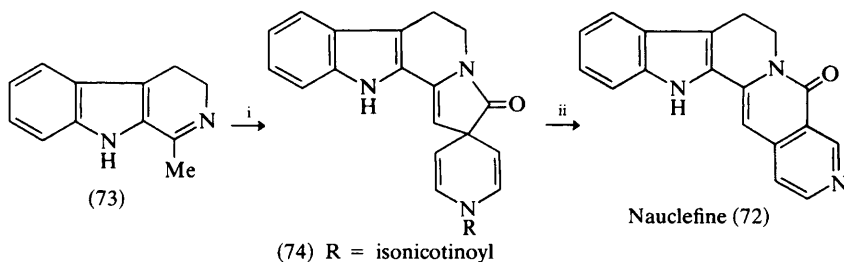


<sup>47</sup> E. J. Shellard, P. J. Houghton, and M. Resha, *Planta Med.*, 1978, **33**, 223.

<sup>48</sup> R. T. Brown and J. Leonard, *Tetrahedron Lett.* 1979, 1805.

which has only small (axial–equatorial and equatorial–equatorial) couplings. The ester group in this epimer of (71) is thus axially disposed, and on treatment with sodium methoxide it can be converted into cyclositsirikine (71). Sitsirikine itself (70) must therefore have the *R* configuration at C-16.

The considerable amount of new synthetic work reported in this area during the past year includes a new synthesis<sup>49</sup> of nauclefine (72) by a modification of the enamide photocyclization route. The reaction of harmalan (73) with an excess of isonicotinoyl chloride gave the spirodihydropyridine derivative (74), which on hydrolysis followed by irradiation gave nauclefine (72) (Scheme 8).



Reagents: i, Isonicotinoyl chloride (excess), NEt<sub>3</sub>; ii, 5% KOH-MeOH; iii, *hν*, PhH, at r.t., 1 h

**Scheme 8**

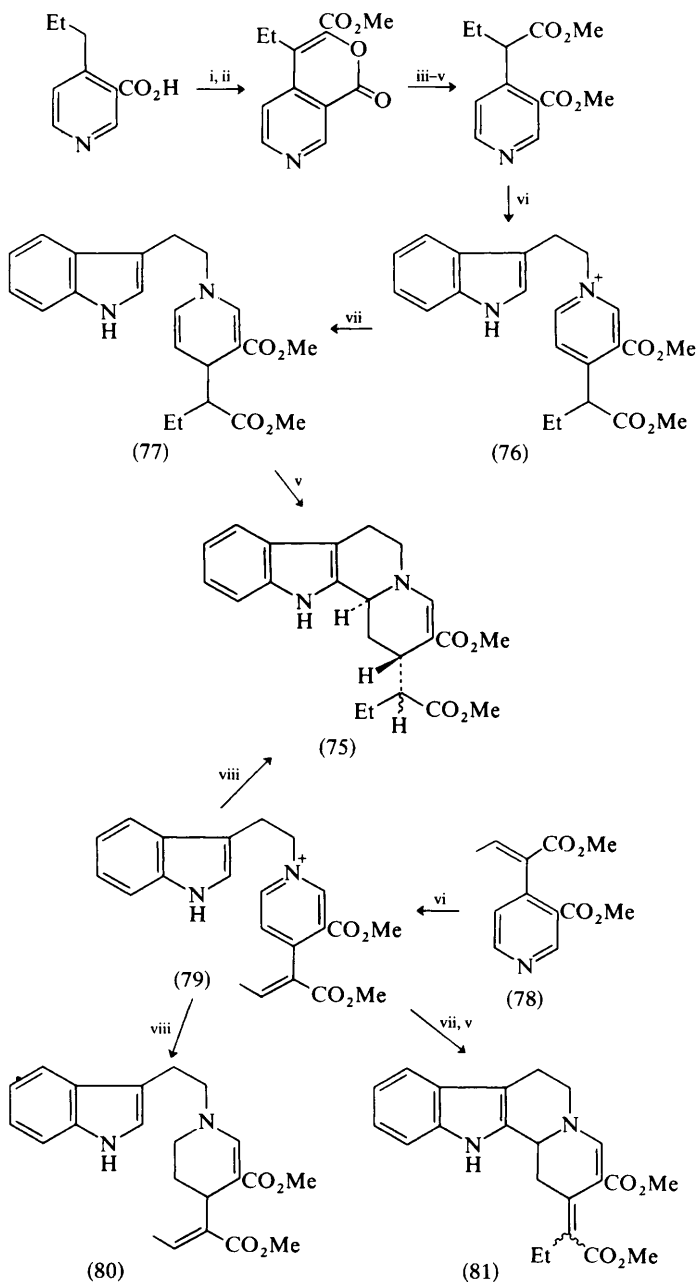
Lounasmaa *et al.*<sup>50</sup> have continued their investigations into the synthesis of indoloquinolizidine derivatives, with particular reference to vallesiachotamine models. The most advanced work in this area to date involves synthesis (Scheme 9) of the closely related vallesiachotamine derivative (75).<sup>50b</sup> The critical stage in this synthesis was the reduction of the pyridinium salt (76) by means of sodium dithionite, which, in buffered (NaHCO<sub>3</sub>) solution, allowed the isolation of the dihydropyridine derivative (77). Cyclization of (77) in the presence of acid gave, preferentially, the desired 3H,15H-*trans*-isomer (75), as had previously been established<sup>50a,c</sup> in model systems. Alternatively, alkylation of the unsaturated ester (78) with tryptophyl bromide gave the pyridinium salt (79), which, on reduction with sodium dithionite in aqueous methanol, gave a mixture of (75) and the uncyclized tetrahydropyridine derivative (80).<sup>50d</sup> When the sodium dithionite reduction medium was buffered (with NaHCO<sub>3</sub>), and the dihydropyridines so obtained were cyclized in acid, the products were the tetracyclic geometrical isomers of structure (81) (Scheme 9).

A new synthesis of flavopereirine, isolated as its perchlorate (82), involves another example of enamide photocyclization (Scheme 10).<sup>51</sup> The intermediate enamide (83) proved to be so unstable that it was cyclized, without purification, to the tetracyclic enamide (84), which was hardly more stable; however, the product (85) obtained following elimination of methanol was stable.

<sup>49</sup> T. Naito, O. Miyata, and I. Ninomiya, *J. Chem. Soc., Chem. Commun.*, 1979, 517.

<sup>50</sup> (a) M. Lounasmaa and R. Jokela, *Tetrahedron*, 1978, **34**, 1841; (b) M. Lounasmaa, P. Juutinen, and P. Kairisalo, *ibid.*, p. 2529; (c) M. Lounasmaa, H. Merikallio, and M. Puhakka, *ibid.*, p. 2995; (d) M. Lounasmaa and R. Jokela, *Tetrahedron Lett.*, 1978, 3609.

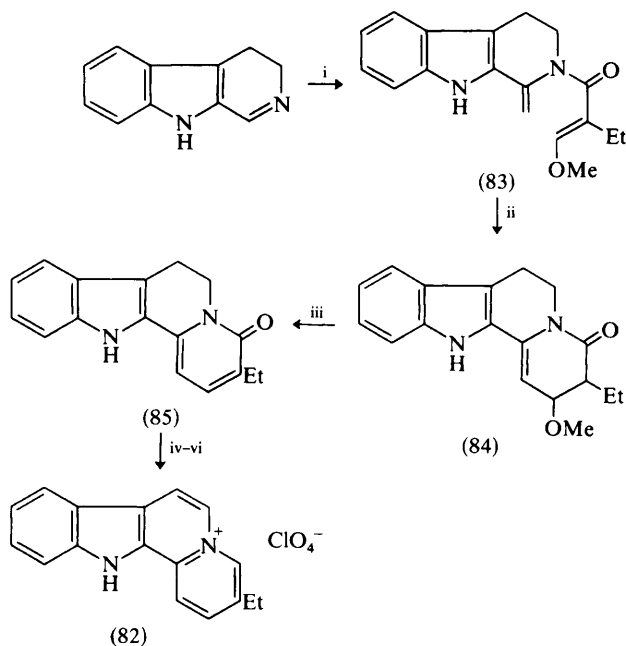
<sup>51</sup> I. Ninomiya, Y. Tada, T. Kiguchi, O. Yamamoto, and T. Naito, *Heterocycles*, 1978, **9**, 1527.



Reagents: **i**,  $(\text{COCl})_2$ ,  $\text{CHCl}_3$ ,  $\text{NEt}_3$ ; **ii**,  $\text{MeOH}$ ,  $\text{CHCl}_3$ ,  $\text{NEt}_3$ ; **iii**,  $\text{KOH-H}_2\text{O}$ ; **iv**,  $\text{H}_2\text{O}_2\text{-KOH}$ ; **v**,  $\text{MeOH}$ ,  $\text{HCl}$ ; **vi**, tryptophyl bromide; **vii**,  $\text{Na}_2\text{S}_2\text{O}_4$ ,  $\text{NaHCO}_3$ ; **viii**,  $\text{Na}_2\text{S}_2\text{O}_4$ ,  $\text{H}_2\text{O}$ ,  $\text{MeOH}$

**Scheme 9**





Reagents: i,  $\text{MeOCH}=\text{C}(\text{Et})\text{COCl}$ ; ii,  $h\nu$ , PhH, at r.t.; iii, 10%  $\text{HCl-H}_2\text{O}$ ; iv,  $\text{LiAlH}_4$ ; v, Pd/C, 280–300 °C; vi,  $\text{HClO}_4$

**Scheme 10**

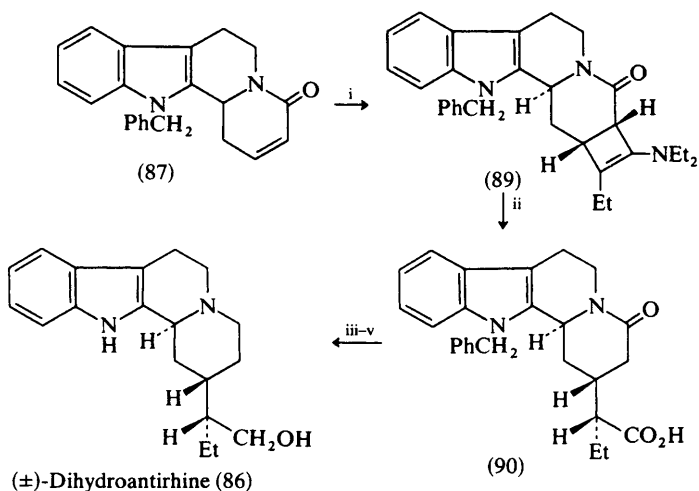
The first stereoselective synthesis of ( $\pm$ )-dihydroantirrhine (86) employs a neat device for stereochemical control, and proceeds in a remarkable overall yield of 40% from the lactam (87).<sup>52</sup> Addition of the ynamine (88) to (87) involves preferentially a transition state in which ring D has a flattened half-chair, rather than a half-boat, conformation, which results in the formation of the intermediate (89). Proton addition to (89) during acid hydrolysis to the lactam-acid (90) occurs predominantly on the more accessible *exo* face; the stereochemistry of (90), and thus of ( $\pm$ )-dihydroantirrhine (86), is thereby assured (Scheme 11).<sup>52</sup>

In connection with partial synthesis in the ring-E-*seco* alkaloids and the heteroyohimbine group, several  $N_b$ -oxides have been prepared. Dihydrocorynantheine, on oxidation with *m*-chloroperbenzoic acid, affords two epimeric  $N_b$ -oxides whereas its *pseudo* isomer, hirsutine, gives only one.<sup>53</sup> Desmethyl-hirsutine  $N_b$ -oxide (91), when treated with trifluoroacetic anhydride in methylene chloride, undergoes the Polonovski reaction; reduction of the product by means of buffered sodium cyanoborohydride then affords a mixture of desmethylcorynantheine (92), 3-*iso*-raunitiveine (93), and akuammigine (94) (Scheme 12).<sup>54</sup> Clearly, formation of an immonium ion can occur in the Polonovski reaction either towards C-3 [ $\rightarrow$ (95)], which results in the ultimate epimeriza-

<sup>52</sup> J. Ficini, A. Guingant, and J. d'Angelo, *J. Am. Chem. Soc.*, 1979, **101**, 1318.

<sup>53</sup> N. Aimi, E. Yamanaka, M. Ogawa, T. Kohmoto, K. Mogi, and S. Sakai, *Heterocycles*, 1978, **10**, 73.

<sup>54</sup> S. Sakai and N. Shinma, *Chem. Pharm. Bull.*, 1978, **26**, 2596.



Reagents: i,  $\text{EtC}\equiv\text{CNEt}_2$  (88),  $\text{MgBr}_2$ ; ii, 10%  $\text{HCl}$ , at r.t., 1 h; iii,  $\text{CH}_2\text{N}_2$ ; iv,  $\text{LiAlH}_4$ , THF; v,  $\text{Na, NH}_3$ .

**Scheme 11**

tion at this centre in the product (92) isolated, or towards C-21 [ $\rightarrow$  (96)], which ultimately gives (93) and (94).

Similar treatment of hirsuteine  $N_b$ -oxide (97) gives corynantheine (98) and 3-*iso*-corynantheidine (65), the latter presumably arising by reduction of the intermediate conjugated dienamine ion (99).<sup>54</sup>

Other partial syntheses of heteroyohimbine alkaloids are based on pteropodine (100), the major alkaloid of *Uncaria florida* Vidal, and the derived 2,3-*seco*-2,3-dihydroakuammigine (101).<sup>55,56</sup> A re-investigation<sup>57</sup> of the oxidative cyclization of (101) by means of mercuric acetate and EDTA was carried out; the products included tetrahydroalstonine (102), and the 'inside' heteroyohimbine and dehydroyohimbine derivatives (103) and (104) (Scheme 13). In contrast to the reports of other workers,<sup>58</sup> no akuammigine (94) was detected. However, the Polonovski reaction of the  $N$ -oxide of (101) gave akuammigine (94), together with (103) and a piperidine derivative (105).

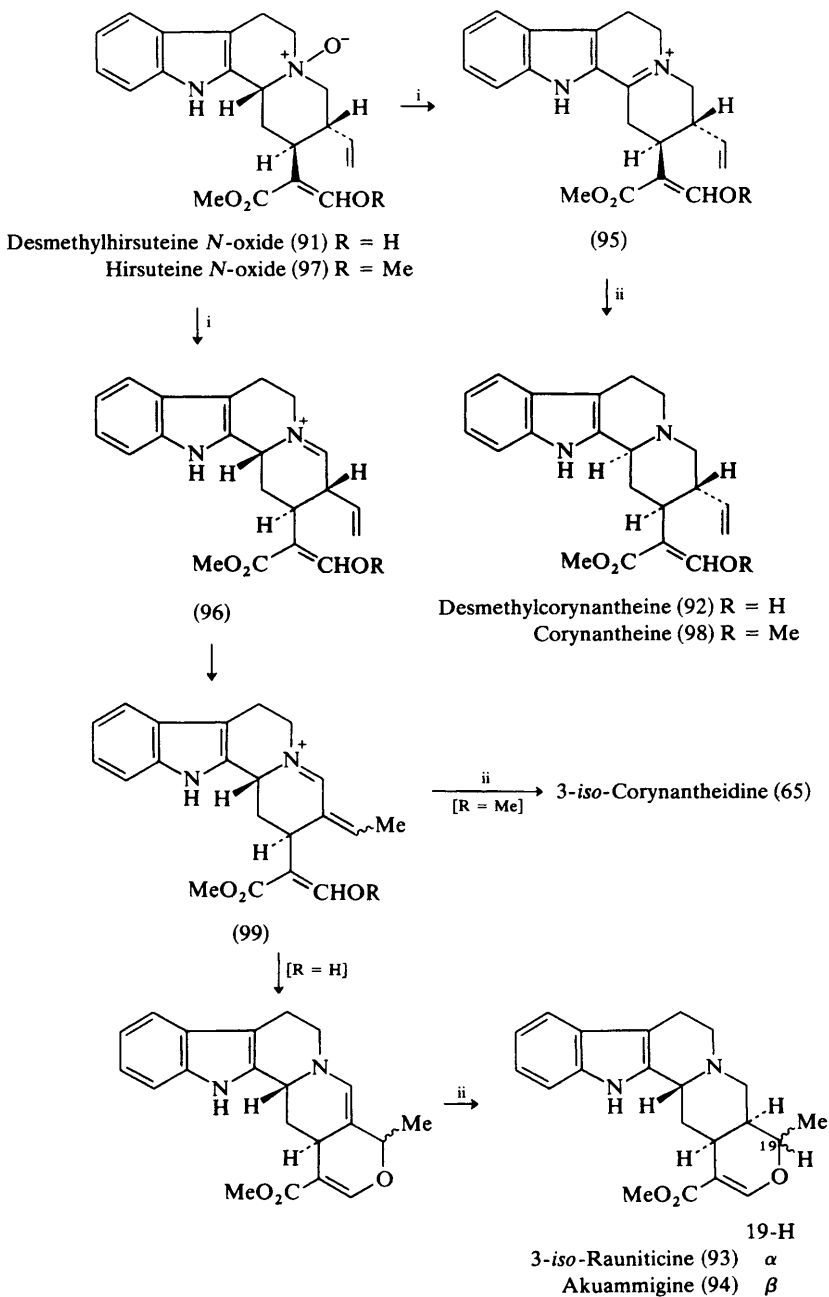
This cleavage of the oxindole alkaloids, *e.g.* (100), or the 2,3-*seco*-derivatives of type (101) to bicyclic piperidine derivatives is of considerable interest, and has provided new pathways for the partial synthesis of other alkaloids. Alternative ways of achieving the cleavage involve the application of the Hobson reaction to pteropodine (100), followed by hydrogenolysis of the intermediate (106) (Scheme 14); a similar sequence of reactions on 2,3-*seco*-2,3-dihydroakuammigine (101)

<sup>55</sup> S. Sakai, N. Aimi, J. Endo, M. Shimizu, E. Yamanaka, K. Katano, M. Kashiwazaki, M. Fujiu, and Y. Yamamoto, *Yakugaku Zasshi*, 1978, **98**, 850 (*Chem. Abs.*, 1978, **89**, 197 771).

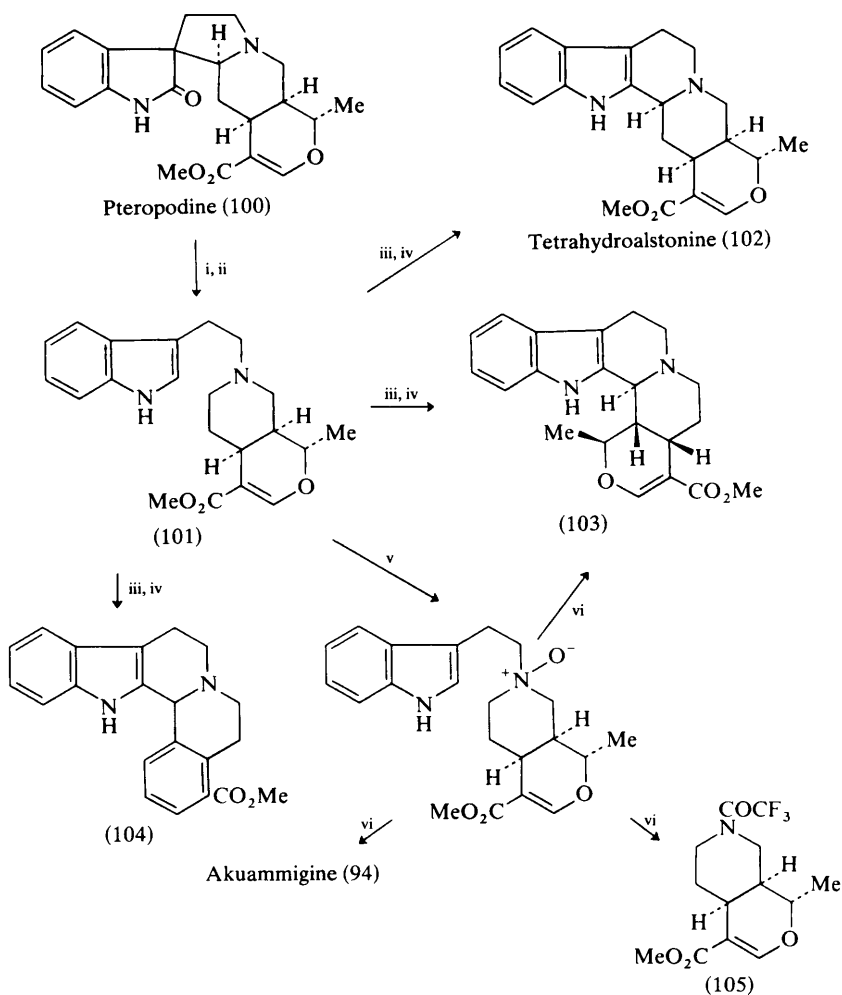
<sup>56</sup> S. Sakai, N. Aimi, J. Endo, M. Shimizu, E. Yamanaka, M. Ogawa, K. Katano, M. Kashiwazaki, M. Fujiu, and Y. Yamamoto, *Heterocycles*, 1979, **12**, 152.

<sup>57</sup> For the earlier investigations see N. Aimi, E. Yamanaka, J. Endo, S. Sakai, and J. Haginiwa, *Tetrahedron Lett.*, 1972, 1081.

<sup>58</sup> J. Gutzwiller, G. Pizzolato, and M. Uskoković, *J. Am. Chem. Soc.*, 1971, **93**, 5907.



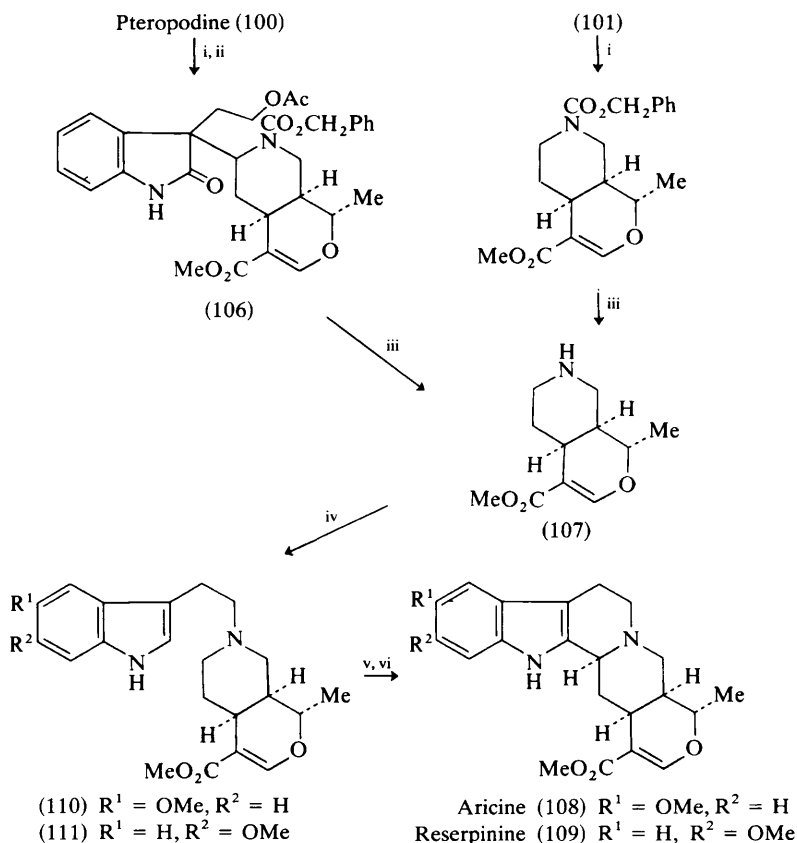
Scheme 12



Reagents: *i*,  $\text{Et}_3\text{O}^+\text{BF}_4^-$ ; *ii*,  $\text{NaBH}_4$ ,  $\text{AcOH}$ ; *iii*,  $\text{Hg}(\text{OAc})_2$ , EDTA; *iv*,  $\text{NaBH}_4$ ; *v*, *m*-CPBA; *vi*,  $(\text{CF}_3\text{CO})_2\text{O}$ , TFA

**Scheme 13**

gave the same product (107). Alkylation of (107) by means of the appropriate methoxytryptophyl bromide then gave the 2,3-seco-heteroyohimbines (110) and (111), which were converted into aricine (108) and reserpine (109) by the familiar oxidative cyclization method; as in the earlier examples of this reaction, some of the 'inside' products, *i.e.* the appropriate methoxy-derivatives of (103) and (104), were obtained (Scheme 14).<sup>55</sup>



Reagents: i, ClCO<sub>2</sub>CH<sub>2</sub>Ph; ii, NaOAc; iii, H<sub>2</sub>, Pd/C; iv, 5- (or 6-)methoxytryptophyl bromide, K<sub>2</sub>CO<sub>3</sub>, DMF; v, Hg(OAc)<sub>2</sub>, EDTA; vi, NaBH<sub>4</sub>

**Scheme 14**

Full details of the partial syntheses of 20 $\alpha$ -ethyl-19,20-dihydro-16-*epi*-pleiocarpamine<sup>59a</sup> and 16-*epi*-pleiocarpamine,<sup>3c</sup> from hirsutine and geissoschizine respectively, have now been published.<sup>60</sup>

The synthesis<sup>61</sup> of (-)-alangimarckine (114) from the tricyclic amino-acid (113), which had previously<sup>62</sup> been prepared from cincholoipon ethyl ester (112), confirms the structure and relative stereochemistry recently deduced,<sup>63a</sup> and also proves that the absolute stereochemistry is as given in (114) (Scheme 15).

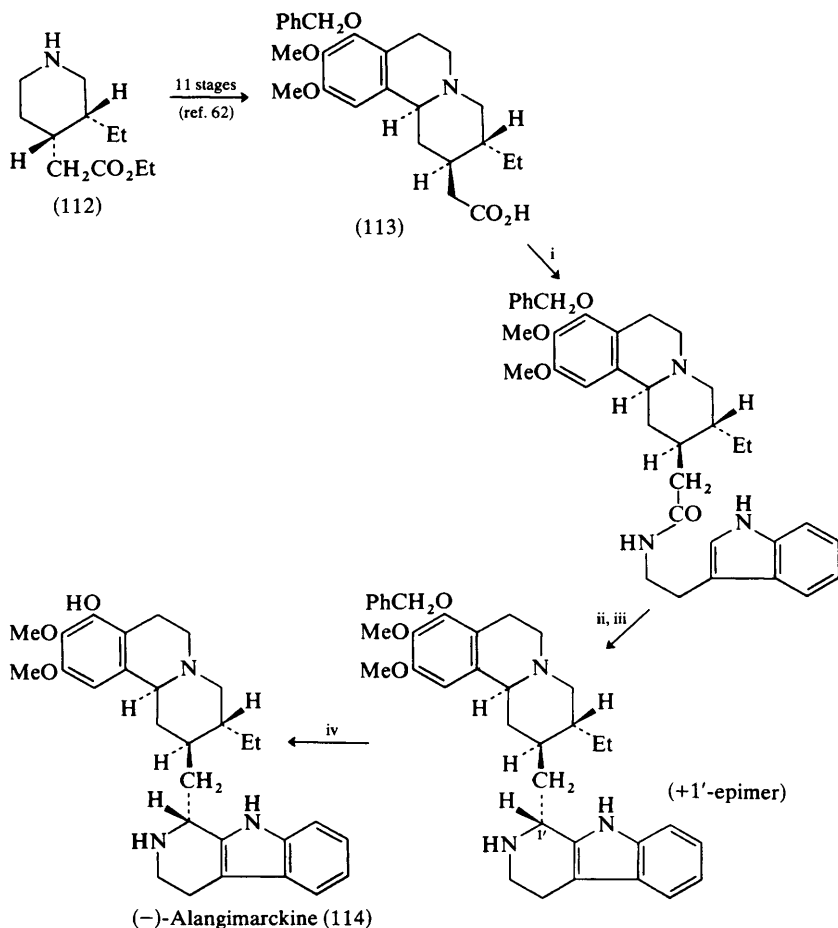
<sup>59</sup> J. E. Saxton, in 'The Alkaloids', ed. M. F. Grondon (Specialist Periodical Reports), The Chemical Society, London, 1976, Vol. 6; (a) pp. 217, 219; (b) p. 192.

<sup>60</sup> S. Sakai and N. Shinma, *Yakugaku Zasshi*, 1978, **98**, 950 (*Chem. Abs.*, 1979, **90**, 55 147).

<sup>61</sup> T. Fujii, H. Kogen, and M. Ohba, *Tetrahedron Lett.*, 1978, 3111.

<sup>62</sup> T. Fujii, S. Yoshifuji, S. Minami, S. C. Pakrashi, and E. Ali, *Heterocycles*, 1977, **8**, 175.

<sup>63</sup> J. E. Saxton, in 'The Alkaloids', ed. M. F. Grondon (Specialist Periodical Reports), The Chemical Society, London, 1979, Vol. 9; (a) p. 180; (b) p. 174; (c) p. 185; (d) p. 188; (e) p. 217; (f) p. 197; (g) p. 212; (h) p. 218.



Reagents: i, Tryptamine,  $\text{NCPO}(\text{OEt})_2$ ,  $\text{NEt}_3$ , DMF, at 28 °C for 6 h; ii,  $\text{POCl}_3$ , PhMe, at 110 °C; iii,  $\text{H}_2$ , Pt, dioxan; iv,  $\text{H}_2$ , Pd/C

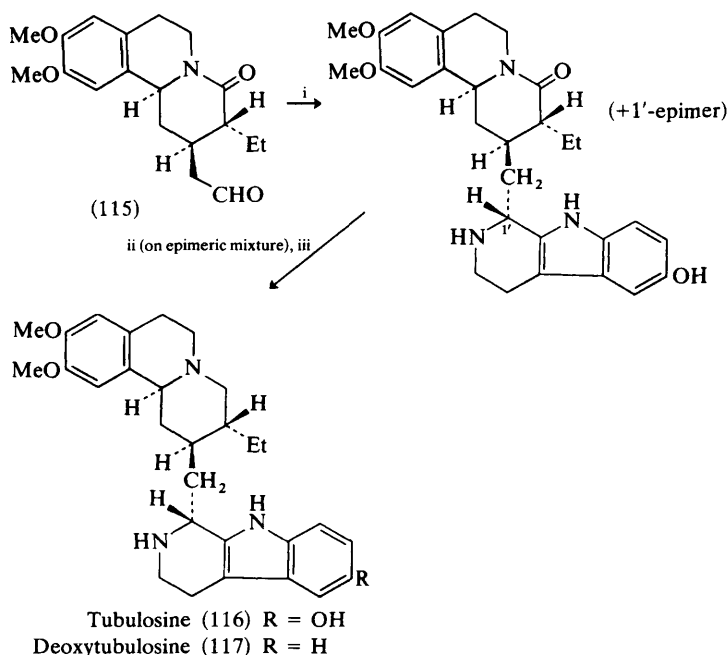
**Scheme 15**

A simple synthesis of ( $\pm$ )-tubulosine (116) results from condensation of ( $\pm$ )-4-oxoprotoemetine (115) with serotonin, followed by reduction of the lactam carbonyl group (Scheme 16); similarly, use of tryptamine instead of serotonin gives ( $\pm$ )-deoxytubulosine (117).<sup>64</sup>

In the yohimbine group, reserpine  $N_b$ -oxide has been found in the aerial parts of *Melodinus balansae* Baillon var. *paucivenosus* (S. Moore) Boiteau,<sup>65</sup> and yohimbine, 18-hydroxy-yohimbine, reserpine, and rescinnamine in the stem bark of *Rauwolfia cumminsii*.<sup>44</sup> Other extractions have resulted in the isolation of yohimbine, methyl reserpate, and (possibly) 18-hydroxy-yohimbine from the stem bark of *R. vomitoria*.<sup>45</sup>

<sup>64</sup> T. Kametani, Y. Suzuki, and M. Ihara, *Heterocycles*, 1978, **11**, 415.

<sup>65</sup> M. H. Mehri, A. Rabaron, T. Sévenet, and M. M. Plat, *Phytochemistry*, 1978, **17**, 1451.



Reagents: i, 5-Hydroxytryptamine, AcOH, at r.t. for 2 days; ii,  $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OMe})_2$ , py, at r.t. for 1 h; iii, chromatographic separation

**Scheme 16**

The  $^{15}\text{N}$  chemical shifts in the natural-abundance spectra of yohimbine, reserpine, and a number of model indoloquinolizidine derivatives have been recorded;<sup>66</sup> the data show that the chemical shifts depend markedly on the nature of the C/D ring junction, and on substituents in a  $\gamma$ -gauche conformation. In the absence of  $\gamma$ -effects, a *cis*-fused quinolizidine nitrogen is shielded by 13–15 p.p.m. compared with nitrogen in a *trans*-fused system. Protonation deshields the nitrogen to a larger extent in the *cis*- than in the *trans*-series, and this criterion can be used to diagnose the geometry of the C/D ring junction.

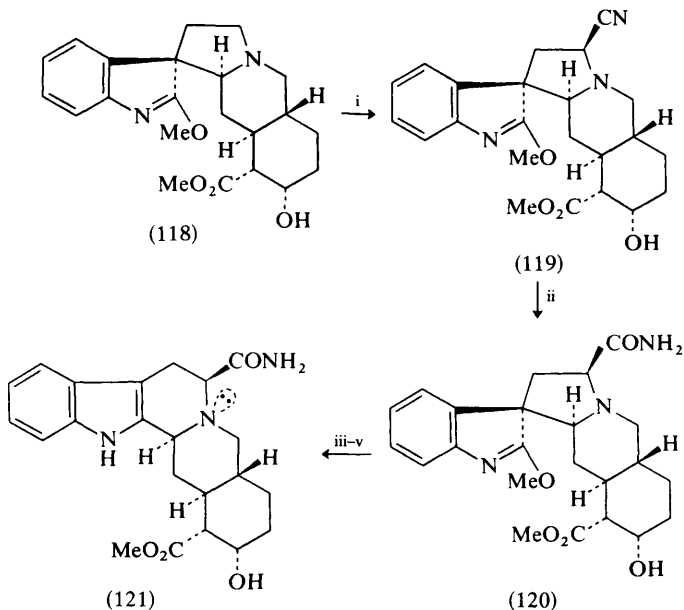
Yohimbine, pseudoyohimbine, and yohimbineone give two  $N_6$ -diastereoisomeric quaternary salts with methyl iodide. The two yohimbine metho-salts give strikingly different, almost enantiomeric, c.d. spectra, which can therefore be used to deduce the nature of the C/D ring junction.<sup>67</sup>

Photo-oxidation of the imino-ether (118) (prepared from yohimbine *via* the 7-chloroindolenine derivative), in the presence of oxygen and potassium cyanide, with Rose Bengal as sensitizer, results in the introduction of a cyano-group into the tryptophan position; the product is thus the  $\alpha$ -amino-nitrile (119), together

<sup>66</sup> S. N. Y. Fanso-Free, G. T. Furst, P. R. Srinivasan, R. L. Lichter, R. B. Nelson, J. A. Panetta, and G. W. Gribble, *J. Am. Chem. Soc.*, 1979, **101**, 1549.

<sup>67</sup> G. Tóth, F. Hetényi, O. Clauder, and M. Kajtár, *Justus Liebigs Ann. Chem.*, 1978, 1096.

with the related amide and their C-5 epimers (Scheme 17).<sup>68</sup> Partial hydrolysis of (119) and its epimer gave a separable mixture of the related amides [(120) and its epimer]. Epimer (120) was then reduced to the corresponding indoline, oxidized (by  $\text{MnO}_2$ ) to the indolenine, and treated with acid, which gave  $5\beta$ -carbox-amidoyohimbine (121). The spectroscopic data indicated that (121) contained a *cis* C/D ring junction.



Reagents: i,  $h\nu$ ,  $\text{O}_2$ , KCN, MeOH, Rose Bengal; ii, MeOH,  $\text{H}_2\text{O}_2$ ,  $\text{H}_2\text{O}$ ; iii,  $\text{NaBH}_3\text{CN}$ ; iv,  $\text{MnO}_2$ ,  $\text{CH}_2\text{Cl}_2$ ; v, AcOH

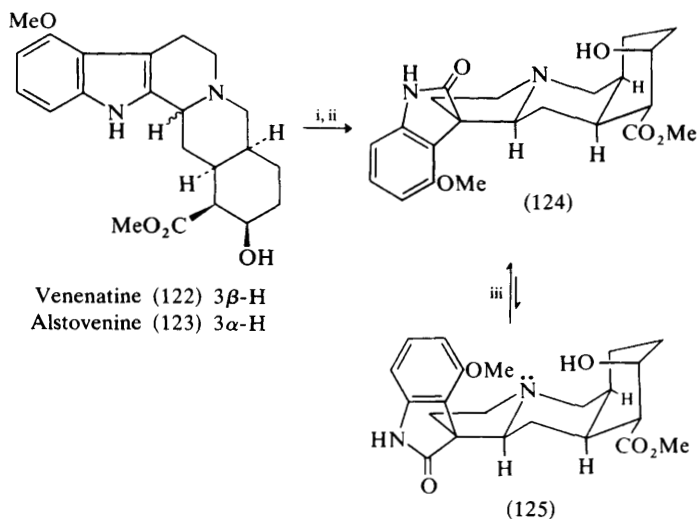
**Scheme 17**

Conversion of the epimeric bases venenatine (122) and alstovenine (123) into the related oxindole gave a single isomer, formulated as (124), instead of the epimeric pair normally produced (Scheme 18).<sup>69</sup> Equilibration of (124) with its stereoisomeric forms proved surprisingly difficult, and a long period (48 h) of reflux in 30% aqueous acetic acid was required to give a mixture containing 30% of an isomer which, however, proved to be unstable and difficult to purify, since it reverted to (124) even on attempted chromatography. On the basis of the spectroscopic data of the mixtures obtained, the isomer was deduced to have the *allo* conformation (125), in which there are considerable non-bonded interactions between the 9-methoxy-group and the lone pair of electrons on  $\text{N}_6$ . The two *epiallo* isomers of (124) and (125) contained even greater non-bonded interactions than (125), and would clearly be expected to be much less stable.<sup>69</sup>

<sup>68</sup> D. Herlem and F. Khuong-Huu, *Tetrahedron*, 1979, **35**, 633.

<sup>69</sup> P. L. Majumder, S. Joardar, and T. K. Chanda, *Tetrahedron*, 1978, **34**, 3341.





Scheme 18

Yohimbine, on oxidation, gives rise to two epimeric  $N_b$ -oxides, of which the major isomer contains a *trans* C/D ring junction. In contrast, pseudoyohimbine, which is its C-3 epimer, can only yield one  $N_b$ -oxide.<sup>53</sup>

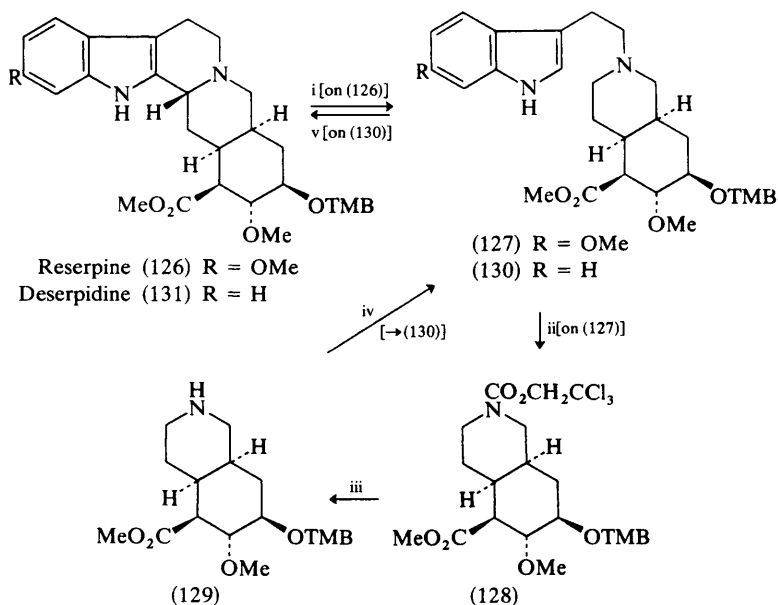
The fission of the 2,3-bond in indole alkaloids, by means of formic acid and formamide,<sup>63b</sup> provides a route for the release of the D/E ring unit, and therefore a method for the interconversion of appropriate alkaloids. Thus, 2,3-seco-2,3-dihydroreserpine (127), prepared in this way from reserpine (126), reacts with trichloroethyl chloroformate to give mainly the urethane (128), reduction of which gives the D/E unit (129). Alkylation of (129) with tryptophyl bromide then gives 2,3-seco-2,3-dihydrodeserpine (130), which one oxidation with mercuric acetate affords a low yield of deserpidine (131), together with a small amount of 3-*iso*-deserpine (Scheme 19).<sup>56,70</sup>

An elegant synthesis<sup>71</sup> of  $\Delta^{15}$ -yohimbenone (132) makes use of the enol ether (133), prepared by Birch reduction of the corresponding anisole derivative. Gentle acid hydrolysis affords the unconjugated enone (134), which reacts with formaldehyde to give yohimbenone. Spectroscopic evidence (u.v.) indicates that the reaction proceeds *via* 3,3-sigmatropic rearrangement of the immonium ion (135) [ $\rightarrow$  (136)], followed by cyclization between C-3 and C-14, rather than by way of a conventional Mannich reaction on the conjugated ketone corresponding to (134) (Scheme 20).

Yamada's approach to asymmetric synthesis<sup>59b</sup> by 1,3-transfer of asymmetry has been adapted to a stereoselective synthesis of yohimbone (137) and allo-

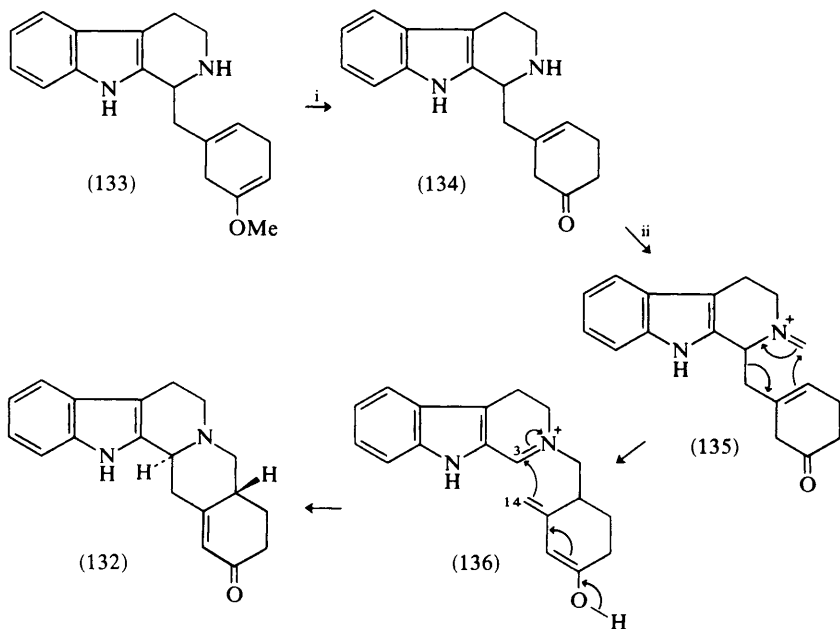
<sup>70</sup> S. Sakai and M. Ogawa, *Heterocycles*, 1978, **10**, 67.

<sup>71</sup> W. Benson and E. Winterfeldt, *Chem. Ber.*, 1979, **112**, 1913.



Reagents: i,  $\text{HCO}_2\text{H}$ ,  $\text{HCONH}_2$ ; ii,  $\text{ClCO}_2\text{CH}_2\text{CCl}_3$ ,  $\text{NaHCO}_3$ ; iii,  $\text{Zn}$ ,  $\text{AcOH}$ ; iv, tryptophyl bromide,  $\text{K}_2\text{CO}_3$ ,  $\text{DMF}$ , at  $70-80^\circ\text{C}$ ; v,  $\text{Hg}(\text{OAc})_2$

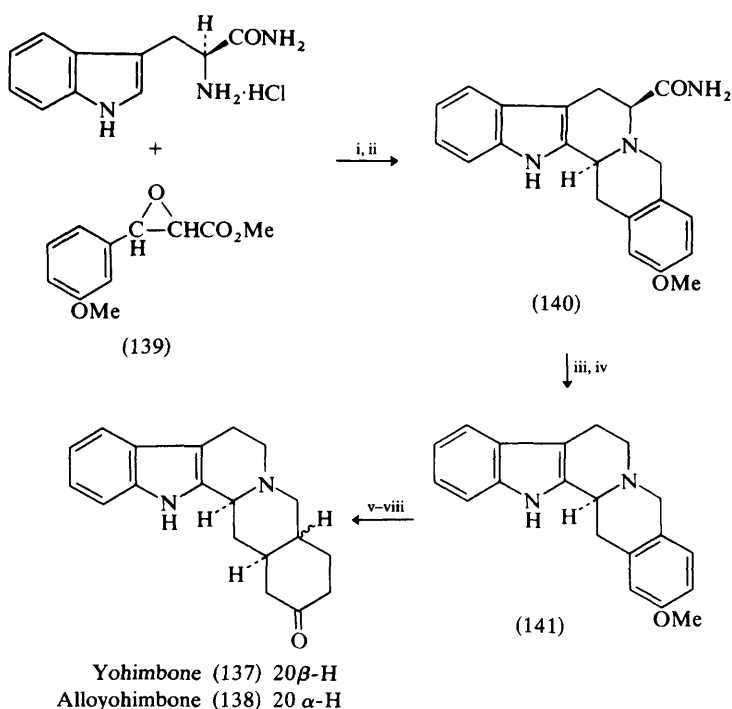
Scheme 19



Reagents: i,  $\text{AcOH}$ ,  $\text{H}_2\text{O}$ , for 1 h, at r.t.; ii,  $\text{CH}_2\text{O}$ ,  $\text{MeOH}$ , at r.t.

Scheme 20

yohimbone (138) (Scheme 21).<sup>72</sup> Condensation of L-tryptophan amide with the glycidic ester (139), followed by cyclization with formaldehyde, gave a separable mixture of the pentacyclic amide (140) and its C-3 epimer. The amide function in (140) was then removed by reduction (by NaBH<sub>4</sub>) of the related  $\alpha$ -amino-nitrile. The product (141) was then elaborated in a routine way to give yohimbone (137), together with some allohyohimbone (138).



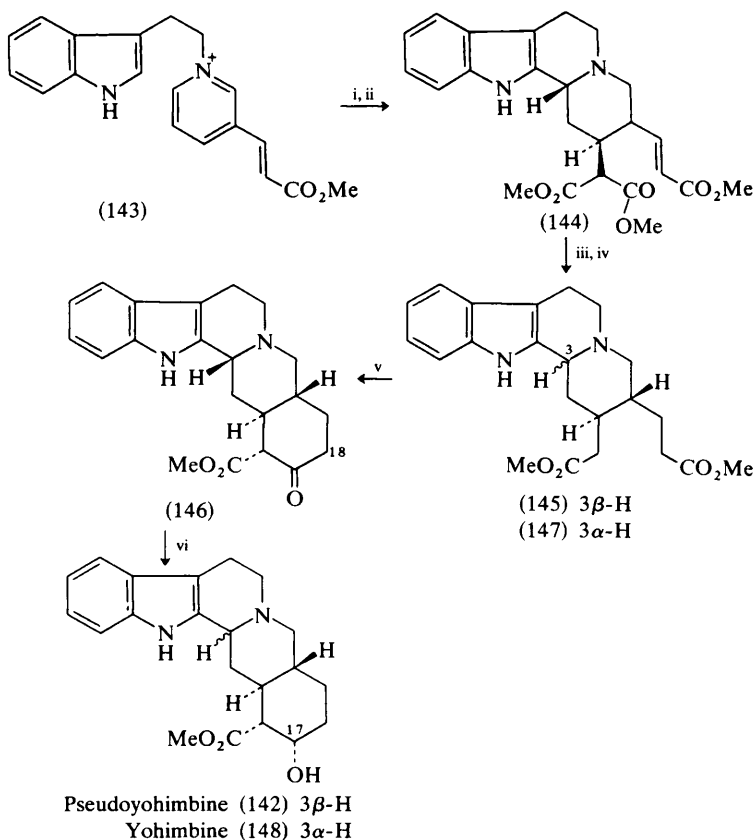
Reagents: i, H<sub>2</sub>O, MeOH, heat for 23 h; ii, CH<sub>2</sub>O, H<sub>2</sub>O, at 50–60 °C for 2 h; iii, POCl<sub>3</sub>, py, DMF; iv, NaBH<sub>4</sub>, py, EtOH; v, Na, Bu'OH, NH<sub>3</sub>; vi, 2M-HCl, H<sub>2</sub>O, MeOH; vii, pyridine, reflux for 2 h; viii, H<sub>2</sub>, Pd/C, AcOH, at r.t. for 4 h

**Scheme 21**

Straightforward modification of Wenkert's route to the ajmalicine group of alkaloids<sup>3d</sup> has allowed the synthesis of pseudoyohimbine (142) to be completed (Scheme 22).<sup>73</sup> Addition of malonic ester to the quaternary salt (143), prepared by an obvious sequence of reactions from nicotinaldehyde, gave a tetrahydropyridine derivative, which cyclized, on acid treatment, to the tetracyclic triester (144). Manipulation of (144) by standard methods ultimately gave ( $\pm$ )-pseudoyohimbine (142); the process, however, loses some elegance by the fact that the Dieckmann cyclization (145)  $\rightarrow$  (146) was not regiospecific, much of the 18-methoxycarbonyl isomer of (146) being formed. Acid-catalysed epimerization of

<sup>72</sup> K. Okamura and S. Yamada, *Chem. Pharm. Bull.*, 1978, **26**, 2305.

<sup>73</sup> E. Wenkert, G. Kunesch, K. Orito, W. A. Temple, and J. S. Yadav, *J. Am. Chem. Soc.*, 1978, **100**, 4894.



Reagents: i,  $\text{NaCH}(\text{CO}_2\text{Me})_2$ , monoglyme; ii,  $\text{HBr}$ ,  $\text{PhH}$ ; iii,  $\text{LiI} \cdot 3\text{H}_2\text{O}$ ,  $\text{DMSO}$ , at  $180^\circ\text{C}$ ; iv,  $\text{H}_2$ ,  $\text{Pt}$ ,  $\text{AcOH}$ ; v,  $\text{NaH}$ ,  $\text{THF}$ ; vi,  $\text{H}_2$ ,  $\text{Pt}$ ,  $\text{MeOH}$ ,  $\text{AcOH}$ .

**Scheme 22**

(145) at C-3 gave the ester (147), which had previously<sup>74</sup> been converted into yohimbine (148) and  $\beta$ -yohimbine (17-isoyohimbine); hence this work constitutes new formal total syntheses of these alkaloids.

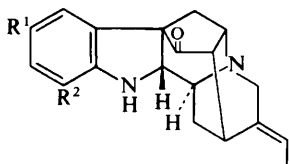
**Sarpagine–Ajmaline–Picraline–Vobasine Group.** The roots and stems of *Rauwolfia schueli* Speg. (*R. boliviana* Mgf.) have been re-examined,<sup>75a</sup> and the ajmaline content has been quantitatively estimated; the conclusion is that this plant constitutes one of the richest sources of ajmaline. Ajmaline also occurs<sup>65</sup> in *Melodinus balansae* Baillon var. *paucivenosus*, normacusine B occurs in *Strychnos nux vomica*,<sup>75b</sup> akuamidine in *M. celastroides*,<sup>76</sup> and pericyclivine and caberine in the aerial parts of *Catharanthus ovalis*.<sup>41a</sup>

<sup>74</sup> L. Töke, K. Honty, and Cs. Szántay, *Chem. Ber.*, 1969, **102**, 3248.

<sup>75</sup> (a) V. S. Martino, A. L. Bandoni, O. Hnatyszyn, R. V. D. Rondina, and J. D. Coussio, *J. Pharm. Pharmacol.*, 1978, **30**, 817; (b) K. H. C. Baser, N. G. Bisset, and P. J. Hylands, *Phytochemistry*, 1979, **18**, 512.

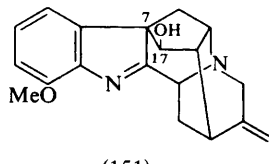
<sup>76</sup> A. Rabaron, M. H. Mehri, T. Sévenet, and M. M. Plat, *Phytochemistry*, 1978, **17**, 1452.

Perakine, norpurpeline (149), dihydronorpurpeline, endolobine (150), purpeline, seredamine, nortetraphyllicine, normacusine B, and desacetyl-picaline have been found in the stem bark of *Rauwolfia cumminsii*;<sup>44</sup> two minor bases were tentatively identified as *O*-methylnormacusine B (17-methoxysarpagan) and its *N*<sub>6</sub>-oxide, and a third, as yet unidentified, is probably also a sarpagan derivative. Sarpagine, normacusine B, purpeline, norpurpeline, norseredamine, nortetraphyllicine, and 10-hydroxynortetraphyllicine occur in *R. vomitoria* stems;<sup>45</sup> an unknown base was provisionally formulated as (151), but the stability of the 7,17-bond in such a structure is very much in doubt.



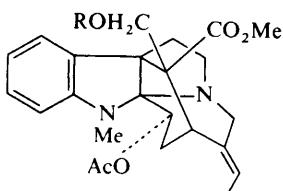
Norpurpeline (149)  $R^1 = \text{H}$ ,  $R^2 = \text{OMe}$

Endolobine (150)  $R^1 = \text{OMe}$ ,  $R^2 = \text{H}$



(151)

The work by the French group on the constituents of Senegalese *Hunteria elliptica* (Stapf.) Pichon has again been summarized, together with new extractions of *H. congolana* Pichon, from Zaïre.<sup>41b</sup> The seeds are particularly rich in alkaloids, and six were isolated, although others are present in trace amounts. Four of these alkaloids belong to this group, and were identified as corymine, acetylcorymine, and two new alkaloids, namely 3-*O*-acetyl-3-*epi*-dihydrocorymine (152) and 3,17-di-*O*-acetyl-3-*epi*-dihydrocorymine (153). The leaves were much less rich in alkaloids, but contained three bases. The first of these was simply shown to be des-*N*<sub>6</sub>-methylisocorymine (154), since methylation gave isocorymine (155). Methylation of the second base, des-*N*<sub>6</sub>-methyleripinal (156),

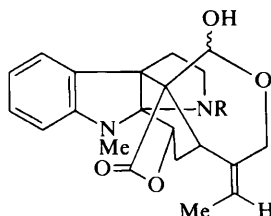


3-*O*-Acetyl-3-*epi*-dihydrocorymine

(152)  $R = \text{H}$

3,17-Di-*O*-acetyl-3-*epi*-dihydrocorymine

(153)  $R = \text{Ac}$



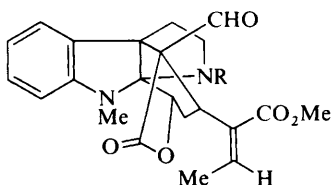
Des-*N*<sub>6</sub>-methylisocorymine (154)  $R = \text{H}$

Isocorymine (155)  $R = \text{Me}$

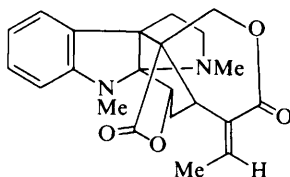
gave the third alkaloid, which was identified as eripinal (157), since reduction (by  $\text{NaBH}_4$ ) gave erinine (158); apparently, eripine, the primary alcohol corresponding to eripinal, was not obtained.<sup>41b</sup>

Details of the extraction from *Pandaca boiteau* Mg. of methuenine, 19, 20-dehydroervatamine, and ervitsine, whose structure elucidation was reported earlier,<sup>63c</sup> have now been published.<sup>77</sup>

<sup>77</sup> M. Andriantsiferana, F. Picot, P. Boiteau, and H. P. Husson, *Phytochemistry*, 1979, **18**, 911.



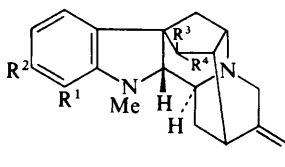
Des-*N<sub>b</sub>*-methyleripinal (156) R = H  
Eripinal (157) R = Me



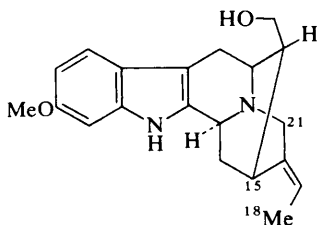
Erinine (158)

The alkaloid of *Rauwolfia reflexa* which was initially claimed<sup>3e</sup> to be purpeline (159) has now been shown,<sup>78</sup> by examination of its <sup>13</sup>C and <sup>1</sup>H n.m.r. spectra, to be the 11-methoxy-isomer (160). It is therefore a new alkaloid, and has been designated rauflexine. The corrected structure for its congener, reflexine, the related secondary alcohol, is therefore (161).

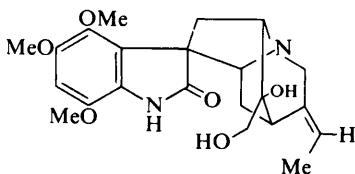
The <sup>13</sup>C n.m.r. spectra of the *Gardneria* alkaloids have been recorded, in a study which was essentially aimed at elucidating the configuration of the double bond.<sup>79</sup> In gardneramine and the alkaloids that have been correlated with it,<sup>63d</sup> this double bond has the unusual (*Z*) configuration, according to the earlier *X*-ray structure determination. However, the sarpagine group, exemplified by gardnerine (162), have the more familiar (*E*) configuration, since C-15 is shielded ( $\gamma$ -effect by C-18) to a greater extent than C-15 in geometrically isomeric analogues of (*Z*) configuration. With regard to C-21, the reverse is true. This accords with the earlier deduction based on a NOE effect in the <sup>1</sup>H n.m.r. spectrum of gardnutine. On the same basis, chitosenine (163) also has the (*E*) configuration about the double bond.



	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>
Purpeline (159)	OMe	H	=O	
Rauflexine (160)	H	OMe	=O	
Reflexine (161)	H	OMe	H	OH



Gardnerine (162)

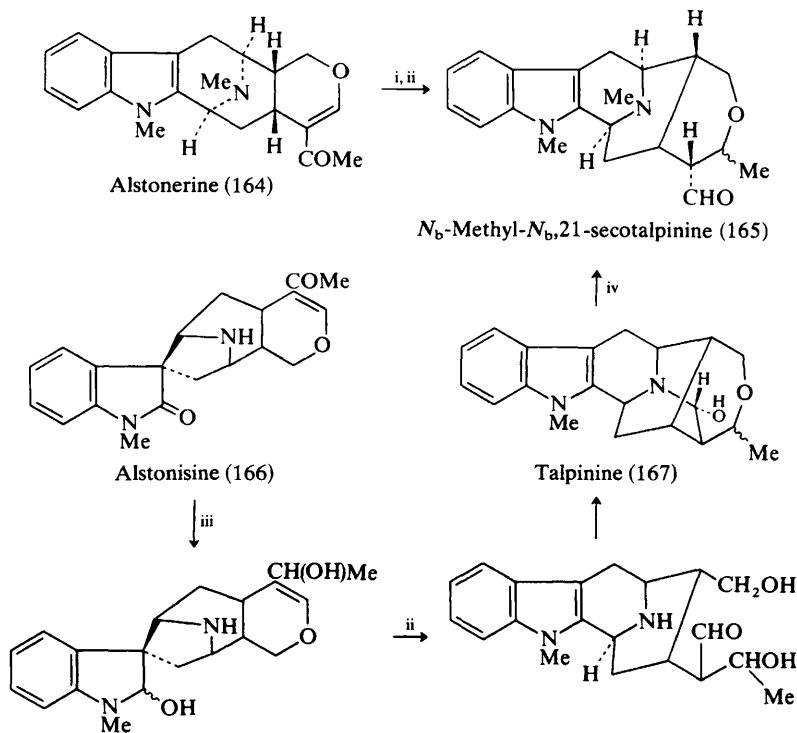


Chitosenine (163)

<sup>78</sup> A. Chatterjee, M. Chakrabarty, A. K. Ghosh, E. W. Hagaman, and E. Wenkert, *Tetrahedron Lett.*, 1978, 3879.

<sup>79</sup> N. Aimi, K. Yamaguchi, S. Sakai, J. Haginiwa, and A. Kubo, *Chem. Pharm. Bull.*, 1978, **26**, 3444.

The biomimetic transformation of macroline into alstonerine, previously reported in brief,<sup>3f</sup> has now been described in detail.<sup>80</sup> Additional, related interconversions simultaneously reported include the reduction of alstonerine (164) by means of sodium borohydride, followed by acid treatment, which gave *N*<sub>6</sub>-methyl-*N*<sub>6</sub>,21-secotalpinine (165), and the two-fold reductive rearrangement of alstonisine (166) into talpinine (167) (Scheme 23).



Reagents: i, NaBH<sub>4</sub>; ii, 0.2 M-HCl; iii, LiAlH<sub>4</sub>; iv, MeI, PhH

**Scheme 23**

The antiviral and local anaesthetic properties of several acyl-indole alkaloids of the vobasine-dregamine group have been discussed in a brief review.<sup>81</sup>

**Strychnine-Akuammicine-Ellipticine Group.** Akuammicine has been found in the seeds of *Hunteria congolana*,<sup>41b</sup> and *N*<sub>a</sub>-methyl-2β,16β-dihydroakuammicine in the leaves of *Vinca minor*.<sup>42</sup> Tubotaiwine and condylocarpine occur in *Aspidosperma album*;<sup>38c</sup> tubotaiwine and apparicine have been isolated from *Catharanthus ovalis*,<sup>41a</sup> tubotaiwine also from *Pandaca boiteau*<sup>77</sup> and *Melodinus aeneus* Baill., in the last of which tubotaiwine *N*<sub>6</sub>-oxide also occurs.<sup>82</sup>

<sup>80</sup> R. L. Garnick and P. W. Le Quesne, *J. Am. Chem. Soc.*, 1978, **100**, 4213.

<sup>81</sup> M. J. Hoizey, L. Le Men-Olivier, J. Le Men, M. Leboeuf, J. P. Fauquet, J. de Jong, E. Morel, and C. Warolin, *Ann. Pharm. Fr.*, 1978, **36**, 519.

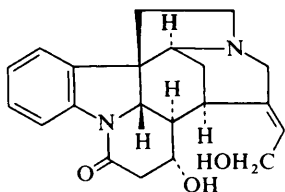
<sup>82</sup> S. Baassou, H. Mehri, and M. Plat, *Phytochemistry*, 1978, **17**, 1449.

New extractions<sup>75b</sup> of the root bark of Sri Lankan *Strychnos nux vomica* have disclosed the presence, besides strychnine, brucine, and isostrychnine, of 12-hydroxystrychnine, 12-hydroxy-11-methoxystrychnine, and a minor base, named protostrychnine (168), because of the obvious possibility that it may be an immediate biosynthetic precursor of strychnine. The overall structure (168), but not necessarily the configuration at C-17, was confirmed by allowing the 18-O-tigloyl ester to react with phosphorus oxychloride in pyridine; saponification of the product, followed by treatment with dilute hydrochloric acid, then gave strychnine.

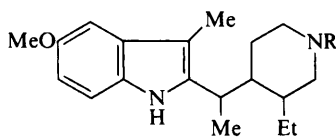
In addition to desacetylretuline and deoxydiaboline (already noted),<sup>3g,11d</sup> the root bark of *S. variabilis* de Wild. contains retuline, isoretuline, and desacetyl-isoretuline.<sup>83</sup>

The leaves of *Ochrosia oppositifolia* contain<sup>84</sup> two new alkaloids, 10-hydroxyapparicine (169) and 10-methoxyapparicine (170), whose overall structures became clear from examination of their mass and 300 MHz n.m.r. spectra. The position of the aromatic substituent in (170), which could not be deduced from the spectroscopic data, follows from the typical 5-methoxyindole u.v. absorption of the secondary base (171) and its  $N_b$ -acetyl derivative (172), produced by saturation of the 16,17 and 19,20 double-bonds in 10-methoxyapparicine and simultaneous hydrogenolysis of the benzylic 6- $N_b$  bond. Methylation of the second, amorphous alkaloid with diazomethane gave (170); consequently it is 10-hydroxyapparicine (169).

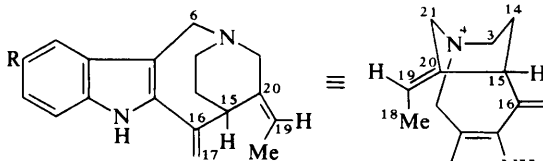
The configuration about the double bond in apparicine (173), which has not previously been rigidly defined, follows<sup>84</sup> from the NOE enhancement of the H-15 absorption on irradiation of the C-18 methyl signal. A similar phenomenon was observed for 10-hydroxyapparicine. In these two alkaloids, and therefore in



Protostrychnine (168)



(171) R = H  
(172) R = Ac



10-Hydroxyapparicine (169) R = OH  
10-Methoxyapparicine (170) R = OMe  
Apparicine (173) R = H

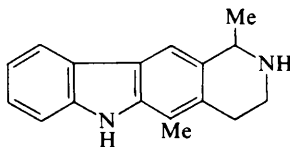
<sup>83</sup> (a) M. J. G. Tits and L. Angenot, *Planta Med.*, 1978, **34**, 57; (b) M. Tits and D. Tavernier, *Plant. Med. Phytother.*, 1978, **12**, 92.

<sup>84</sup> L. Akhter, R. T. Brown, and D. Moorcroft, *Tetrahedron Lett.*, 1978, 4137.



10-methoxyapparicine (170) also, the double bond has the usual (*E*) configuration, in which C-18 (a methyl group) is in close proximity to H-15; in the alternative (*Z*) configuration, an NOE enhancement would be expected for one of the protons at C-21, rather than for one at C-15.

Janetine, a constituent of *Ervatamia coronaria*,<sup>85</sup> is simply tetrahydro-olivacine (174).



Janetine (174)

More n.m.r. data have been recorded and analysed; the most recent include the <sup>1</sup>H n.m.r. spectra of retuline, isoretuline, and their derivatives,<sup>86a</sup> and the <sup>13</sup>C n.m.r. spectra of strychnine, brucine,<sup>86b</sup> and the ellipticine group of alkaloids.<sup>86c</sup>

An improved preparation of the Wieland–Gumlich aldehyde from isonitrosostrychnine on a polymer support has been reported.<sup>87</sup> Quaternization of isonitrosostrychnine with chloroacetylated styrene–divinylbenzene copolymer, followed by Beckmann rearrangement with thionyl chloride, then release of the base from the polymer, affords the aldehyde in 75% yield.

A neat, biogenetically-patterned conversion of stemmadenine (175) and its *O*-acetate (176) into vallesamine (177) and its *O*-acetate (178) provides yet another application of the Polonovski reaction in indole alkaloid synthesis (Scheme 24).<sup>88</sup> The facility of this transformation suggests that the *N*<sub>5</sub>-oxides may be the actual biogenetic precursors of the alkaloids lacking C-5, and that decarboxylative loss of C-22, implicit in the biogenetic pathway proposed earlier<sup>89</sup> for apparicine, is not necessary.

Details of the synthesis<sup>3h</sup> of ellipticine and related pyridocarbazole alkaloids by Gilbert *et al.* have now been published.<sup>90a</sup>

Bergman and Carlsson have adapted their brief ellipticine synthesis to a new synthesis of olivacine (179).<sup>90b</sup> Condensation of 2-ethylindole with 2-methyl-3-methylpyridine gave the bis-indolyl condensation product (180), which lost 2-ethylindole on pyrolysis, and cyclized to give olivacine directly (Scheme 25).

**Aspidospermine–Aspidofractine–Eburnamine Group.** Details of the extraction of the enantiomeric vincadines and their C-16 epimers from the leaves of *Amsonia tabernaemontana* have been published.<sup>91</sup>

<sup>85</sup> C. G. Gonzalez and S. C. Rodriguez, *Rev. Cubana Farm.*, 1978, **12**, 177 (*Chem. Abs.*, 1979, **90**, 138 069).

<sup>86</sup> (a) D. Tavernier, M. J. Anteunis, M. J. Tits, and L. J. Angenot, *Bull. Soc. Chim. Belg.*, 1978, **87**, 595; (b) S. P. Singh, V. I. Stenberg, S. S. Parmar, and S. A. Farnum, *J. Pharm. Sci.*, 1979, **68**, 89; (c) A. Ahond, C. Poupat, and P. Potier, *Tetrahedron*, 1978, **34**, 2385.

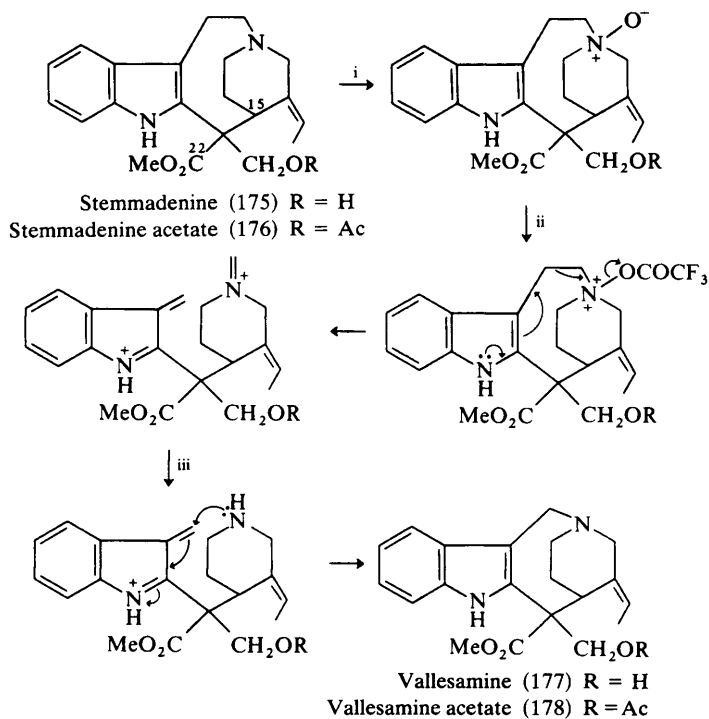
<sup>87</sup> L. Szabó and O. Clauder, *Acta Chim. Acad. Sci. Hung.*, 1977, **95**, 85 (*Chem. Abs.*, 1978, **89**, 43 889).

<sup>88</sup> A. I. Scott, C. L. Yeh, and D. Greenslade, *J. Chem. Soc., Chem. Commun.*, 1978, 947.

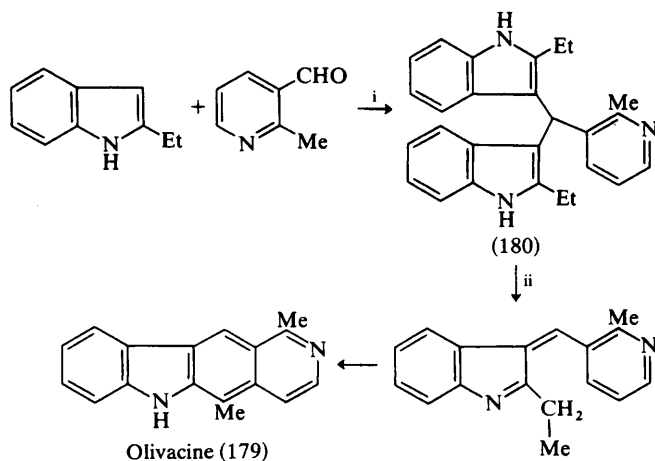
<sup>89</sup> A. Ahond, A. Cavé, C. Kan-Fan, Y. Langlois, and P. Potier, *J. Chem. Soc., Chem. Commun.*, 1970, 517.

<sup>90</sup> (a) J. Gilbert, D. Rousselle, C. Gansser, and C. Viel, *J. Heterocycl. Chem.*, 1979, **16**, 7; (b) J. Bergman and R. Carlsson, *Tetrahedron Lett.*, 1978, 4055.

<sup>91</sup> B. Zsador, J. Tamás, M. Szilasi, Z. Majer, and P. Kaposi, *Acta Chim. Acad. Sci. Hung.*, 1978, **96**, 167.



Scheme 24



Scheme 25

Attention may be drawn to a useful and extensive review<sup>35b</sup> of the alkaloids of *Alstonia venenata*, which include a number of derivatives of aspidospermidine and vincadifformine. Three new alkaloids, echitoveniline (181), 11-methoxyechitoveniline (182), and 11-methoxyechitovenidine (183), occur<sup>35b,92</sup> in the fruits of this plant, although the leaves are a better source of (182). In consonance with these structures, ester exchange with sodium methoxide affords (-)-mino-vincinine (184) [from (181)] and (-)-11-methoxyminovincinine (185) [from (182) and (183)], whose physical constants show excellent agreement with those reported for (19*R*)-(184) and (19*R*)-(185).

In other extractions, (+)-vincadifformine, (-)-tabersonine, (-)-11-methoxytabersonine, (-)-lochnericine, (-)-lochnerinine, 14,15-dehydro-16-*epi*-vincamine, and 14,15-dehydro-16-*epi*-vincine have been isolated from *Melodinus aeneus* Baill.,<sup>82</sup> venalstonine and venalstonidine from the leaves of *M. balansae* var. *paucivenosus*,<sup>65</sup> and vincadifformine from the seeds of *Hunteria congolana*.<sup>41b</sup> The leaves and stem bark of *Geissospermum argenteum* Wood., from French Guyana, contain (-)-desmethoxyaspidospermine, (-)-aspidospermine, (+)-aspidocarpine, and (+)-desmethylassidospermine,<sup>93</sup> both antipodal series of alkaloids are thus represented in this plant. *G. argenteum* differs from the other *Geissospermum* species hitherto studied (*G. vellosii* and *G. laeve*), which elaborate only alkaloids of the corynane type, e.g. geissoschizoline and geissospermine, in which the secologanin-derived unit has not rearranged. Aspidospermidine derivatives are well represented in *Catharanthus ovalis*, and include<sup>41a</sup> vindoline, vindorosine, vindolinine, 19-*epi*-vindolinine, cathovaline, desacetylcathovaline, 14-hydroxycathovaline, 15-hydroxykopsinine (186), venalstonine, venalstonidine, (19*R*)- and (19*S*)-hydroxytabersonine, and cathovalinine. 15-Hydroxykopsinine (186) has apparently also been found in *C. longifolius*.<sup>94</sup> The two alkaloids of structure (187) and (188), previously described,<sup>95</sup> are now referred to as kitramine (19*R*) and kitraline (19*S*).<sup>41a</sup>

The branches and leaves of *Melodinus celastroides* have yielded<sup>76</sup> 19-*epi*-vindolinine, (19*R*)- and (19*S*)-hydroxytabersonine, (-)-tabersonine, (-)-venalstonine, (-)-vindolinine, and five new alkaloids, which are 14,15-dehydroisoeburnamine, buxomeline (189), and three alkaloids whose structures have not yet been disclosed, viz. melonine, melonine *N*<sub>b</sub>-oxide, and methylene-bis-1,1'-melonine. The structure (189) of buxomeline was deduced almost entirely from its spectroscopic properties; the presence of both *N*<sub>b</sub>-carbinolamine and carbinolamine ether functions is unusual.

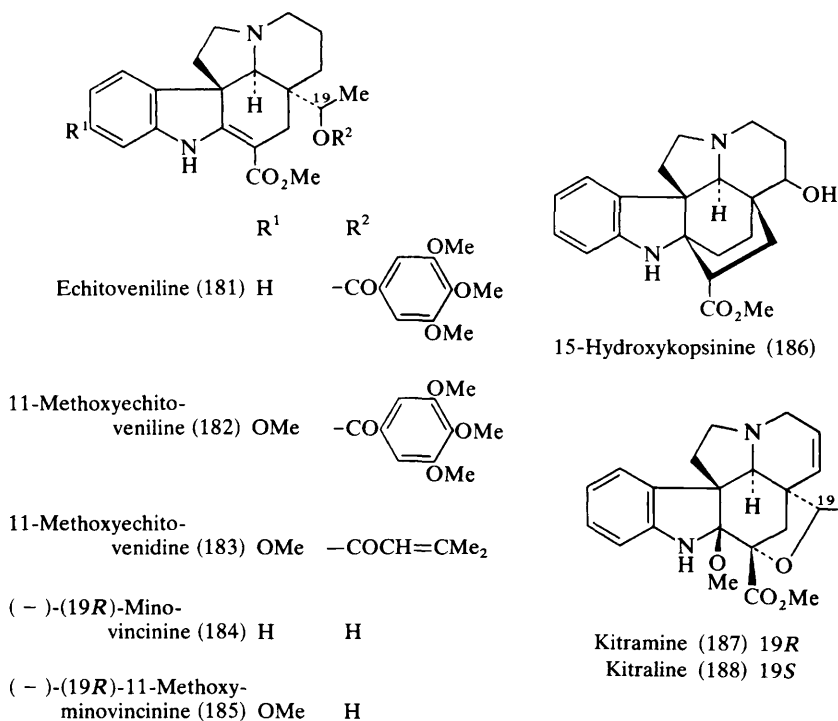
In previous work the stem bark of *Aspidosperma album* (Vahl) R. Bent. was examined, and ten alkaloids were isolated; attention has now been diverted to the seeds, from which no fewer than twenty-five alkaloids were obtained.<sup>38c</sup> Of these, fourteen were identified, including (-)-quebrachamine, (+)-aspidolimidine, and (+)-fendlerine, which are known to occur in the stem bark of the same plant. Other *Aspidosperma* bases identified were (+)-aspidospermidine, (+)-lima-

<sup>92</sup> P. L. Majumder, S. Joardar, T. K. Chanda, B. N. Dinda, M. Banerjee, A. B. Ray, A. Chatterjee, P. Varenne, and B. C. Das, *Tetrahedron*, 1979, **35**, 1151.

<sup>93</sup> J. P. Paccioni and H. P. Husson, *Phytochemistry*, 1978, **17**, 2146.

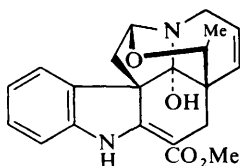
<sup>94</sup> P. Rasoanaivo, unpublished work, reported in ref. 41a.

<sup>95</sup> R. Z. Andriamialisoa, N. Langlois, and P. Potier, *Tetrahedron Lett.*, 1976, 163.

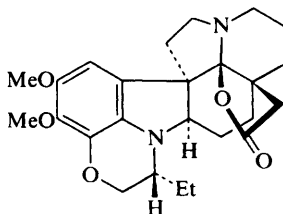


spermine, (+)-11-methoxylimaspermine, (-)-12-desmethoxyaspidospermine, and (+)-*O*-methyl-18-oxoaspidalbine, while the following are new to the genus *Aspidosperma*: (+)-vincadifformine, (±)-vincamine, and (±)-andranginine.

Alalakine, the remaining *Aspidosperma*-type alkaloid to be identified, is new, and exhibits an ultraviolet spectrum similar to that of obscurinvine. Its i.r. spectrum contains a double absorption in the carbonyl region that is reminiscent of the  $\gamma$ -lactone absorption of 18-oxoaspidalbine derivatives, while its mass spectrum contains peaks similar to those derived from the aromatic portion of obscurinvine and the hydroaromatic part of *O*-methyl-18-oxoaspidalbine. On the basis of these data, and the 400 MHz  $^1\text{H}$  n.m.r. spectrum, alalakine is formulated as (190).<sup>38c</sup>

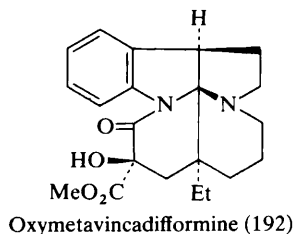
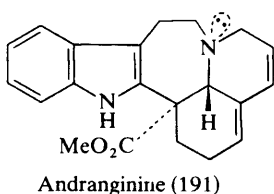


Buxomeline (189)



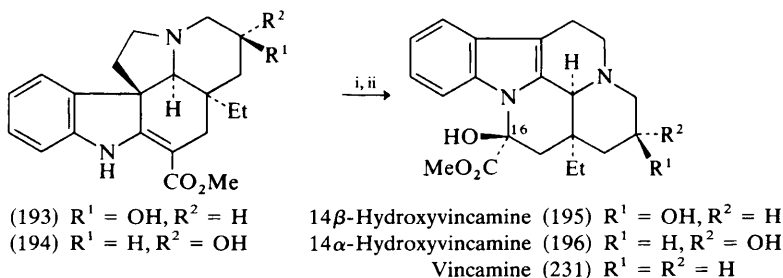
Alalakine (190)

The structure and stereochemistry of andranginine (191)<sup>96</sup> and oxy-metavincadifformine (192),<sup>97a</sup> the name now given to the oxidative rearrangement product of vincadifformine,<sup>97b</sup> have been confirmed by X-ray crystal-structure analysis.



Hydroboration-oxidation of tabersonine gives mainly 14 $\beta$ -hydroxyvincadifformine (193), together with a small amount of the 14 $\alpha$ -hydroxy-epimer (194).<sup>98</sup> The regioselectivity of this reaction is presumably a consequence of initial quaternization of N<sub>6</sub> by borane. If this reaction is accompanied by inversion of N<sub>6</sub>, as occurs in the quaternization of aspidospermine, the  $\alpha$ -face will be less accessible to reagent than the  $\beta$ -face, so that hydroboration must necessarily give rise to a 14 $\beta$ -hydroxy-derivative preferentially. The inductive effect of the positively charged N<sub>6</sub> no doubt results in a transition state of lower energy for the introduction of boron to C-14, rather than C-15. The rearrangement of vincadifformine derivatives to vincamine derivatives, *i.e.* by oxidation at C-16 and N<sub>6</sub> by means of peracid, followed by deoxygenation of the N<sub>6</sub>-oxide function (with PPh<sub>3</sub>) and rearrangement in acid, proceeds well with (193) and (194). The products, (195) and (196) respectively, are accompanied by their C-16 epimers (Scheme 26).<sup>98</sup>

14-Hydroxycathovaline, for which the structure and relative stereochemistry have been established earlier, has the absolute configuration shown in (197), since its c.d. spectrum is closely similar to that of cathovaline, which is known to have



Reagents: i, 2  $\times$  *p*-NPBA, PhH; ii, PPh<sub>3</sub>, AcOH, H<sub>2</sub>O

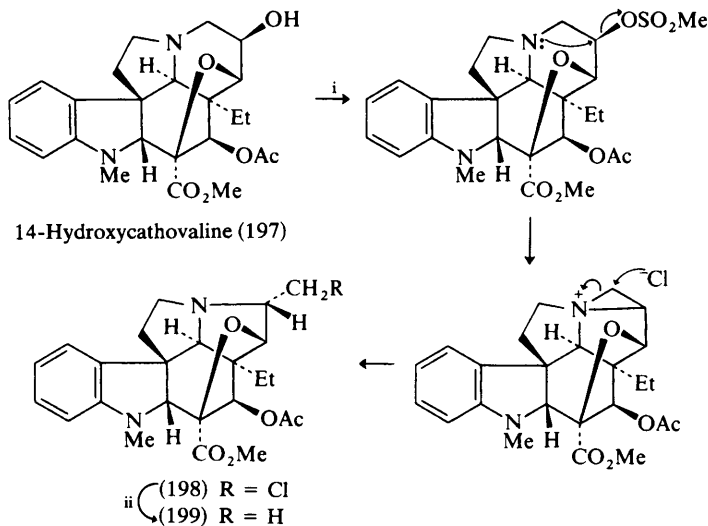
**Scheme 26**

<sup>96</sup> C. Riche and C. Pascard-Billy, *Acta Crystallogr., Sect. B*, 1979, **35**, 666.

<sup>97</sup> (a) N. Rodier, R. Céolin, G. Croquelois, N. Kunesch, and J. Poisson, *Acta Crystallogr., Sect. B*, 1978, **34**, 3682; (b) G. Croquelois, N. Kunesch, and J. Poisson, *Tetrahedron Lett.*, 1974, 4427.

<sup>98</sup> C. Caron-Sigaut, L. Le Men-Olivier, G. Hugel, J. Lévy, and J. Le Men, *Tetrahedron*, 1979, **35**, 957.

the same absolute stereochemistry as vindorosine.<sup>99</sup> In an attempt to correlate (197) with cathovaline, the oxidation of the 14-hydroxy-group was studied. However, oxidation tended to occur at the  $N_2$ -methyl group or at C-3, and the desired 14-oxo-compound could not be obtained. In the course of this work it was noted that the reaction of 14-hydroxycathovaline with mesyl chloride gave not a 14-mesylate but a primary chloride (198), in which ring D had suffered contraction; the proton n.m.r. spectra of (198) and the corresponding reduction product (199) served to confirm the structures and configurations assigned. The most likely mechanism for the change (197)  $\rightarrow$  (198) invokes the participation of an aziridinium ion (Scheme 27).<sup>99</sup>



Reagents: i, MeSO<sub>2</sub>Cl; ii, H<sub>2</sub>, Pd/C

Scheme 27

The selective cleavage of the 11-methoxy-group in vindoline can be achieved in 33% yield by the micro-organism *Sepedonium chrysospermum* ATCC; the product, *O*-desmethylvindoline, is apparently not contaminated with by-products.<sup>100a</sup> The vindoline dimer obtained<sup>63e</sup> on incubation of *Streptomyces griseus* in the presence of vindoline is presumably obtained *via* vindoline 3,14-enamine. Evidence in support of this view comes from the isolation of this very sensitive enamine from the fermentation extracts. Subsequent chromatography of the crude enamine on silica gel or alumina resulted in complete conversion into the previously isolated dimer.<sup>100b</sup>

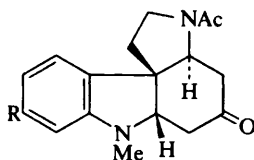
Kutney's work on the manipulation of the functional groups of vindoline, as a preliminary to the partial synthesis of vinblastine analogues, and the synthesis, in

<sup>99</sup> N. Langlois and P. Potier, *Bull. Soc. Chim. Fr., Part 2*, 1978, 144.

<sup>100</sup> (a) G. S. Wu, T. Nabih, L. Youel, W. Peczynska-Czoch, and J. P. Rosazza, *Antimicrobial Agents Chemother.*, 1978, **14**, 601; (b) M. E. Gustafson and J. P. Rosazza, *J. Chem. Res.*, 1979, (S), 166; (M), 1834.

the same laboratory, of 16,17-dihydrosecodine-17-ol and secodine, have been published in detail.<sup>101,102</sup> Other work described in detail includes Sundberg's synthesis<sup>103</sup> of 20-desethylquebrachamine, Winterfeldt's ingenious new route to eburnamonine and eburnamine,<sup>104</sup> and Schlessinger's synthesis of eburnamonine and vincamine.<sup>105</sup>

Takano *et al.* have published a second preliminary communication<sup>106</sup> in which new approaches to the intermediates (200) and (201)<sup>63f</sup> in Büchi's vindorosine/vindoline synthesis are described.



(200) R = H

(201) R = OMe

The synthesis of vindoline (202), by Kutney *et al.*,<sup>107</sup> from (±)-vincaminoridine (203) or (±)-16-*epi*-vincaminoridine (204), also constitutes a formal total synthesis, and affords a striking illustration of functional group transformation in this pentacyclic series. Oxidative cyclization of (203) or (204) gave 11-methoxy-*N*<sub>a</sub>-methylvincadifformine (205), whose structure was established by preparation from vindoline (202) (Scheme 28); subsequently, (205) was used as the relay intermediate, and was converted into vindoline *via* the 16-ketone (206). Ketone transposition gave the isomeric 17-ketone (207), also obtainable by the degradation of vindoline. Substitution in ring C was completed as in the Büchi synthesis to give dihydrovindoline (208), and the final problem was then the introduction of the 14,15 double-bond. This was achieved *via* oxidation of (208) to the lactam-ether (209), which on  $\beta$ -elimination and acetylation gave 3-oxovindoline 16-acetate (210); removal of the 3-oxo-group and partial deacetylation finally gave vindoline (202) (Scheme 28).<sup>107</sup>

Another impressive contribution to synthesis in this area is the total synthesis of vincadifformine (211) and ervinceine (212) (=11-methoxyvincadifformine) by

<sup>101</sup> J. P. Kutney, J. Balsevich, T. Honda, P. H. Liao, H. P. M. Thiellier, and B. R. Worth, *Can. J. Chem.*, 1978, **56**, 2560.

<sup>102</sup> J. P. Kutney, R. A. Badger, J. F. Beck, H. Bosshardt, F. S. Matough, V. E. Ridauro-Sanz, Y. H. So, R. S. Sood, and B. R. Worth, *Can. J. Chem.*, 1979, **57**, 289.

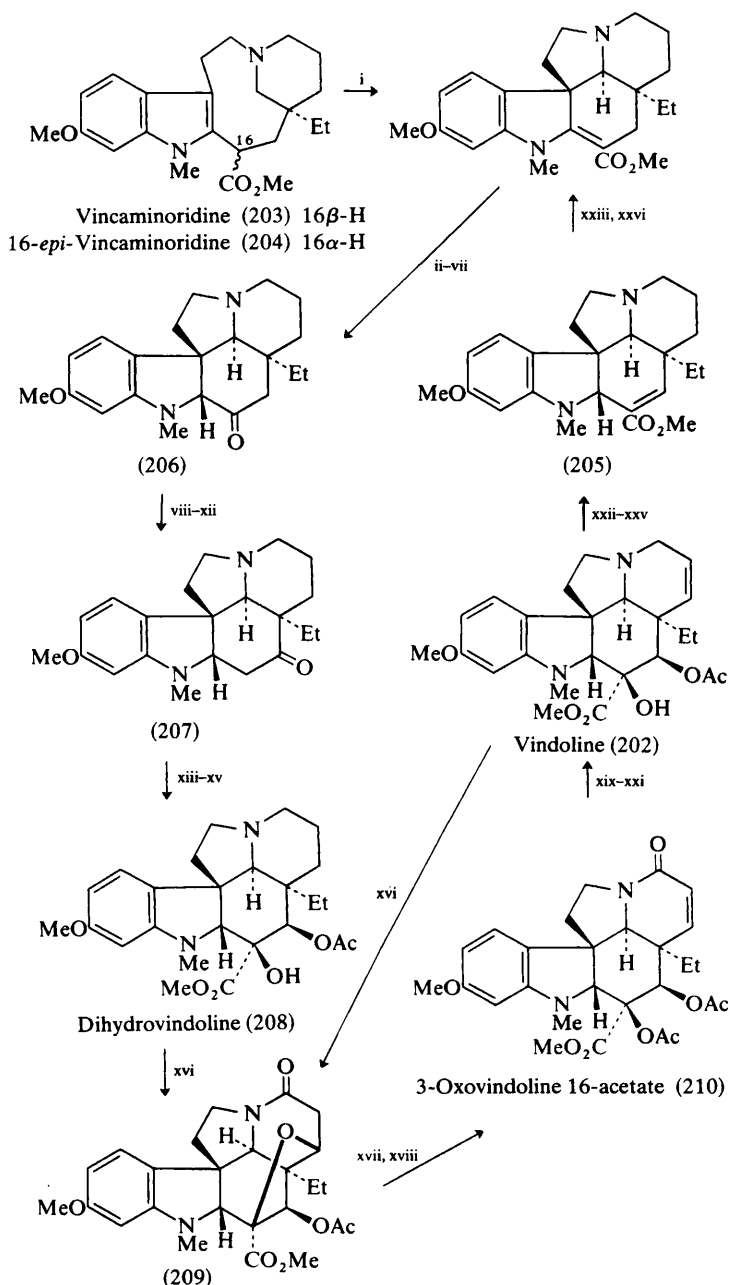
<sup>103</sup> R. J. Sundberg, J. G. Luis, R. L. Parton, S. Schreiber, P. C. Srinivasan, P. Lamb, P. Forcier, and R. F. Bryan, *J. Org. Chem.*, 1978, **43**, 4859.

<sup>104</sup> R. Becker, G. Benz, M. Rösner, U. Rosentreter, and E. Winterfeldt, *Chem. Ber.*, 1979, **112**, 1879; H. Hammer, M. Rösner, U. Rosentreter, and E. Winterfeldt, *ibid.*, p. 1889; E. Bölsing, F. Klatte, U. Rosentreter, and E. Winterfeldt, *ibid.*, p. 1902.

<sup>105</sup> J. L. Herrmann, R. J. Cregge, J. E. Richman, G. R. Kieczkowski, S. N. Normandin, M. L. Quesada, C. L. Semmelhack, A. J. Poss, and R. H. Schlessinger, *J. Am. Chem. Soc.*, 1979, **101**, 1540.

<sup>106</sup> S. Takano, K. Shishido, M. Sato, K. Yuta, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1978, 943.

<sup>107</sup> J. P. Kutney, U. Bunzli-Trepp, K. K. Chan, J. P. de Souza, Y. Fujise, T. Honda, J. Katsube, F. K. Klein, A. Leutwiler, S. Morehead, M. Rohr, and B. R. Worth, *J. Am. Chem. Soc.*, 1978, **100**, 4220.





Kuehne *et al.*<sup>108</sup> (Scheme 29). The basic strategy involved the construction of a spirocyclic quaternary ammonium ion (213) which, on fragmentation, was expected to yield the fugitive secodine (214); spontaneous biomimetic cyclization of (214) should then yield (±)-vincadifformine (211). This concept was brilliantly executed, and high yields of vincadifformine were obtained from the intermediate indolazepinedicarboxylic ester (215).<sup>108a</sup> The preparation of (215) from *N*-benzyltetrahydro- $\beta$ -carboline (216) was also an ingenious process which presumably involved the spiropyrrolidino-derivative (217) (not isolated). Evidence that (217) was involved was obtained from an alternative preparation of (218) from the  $\gamma$ -carboline isomer (219) of (216); the two conversions (216)  $\rightarrow$  (218) and (219)  $\rightarrow$  (218) must proceed *via* a common intermediate, which can only be the spirocyclic compound (217).<sup>108b</sup>

Subsequently, the independent hydrolysis and monodecarboxylation of esters of type (215) was found to be unnecessary, and an even more direct approach to vincadifformine was developed using the dimethyl ester (218), which underwent spiro-alkylation, hydrolysis, and decarboxylation *in situ*, followed by fragmentation and recyclization, to give vincadifformine (211) (Scheme 29).<sup>108b</sup>

Extension to the synthesis of ervinceine (212) involved as starting material the methoxytetrahydro- $\gamma$ -carboline derivative (220), which is more readily accessible, by synthesis from *N*-benzyl-4-piperidone, than the isomeric  $\beta$ -carboline derivative.<sup>108b</sup>

Wenkert's new route<sup>109</sup> to eburnamonine (221) (Scheme 30) involves a neat extension of the preparation of 1,4-diketones, *via* cyclopropanoid intermediates, which allows the formation of  $\gamma$ -imino- or  $\gamma$ -keto-acids. Two variations of this approach were reported, all the stages in which were high-yielding, given the essential starting materials (222) and (223). In both variations the intermediate  $\gamma$ -substituted acid was stabilized by cyclization, *i.e.* as (224) or (225). Condensation with the appropriate indolyethyl derivative then led to the common intermediate (226), which on thermolysis gave (±)-eburnamonine (221).

Yet another new synthesis<sup>110</sup> of (±)-eburnamonine (221) employs two routes to the preparation of the tetracyclic unsaturated ester (227). One of these involved the first application of the Wadsworth–Emmons reaction to an enol ester (228). This neatly introduced the future C-16 and C-17 to give a *trans*-quinolizidine derivative, which, on 1,4-addition of ethyl magnesium bromide, completed the carbon skeleton with formation of the desired *cis* C/D quinolizidine ester; cyclization on to the indole nitrogen then gave (±)-eburnamonine (221) (Scheme 31).

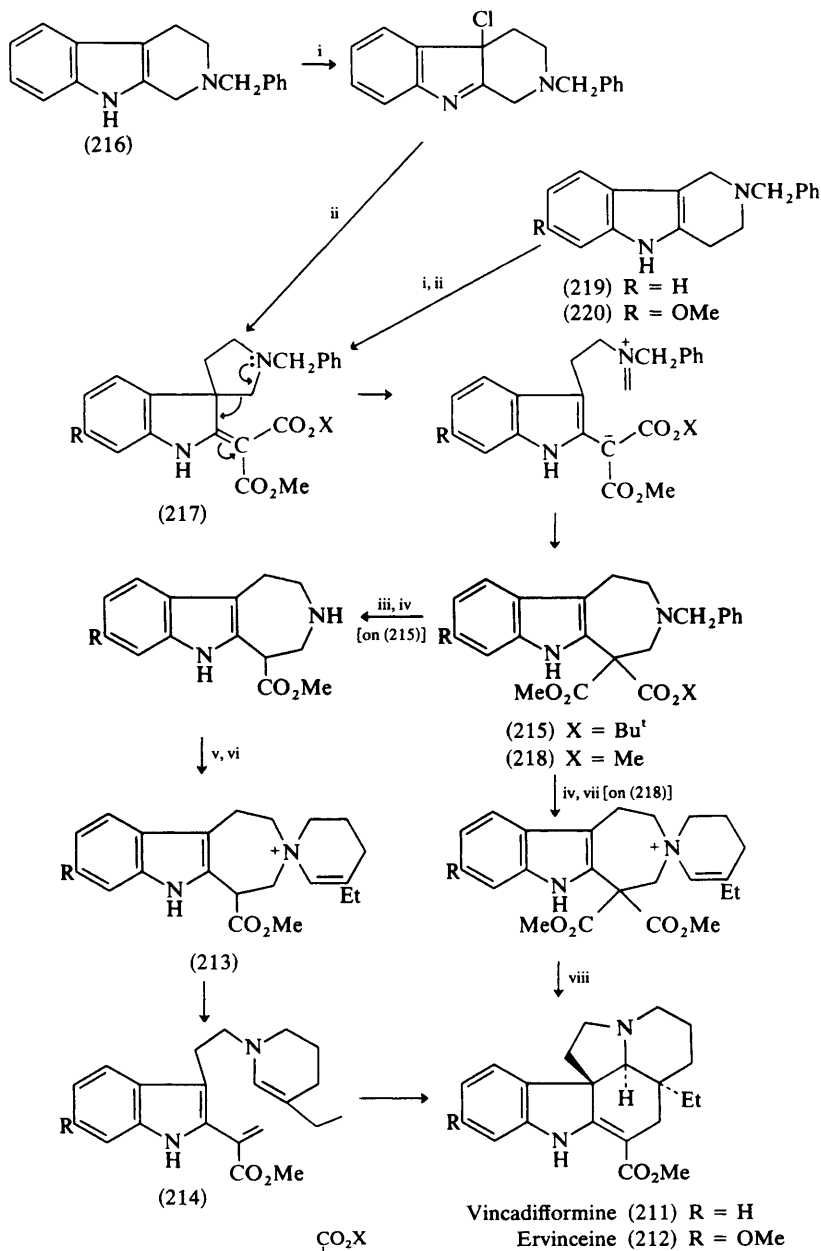
<sup>108</sup> (a) M. E. Kuehne, D. M. Roland, and R. Hafter, *J. Org. Chem.*, 1978, **43**, 3705; (b) M. E. Kuehne, T. H. Matsko, J. C. Bohnert, and C. L. Kirkemo, *ibid.*, 1979, **44**, 1063.

<sup>109</sup> E. Wenkert, T. Hudlický, and H. D. H. Showalter, *J. Am. Chem. Soc.*, 1978, **100**, 4893.

<sup>110</sup> G. Costerousse, J. Buendia, E. Toromanoff, and J. Martel, *Bull. Soc. Chim. Fr., Part 2*, 1978, 355.

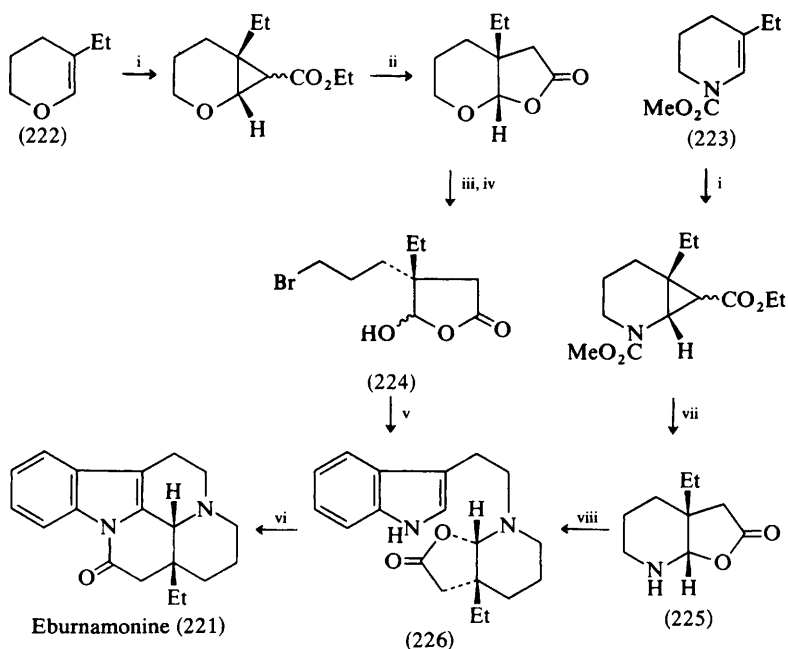
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KOBu<sup>t</sup>; xv, NaAl(OCH<sub>2</sub>CH<sub>2</sub>OMe)<sub>2</sub>H<sub>2</sub>, AlCl<sub>3</sub>, THF, at -20 °C; xvi, Hg(OAc)<sub>2</sub>, dioxan; xvii, Ph<sub>3</sub>CLi, THF; xviii, Ac<sub>2</sub>O, THF; xix, Me<sub>3</sub>O<sup>+</sup> BF<sub>4</sub><sup>-</sup>, CH<sub>2</sub>Cl<sub>2</sub>; xx, NaBH<sub>4</sub>, EtOH; xxi, silica gel, H<sub>2</sub>O; xxii, HCl, H<sub>2</sub>O; xxiii, H<sub>2</sub>, Pt; xxiv, *NN'*-thiocarbonyldi-imidazole, MeCOEt, heat; xxv, Raney nickel, THF; xxvi, Pb(OAc)<sub>4</sub>.



Reagents: i, PhH, NEt<sub>3</sub>, Bu'OCl; ii, TiHCO<sub>2</sub>Me, PhH; iii, TFA, ClCH<sub>2</sub>CH<sub>2</sub>Cl, N<sub>2</sub>, heat for 3.5 h; iv, H<sub>2</sub>, Pd/C, AcOH; v, Br(CH<sub>2</sub>)<sub>3</sub>CHEtCHO, MeOH, N<sub>2</sub>, at r.t. for 1 h; vi, NEt<sub>3</sub>, MeOH, at 40 °C for 12 h; vii, Br(CH<sub>2</sub>)<sub>3</sub>CHEtCHO, TsOH, MeOH, N<sub>2</sub>, at 40 °C for 10 h; viii, NEt<sub>3</sub>, MeOH, at 60 °C for 4 h

Scheme 29



Reagents: i,  $\text{N}_2\text{CHCO}_2\text{Et}$ , Cu; ii,  $\text{H}^+$ ,  $\text{H}_2\text{O}$ ; iii,  $\text{BBr}_3$ ,  $\text{CH}_2\text{Cl}_2$ , at r.t. for 14 h; iv, 1% HCl, dioxan, at  $80^\circ\text{C}$  for 20 h; v, tryptamine-HCl, DMSO, at  $55^\circ\text{C}$  for 12 h, 3A molecular sieves; vi,  $250^\circ\text{C}$ , 0.01 mmHg for 0.5h; vii, KOH,  $\text{H}_2\text{O}$ ,  $\text{HOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$ , at  $100^\circ\text{C}$  for 12 h; viii, tryptophyl bromide, NaOH,  $\text{Et}_3\text{NCH}_2\text{Ph Cl}^-$ , PhH, at  $35^\circ\text{C}$  for 6 h

**Scheme 30**

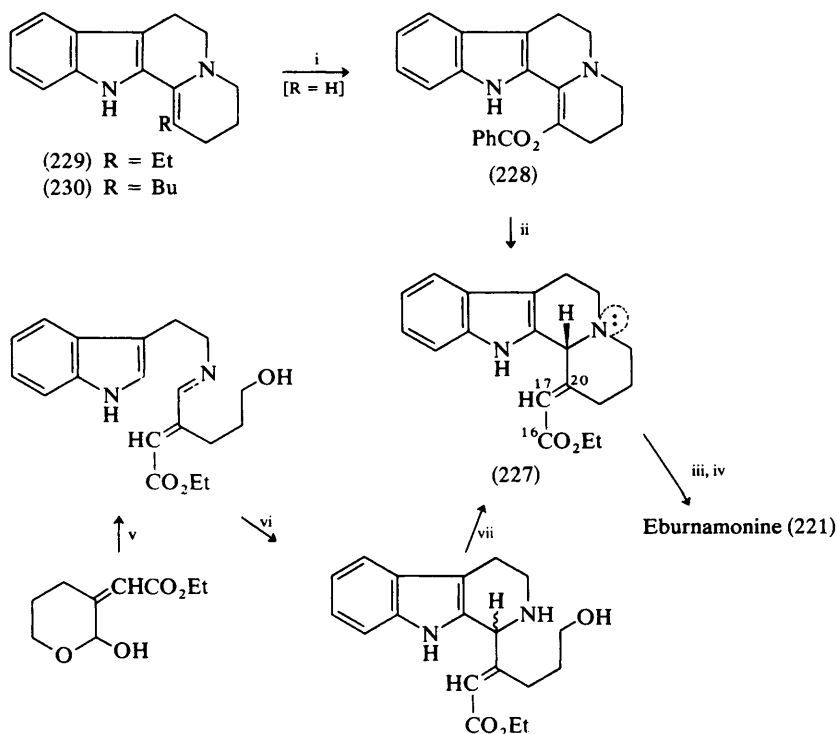
The enamine (229) has in the past served as a useful intermediate in a number of eburnamine–vincamine syntheses. Recent applications of this same enamine have resulted in the synthesis of homoeburnamine,<sup>111</sup> ( $\pm$ )-ethyl apovincamine,<sup>112a</sup> several 16-deoxy-21-*epi*-vincamine derivatives, together with two butyl analogues derived from the enamine (230),<sup>112b</sup> and the butyl analogue of vincamine, also derived from the enamine (230).<sup>112c</sup>

The oxidative rearrangement of vincadifformine (211) to vincamine (231) (whose structure is shown in Scheme 26) can be done directly and in approximately 30% yield, by the use of oxygen in the presence of metal salts (e.g. copper sulphate, ferric chloride, or cobalt stearate) and dilute hydrochloric acid; some 16-*epi*-vincamine is naturally also obtained. Tabersonine likewise gives 14,15-dehydrovincamine and its 16-epimer.<sup>113</sup> This method avoids the undesired

<sup>111</sup> A. Buzas, C. Retourne, J. P. Jacquet, and G. Lavielle, *Tetrahedron*, 1978, **34**, 3001.

<sup>112</sup> (a) G. Kalaus, P. Györy, L. Szabó, and Cs. Szántay, *Acta Chim. Acad. Sci. Hung.*, 1978, **97**, 429; (b) G. Kalaus, L. Szabó, Cs. Szántay, E. Kárpáty, and L. Szporny, *Arch. Pharm. (Weinheim, Ger.)*, 1979, **312**, 312; (c) G. Kalaus, P. Györy, L. Szabó, and Cs. Szántay, *Acta Chim. Acad. Sci. Hung.*, 1978, **96**, 385.

<sup>113</sup> S. Paracchini and E. Pesce, *Farmaco, Ed. Sci.*, 1978, **33**, 573.



Reagents: i, (PhCO<sub>2</sub>)<sub>2</sub>, hydroquinone, dioxan, at 25 °C for 30 min, then NH<sub>4</sub>OH; ii, (EtO)<sub>2</sub>POCH<sub>2</sub>-CO<sub>2</sub>Et, NaH, DME, N<sub>2</sub>; iii, EtMgBr, CuCl<sub>2</sub>, THF, Et<sub>2</sub>O, N<sub>2</sub>; iv, NH<sub>4</sub>Cl, H<sub>2</sub>O; v, tryptamine, PhH, N<sub>2</sub>; vi, EtOH, HCl; vii, SOCl<sub>2</sub>, py, PhH

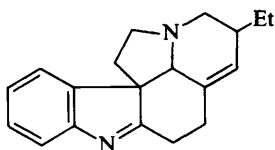
**Scheme 31**

oxidation at N<sub>6</sub>, and the necessity to remove the N<sub>6</sub>-oxide function so produced, by means of triphenylphosphine, which was a feature of the earlier procedure.

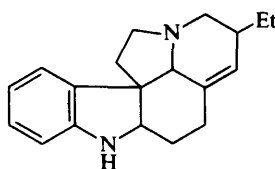
**Catharanthine-Ibogamine-Cleavamine Group.** New extractions have resulted in the isolation of (+)-(20*R*)- and (-)-(20*S*)-dihydrocleavamine, (+)-(20*S*)-1,2-dehydropseudoaspidospermidine, and (+)-(20*R*)- and (-)-(20*S*)-pseudoaspidospermidine, from the leaves, stem bark, and root bark of *Pandaca boiteau*,<sup>77</sup> and ibogamine and 20-*epi*-ibogamine from *Melodinus aeneus*.<sup>82</sup> Of five new, minor alkaloids isolated from the leaves and stem bark of *Capuronetta elegans* Mgf., two are monomeric, and prove to be 14,15-anhydrocapuronidine (232) and 14,15-anhydro-1,2-dihydrocapuronidine (233).<sup>114</sup> The occurrence of catharanthine and (-)-coronaridine in the same plant, *Catharanthus ovalis*, in association with 22 other alkaloids, is of some interest, since they belong to enantiomeric series.<sup>41a</sup>

Further investigations into the constituents of *Tabernaemontana apoda* Wt. ex Sauv. (*Peschiera apoda* Mgf.) have revealed the presence of voacangine hydr-

<sup>114</sup> I. Chardon-Loriaux, M. M. Debray, and H. P. Husson, *Phytochemistry*, 1978, **17**, 1605.



14,15-Anhydrocapuronidine (232)



14,15-Anhydro-1,2-dihydrocapuronidine (233)

oxyindolenine, voacristine, and voacangine pseudoindoxyl in the root bark,<sup>115a</sup> and coronaridine, ibogamine, voacangine,<sup>115b</sup> voacristine, voacangine hydroxyindolenine, voacristine hydroxyindolenine, and voacristine pseudoindoxyl<sup>115c</sup> in the fruits.

Further reactions of catharanthine (234) have been studied in the search for suitable substrates for the partial synthesis of vinblastine derivatives.<sup>116</sup> Since access to the  $\alpha$ -face of catharanthine is severely hindered, the only reliable method of obtaining 20 $\alpha$ -hydroxy-derivatives, required for a possible synthesis of vinblastine itself, is *via* catharanthine lactone (235). A new preparation of (235) uses the oxidation of catharanthine acid (236) by means of mercuric acetate in *dry* THF; reduction of the intermediate mercurio-lactone (237) with tetrabutylammonium borohydride then gives catharanthine lactone (235). When the proportions of solvents used in this reduction were varied, the epimeric hydroxy-lactones (238) were obtained (Scheme 32).

In aqueous methanol, the oxidation of catharanthine acid (236) with mercuric acetate gives a product (239), obtained by oxidative decarboxylation and rearrangement. A possible mechanism for this reaction is illustrated (Scheme 32). An alternative preparation of (239) involves the von Braun degradation of catharanthine (234), which severs the 21-N<sub>6</sub> bond to give a cyanamide derivative (240). Saponification of (240) followed by bromodecarboxylation and removal of the *N*-cyano-group affords a tetracyclic amino-diene (241) which, on oxidation in methanol solution, gives the epimers (239).<sup>116</sup>

In connection with total synthesis in this subgroup, mention may be made of a model synthesis of 5-oxodesethylcatharanthine (242) by the photocyclization of the chloro-amide (243).<sup>117</sup> Extension of this approach to the synthesis of catharanthine is at present being hindered by the non-availability of the dihydropyridine derivative required for the preparation of the 20-ethyl analogue of (243).

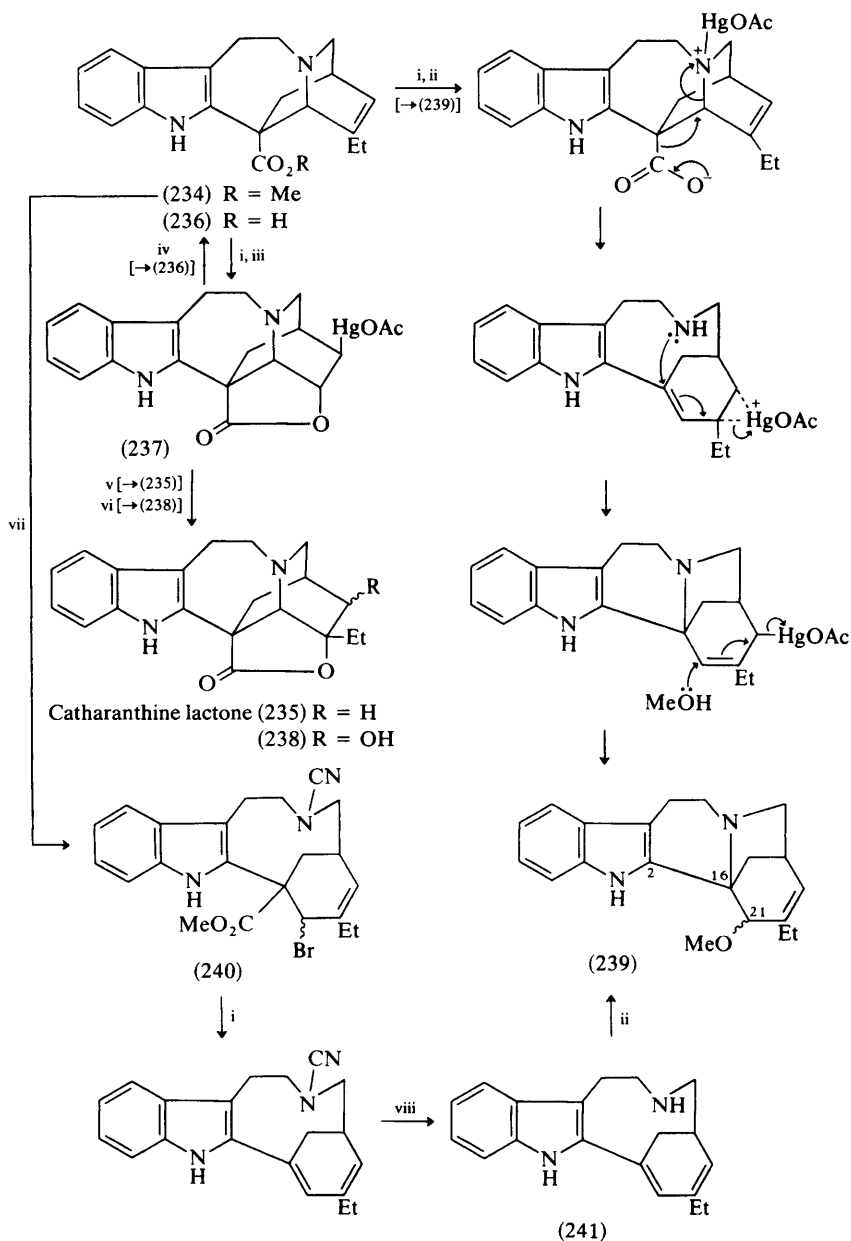
Quite the most outstanding contribution to synthesis in this group in recent years is the asymmetric synthesis of ibogamine by Trost *et al.*<sup>118</sup> Starting from the optically active diene (244), ibogamine (245) was obtained in only four stages in an astonishing overall yield of 17%. Two of these stages involved transition-metal (palladium)-catalysed cyclizations, the second being assisted also by silver in a new olefin arylation procedure (Scheme 33).

<sup>115</sup> (a) P. Sierra, R. Iglesias, and I. Perez, *Rev. CENIC, Cienc. Fis.*, 1977, **8**, 47; (b) A. Lagunas and R. Iglesias, *ibid.*, p. 61; (c) A. Lagunas and R. Iglesias, *ibid.*, p. 67 (*Chem. Abs.*, 1979, **90**, 100 129, 100 131, and 100 132).

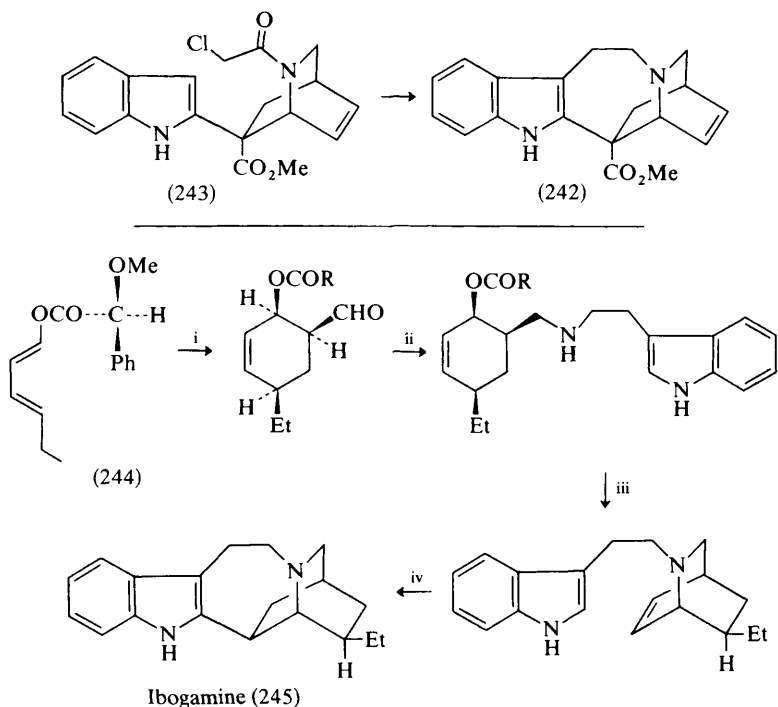
<sup>116</sup> P. Mangeney and Y. Langlois, *Tetrahedron Lett.*, 1978, 3015.

<sup>117</sup> R. J. Sundberg and J. D. Bloom, *Tetrahedron Lett.*, 1978, 5157.

<sup>118</sup> B. M. Trost, S. A. Godleski, and J. P. Genêt, *J. Am. Chem. Soc.*, 1978, **100**, 3930.



Scheme 32



Reagents: i,  $\text{CH}_2=\text{CHCHO}$ ,  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ ; ii, tryptamine,  $\text{NaBH}_4$ ; iii,  $[\text{Pd}(\text{PPh}_3)_4]$ ,  $\text{MeCN}$ , at  $70^\circ\text{C}$ ; iv,  $[(\text{MeCN})_2\text{PdCl}_2]$ ,  $\text{AgBF}_4$ , then  $\text{NaBH}_4$

**Scheme 33**

### 3 Bis-indole Alkaloids

Staurosporine (AM-2282), a constituent<sup>119a</sup> of *Streptomyces staurosporus*, which exhibits both strong hypotensive and antimicrobial activity, has the novel structure (246), according to X-ray crystal-structure analysis.<sup>119b</sup>

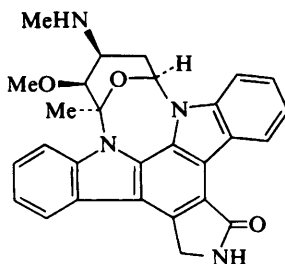
Details of the elucidation<sup>3i</sup> of the structure of chetomin have now been published.<sup>120</sup>

A new synthesis<sup>121</sup> of folicanthine (247) and chimonanthine (248) has been reported, in which the dimeric structure is obtained by the proflavine-sensitized photo-oxygenation of  $N_6$ -methoxycarbonyltryptamine in formic acid (Scheme 34). The product proved to be a mixture of the  $N_6$ -formyl-3a-hydroxy-pyrroloindole (249) and the dimeric compounds (250), separable into racemic (250a) and *meso* (250b) forms. Reduction (by  $\text{LiAlH}_4$ ) of the mixture of (250a)

<sup>119</sup> (a) S. Omura, Y. Iwai, A. Hirano, A. Nakagawa, J. Awaya, H. Tsuchiya, Y. Takahashi, and R. Masuma, *J. Antibiot.*, 1977, **30**, 275; (b) A. Furusaki, N. Hashiba, T. Matsumoto, A. Hirano, Y. Iwai, and S. Omura, *J. Chem. Soc., Chem. Commun.*, 1978, 800.

<sup>120</sup> D. Brewer, A. G. McInnes, D. G. Smith, A. Taylor, J. A. Walter, H. R. Loosli, and Z. L. Kis, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1248.

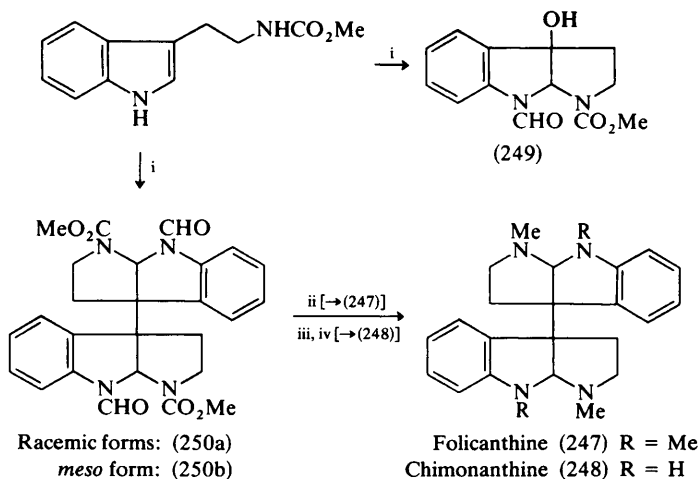
<sup>121</sup> T. Hino, S. Kodato, K. Takahashi, H. Yamaguchi, and M. Nakagawa, *Tetrahedron Lett.*, 1978, 4913.



Staurosporine (246)

and (250b) gave ( $\pm$ )-folicanthine (247), while reduction of the *meso* form (250b) gave *meso*-folicanthine, not previously prepared.

Removal of the  $N_4$ -formyl groups in (250a) by hydrolysis, then reduction by means of lithium aluminium hydride, gave ( $\pm$ )-chimonanthine (248); similar treatment of the mixture of (250a) and (250b) gave ( $\pm$ )-chimonanthine and *meso*-chimonanthine. Since ( $\pm$ )-chimonanthine can be converted into ( $\pm$ )-calycanthine in boiling acetic acid, this also constitutes a total synthesis of calycanthine.<sup>121</sup>



Reagents: i,  $O_2$ ,  $HCO_2H$ ,  $h\nu$ , proflavine hemisulphate, 10–15 °C, 1 h; ii,  $LiAlH_4$ ,  $Et_2O$ , 20 h; iii, 10%  $NaOH$ ,  $MeOH$ ; iv,  $LiAlH_4$ ,  $THF$

Scheme 34

The notable work<sup>122a</sup> by Parry and Smith on the structure of quadrigemines A and B, two minor alkaloids of *Hodgkinsonia frutescens* F. Muell., has been published.<sup>122b</sup> Both alkaloids are composed of four  $N_6$ -methyltryptamine units, and are the first tetrameric structures to be encountered. The structure of quadrigemine A (251) follows from its facile Hofmann degradation to a tetra-

<sup>122</sup> (a) K. P. Parry, Ph.D. Thesis, Univ. of Manchester, 1968; (b) K. P. Parry and G. F. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1671.



methine base (252), which is cleanly reduced by potassium borohydride to a single product, the indolyindoline (253), identical with that derived from degradation of hodgkinsine.

The mass spectral evidence, as well as this chemical evidence, indicates that quadrigemine A has a symmetrical structure, but the n.m.r. evidence indicates that it is probably a mixture of diastereoisomers. On the basis of the optical rotation evidence derived from quadrigemine A, the degradation product (253), and the dimeric alkaloids (247), (248), and calycanthidine, it has been suggested that quadrigemine A is a mixture of the (*RRSR*) diastereoisomer illustrated (251), together with one or both of the *meso* diastereoisomers (*RRSS*) and (*RSRS*).

Quadrigemine B (254) exhibits an n.m.r. spectrum similar to that of quadrigemine A, but shows a marked difference in its mass spectrum, which reveals a fragmentation into mono-tryptamine and trimeric tryptamine units. This is confirmed by Hofmann degradation followed by reduction (with  $\text{KBH}_4$ ), which gave high yields of  $N_bN_b$ -dimethyltryptamine and a trimeric indolyl-bisindoline base of probable structure (255). The mode of attachment of the tryptamine units in (255) was deduced from the spectral evidence, deuteration experiments, and from the electronic spectra of the product of  $N_a$ -formylation and nitration of (255). On the basis of these data, the structure (254) (no stereochemistry implied) was proposed for quadrigemine B.<sup>122</sup>

Borreverine (256) occurs, together with an isomer, isoborreverine (257), in the leaves and stems of *Flindersia fournieri* Panch. et Seb.,<sup>123a</sup> both alkaloids occur, together with the monomer, borrerine (258), in *Borreria verticillata*.<sup>123b</sup> The structure of isoborreverine follows<sup>123a</sup> from its acetylation to a diacetyl derivative (259), whose structure was earlier established<sup>3j</sup> by the X-ray method, since it is also the acetylation product of borreverine. Both borreverine (256) and isoborreverine (257) may be synthesized by the acid-catalysed (HCl, MeOH, TFA) dimerization of borrerine (258) and, under similar conditions, borreverine can be quantitatively converted into isoborreverine.<sup>123b</sup>

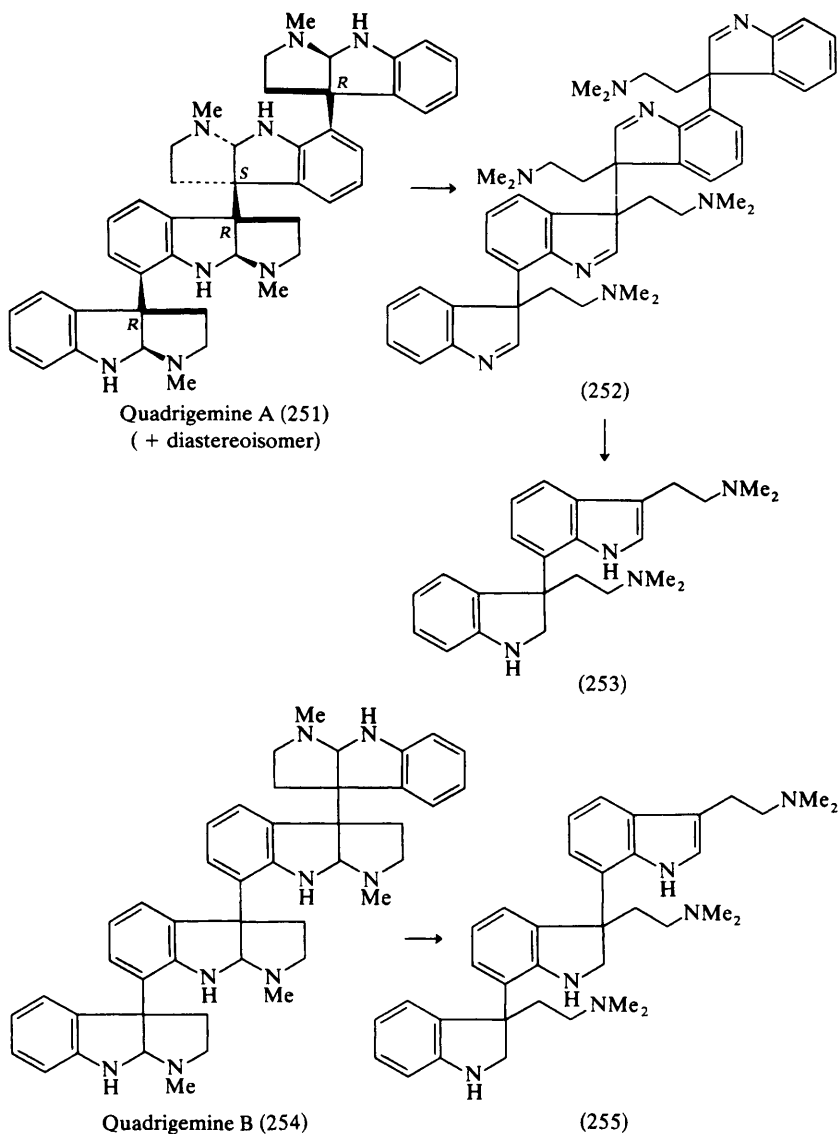
The synthesis<sup>124</sup> of the four epimers of the structure (260), from  $N_b$ -methyl-tryptamine and ( $\pm$ )-geissoschizal or ( $\pm$ )-3-*epi*-geissoschizal, reveals that the structure (260) earlier proposed for usambarine is incorrect. The  $^1\text{H}$  n.m.r. spectrum of usambarine shows significant differences from the spectra of the synthetic bases (260), particularly in the olefinic region, and it now appears that usambarine contains a vinyl group; this is supported by the i.r. absorption at  $918\text{ cm}^{-1}$ . Usambarine is therefore regarded as being (261), the absolute configuration at C-3 and C-17 being based on a comparison of the c.d. spectra of (261) and ochrolifuanine B.

The configuration at C-20 is, perhaps, less secure, there being at present no unequivocal evidence relating to this point. It is therefore of interest to note that the structure (261) has also been assigned to 18,19-dehydronigritanine, one of four alkaloids isolated<sup>125</sup> from the leaves of *Strychnos nigritana* Bak. Again no

<sup>123</sup> (a) F. Tillequin, M. Koch, M. Bert, and T. Sévenet, *J. Nat. Prod.*, 1979, **42**, 92; (b) F. Tillequin, M. Koch, J. L. Pousset, and A. Cavé, *J. Chem. Soc., Chem. Commun.*, 1978, 826.

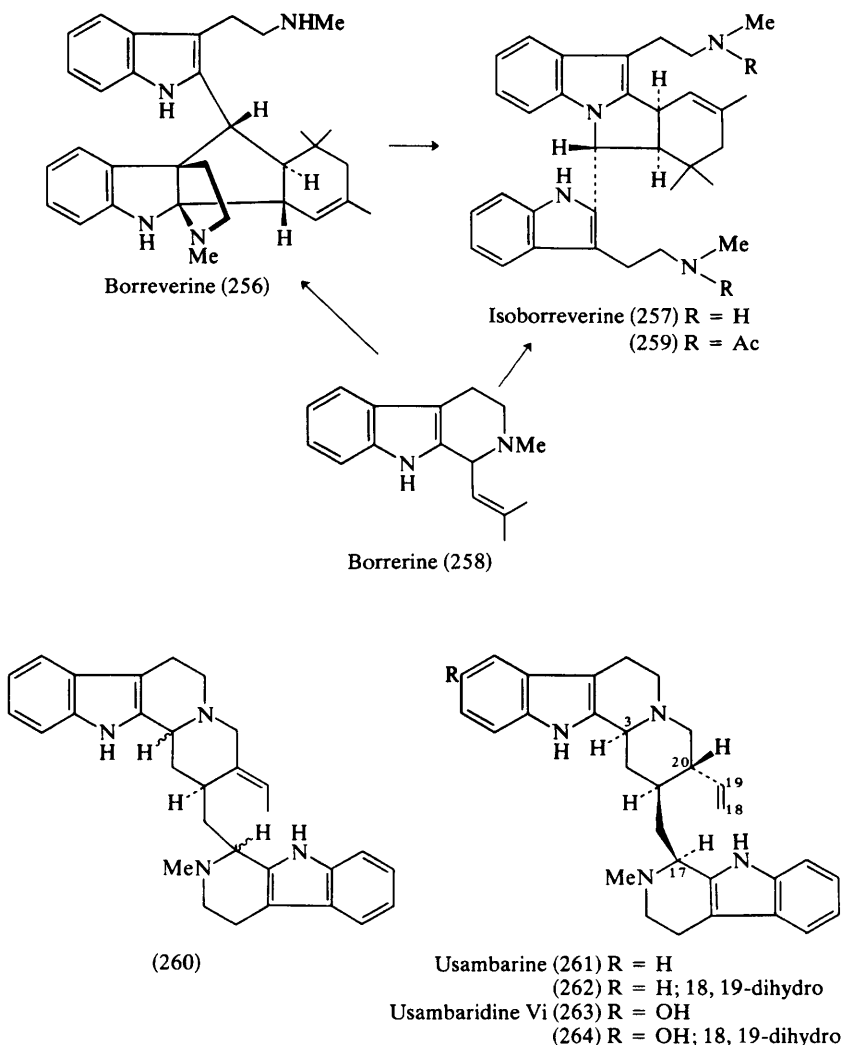
<sup>124</sup> L. J. G. Angenot, C. A. Coune, M. J. G. Tits, and K. Yamada, *Phytochemistry*, 1978, **17**, 1687.

<sup>125</sup> J. U. Oguakwa, C. Galeffi, I. Messina, R. La Bua, M. Nicoletti, and G. B. Marini-Bettòlo, *Gazz. Chim. Ital.*, 1978, **108**, 615.



direct evidence was available relating to the configuration at C-20. It is possible that 18-dehydronigritanine and usambarine are identical, or they may be epimers at C-20; the Italian workers commented on the almost complete identity of the mass spectra of the two alkaloids, although they were working on the assumption that usambarine is (260).

The other three alkaloids obtained<sup>125</sup> from *S. nigritana* are nigritanine (262), which is the 18,19-dihydro-derivative of (261), the 10-hydroxy-derivative (263) of (261), and 10-hydroxynigritanine (264).



Following a re-examination of the  $^1\text{H}$  n.m.r. spectrum of usambaridine Vi at 300 MHz, Angenot *et al.*<sup>126</sup> have concluded that this alkaloid also has the structure and stereochemistry (263), in which case it is identical to 10-hydroxy-18,19-dehydronigritanine.

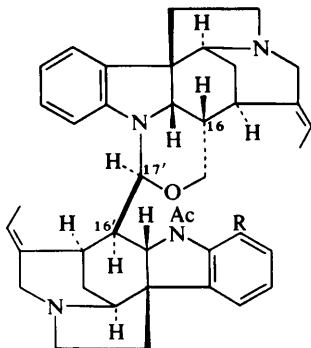
A second brief account of the isolation of the oxindole alkaloids strychnofoline, isostrychnofoline, strychnophylline, and isostrychnophylline, and the X-ray crystal-structure determination of strychnofoline, have been published.<sup>127</sup>

<sup>126</sup> L. Angenot, C. Coune, and M. Tits, *J. Pharm. Belg.*, 1978, **33**, 284.

<sup>127</sup> L. Angenot, *Plant. Med. Phytother.*, 1978, **12**, 123.

Extracts of *S. dolichothyrsa* show marked muscle-relaxant activity, and contain a wide range (>60) of alkaloids. Bis-strychninoid alkaloids that are present include bisnordihydrotoxiferine, bisnor-C-alkaloid H, and caracurine V.<sup>128</sup>

Bisnordihydrotoxiferine is also found in the root bark of *S. variabilis*,<sup>83</sup> together with strychnobiline (265), isostrychnobiline (266), and 12'-hydroxyisostrychnobiline (267).<sup>129</sup> As an internal carbinolamine ether, strychnobiline can be hydrolysed by acid to the component aldehyde and amino-alcohol, which are 18-deoxydiaboline and desacetylretuline,<sup>83</sup> since these bases also occur in *S. variabilis*, the possibility that (265) is an artefact cannot be excluded.



Strychnobiline (265) R = H

(stereochemistry at C-16, -16', and -17' is unspecified)

Isostrychnobiline (266) R = H

12'-Hydroxyisostrychnobiline (267) R = OH

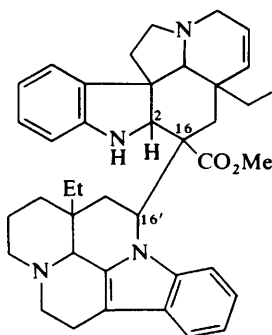
Isostrychnobiline (266) and its 12'-hydroxy-derivative (267) presumably differ from strychnobiline (265) at one or more of the centres C-16, -16', and -17'. The similarity between the n.m.r. spectra of the stereochemically analogous bases (266) and (267) is obscured partly by the fact that (266) exists as two principal amide rotamers in solution, whereas the hydrogen-bonding between the amide function and the cryptophenolic hydroxy-group in (267) results in only one rotamer in solution. Nevertheless, comparison of the n.m.r. spectra of (266) and (267) with retuline and appropriate derivatives, including 16-iso-retuline, reveals that (266) and (267) are composed of one retuline and one isoretuline component, the complete stereochemistry being as shown.<sup>86a,129</sup>

Methylene-bis-1,1'-melonine is a new constituent of *Melodinus celastroides* whose structure has not yet been revealed.<sup>76</sup>

Paucivenine (268), an amorphous alkaloid of *M. balansae* var. *paucivenosus*,<sup>65</sup> contains indole, indoline, and saturated ester chromophores, and in its mass spectrum exhibits peaks characteristic of eburnane and tabersonine (both of which could be generated by transfer of H-2 to C-16' with fission of the 16-16' bond) together with peaks reminiscent of tabersonine. On the basis of these data,

<sup>128</sup> R. Verpoorte, *Pharm. Weekbl.*, 1978, **113**, 1249 (*Chem. Abs.*, 1979, **90**, 109 840).

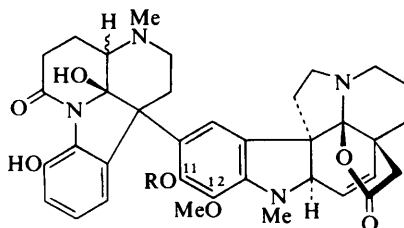
<sup>129</sup> M. Tits, D. Tavernier, and L. Angenot, *Phytochemistry*, 1979, **18**, 515.



Paucivenine (268)

the structure (268) has been proposed; the small amount of material available precluded elucidation of the stereochemistry by analysis of the n.m.r. spectrum.

Cimiciphytine and norcimiciphytine are two minor, lactonic alkaloids isolated from *Haplophyton cimidum*.<sup>130</sup> Both alkaloids contain an unrearranged canthiphytine unit, since cimiciphytine (269) can be obtained by mild reduction of haplophytine in acid solution (Zn-AcOH), and norcimiciphytine (270) affords (269) on methylation with diazomethane. The free phenolic hydroxy-group in (270) is placed at position 11, rather than position 12, since the n.m.r. spectrum of norcimiciphytine reveals the absence of a highly shielded methoxy-group, in contrast to the n.m.r. spectra of (269) and haplophytine.<sup>130</sup>



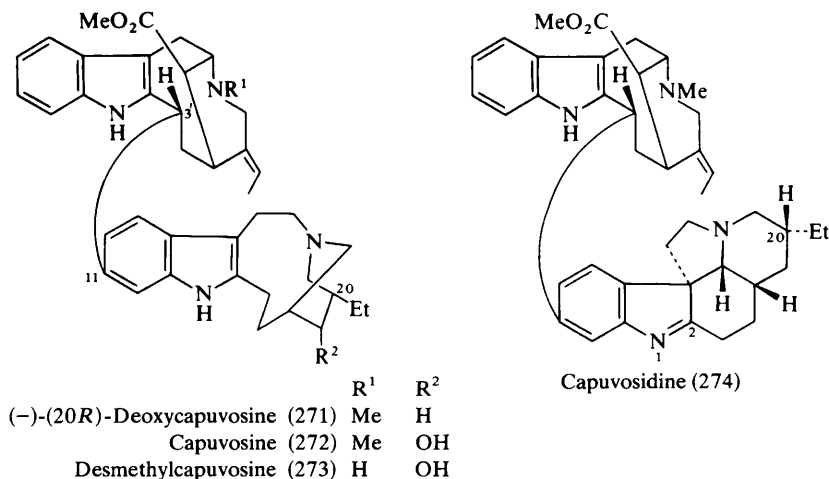
Cimiciphytine (269) R = Me  
Norcimiciphytine (270) R = H

Three new dimeric alkaloids have been found among the minor bases of *Capuronetta elegans*.<sup>114</sup> (-)-(20R)-Deoxycapuvosine (271) differs from the major alkaloid, capuvosine (272), only in the absence of a hydroxy-group at C-15, and desmethylcapuvosine (273) differs from (272) only in the absence of the *N*<sub>6</sub>-methyl group. Capuvosidine (274), the third alkaloid, contains a vobasine unit attached to a pentacyclic 1,2-dehydropseudoaspidospermidine unit, and thus exhibits indole plus indolenine u.v. absorption. Reduction (by NaBH<sub>4</sub>) affords an indoline derivative, which shows the characteristic fragmentation pattern of a pseudoaspidospermidine derivative. The similarity of the n.m.r. spectra of (271)–(274) indicates both the identity of the configuration at C-3' in all four

<sup>130</sup> M. V. Lakshmikantham, M. J. Mitchell, and M. P. Cava, *Heterocycles*, 1978, **9**, 1009.

bases and that there is the same attachment of the two component bases between positions 3' and 11.

Unfortunately, the reduction of the indolenine unit in capuvosidine to an indole derivative by means of sodium borohydride in protic solvents (cf. 1,2-dehydroaspidospermidine  $\rightarrow$  quebrachamine) was not reported; if C-20 has the (*R*) configuration, as shown in (274),<sup>114</sup> the product would have been deoxycapuvosine (271). The relevance of this transformation stems from the report<sup>77</sup> that (–)-(20*R*)-deoxycapuvosine (271) and capuvosidine, identical with the bases obtained from *Capuronetta elegans*, also occur in *Pandaca boiteaui*; capuvosidine from this source is described, however, as (–)-(20*S*)-capuvosidine, i.e. the 20-epimer of (274), but without supporting evidence. Other bases present in

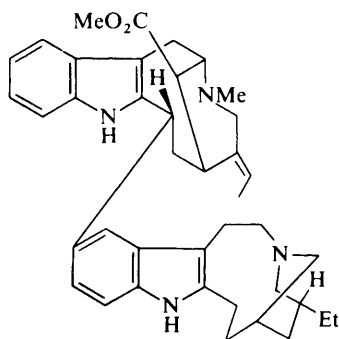
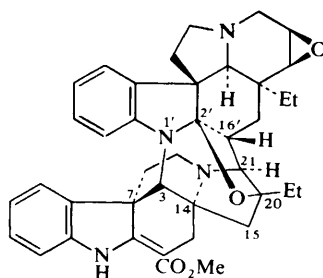


*P. boiteaui*<sup>77</sup> are voacamine, desmethoxycarbonylvoacamine, 1,2-dihydro-capuvosidine, and (–)-(20*R*)-isodeoxycapuvosine (275); in this last base the attachment between the two monomeric components is *via* positions 3' and 10.

The leaves of *Stenosolen heterophyllus* (Vahl) Mgf. (family Apocynaceae), from French Guyana, contain<sup>131</sup> seven dimeric alkaloids, of which ervafoline is identical with the alkaloid previously isolated<sup>132</sup> by Lévy and his collaborators from *Ervatamia pandacaqui*. The structure of ervafoline (276), elucidated by the *X*-ray method, is novel, and contains an aspidospermidine unit attached to a pandoline component *via* three bonds, namely  $N_a$  to C-3, C-16' to C-21, and C-2' to oxygen attached to C-20. A characteristic feature of this new dimeric ring system is the extraordinarily small chemical shift (5.65 p.p.m.) of the signal owing to the proton attached to C-12' as a result of shielding by the aromatic ring of the pandoline unit. The stereostructure (276) also represents the absolute configuration of ervafoline.<sup>131</sup>

<sup>131</sup> A. Henriques, C. Kan-Fan, A. Ahond, C. Riche, and H. P. Husson, *Tetrahedron Lett.*, 1978, 3707.

<sup>132</sup> P. Lathuillière, L. Olivier, J. Lévy, and J. Le Men, *Ann. Pharm. Fr.*, 1970, **28**, 57.

(-)-(20*R*)-Isodeoxycapuvosine (275)

Ervafoline (276)

High-performance liquid chromatography is recommended<sup>133</sup> for the analysis of mixtures containing desacetylvinblastine amide (vindesine); the method permits the detection of the corresponding dihydro-derivative and the related *N*<sub>b</sub>-oxide, which are the principal by-products in the chemical conversion of vinblastine into desacetylvinblastine amide.

A total of 37 desacetylvinblastine amide derivatives substituted on the amide nitrogen atom have been prepared and examined in connection with investigations into structure-antitumour activities in this area.<sup>134</sup>

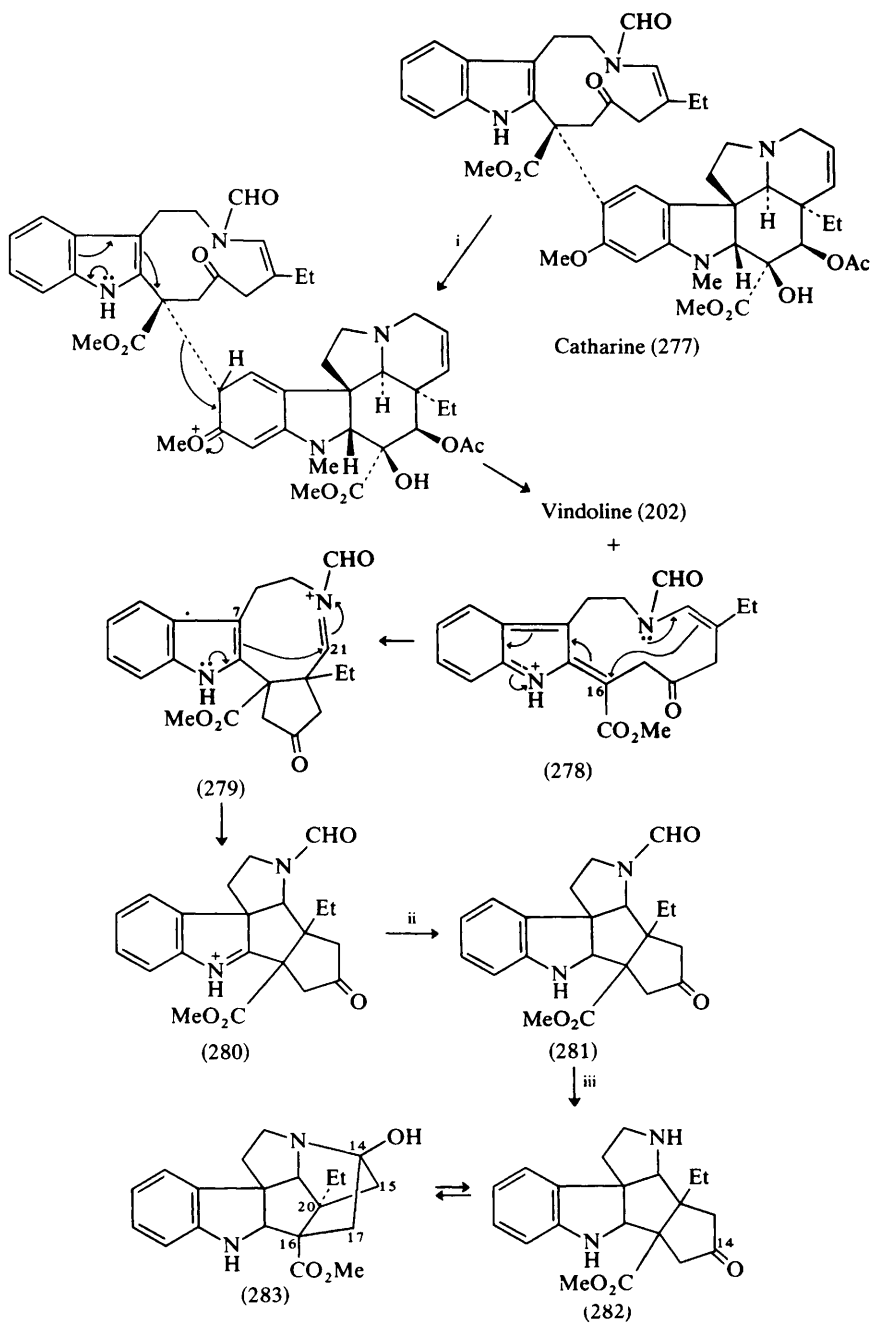
In trifluoroacetic acid, catharine (277) undergoes a fascinating and unexpected sequence of reactions.<sup>135</sup> The initial fission of the molecule, not surprisingly, results in release of vindoline; the other component, however, undergoes a double cyclization, with formation of the pentacyclic intermediate (280). Evidently the double bond in the enamide (278) initially generated is sufficiently nucleophilic to attack C-16, with formation of the 16–20 bond; the *N*-formylimmonium ion (279) so produced is, predictably, sufficiently electrophilic to allow formation of the 7–21 bond. The product isolated from this reaction, following reduction by means of sodium cyanoborohydride, is therefore the pentacyclic compound (281). The consequences of removal of the *N*-formyl group in (281) are also of interest. In the product (282), *N*<sub>b</sub> is sufficiently close to C-14 to allow cyclization to the carbinolamine form (283), the structure of which was established unequivocally by the X-ray method. The hexacyclic form (283) also appears to be preferred in solution, since the molecule does not contain a ketonic carbonyl group (<sup>13</sup>C n.m.r. spectrum). In basic solution, however, (283) must be in equilibrium with (282), since the four protons on C-15 and C-17 can be exchanged for deuterium; and the secondary alcohol related to (282) is the product of reduction by means of sodium borohydride (Scheme 35).<sup>135</sup>

Details have been published<sup>101</sup> of the synthesis of analogues of vinblastine by Polonovski coupling of catharanthine *N*-oxide and various transformation products of vindoline, and a synthesis of catharinine (vinamidine) has been

<sup>133</sup> R. L. Hussey and W. M. Newlon, *J. Pharm. Sci.*, 1978, **67**, 1319.

<sup>134</sup> R. A. Conrad, G. J. Cullinan, K. Gerzon, and G. A. Poore, *J. Med. Chem.*, 1979, **22**, 391.

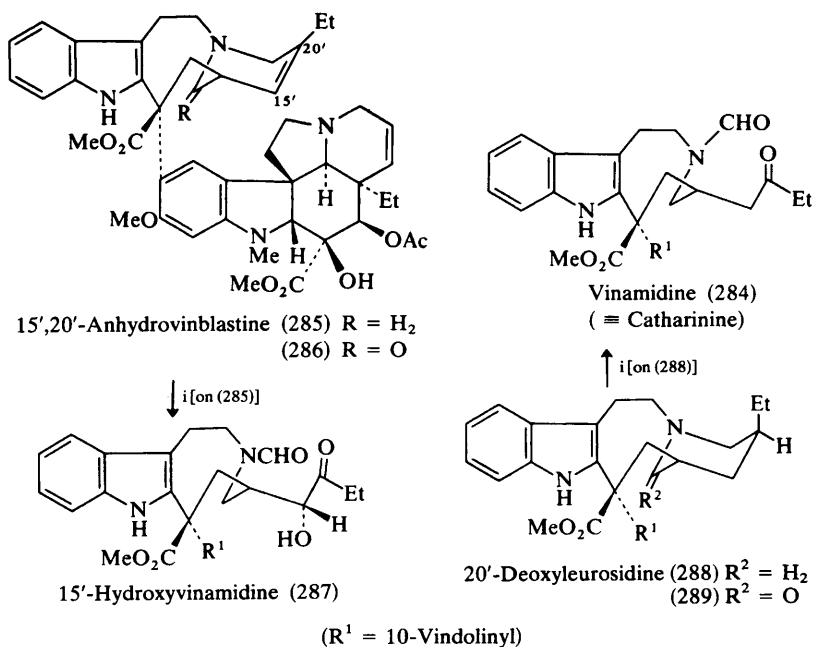
<sup>135</sup> P. Rasoanaivo, N. Langlois, A. Chiaroni, and C. Riche, *Tetrahedron*, 1979, **35**, 641.



Scheme 35



developed.<sup>136</sup> Vinamidine (284) may well arise by oxidative fission of the piperidine ring in anhydrovinblastine (285), or a close relative. However, oxidation of either 15',20'-anhydrovinblastine (285) or leurosine (the related 15',20'- $\alpha$ -epoxide) with potassium permanganate gave the related 3'-lactams (286 and its 15',20'- $\alpha$ -epoxide) together with a ketol (287), containing a formamide group, which was shown to be 15'-hydroxyvinamidine. Fission of the ketol system in (287) by means of sodium periodate gave an aldehyde by loss of three carbon atoms, thus confirming that the oxidation of (285) had resulted in cleavage of the 20'-21' bond, with formation of a 15'-hydroxy-20'-oxo pattern of oxidation in the product. The (15'*R*) configuration postulated in (287) was assumed on the basis of retention of configuration at this position in the oxidation of leurosine. Evidently the ketol (287) is in a higher oxidation state than vinamidine, and since the 15'-hydroxy-group in (287) could not be removed, the oxidation of a substrate with a lower oxidation state was investigated. In fact, oxidation of 20'-deoxy-leurosine (288) by permanganate gave some 3'-lactam (289), together with 25% of a ring D cleavage product, identified as vinamidine (284) (Scheme 36).<sup>136</sup>



Reagents: i,  $KMnO_4$ , acetone

**Scheme 36**

15',20'-Anhydrovinblastine (285) has for some time been regarded as the biosynthetic precursor of the vinblastine group of alkaloids, although its presence in the plant has never previously been established, probably owing to the facility with which it can be transformed into other dimeric alkaloids, e.g. leurosine and

<sup>136</sup> J. P. Kutney, J. Balsevich, and B. R. Worth, *Heterocycles*, 1978, **11**, 69.

catharine.<sup>63g</sup> Evidence has now been obtained, however, that anhydrovinblastine is a natural product, and can actually be isolated from *Catharanthus roseus*, provided that the extraction procedure is carried out quickly.<sup>137</sup> Evidence has also been provided which demonstrates that catharine is a *bona fide* alkaloid, and not an artefact.<sup>138</sup>

Leurosine, the 15',20'- $\alpha$ -epoxide of (285), can be prepared by oxidation of 15',20'-anhydrovinblastine (285) with hydrogen peroxide in the presence of either horseradish peroxidase or cell-free extracts of *C. roseus* plants; the evidence has been interpreted as indicating that leurosine is also a true natural product, not an artefact.<sup>139</sup>

Whether leurosine, catharine, and their congeners are true alkaloids, or artefacts derived from anhydrovinblastine, the fact remains that the aerial oxidation of anhydrovinblastine is a facile process which does not need to be enzyme-mediated, and a further examination of this reaction has revealed<sup>140</sup> that all the alkaloids of the vinblastine group are produced. The oxidations were performed in acetonitrile solution, and in one experiment, conducted at 26 °C for 48 hours, the composition of the alkaloid mixture obtained was roughly similar to the relative abundances of the dimeric alkaloids isolated from *Catharanthus* species. In the oxidation the lone electrons on N<sub>6</sub>' are presumably involved, since anhydrovinblastine N<sub>6</sub>'-oxide is inert towards oxidation by air, and while the presence of moisture promotes the reaction, oxygen from the water is not incorporated into the oxidized alkaloids. On the basis of the available evidence, a mechanism, shown in truncated form in Scheme 37, was proposed for the oxidative transformation of anhydrovinblastine into the various alkaloids isolated.<sup>140</sup>

The long series of experiments involving the synthesis of vinblastine analogues by the Polonovski coupling of catharanthine N<sub>6</sub>-oxide derivatives with vindoline has culminated in the synthesis of vinblastine (290) itself,<sup>141</sup> and this forms a fitting climax to any report on the past year's progress in indole alkaloid chemistry.

The rather unstable enamine (291) has already been prepared *in situ* by the Polonovski coupling reaction, and intercepted by means of osmium tetroxide; reduction of the ensuing hydroxycarbinolamine (by NaBH<sub>4</sub>) then completed the first synthesis of leurosidine (292).<sup>142</sup> The enamine (291) can also be obtained by the hydrogenation of 15',20'-anhydrovinblastine (285), which results in preferential addition of hydrogen at the  $\alpha$ -face of the double bond, followed by oxidation (with *m*-chloroperbenzoic acid) to the N<sub>6</sub>'-oxide (293), and Polonovski reaction with trifluoroacetic anhydride. The effect of various oxidizing agents on (291) was then examined. The earlier synthesis of leurosidine following oxidation by osmium tetroxide was confirmed, but a completely different result was observed when thallium triacetate was used as the oxidant. Attack now occurred

<sup>137</sup> A. I. Scott, F. Gueritte, and S. L. Lee, *J. Am. Chem. Soc.*, 1978, **100**, 6253.

<sup>138</sup> K. L. Stuart, J. P. Kutney, T. Honda, and B. R. Worth, *Heterocycles*, 1978, **9**, 1391.

<sup>139</sup> K. L. Stuart, J. P. Kutney, and B. R. Worth, *Heterocycles*, 1978, **9**, 1015.

<sup>140</sup> N. Langlois and P. Potier, *J. Chem. Soc., Chem. Commun.*, 1979, 582.

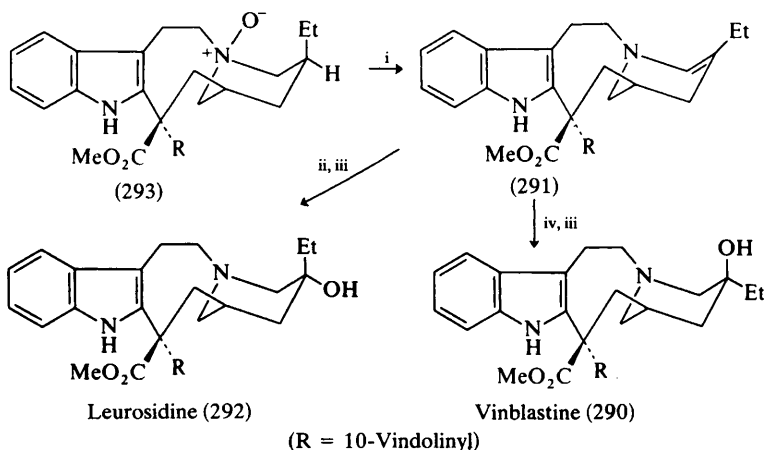
<sup>141</sup> P. Mangeney, R. Z. Andriamialisoa, N. Langlois, Y. Langlois, and P. Potier, *C.R. Hebd. Seances Acad. Sci., Ser. C*, 1979, **288**, 129; *J. Am. Chem. Soc.*, 1979, **101**, 2243.

<sup>142</sup> N. Langlois and P. Potier, *Tetrahedron Lett.*, 1976, 1099.



#### 4 Biogenetically Related Quinoline Alkaloids

20-Deoxycamptothecin (294), 20-hexanoylcamptothecin (295), and 20-hexanoyl-10-methoxycamptothecin (296) are new constituents of *Camptotheca*

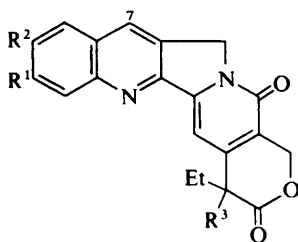


Reagents: i, (CF<sub>3</sub>CO)<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>; ii, OsO<sub>4</sub>; iii, NaBH<sub>4</sub>; iv, Tl(OAc)<sub>3</sub>

**Scheme 38**

*acuminata*;<sup>143</sup> the presence of 10-methoxycamptothecin (297) has been confirmed, and 11-hydroxycamptothecin (298) found in the same plant.<sup>144</sup>

Single-crystal X-ray diffraction studies have been reported for cinchonine<sup>145</sup> and quinidine.<sup>146</sup>



	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>
20-Deoxycamptothecin (294)	H	H	H
20-Hexanoylcamptothecin (295)	H	H	O <sub>2</sub> C(CH <sub>2</sub> ) <sub>4</sub> Me
20-Hexanoyl-10-methoxycamptothecin (296)	H	OMe	O <sub>2</sub> C(CH <sub>2</sub> ) <sub>4</sub> Me
10-Methoxycamptothecin (297)	H	OMe	OH
11-Hydroxycamptothecin (298)	OH	H	OH

High-performance liquid chromatography provides a rapid, specific, and sensitive method for the determination of quinidine and dihydroquinidine in human plasma; it is reported that as little as 1 ng of quinidine can be detected.<sup>147</sup>

<sup>143</sup> J. A. Adamovics, J. A. Cina, and C. R. Hutchinson, *Phytochemistry*, 1979, **18**, 1085.

<sup>144</sup> L. T. Lin, C. C. Sung, and J. S. Hsu, *Hua Hsueh Tung Pao*, 1978, 327 (*Chem. Abs.*, 1979, **90**, 109 842).

<sup>145</sup> B. Oleksyn, L. Lebiada, and M. Ciechanowicz-Rutkowska, *Acta Crystallogr., Sect. B*, 1979, **35**, 440.

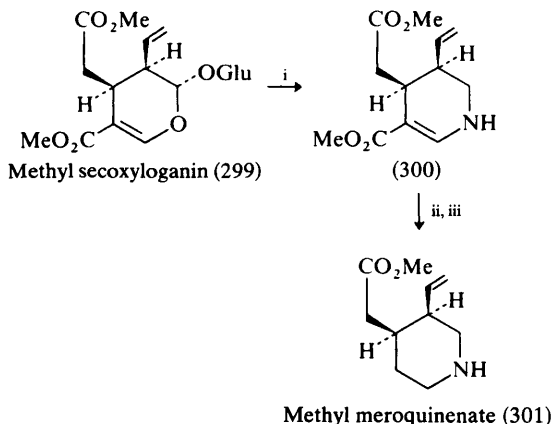
<sup>146</sup> R. Doherty, W. B. Benson, M. Maienthal, and J. McD. Stewart, *J. Pharm. Sci.*, 1978, **67**, 1698.

<sup>147</sup> B. J. Kline, V. A. Turner, and W. H. Barr, *Anal. Chem.*, 1979, **51**, 449.

The copolymerization of *Cinchona* alkaloids with acrylonitrile affords copolymers which behave as very useful catalysts in asymmetric synthesis, arguably the most effective reported to date.<sup>148</sup> For example, in the addition of dodecanethiol to isopropenyl methyl ketone a 57% enantiomer excess was reported; this is the highest value ever recorded for an asymmetric synthesis that is catalysed by an organic polymer.

Quinine, as a  $\beta$ -amino-alcohol, cannot be satisfactorily oxidized under standard Oppenauer conditions; however, it can be oxidized completely at room temperature to quinidinone in dry, deoxygenated DMF, by fluorenone and sodium hydride.<sup>149</sup> It is of interest that little fluorenone is obtained as a result of the hydride transfer, and virtually none (only 1%) is obtained if the oxidation is conducted at  $-50^\circ\text{C}$ ; instead the major reduction product is the pinacol derived from fluorenone. This presumably arises by condensation of the carbanion, derived from fluorenone in the presence of strong base, with unchanged fluorenone.

Following their earlier conversion of dihydrosecologanin into dihydro-meroquinene,<sup>63h</sup> Brown and Leonard have succeeded in carrying out a similar transformation with secologanin, in which the double bond remains intact, to afford a valuable stereoconservative synthesis of meroquinene derivatives (Scheme 39).<sup>150</sup> In a 'one-pot' process, methyl secoxylogananin (299) was subjected



Reagents: i,  $\beta$ -Glucosidase,  $\text{NaBH}_3\text{CN}$ ,  $\text{NH}_4\text{OAc}$ , pH 6.5; ii, 1%  $\text{HCl}$ ,  $\text{H}_2\text{O}$ ,  $\text{MeOH}$ ; iii,  $\text{NaBH}_4$

**Scheme 39**

to glucolysis and reductive amination, under conditions of carefully controlled pH, to give the vinyl compound (300) in 60% yield. Under other conditions, *e.g.* with trimethylamine-borane at pH 6–7, the isomeric ethylidene compound was obtained, and at pH 5 with sodium cyanoborohydride the vinyl double-bond suffered reduction. Hydrolysis and decarboxylation of (300), followed by reduc-

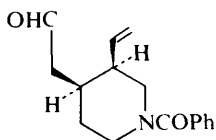
<sup>148</sup> N. Kobayashi and K. Iwai, *J. Am. Chem. Soc.*, 1978, **100**, 7071.

<sup>149</sup> J. J. Koenig, J. de Rostolan, J. C. Bourbier, and F. X. Jarreau, *Tetrahedron Lett.*, 1978, 2779.

<sup>150</sup> R. T. Brown and J. Leonard, *J. Chem. Soc., Chem. Commun.*, 1978, 725.

tion, then gave an almost quantitative yield of methyl meroquinenate (301), whose *N*-benzoyl derivative was identical with that prepared by degradation of quinine.

Other synthetic work in this area includes a new synthesis of ( $\pm$ )-*N*-benzoyl-meroquinene aldehyde (302), in eighteen steps, from ( $\pm$ )-norcamphor.<sup>151</sup> The lack of stereospecificity in an intermediate reduction stage afforded also a synthesis of the diastereoisomer of (302).



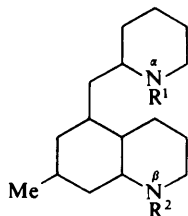
(302)

Finally, appropriate modification of an earlier synthesis of camptothecin has allowed the total synthesis of 7-methoxycamptothecin and some *C*-20-alkyl analogues.<sup>152</sup>

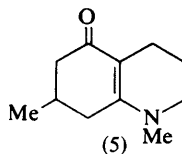
<sup>151</sup> S. Takano, M. Takahashi, S. Hatakeyama, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1979, 556.

<sup>152</sup> E. Baxmann and E. Winterfeldt, *Chem. Ber.*, 1978, **111**, 3403.

Since the review two years ago,<sup>1</sup> several significant developments have occurred, both on the structural side and in synthesis. Turning first to the structural studies, Braekman and co-workers have discovered a new series of bases, the parent of which is the C<sub>16</sub> alkaloid phlegmarine (1), isolated, along with N<sub>β</sub>-methylphlegmarine (2), from *L. phlegmaria*.<sup>2</sup> N<sub>α</sub>-Acetyl-N<sub>β</sub>-methylphlegmarine (3) was isolated from *L. clavatum* var. *borbonicum* and N<sub>α</sub>-methylphlegmarine (4) from *L. cernuum*. The compounds were correlated by appropriate transformations, and mass spectrometry and mass-analysed ion kinetic energy (MIKE) spectrometry were used to deduce the structures.<sup>2</sup> A stereoisomer of (3) was synthesized, starting from the known unsaturated ketone (5).<sup>3</sup> The stereoisomer was not identical with (3) [the stereochemistry of compounds (1)–(4) has not been determined], but it showed identical mass, MIKE, and collision-induced decomposition spectra. The authors suggest that phlegmarine (1) or a closely related compound may be a key intermediate in the biosynthesis of the C<sub>16</sub> *Lycopodium* alkaloids.<sup>2</sup> *L. phlegmaria* also produces the known alkaloids lycodoline, anhydrolycodoline, lycoflexine, lycopodine, and gnidioidine and *L. clavatum* var. *borbonicum* yields, in addition to (3), lycopodine, anhydrolycopodine, dihydrolycopodine, acetyldihydrolycopodine, lycodoline, and lycoflexine.<sup>2,4</sup>



- (1) R<sup>1</sup> = R<sup>2</sup> = H  
 (2) R<sup>1</sup> = H, R<sup>2</sup> = Me  
 (3) R<sup>1</sup> = Ac, R<sup>2</sup> = Me  
 (4) R<sup>1</sup> = Me, R<sup>2</sup> = H



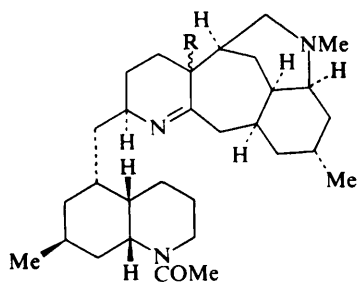
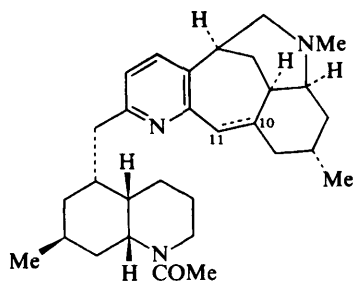
<sup>1</sup> W. A. Ayer, in 'The Alkaloids', ed. M. F. Grondon (Specialist Periodical Reports), The Chemical Society, London, 1977, Vol. 8, Ch. 12.

<sup>2</sup> L. Nyembo, A. Goffin, C. Hootelé, and J. C. Braekman, *Can. J. Chem.*, 1978, **56**, 851.

<sup>3</sup> H. Dugas, R. A. Ellison, Z. Valenta, K. Wiesner, and C. M. Wong, *Tetrahedron Lett.*, 1965, 1279.

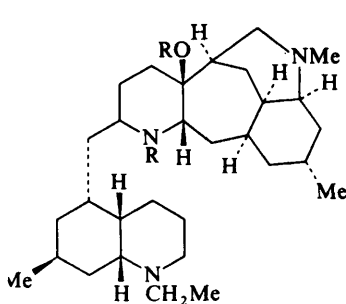
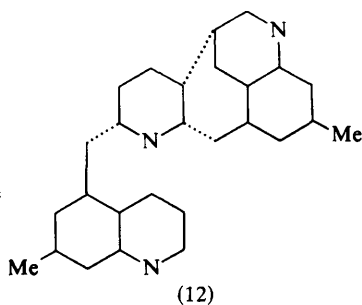
<sup>4</sup> For the structures of the known alkaloids see reference 1 and W. A. Ayer, *MTP International Review of Science*, Series 1, Volume 9, ed. D. H. Hey and K. Wiesner, University Park Press, Baltimore, 1973, p. 1.

Details of the structures of the most complex type of *Lycopodium* alkaloids yet reported, a group of  $C_{30}N_3$  bases, have begun to appear.<sup>5</sup> These compounds, which show a relationship to the simpler phlegmarine-type bases, are lucidine B (6), lycolucine (7), and dihydrolycolucine (8).<sup>5</sup> Lucidine B (6) undergoes facile aerial oxidation to oxolucidine B (9), which when reduced with  $LiAlH_4$  provides dihydrodeoxyoxolucidine B (10). The structure of the *O,N*-di-*p*-bromobenzoate (11) of (10) was determined by X-ray crystallography, and this led to the proposal of structure (6) for lucidine B. Mild catalytic dehydrogenation of (6) gave dihydrolycolucine (8), which was also obtained by catalytic hydrogenation of the C-10–C-11 double bond in lycolucine (7).<sup>5</sup> Whereas phlegmarine has one  $C_{11}N$  unit attached to a piperidine ring, the  $C_{30}N_3$  compounds have two of the  $C_{11}N$  units fused to a piperidine (or pyridine) ring system, as indicated by the dotted lines in (12). Assuming that there is a biogenetic relationship between phlegmarine (1) and lucidine B (6), it is tempting to speculate that phlegmarine has the stereochemistry shown in (13).

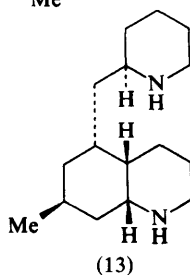
(6)  $R = H$ (9)  $R = \beta\text{-OH}$ 

(7) 10,11 double bond

(8) 10,11 single bond

(10)  $R = H$ (11)  $R = \text{CO}-\text{C}_6\text{H}_4\text{Br}$ 

(12)

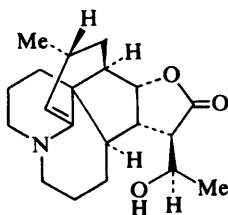


(13)

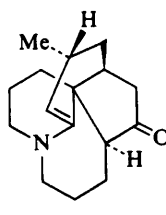
<sup>5</sup> W. A. Ayer, L. M. Browne, Y. Nakahara, M. Tori, and L. T. J. Delbaere, *Can. J. Chem.*, 1979, **57**, 1105.



Another new skeletal type, this one with twenty carbon atoms, is represented by megastachine (14), isolated from *L. megastachyum* collected in Madagascar.<sup>6</sup> The structure of (14) was determined by an X-ray crystallographic study of its methiodide. Megastachine contains the sixteen-carbon framework of fawcettidine (15) in which the (reduced) oxygen function has been replaced by a (reduced) acetoacetate unit.<sup>6</sup>



(14)



(15)

The bases of *L. clavatum* of Polish origin have been re-examined and the known compounds lycopodine, flabelliformine, lycodoline, dihydrolycopodine, clavonine, and des-*N*-methyl- $\alpha$ -obscurine isolated.<sup>7</sup> Interestingly, nicotine, which was isolated several times from this family in the 1940's,<sup>8</sup> but not reported in more recent investigations, was also isolated in this study.<sup>7</sup>

The past two years have seen the completion of two new syntheses of lycopodine, the most widely occurring alkaloid of the group. A very elegant total synthesis, in which ( $\pm$ )-lycopodine is obtained in 17.7% yield from the cyanoenone (16), has been reported by Heathcock *et al.*<sup>9</sup> and is summarized in Scheme 1. Enone (16) is available in high yield from dihydro-orcinol.<sup>10</sup> Treatment of (16) with dimethylallylcopper lithium followed by ozonolysis of the resulting keto-olefin provided (17) as a 1:1 mixture of the C-2 epimers. Alternatively, (17) could be prepared by conjugate addition of the cuprate derived from lithiated acetone *NN*-dimethylhydrazone followed by acid hydrolysis. Diketone (17) was transformed into the amine (19), *via* the acid (18), as indicated in Scheme 1. Treatment of (19) (mixture of C-2 epimers) with methanolic HCl results in slow intramolecular Mannich cyclization to a *single* tricyclic amine ketone (20), in 65% yield. Catalytic debenzylation of (20) followed by Oppenauer oxidation and concurrent cyclization afforded 3,4-dehydrolycopodine (21). Hydrogenation of (21) gave *dl*-lycopodine (22), completing the nine-step transformation of (16) into the racemic alkaloid.

An interesting synthesis of anhydrolycodoline (23) has recently been described.<sup>11,12</sup> Since anhydrolycodoline has already been transformed into lycopodine, albeit in low yield, this also represents a total synthesis of lycopodine (22).

<sup>6</sup> J. C. Braekman, C. Hootel , N. Miller, J. P. Declercq, G. Germain, and M. van Meerssche, *Can. J. Chem.*, 1979, **57**, 1691.

<sup>7</sup> W. J. Rodewald and G. Gryniewicz, *Rocz. Chem.*, 1977, **51**, 1271.

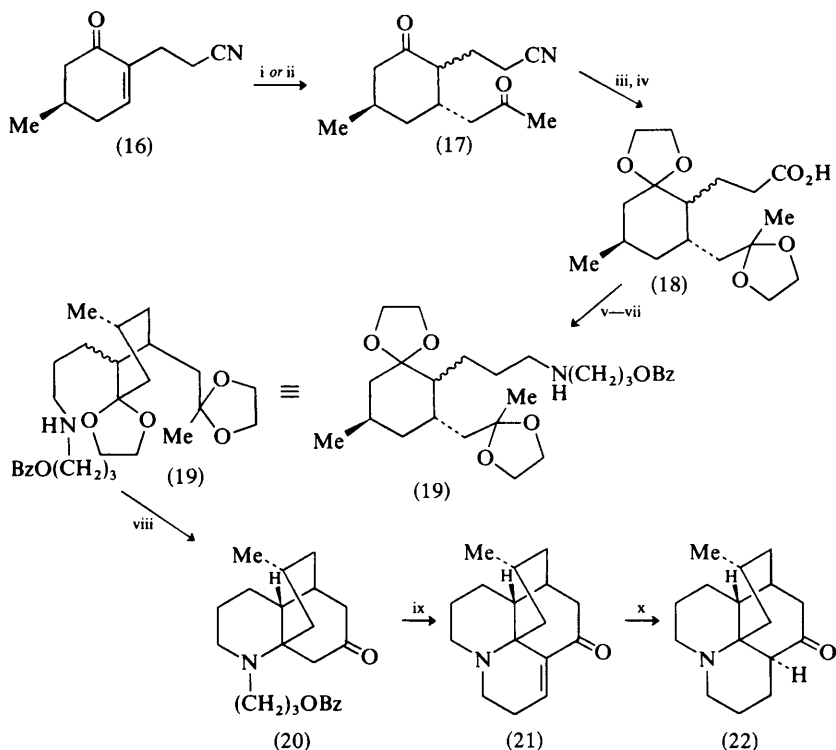
<sup>8</sup> D. B. MacLean, in 'The Alkaloids', Vol. 10, ed. R. M. Manske, Academic Press, New York, 1968, p. 313.

<sup>9</sup> C. H. Heathcock, E. Kleinman, and E. S. Binkley, *J. Am. Chem. Soc.*, 1978, **100**, 8037.

<sup>10</sup> R. D. Clark and C. H. Heathcock, *J. Org. Chem.*, 1976, **41**, 636.

<sup>11</sup> S. W. Kim, Y. Bando, and Z. Horii, *Tetrahedron Lett.*, 1978, 2293.

<sup>12</sup> S. W. Kim, Y. Bando, N. Takahashi, and Z. Horii, *Chem. Pharm. Bull.*, 1978, **26**, 3150.



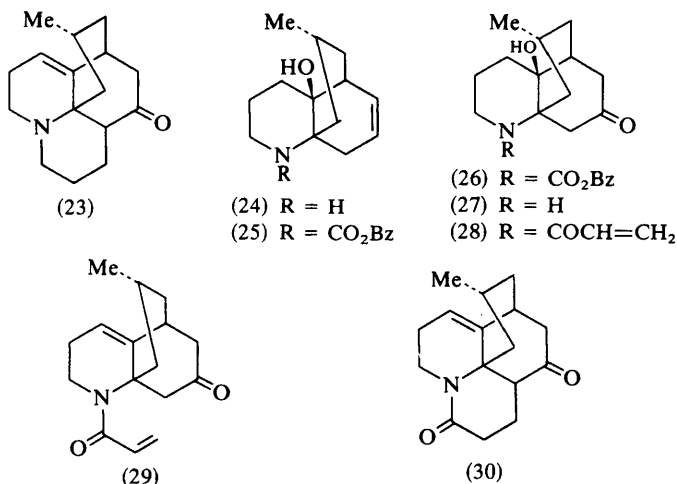
Reagents: *i*, dimethylallylcopper lithium, at  $-78^{\circ}\text{C}$ , then  $\text{O}_3$ ; *ii*, lithiated cuprate of acetone *NN*-dimethylhydrazone, then  $\text{H}_3\text{O}^+$ ; *iii*,  $\text{HOCH}_2\text{CH}_2\text{OH}, \text{H}^+$ ; *iv*,  $\text{KOH}$ , aq.  $\text{EtOH}$ ; *v*,  $\text{ClCO}_2\text{Et}$ ,  $\text{NEt}_3$ ; *vi*,  $\text{BzO}(\text{CH}_2)_3\text{NH}_2$ ; *vii*,  $\text{LiAlH}_4$ , THF; *viii*,  $\text{HCl}$ ,  $\text{MeOH}$ , reflux, 12 d; *ix*, benzophenone,  $\text{Bu}^t\text{OK}$ ,  $\text{PhH}$ ; *x*,  $\text{H}_2$ ,  $\text{Pt}$ ,  $\text{EtOH}$

**Scheme 1**

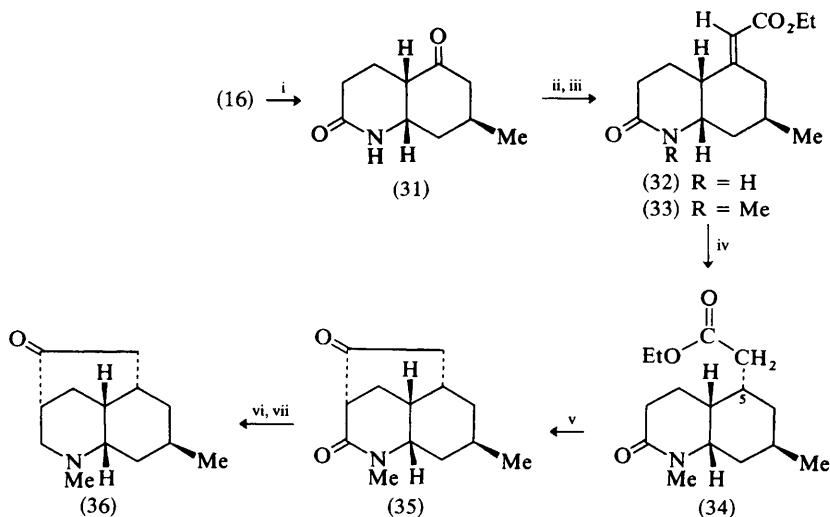
The tricyclic olefin (24), the preparation of which has been described previously in this series,<sup>13</sup> was the starting point for this synthesis. Compound (24) was first transformed into the benzylurethane (25). Hydroboration followed by oxidation gave the hydroxy-ketone (26). Reductive removal of the protecting group gave the amine (27), which was transformed into the acrylyl amide (28). All attempts to cyclize (28) by internal Michael addition were unsuccessful, probably for stereoelectronic reasons.<sup>14</sup> Dehydration of (28), however, gave the olefin (29), and this, when treated with a catalytic amount of sodium ethoxide and dicyclohexyl-18-crown-6 in boiling DMF, cyclized to the lactam (30) in 56% yield. Reduction of (30) with  $\text{LiAlH}_4$  followed by Jones oxidation gave *dl*-anhydrolycodoline (23) in 63% yield.

<sup>13</sup> V. A. Snieckus, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1973, Vol. 2, p. 242.

<sup>14</sup> T. Momose, S. Uchida, T. Imanashi, S. W. Kim, N. Takahashi, and Z. Horii, *Heterocycles*, 1977, **6**, 1105.



The third total synthesis of luciduline has been reported and is outlined in Scheme 2.<sup>15</sup> The starting material is the same keto-nitrile (16) used in Heathcock's lycopodine synthesis described above. Treatment of (16) with methanolic sodium hydroxide led directly to a mixture of the *cis*-lactam (31) and the corresponding *trans*-isomer (ratio ~5:1). Condensation of (31) with ethyl trimethylsilylacetae furnished the unsaturated ester (32), which was *N*-methylated to (33). Catalytic hydrogenation of (33) provided a 1:1 mixture of (34) and its C-5



Reagents: i, NaOH, MeOH; ii, Me<sub>3</sub>SiCH<sub>2</sub>CO<sub>2</sub>Et, lithium isopropylcyclohexylamide; iii, lithium isopropylcyclohexylamide, Me<sub>2</sub>SO<sub>4</sub>; iv, H<sub>2</sub>, Pt; v, lithium isopropylcyclohexylamide, THF; vi, LiAlH<sub>4</sub>, Et<sub>2</sub>O; vii, Jones' reagent

Scheme 2

<sup>15</sup> J. Szychowski and D. B. MacLean, *Can. J. Chem.*, 1979, **57**, 1631.

epimer. Lactam (34) readily cyclized when treated with base to give ( $\pm$ )-luciduline lactam (35), and this was transformed into ( $\pm$ )-luciduline by hydride reduction followed by Jones oxidation.<sup>15</sup>

This review is dedicated to the memory of R.H.F. Manske, a pioneer in the field of *Lycopodium* alkaloids, who passed away in 1978.

## Diterpenoid Alkaloids

BY S. William PELLETIER & Samuel W. PAGE

### 1 Introduction

During the past year the diterpenoid alkaloids have attracted more interest than in previous years. Reports have appeared on the alkaloids of *Aconitum* and *Delphinium* species found in Bulgaria, Canada, Japan, Norway, Spain, the Peoples Republic of China, several regions of the Soviet Union, and the south-eastern and western United States.

There has been a notable increase in the chemotaxonomical screening of these species for alkaloid content. That the toxicity (*e.g.* the notorious lethal mediaeval potions and the livestock poisons) and the beneficial pharmacological effects of some of these plants result solely from the diterpenoid alkaloids present is being questioned. Japanese workers<sup>1</sup> have identified the active heart-stimulant and diuretic principle in *A. japonicum* Thumb. (the Japanese Bushi herb) as higenamine, a benzyloisoquinoline alkaloid. Magnoflorine and several other aporphine alkaloids have been isolated from *Delphinium* species,<sup>2,3</sup> and phenyl-2-naphthylamine has been isolated from *A. karakolicum*.<sup>4</sup> The alkaloid content varies with both the species and the habitat. In the light of better chemotaxonomical studies, and because of some confusion in the speciation of several plant specimens under investigation, the importance of careful identification and the submission of herbarium specimens should be emphasized.

A detailed review of the chemistry of C<sub>19</sub> diterpenoid alkaloids<sup>5</sup> has appeared.

There were no new reports on alkaloids from *Daphniphyllum* species received by our laboratories.

Following the previous conventions, the numbering systems for the aconitine, lycotonine, atisine, and veatchine skeletons are shown in structures A, B, C, and D, respectively.

### 2 C<sub>19</sub> Diterpenoid Alkaloids

**Alkaloids of *Aconitum gigas* Lev. et Van.**—A full report<sup>6</sup> on the structure elucidation of the alkaloids from this species has appeared (*cf.* Vol. 9, p. 221).

<sup>1</sup> T. Kosuge, M. Yokota, and M. Nagasawa, *Yakugaku Zasshi*, 1978, **98**, 1370.

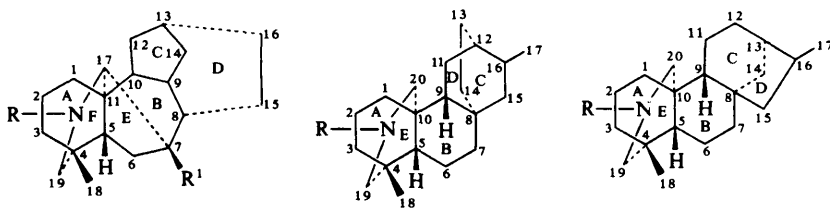
<sup>2</sup> B. T. Salimov, N. D. Abdullaev, M. S. Yunusov, and S. Yu. Yunusov, *Khim. Pri. Soedin.*, 1978, 235.

<sup>3</sup> V. N. Aiyar, M. Benn, Y. Y. Huang, J. M. Jacyno, and A. J. Jones, *Phytochemistry*, 1978, **17**, 1453.

<sup>4</sup> M. N. Sultankhodzhaev, L. Beshitaishvili, M. S. Yunusov, and S. Yu. Yunusov, *Khim. Pri. Soedin.*, 1978, 479.

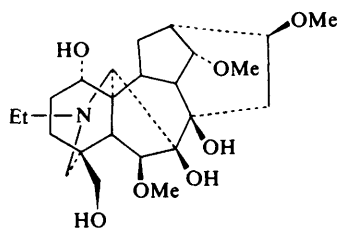
<sup>5</sup> S. W. Pelletier and N. V. Mody, in 'The Alkaloids', ed. R. H. F. Manske and R. G. A. Rodrigo, Academic Press, New York, 1979, Vol. 17, Chapter 1, p. 1.

<sup>6</sup> S. Sakai, N. Shinma, S. Hasegawa, and T. Okamoto, *Yakugaku Zasshi*, 1978, **98**, 1376.

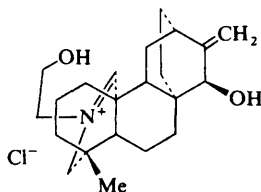


(A) Aconitine skeleton,  $R^1 = H$  (C) Atisine skeleton (D) Veatchine skeleton  
 (B) Lycoctonine skeleton,  $R^1 = OR^2$

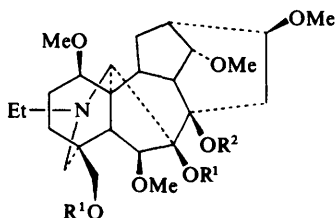
Gigactonine (1), atisine hydrochloride (2), lycoctonine (3), lycaconitine (4), and two artifacts from lycaconitine, *i.e.* (5) and (6), were isolated from plants collected in Hokkaido, Japan. The  $^{13}C$  n.m.r. chemical shifts and assignments for compounds (1), (3), 7,18-di-*O*-methyl-lycoctonine (7), and neoline (8) were presented. Methylation of gigactonine with KH-DMSO-MeI yielded a mixture of the di- (9) and tri-methylated (10) derivatives. Methylation with NaH-DMF-MeI afforded (9) and delsoline (11). Acetylation of gigactonine with acetic anhydride-pyridine gave the 1,18-diacetyl derivative (12). Acetylation of the 7,18-dimethyl derivative (9) and delsoline (11) formed compounds (13) and (14), respectively. Oxidation of gigactonine with *N*-chlorosuccinimide and dimethyl sulphate gave gigactonal (15). Cornforth oxidation of (11) produced a mixture of compounds (16) and (17). Methylation of delcosine (18) with NaH-dioxan-MeI gave delsoline (11). These results demonstrate that 18-*O*-methylgigactonine, 14-*O*-methyldecosine, and delsoline are identical.



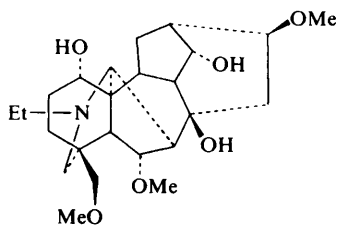
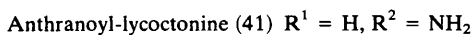
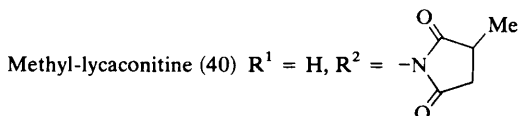
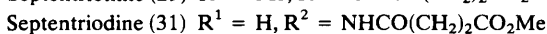
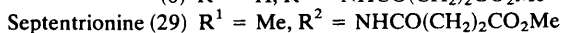
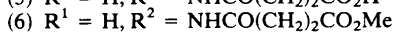
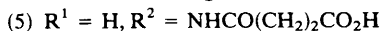
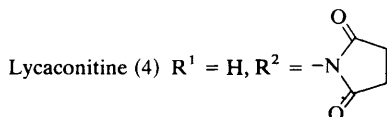
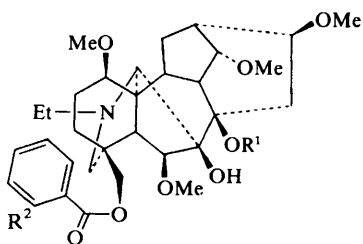
Gigactonine (1)



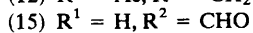
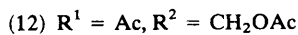
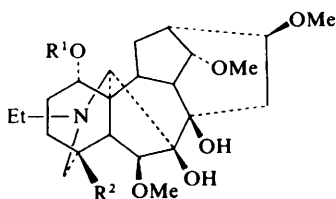
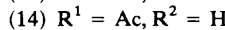
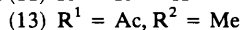
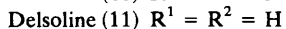
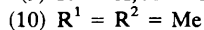
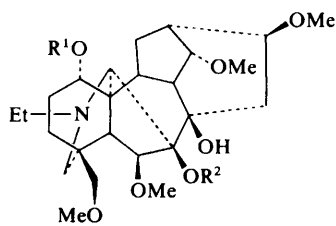
Atisinium chloride (2)

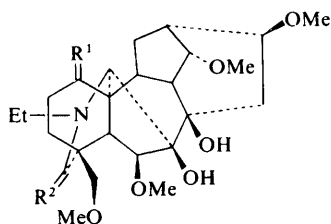


Lycoctonine (3)  $R^1 = R^2 = H$   
 (7)  $R^1 = Me, R^2 = H$   
 (30)  $R^1 = H, R^2 = Me$



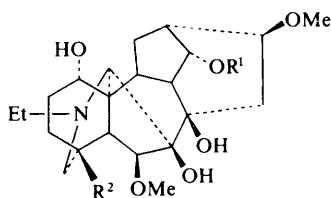
Neoline (8)





(16)  $R^1 = O, R^2 = H_2$

(17)  $R^1 = R^2 = O$

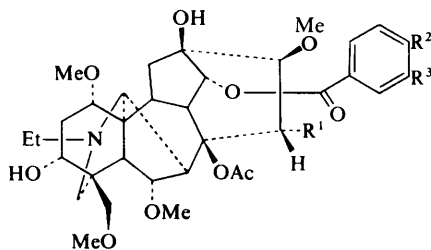


Delcosine (18)  $R^1 = H, R^2 = CH_2OMe$

Acetyldecosine (33)  $R^1 = Ac, R^2 = CH_2OMe$

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

**Alkaloids of *Aconitum hemisleyanum*: Yunaconitine.**—Research carried out in the Peoples Republic of China<sup>7</sup> has resulted in the isolation of a new alkaloid from *A. hemisleyanum* Pritz. var. *circinatum* W. T. Wang and from *A. geniculatum* Flet. et Laue. var. *unguiculatum* W. T. Wang. The structure of yunaconitine (19) [ $C_{35}H_{49}NO_{11}$ ; m. pt. 141—143 °C (perchlorate: m. pt. 226—230 °C, nitrate: m. pt. 198—200 °C)] was assigned on the basis of the i.r., u.v., and <sup>1</sup>H n.m.r. spectral data. Hydrolysis of yunaconitine (19) gave pseudoaconine (20). The n.m.r. spectral comparisons of yunaconitine, aconitine (21), jesaconitine (22), pseudoaconitine (23), and pseudoaconine (20) strongly support this structural assignment.

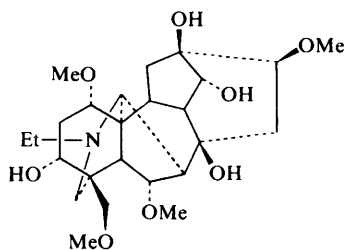


Yunaconitine (19)  $R^1 = R^3 = H, R^2 = OMe$

Aconitine (21)  $R^1 = OH, R^2 = R^3 = H$

Jesaconitine (22)  $R^1 = OH, R^2 = OMe, R^3 = H$

Pseudoaconitine (23)  $R^1 = H, R^2 = R^3 = OMe$



Pseudoaconine (20)

**Alkaloids of *Aconitum ranunculaefolium*: Ranaconitine.**—Mollov and co-workers<sup>8</sup> isolated lappaconitine (24) and ranaconitine [ $C_{32}H_{44}N_2O_9$ ; m. pt. 132—134 °C] from plants of *A. ranunculaefolium*, a species native to Bulgaria. The structures of lappaconitine and its hydrolysis-product lappaconine (25) had previously been determined.<sup>9</sup> Because of the instability of ranaconitine in solution and the limited quantity available, its structure was not assigned. Recent work,<sup>10</sup> relying primarily on <sup>13</sup>C n.m.r. analyses, has shown the structure of

<sup>7</sup> S.-Y. Chen, Hua Hsueh Hsueh Pao, 1979, 37, 15.

<sup>8</sup> N. Mollov, M. Haimova, P. Tscherneva, N. Pecigargova, I. Ognjanov, and P. Panov, C. R. Acad. Bulg. Sci., 1964, 17, 251.

<sup>9</sup> N. Mollov, M. Tada, and L. Marion, Tetrahedron Lett., 1969, 2189.

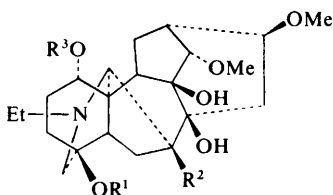
<sup>10</sup> S. W. Pelletier, N. V. Mody, A. P. Venkov, and N. M. Mollov, Tetrahedron Lett., 1978, 5045.



ranaconitine to be (26). On alkaline hydrolysis, ranaconitine gives ranaconine (27) and *N*-acetylthranilic acid. The  $^{13}\text{C}$  n.m.r. chemical shifts and assignments for ranaconitine and lappaconitine are presented.<sup>10</sup> Correlation of these spectra with those of other  $\text{C}_{19}$  diterpenoid alkaloids supports structure (26) for ranaconitine. This co-occurrence of an aconitine-type alkaloid (no oxygen-containing group at C-7) and a lycoctonine-type alkaloid (which has an oxygen functionality at C-7) has not been noted in recent phytochemical investigations.

**Alkaloids of *Aconitum septentrionale*: Septentrionine and Septentriodine.**—

Further investigations<sup>11</sup> into the alkaloids of *A. septentrionale* Koelle collected in Norway have elucidated the structures of two new alkaloids from these plants. Lappaconitine (24) and desacetyl-lappaconitine (28) had previously been identified.<sup>12</sup> Septentrionine [ $\text{C}_{38}\text{H}_{54}\text{N}_2\text{O}_{11}$ ; m. pt. 123–125 °C] was shown to have structure (29) from the i.r. and  $^1\text{H}$  and  $^{13}\text{C}$  n.m.r. spectral data. Alkaline hydrolysis of septentrionine (29) gave (30) and *N*-succinoylanthranilic acid. Septentrionine is probably the Alkaloid 'A' described in the earlier investigations<sup>12</sup> of *A. septentrionale*. Septentriodine [ $\text{C}_{37}\text{H}_{52}\text{N}_2\text{O}_{11}$ ; amorphous] was assigned structure (31) from the i.r.,  $^1\text{H}$  and  $^{13}\text{C}$  n.m.r., and mass spectral data. Hydrolysis of septentriodine (31) with 5% methanolic KOH gave lycoctonine (3) and *N*-succinoylanthranilic acid. The  $^{13}\text{C}$  n.m.r. chemical shifts and assignments for (29), (30), (31), and several structurally related alkaloids have been presented.<sup>11</sup> Septentrionine and septentriodine are comparable to the acid (5) and corresponding ester (6) that were reported as artifacts of lyaconitine from *A. gigas*.<sup>6</sup> These are the first  $\text{C}_{19}$  diterpenoid alkaloids that bear a carboxyl function in the amide side-chain to have been reported.



Lappaconitine (24)  $\text{R}^1 = \text{COC}_6\text{H}_4\text{-}o\text{-NHAc}$ ,  $\text{R}^2 = \text{H}$ ,  $\text{R}^3 = \text{Me}$

Lappaconine (25)  $\text{R}^1 = \text{R}^2 = \text{H}$ ,  $\text{R}^3 = \text{Me}$

Ranaconitine (26)  $\text{R}^1 = \text{COC}_6\text{H}_4\text{-}o\text{-NHAc}$ ,  $\text{R}^2 = \text{OH}$ ,  $\text{R}^3 = \text{Me}$

Ranaconine (27)  $\text{R}^1 = \text{H}$ ,  $\text{R}^2 = \text{OH}$ ,  $\text{R}^3 = \text{Me}$

Desacetyl-lappaconitine (28)  $\text{R}^1 = \text{COC}_6\text{H}_4\text{-}o\text{-NH}_2$ ,  $\text{R}^2 = \text{H}$ ,  $\text{R}^3 = \text{Me}$

Lappaconidine (50)  $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$

[Structures (29), (30), and (31) appear with structures (3) and (4)]

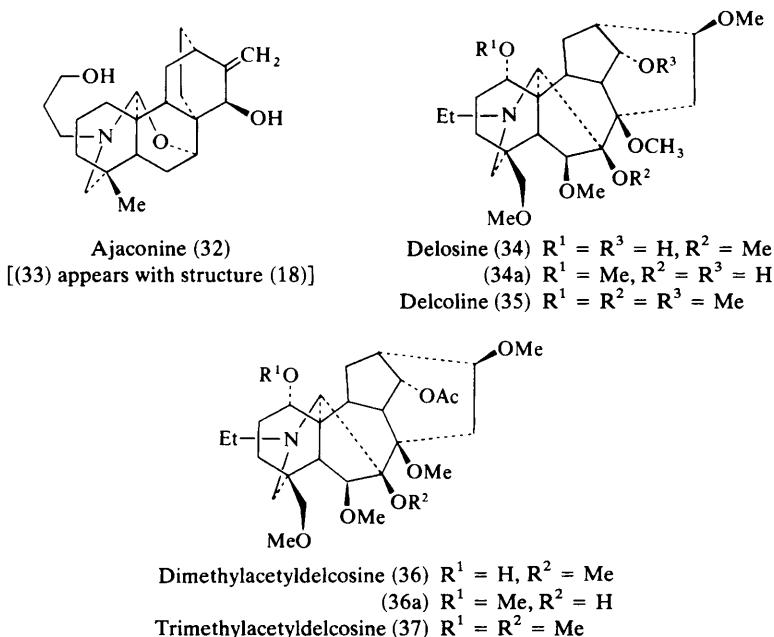
**Alkaloids of '*Delphinium ajacis*' (syn. *Consolida ambigua*).**—Waller and Lawrence<sup>13</sup> have reported further isolation and mass spectral studies of alkaloids from the 'common larkspur'. Ajaconine (32), delcosine (18), acetyldelcosine (33),

<sup>11</sup> S. W. Pelletier, R. S. Sawhney, and A. J. Aasen, *Heterocycles*, 1979, **12**, 377.

<sup>12</sup> L. Marion, L. Fonze, C. K. Wilkins, Jr., J. P. Boca, F. Sandberg, R. Thorsen, and E. Linden, *Can. J. Chem.*, 1967, **45**, 969.

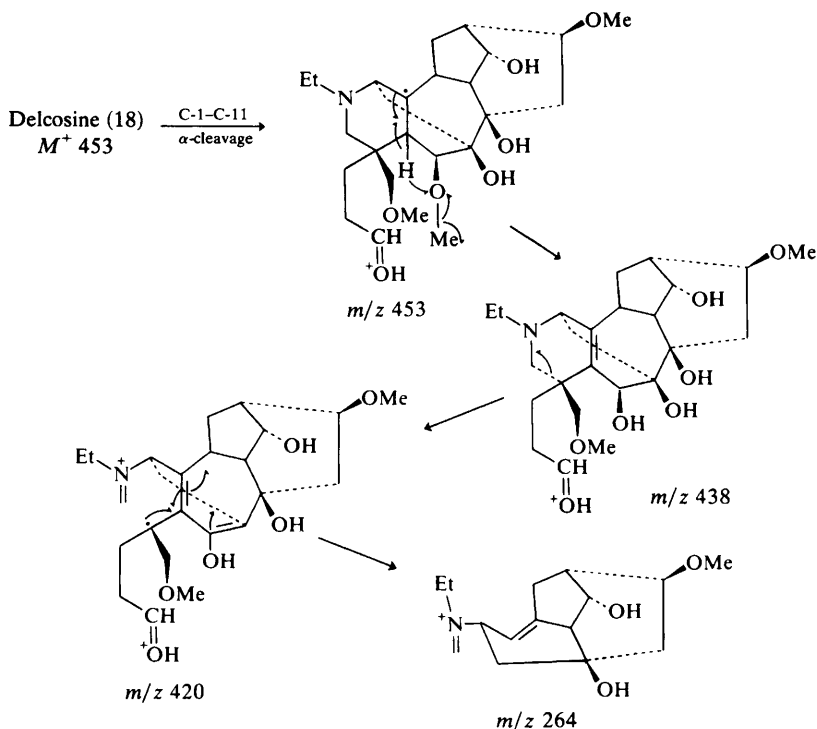
<sup>13</sup> G. R. Waller and R. H. Lawrence, Jr., in 'Recent Developments in Mass Spectrometry in Biochemistry and Medicine,' ed. A. Fierio, Plenum, New York, 1978, p. 429.

and delsoine (11) were previously identified from this species. The isolation procedure included extraction of the powdered dry plant material with 10% acetic acid. The acid extract was washed with  $\text{CCl}_4$  and then, with cooling to  $10^\circ\text{C}$ , was made basic with 5N-NaOH (to pH 13). The chloroform extract of this basic solution was analysed directly by t.l.c., g.c., and g.c.-m.s. A key feature of the g.c. and g.c.-m.s. analyses was the use of all-glass systems to prevent dehydration and epimerization. The t.l.c. analyses indicated the presence of eight alkaloids, including (11), (18), (32), and (33). The mass spectra of these and the four unknown bases were determined by g.c.-m.s. or by direct-probe m.s. analyses of the material isolated from t.l.c. plates. The following structures and names for the unknown alkaloids were proposed, on the basis of the mass spectral data and from biosynthetic considerations:  $m/z$  481, delosine (34);  $m/z$  509, delcoline (35);  $m/z$  523, dimethylacetyldecosine (36); and  $m/z$  537, trimethylacetyldecosine (37). The possibility that other combinations of the oxygen functionalities could exist in (34), (35), and (37) was noted. To account for the presence of the  $[M - 189]$  ion in the mass spectra of compounds (18), (33), and (11) [no methoxy-group at C-7] and its absence in compounds (34), (35), (36), and (37), the route of formation as shown in Scheme 1 was postulated. The biosyntheses and interconversion of these alkaloids were also discussed.



No additional physical or chemical data for the new alkaloids were given. However, the base peak in the mass spectra of these bases was the  $[M - 31]$  ion, corresponding to the loss of OMe. From previous mass spectral studies of the diterpenoid alkaloids,<sup>14</sup> a loss such as this resulting in the base peak generally

<sup>14</sup> M. S. Yunusov, Ya. V. Rashkes, V. A. Telnov, and S. Yu. Yunusov, *Khim. Pri. Soedin.*, 1969, 515.



Scheme 1

indicated the presence of a methoxy-group at C-1. Therefore, structures (34a) and (36a) for delcosine and dimethylacetyldelcosine, respectively, seem more likely than the structures proposed.

Some taxonomical confusion exists regarding the speciation of 'common larkspur', formerly known as *D. ajacis*, but renamed *Consolida ambigua* (cf. Vol. 9, p. 223). Given this situation, and the uncertainty in the assignments of the configurations of the methoxy-group at C-1, it is possible that dimethylacetyldelcosine and ambiguiine (38)<sup>15</sup> are identical.

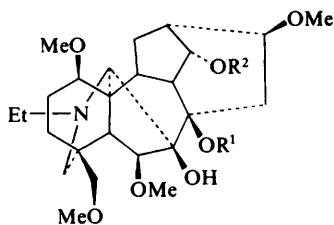
**Alkaloids of *Delphinium brownii* (*Delphinium glaucum*).**—Further investigations<sup>3</sup> of the alkaloids of *D. brownii* have shown the presence, in addition to the previously reported methyl-lycaconitine and browniine, of the diterpenoid alkaloid 14-acetylbrowniine (39) and the aporphine alkaloid magnoflorine. 14-Acetylbrowniine has recently been isolated from plants of *D. oreophilum*<sup>16</sup> and *D. ajacis* (syn. *Consolida ambigua*).<sup>17</sup> The Canadian report<sup>3</sup> noted that this larkspur (native to Alberta) is probably better regarded as a local form of *D. glaucum* S. Wats.

<sup>15</sup> S. W. Pelletier, R. S. Sawhney, and N. V. Mody, *Heterocycles*, 1978, **9**, 1241.

<sup>16</sup> V. G. Kazlikhin, V. A. Tel'nov, M. S. Yunusov, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 1977, 869.

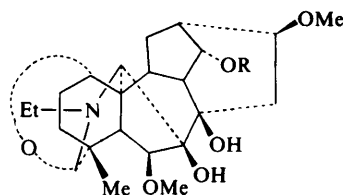
<sup>17</sup> S. W. Pelletier, N. V. Mody, R. S. Sawhney, and J. Bhattacharyya, *Heterocycles*, 1977, **7**, 327.

**Alkaloids of *Delphinium confusum*.**—Extraction of the roots of plants of *D. confusum* M. Pop. with chloroform gave a total of 2.5% of the weight of the plant as alkaloids.<sup>18</sup> pH-Gradient extraction and chromatography on aluminium oxide gave three alkaloids, i.e. methyl-lycaconitine (40), anthranoyl-lycoctonine (41), and a new base,  $C_{30}H_{41}N_2O_8$ , m. pt. 157–159 °C (hydrochloride: m. pt. 162–165 °C). The i.r. and <sup>1</sup>H n.m.r. spectra of this alkaloid indicated the presence of an *N*-ethyl group, four methoxy-groups, an aromatic ring, an ester carbonyl, and hydroxy-groups. Extraction of the aerial parts gave a total of 0.43% of alkaloids, in which methyl-lycaconitine was identified.



Ambiguine (38)  $R^1 = \text{Me}, R^2 = \text{Ac}$

14-Acetylbrowniine (39)  $R^1 = \text{H}, R^2 = \text{Ac}$



Gadesine (42)  $R = \text{H}$

(43)  $R = \text{Ac}$

[Structures (40) and (41) appear with structure (4)]

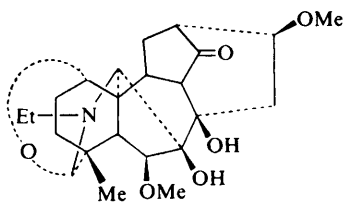
**Alkaloids of *Delphinium pentagynum*.**—Researchers in Spain have isolated<sup>19</sup> a new diterpenoid alkaloid from plants of *D. pentagynum* Lam. collected in southern Spain. Gadesine [ $C_{23}H_{35}NO_6$ ; m. pt. 174–177 °C] was assigned structure (42) on the basis of the chemical, i.r., <sup>1</sup>H n.m.r., and mass spectral data, and from biogenetic considerations. This structure was confirmed by an X-ray crystallographic structure determination. Chemical studies included treatment of gadesine with acetic anhydride and pyridine, which gave the monoacetate (43). Oxidation of gadesine with Cornforth's reagent afforded 14-ketogadesine (44), while reduction with  $\text{LiAlH}_4$  gave the amino-alcohol (45). As is the case with most diterpenoid alkaloids with an  $\alpha$ -hydroxy-group at C-1, oxidation of (45) with potassium permanganate regenerated the cyclic carbinolamine ether. Although several  $C_{20}$  diterpenoid alkaloids with the C-1–O–C-19 bond have been isolated, this is the first reported naturally occurring  $C_{19}$  diterpenoid alkaloid that contains this extremely rigid ring A system.

**Alkaloids of *Delphinium ternatum* Huth.**—Narzullaev and co-workers<sup>18</sup> have reported that extraction of the roots and the aerial parts of these plants with chloroform produced totals of 0.16 and 0.14% of alkaloids, respectively. Fractionation of the root extract by chromatography on silica gel and pH-gradient extraction gave the known alkaloid methyl-lycaconitine (40) and a new alkaloid,  $C_{26}H_{41}NO_7$ , of m.pt. 195–198 °C. The i.r. data indicated the presence of a hydroxy-group and a carboxy-ester. The mass spectrum of this base (mol. wt. 497) was characteristic of a lycoctonine-type alkaloid with a methoxy-group at C-1.

<sup>18</sup> A. S. Narzullaev, Yu. D. Sadykov, and M. Khodzhimatov, *Izv. Akad. Nauk Tadzh. SSR, Otd. Fiz.-Mat. Geol.-Khim. Nauk*, 1978, 87.

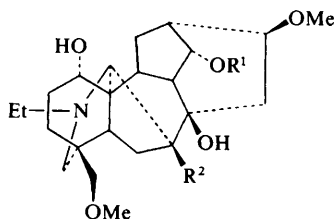
<sup>19</sup> A. G. Gonzalez, G. de la Fuente, and R. Diaz, *Tetrahedron Lett.*, 1979, 79.

**Alkaloids of *Delphinium virescens*.**—A recent study<sup>20</sup> of the diterpenoid alkaloids of *D. virescens* Nutt., a plant native to the southeastern United States, has resulted in the isolation of four bases. The major alkaloid was ajaconine (32). Three minor lycoctonine-type bases that were isolated were browniine and two new alkaloids, *i.e.* virescine (46) [ $C_{23}H_{37}NO_6$ ; m. pt. 68—70 °C (ether–hexane)] and 14-acetylvirescine (47) [ $C_{25}H_{39}NO_7$ ; m. pt. 157—159 °C]. The structures of these compounds were assigned from their i.r. and  $^1H$  and  $^{13}C$  n.m.r. spectral data. Comparisons of the  $^{13}C$  n.m.r. data with those of other lycoctonine-type alkaloids, particularly isotalatizidine (48) and condelphine (49), supported these structures. Treatment of compound (47) with 5% KOH in methanol afforded the amino-alcohol virescine (46).



(44)

[Structure (45) appears with (18)]

Virescine (46)  $R^1 = H, R^2 = OH$ (47)  $R^1 = Ac, R^2 = OH$ Isotalatizidine (48)  $R^1 = R^2 = H$ Condelphine (49)  $R^1 = Ac, R^2 = H$ 

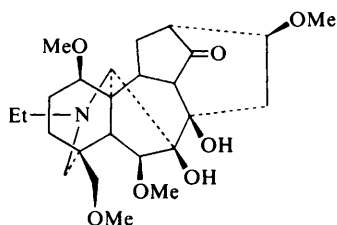
**$^{13}C$  N.M.R. Studies of  $C_{19}$  Diterpenoid Alkaloids.**—Additional spectral analyses that applied to the structure elucidation of the  $C_{19}$  diterpenoid alkaloids have been published.<sup>21</sup> Using noise-decoupling and single-frequency off-resonance decoupling techniques and additivity relationships, the carbon resonances for the following alkaloids were assigned: lappaconitine (24), lappaconine (25), lappaconidine (50), ranaconine (27), 14-dehydrobrowniine (51), aconine (52), pseudoaconine (20), deoxyaconine (53), and hypaconine (54). The configuration of the hydroxy-group at C-1 affected the chemical shifts of the other carbon atoms of ring A. From these data, the authors proposed that, in those alkaloids with an  $\alpha$ -hydroxy-group at C-1, a hydrogen bond exists between this hydroxyl and the nitrogen atom, thus stabilizing ring A in a boat form. When the hydroxyl is of  $\beta$  configuration, ring A remains in a chair form. This idea was supported by the observation that the spectra of lappaconidine (50) in chloroform and in pyridine were almost identical. However, for aconine (52) and pseudoaconine (20), the shifts of the C-2, C-3, and C-4 resonances were significantly different in chloroform *versus* pyridine.

**Reactions of Some Aconitine-type Alkaloids.**—Ichinohe *et al.*<sup>22</sup> have reported a study of some reactions of  $C_{19}$  diterpenoid alkaloids. They attempted to correlate

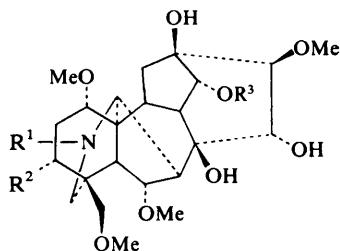
<sup>20</sup> S. W. Pelletier, N. V. Mody, A. P. Venkov, and S. B. Jones, Jr., *Heterocycles*, 1979, **12**, 779.

<sup>21</sup> S. W. Pelletier, N. V. Mody, and R. S. Sawhney, *Can. J. Chem.*, 1979, **57**, 1652.

<sup>22</sup> Y. Ichinohe, H. Sakamaki, M. Hosoda, M. Aimi, T. Takido, T. Sato, and M. Hasegawa, *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu*, 1978, **21**, 74 (*Chem. Abs.* 1979, **90**, 152 421).

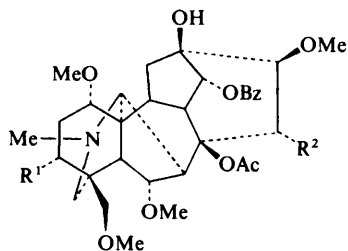


14-Dehydrobrowniine (51)  
 [(50) appears with (24)]

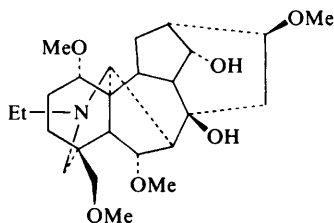


Aconine (52)  $R^1 = \text{Et}, R^2 = \text{OH}, R^3 = \text{H}$   
 Deoxyaconine (53)  $R^1 = \text{Et}, R^2 = R^3 = \text{H}$   
 Hypaconine (54)  $R^1 = \text{Me}, R^2 = R^3 = \text{H}$   
 Mesaconine (95)  $R^1 = \text{Me}, R^2 = \text{OH}, R^3 = \text{H}$   
 Benzoylaconine (96)  $R^1 = \text{Et}, R^2 = \text{OH}, R^3 = \text{Bz}$

delphinine (55) with chasmanine (56). In addition, the hydrogenation of aconitine (21), jesaconitine (22), and mesaconitine (57) to the corresponding deoxy-compounds was described.

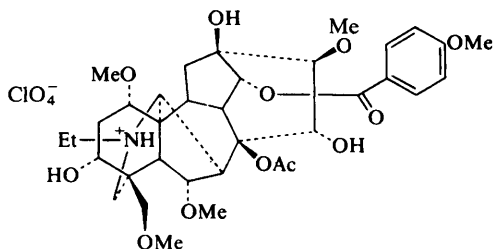


Delphinine (55)  $R^1 = R^2 = \text{H}$   
 Mesaconitine (57)  $R^1 = R^2 = \text{OH}$   
 Hypaconitine (92)  $R^1 = \text{H}, R^2 = \text{OH}$



Chasmanine (56)

**Crystal Structure of Jesaconitine Perchlorate.**—An X-ray crystallographic structure determination of the perchlorate salt of jesaconitine has confirmed its structure as (58).<sup>23</sup> Ring A was determined to have a boat conformation, stabilized by intramolecular hydrogen bonds between the nitrogen and the oxygen substituents at C-1 and C-3. Ring C is in an envelope conformation, with C-14 at the flap. Ring D is a distorted boat that has the C-15 end flattened.

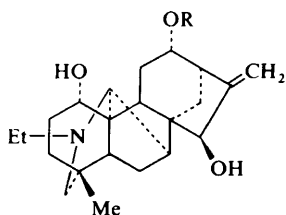


Jesaconitine perchlorate (58)

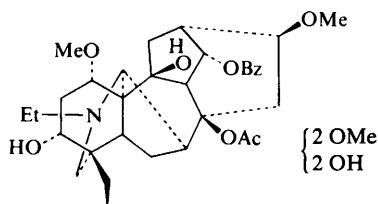
<sup>23</sup> S. W. Pelletier, W. H. De Camp, J. Finer-Moore, and Y. Ichinohe, *Cryst. Struct. Commun.*, 1979, **8**, 299.

### 3 C<sub>20</sub> Diterpenoid Alkaloids

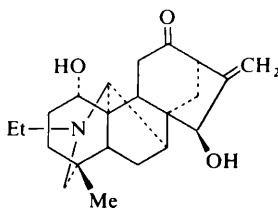
**Alkaloids of *Aconitum karakolicum*.**—Yunusov and co-workers<sup>4</sup> have published the full paper on the structure elucidation of 12-acetylnapelline (59) [C<sub>24</sub>H<sub>35</sub>NO<sub>4</sub>; m. pt. 205—206 °C] in further studies of the alkaloids of *A. karakolicum* (cf. Vol. 8, p. 236). These plants were collected in the Kirghiz S.S.R. Also isolated from the epigeal parts were aconitine (21), aconifine (60), songorine (61), napelline (62), and phenyl-2-naphthylamine.



12-Acetylnapelline (59) R = Ac  
Napelline (62) R = H

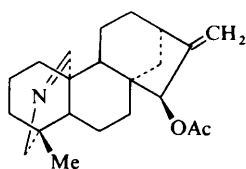


Aconifine (60)

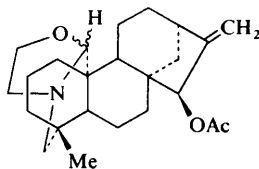


Songorine (61)

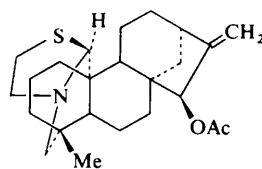
**Formation of the Oxazolidine and Thiazolidine Ring in C<sub>20</sub> Diterpenoid Systems.**—A convenient method for the construction of oxazolidine and thiazolidine rings from the imine-containing diterpenoids has been reported.<sup>24</sup> Treatment of the imine, e.g. lindheimerine (63), with ethylene oxide in glacial acetic acid or with excess neat ethylene sulphide gave the corresponding oxazolidine [e.g. ovatine (64)] and thiazolidine [e.g. (65)], respectively, in yields of 90—98%.



Lindheimerine (63)



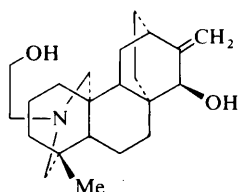
Ovatine (64)



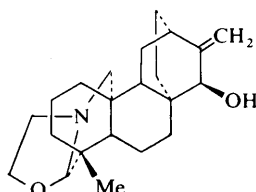
(65)

<sup>24</sup> S. W. Pelletier, J. Nowacki, and N. V. Mody, *Synth. Commun.*, 1979, **9**, 201.

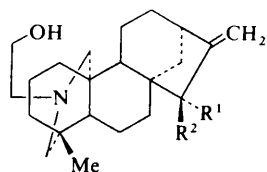
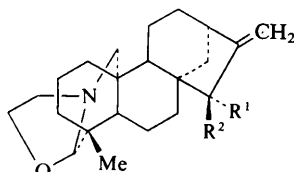
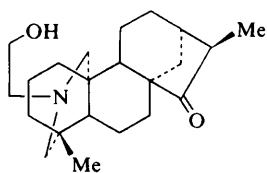
**Formation of the Isoxazolidine Ring in  $C_{20}$  Diterpenoid Systems.**—A new method for the conversion of the *N*-2-hydroxyethyl group into the corresponding isoxazolidine-ring-containing alkaloids has been developed.<sup>25</sup> For example, treatment of dihydroatisine (66) in chloroform with active manganese dioxide at room temperature gave isoatisine (67) in yields of 55–61%. Analogous results were obtained in transforming dihydroveatchine (68) into garryine (69), dihydrogarryfoline (70) into isogarryfoline (71), and dihydrocuauchichicine (72) into isocuauchichicine (73). This procedure is a considerable improvement over the use of osmium tetroxide or mercuric acetate.



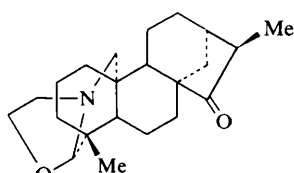
Dihydroatisine (66)



Isoatisine (67)

Dihydroveatchine (68)  $R^1 = OH, R^2 = H$   
Dihydrogarryfoline (70)  $R^1 = H, R^2 = OH$ Garryine (69)  $R^1 = OH, R^2 = H$   
Isogarryfoline (71)  $R^1 = H, R^2 = OH$ 

Dihydrocuauchichicine (72)



Isocuauchichicine (73)

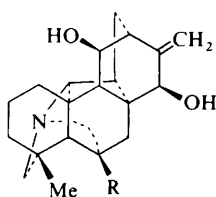
**Chemical Conversions of Kobusine.**—Okamoto and co-workers<sup>26</sup> have reported some of their recent studies of the chemistry of kobusine (74), a C-14–C-20-bridged atisine-type diterpenoid alkaloid. Since this bond constitutes a bicyclo-[3.2.1]octane system, and conversion into a double bond would violate Bredt's rule, there would appear to be no simple way to cleave it. Kobusine was reduced to (75) with sodium in *n*-propanol to protect the allylic alcohol. Acetylation of

<sup>25</sup> S. W. Pelletier, N. V. Mody, and J. Bhattacharyya, *Tetrahedron Lett.*, 1978, 5187.

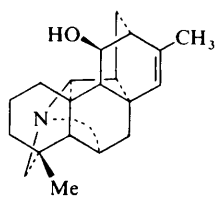
<sup>26</sup> T. Yatsunami, S. Furuya, and T. Okamoto, *Chem. Pharm. Bull.*, 1978, **26**, 3199; *cf. ibid.*, 1975, **23**, 3030.



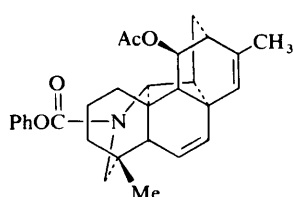
compound (75) followed by treatment with excess phenyl chloroformate gave (76). Hydrogenation of the latter with palladium/carbon gave compound (77), which was further reduced to (78) with platinum black in acetic acid. Acid hydrolysis of (78) gave (79). Ester exchange with benzyl alcohol plus NaH yielded (80), which underwent hydrogenolysis to (81). Chlorination of this amine with *N*-chlorosuccinimide produced the chloramine (82). Refluxing the latter with sodium ethoxide gave a mixture of (83), (84), and (85) (in 38, 28, and 13% yield, respectively). The structure of (83) was assigned on the basis of a series of chemical conversions and was confirmed by an X-ray crystallographic analysis. The structures of (84) and (85) were determined from spectral data and chemical transformations. An anionic nitrogen intermediate (86) for this reaction was tentatively proposed for the following reasons: (i) a nitrenium intermediate was ruled out, because (83) was not formed when (82) reacted with silver tetrafluoroborate; (ii) a homolytic mechanism appeared to be unlikely because (83) was not formed in the presence of a radical initiator or under Hofmann-Loeffler conditions; and (iii) treatment of (82) with sodium methoxide in the presence of *N*-bromoacetamide gave a mixture of (83) and (87). The C-14-C-20 bond was regenerated by refluxing (83) with lithium in THF. These studies may prove useful



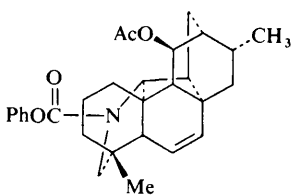
Kobusine (74) R = H  
Pseudokobusine (93) R = OH



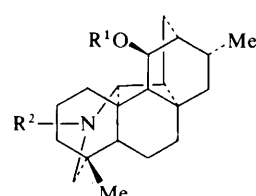
(75)



(76)



(77)



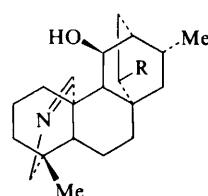
(78) R<sup>1</sup> = Ac, R<sup>2</sup> = PhO<sub>2</sub>C—

(79) R<sup>1</sup> = H, R<sup>2</sup> = PhO<sub>2</sub>C—

(80) R<sup>1</sup> = H, R<sup>2</sup> = PhCH<sub>2</sub>O<sub>2</sub>C—

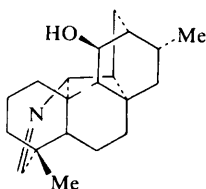
(81) R<sup>1</sup> = R<sup>2</sup> = H

(82) R<sup>1</sup> = H, R<sup>2</sup> = Cl

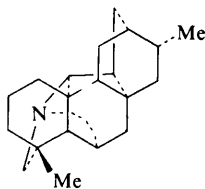


(83) R = Cl

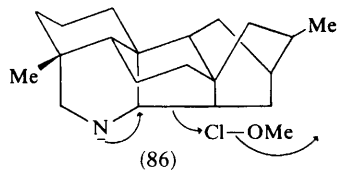
(87) R = Br



(84)



(85)



(86)

in the total synthesis of kobusine and related alkaloids because the formation of both the C-6-N and the C-14-C-20 bonds from the atisine-type skeleton are key reactions.

**An Unusual Rearrangement of Ajaconine.**—When ajaconine (32) was heated under reflux in methanol or aqueous methanol, it rearranged *via* a 5-*endo*-trigonal ring-closure to a new compound, identified as 7 $\alpha$ -hydroxy-isoatisine (88) [C<sub>22</sub>H<sub>33</sub>NO<sub>3</sub>; m. pt. 118–122 °C].<sup>27</sup> These reaction conditions are analogous to those which effect the atisine to isoatisine-type rearrangement, *i.e.* (89; R = H)  $\longrightarrow$  (67). Incidentally, this product (88) was not identified in previous studies<sup>28</sup> of the chemistry of ajaconine. Ajaconine (32) forms an immonium salt (90) instead of a protonated-type (*i.e.* NH<sup>+</sup>) salt when treated with HCl. Treatment of (90; X = Cl) with cold base regenerated ajaconine instead of (89; R = OH), which is the product which would parallel that expected from the chemistry of atisine. <sup>13</sup>C n.m.r. spectral studies indicated that, in hydrogen-bonding-type solvents, the ether linkage of ajaconine ionizes and covalent solvation occurs. This observation accounts for the high pK<sub>a</sub> value of ajaconine (11.8) in aqueous solution and the formation of immonium salts. Reduction of (88) with borohydride gave dihydroajaconine. Refluxing of ajaconine in deuteriated methanol gave a mixture of C-19- and C-20-deuteriated ajaconine and C-19- and C-20-deuteriated 7 $\alpha$ -hydroxyisoatisine (88). From these data, the mechanism for the rearrangement of ajaconine (32) to 7 $\alpha$ -hydroxyisoatisine (88) that is outlined in Scheme 2 was proposed. In ionizing solvents, the closure of the salt (90; X = MeO) to the oxazolidine (89; R = OH) is much slower than the closure to ajaconine (32). However, upon isomerization to (91), which is a reaction analogous to that occurring in the atisine to isoatisine-type rearrangement, this species can readily close to the oxazolidine (88), in spite of the closure being partially disfavoured, because there is no faster process in competition with this ring-closure. The rearrangement of ajaconine is an example of a ‘Baldwin-rule-disfavoured’ 5-*endo*-trigonal ring-closure. The authors state that the Baldwin cyclization rules appear to be less prohibitive for quaternary immonium salts bearing a charge on the nitrogen, because these salts resemble carbo-cations more than uncharged groups.

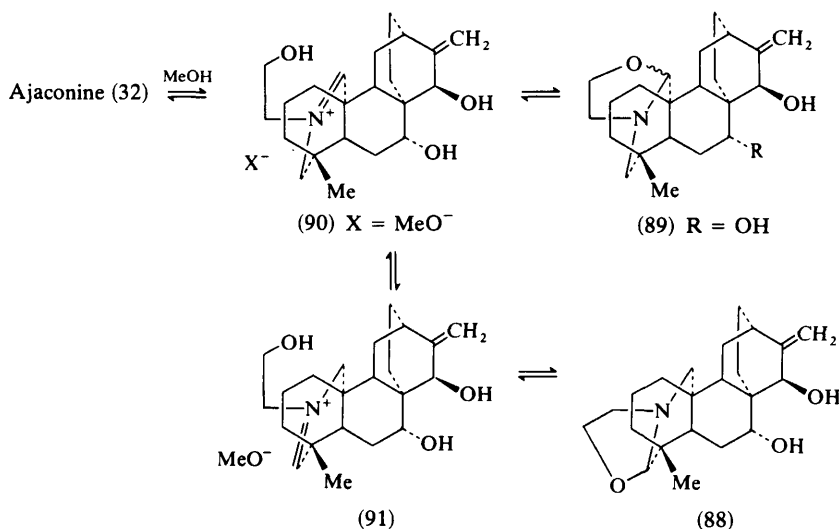
#### 4 Chemotaxonomical Studies

Researchers in Japan<sup>29</sup> have reported the separation and quantitative analyses of the diterpenoid alkaloids in the roots of *A. mitakense* Nakai and *A. yezoense* Nakai. For the quantitative t.l.c. analyses, a dual-wavelength thin-layer scanner (the silica-gel plates were developed with ether saturated with 25% NH<sub>4</sub>OH) was used. For the gas-chromatographic analyses, 1.5% OV-101 and 1.5% SE-30 liquid phases were employed. The alkaloid contents of the roots of *A. mitakense* and *A. yezoense* (from two locations) were measured during the growing season. The levels of hypaconitine (92), aconitine (21), jesaconitine (22), mesaconitine (57), kobusine (74), pseudokobusine (93), lucidusculine (94), chasmanine (56),

<sup>27</sup> S. W. Pelletier and N. V. Mody, *J. Am. Chem. Soc.*, 1979, **101**, 492.

<sup>28</sup> D. Dvornik and O. E. Edwards, *Tetrahedron*, 1961, **14**, 54.

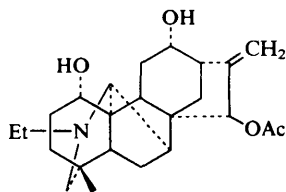
<sup>29</sup> F. Kurosaki, T. Yatsunami, T. Okamoto, and Y. Ichinohe, *Yakugaku Zasshi*, 1978, **98**, 1267.



Scheme 2

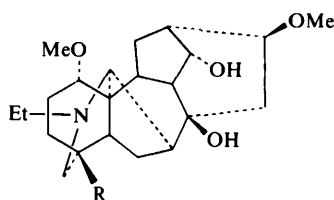
and neoline (8) were monitored. In general, the highest levels occurred early in the growing season (May) and during flowering (August).

Muramatsu and co-workers,<sup>30</sup> in studies associated with livestock poisonings, examined the alkaloids of the leaves and roots of *A. chinense* collected at various growth stages. They reported on the levels of mesaconine (95), aconitine (21), benzoylmesaconine, and benzoylaconine (96). The highest levels of alkaloids in the roots occurred during September. For the leaves, the highest levels occurred in May and October.



Lucidusculine (94)

[Structure (92) is with (55);  
(93) with (74)]

Aconosine (97)  $R = \text{H}$ 

Talatisamine (98)  $R = \text{CH}_2\text{OMe}$   
[Structures (95) and (96) are with (52)]

Soviet researchers<sup>31,32</sup> have reported chemotaxonomical studies of *Aconitum* species native to the Far East. The number and levels of alkaloids varied with both the species and the habitat. Some of their results are presented in Table 1.

<sup>30</sup> U. Muramatsu, M. Takahashi, H. Shibata, and K. Watanabe, *Tochigi-ken Kachiku Eisei Kenkyusho Nempo*, 1977, **12**, 31 (*Chem. Abs.*, 1979, **90**, 183 148).

<sup>31</sup> N. M. Golubev, V. A. Tel'nov, M. S. Yunusov, N. K. Fruentov, and S. Yu. Yunusov, *Vopr. Farm. Dal'nem. Vostoke*, 1977, **2**, 10 (*Chem. Abs.*, 1979, **90**, 164 757).

<sup>32</sup> N. M. Golubev, *Vopr. Farm. Dal'nem Vostoke*, 1977, **2**, 37 (*Chem. Abs.*, 1979, **90**, 164 758).

**Table 1** Alkaloids found in *Aconitum* species grown in two areas of the lower Amur basin<sup>a</sup>

Species	Area 1		Area 2		Number of bases <sup>32</sup>	Alkaloids identified <sup>31</sup>
	Total alkaloids (%)	Total alkaloids (%)	Total alkaloids (%)	Total alkaloids (%)		
<i>A. arcuatum</i>	0.86 <sup>b</sup>	0.43 <sup>b</sup>	—	—	—	Aconosine (97), talatisamine (98)
<i>A. fischeri</i>	1.04	0.26	—	0.52 <sup>c</sup>	13	Talatisamine, aconosine
<i>A. sczukini</i>	0.95	0.126	—	—	11	Mesaconitine (57), neoline (8)
<i>A. umbrosum</i>	0.46	0.59	2.35	0.99	10	Lycaconitine (4)

(a) The percentages shown are percentages of the total weight of the plants. (b) Plants were collected during the period of formation of flower buds through to the beginning of flowering. (c) Leaves only.

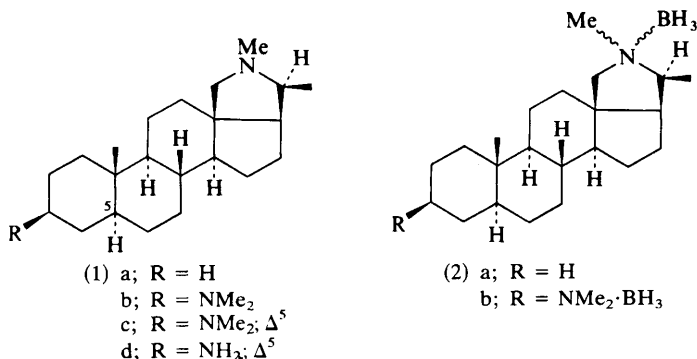
Karawya and Diab<sup>33</sup> have published details of a colorimetric method for the estimation of aconitine in the presence of aconine (52) and benzoyleaconine (96) in plant extracts that are used as pharmaceutical formulations. This method involved the formation of an iron hydroxalate complex and the measurement of the absorbance at 530 nm. Other alkaloids with a group that may react with the hydroxylamine reagent would interfere with the specific analysis for aconitine.

**Acknowledgment:** The authors express their appreciation to Dr. Naresh V. Mody for reviewing the manuscript and making several helpful suggestions.

<sup>33</sup> M. S. Karawya and A. M. Diab, *J. Pharm. Sci.*, 1977, **66**, 1331.

## 1 Alkaloids of the Apocynaceae

Conanine (1a) readily yielded the diastereoisomeric borane complexes (2a) on reaction with borane in tetrahydrofuran.<sup>1</sup> The starting material was re-formed when a solution of (2a) in ethanol was refluxed. The utility of borane as a protecting group for a tertiary amine function was demonstrated by the preparation of dihydroconessimine (4) from dihydroconessine (1b). The intermediate mono-borane complex (3) could be prepared by selective boronation of dihydroconessine, but was obtained in higher yield by selective deprotection of the bis-borane complex (2b), as depicted in Scheme 1. Dihydroconessine *N*-oxide also was prepared from the borane complex (3) by oxidation with a peracid followed by deprotection as before.<sup>1</sup>

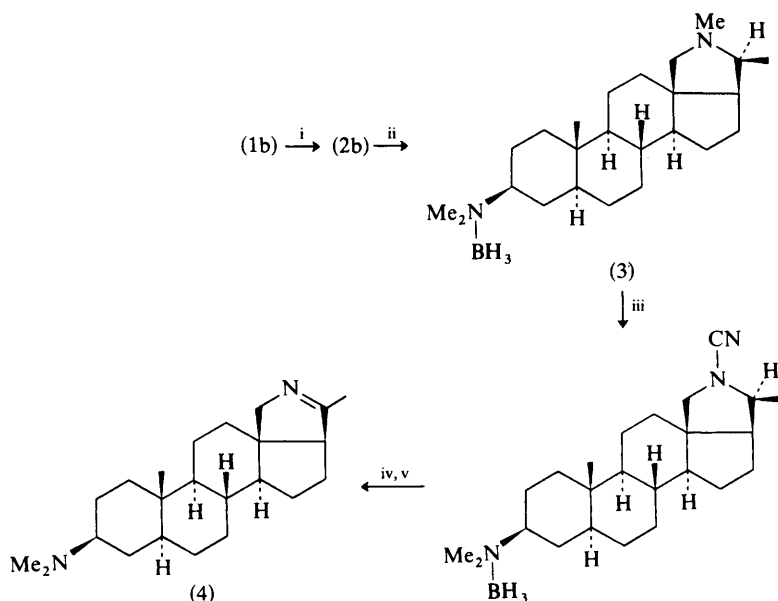


The reaction of conanine (1a) and of related compounds with a number of halogenating agents has been studied.<sup>2</sup> With an excess of bromine in methylene chloride the major product was the lactam (5a), while the desmethyl lactam (5b) and the chlorinated imines (6a) and (6b) were also formed when sodium hypochlorite was used as the oxidant. Treatment of conanine with iodine and sodium bicarbonate in THF gave the ring-expanded heterocycle (7) as the major product;<sup>2</sup> a similar reaction had been observed previously during the oxidation of dihydroconessine.<sup>3</sup>

<sup>1</sup> A. Picot and X. Lusinchi, *Bull. Soc. Chim. Fr.*, 1977, 1227.

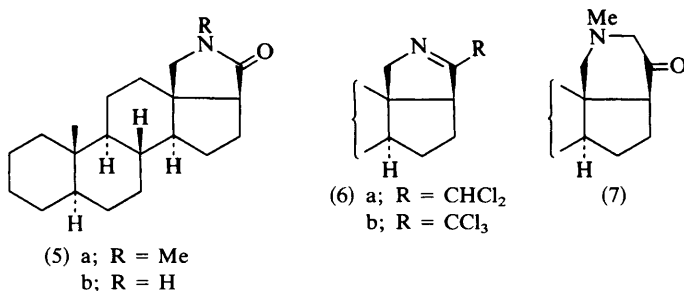
<sup>2</sup> A. Picot and X. Lusinchi, *Tetrahedron*, 1978, **34**, 2747.

<sup>3</sup> M. M. Janot, C. Conreur, and R. Goutarel, *Bull. Soc. Chim. Fr.*, 1962, 2234.



Reagents: i,  $\text{THF} \cdot \text{BH}_3$ ; ii,  $\text{MeCN}$ , heat; iii,  $\text{BrCN}$ ; iv,  $\text{EtOH}$ , heat; v,  $\text{HCl}$ ,  $\text{AcOH}$ , heat

**Scheme 1**

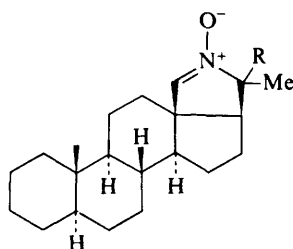


The hydroxy-nitrone (8a) gave the isomeric hydroxy-nitrone (9) on treatment with acid. The latter hydroxy-nitrone underwent base-catalysed deuteration at C-21, presumably *via* the dihydroxy-enamine tautomer. Treatment of either hydroxy-nitrone with methanolic sulphuric acid gave the unstable methoxy-nitrone (10), which yielded the dimeric compound (11) on attempted crystallization.<sup>4</sup> The reaction of nitrone (8b) with dialkyl phosphite derivatives was reported earlier;<sup>5</sup> details of this study have now been published.<sup>6</sup>

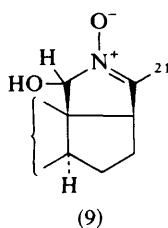
<sup>4</sup> H. Dadoun, J. P. Alazard, J. Parello, and X. Lusinchi, *Tetrahedron*, 1978, **34**, 2639.

<sup>5</sup> P. Milliet and X. Lusinchi, *C. R. Hebd. Seances Acad. Sci., Ser. C.*, 1975, **280**, 1319; cf. F. Khuong-Huu and R. Goutarel, in 'The Alkaloids', ed. M. F. Grundon, (Specialist Periodical Reports), The Chemical Society, London, 1977, Vol. 7, p. 274.

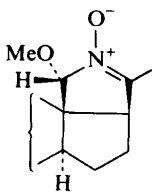
<sup>6</sup> P. Milliet and X. Lusinchi, *Tetrahedron*, 1979, **35**, 43.



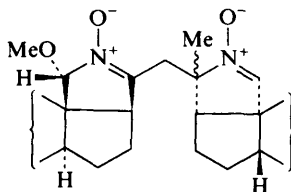
(8) a; R = OH  
b; R = H



(9)



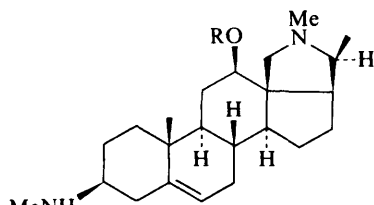
(10)



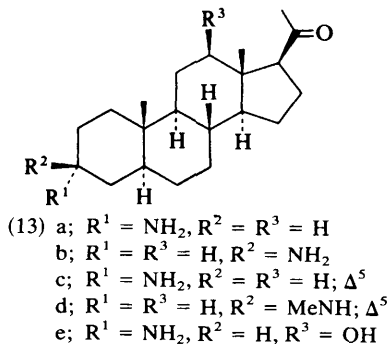
(11)

A new alkaloid, holarrhesine (12a), has been isolated from the bark of *Holarrhena floribunda*, together with the known constituents holadienine and conessine (1c). The new alkaloid was assigned the structure indicated on the basis of spectroscopic studies and the formation of the known compound holarrhelin (12b) on base-catalysed hydrolysis.<sup>7</sup>

A comparison of the alkaloid content of *H. congolensis* with that of *H. floribunda* supported the view that these are distinct species.<sup>8</sup> The major alkaloid in leaves of *H. congolensis*, namely funtumine (13a), was accompanied by dihydroholaphyllamine (13b), holamine (13c), holaphylline (13d), bokitamine (13e), and a new alkaloid, kisantamine (14a). The structure of the latter was deduced solely by spectroscopic studies performed on the *N*-acetyl derivative (14b).<sup>8</sup>



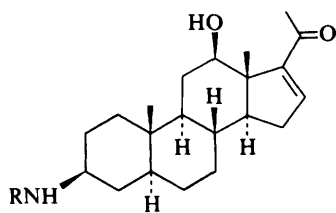
(12) a; R = COCH<sub>2</sub>CH=CHMe<sub>2</sub>  
b; R = H



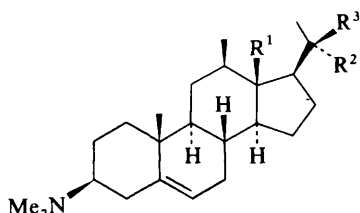
(13) a; R<sup>1</sup> = NH<sub>2</sub>, R<sup>2</sup> = R<sup>3</sup> = H  
b; R<sup>1</sup> = R<sup>3</sup> = H, R<sup>2</sup> = NH<sub>2</sub>  
c; R<sup>1</sup> = NH<sub>2</sub>, R<sup>2</sup> = R<sup>3</sup> = H; Δ<sup>5</sup>  
d; R<sup>1</sup> = R<sup>3</sup> = H, R<sup>2</sup> = MeNH; Δ<sup>5</sup>  
e; R<sup>1</sup> = NH<sub>2</sub>, R<sup>2</sup> = H, R<sup>3</sup> = OH

<sup>7</sup> G. A. Hoyer, A. Huth, I. Nitschke, and C. von Szczepanski, *Planta Med.*, 1978, **34**, 47.

<sup>8</sup> H. Dadoun and A. Cavé, *Plant. Med. Phytother.*, 1978, **12**, 225.



(14) a; R = H  
b; R = Ac



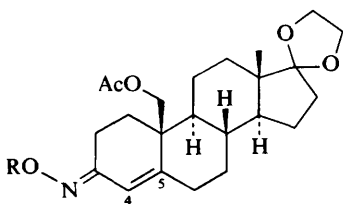
(15) a; R<sup>1</sup> = CH<sub>2</sub>OH, R<sup>2</sup> = NMe<sub>2</sub>, R<sup>3</sup> = H  
b; R<sup>1</sup> = Me, R<sup>2</sup> = H, R<sup>3</sup> = NMe<sub>2</sub>

The major alkaloids of the seed of *Funtumia elastica* are irehdiamines A, B, C, and D.<sup>9</sup> Four minor alkaloids, i.e. conamine (1d), conessine (1c), tetramethyl-horrrhimine (15a), and a new base, 20-*epi*-irehdiamine I (15b), have now been isolated from seeds of this plant. The structure of the latter base was assigned on the basis of its n.m.r. and mass spectra, and confirmed by its synthesis from progesterone by an unexceptional route.<sup>10</sup>

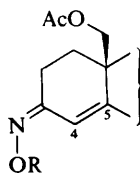
## 2 Salamandra Alkaloids

The synthesis of this group of alkaloids has been reviewed.<sup>11</sup>

The isomeric tosyloximes (16a) and (17a) equilibrate rapidly when dissolved in polar solvents.<sup>12</sup> When the mixture of *syn*- and *anti*-tosyloximes was treated with hydrogen chloride in acetic acid, the product (18) of Beckmann rearrangement of the minor isomer (17a) was isolated in high yield; presumably the rate of Beckmann rearrangement of tosyloxime (16a) is lower than that of the isomeric compound (17a), and is also lower than the rate of its interconversion with the



(16) a; R = Ts  
b; R = H; 4,5β-dihydro



(17) a; R = Ts  
b; R = H; 4,5β-dihydro

latter isomer. Lactam (18) is a possible starting point for the synthesis of salamander alkaloids.<sup>12</sup> In a recent synthesis of cycloneosamandione the *syn*- and *anti*-oximes, (17b) and (16b) respectively, were first separated and the *syn*-isomer was converted into its tosyl derivative prior to Beckmann rearrangement, which furnished the dihydro-analogue of lactam (18).<sup>13</sup> A revised structure (19)

<sup>9</sup> J. Hentchoya-Hemo, Thèse Doctorat, University of Paris, 1970 (Cited by M. D. L. Tolela and P. Foche in ref. 10).

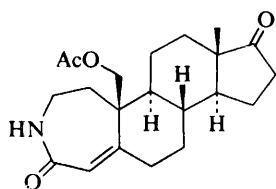
<sup>10</sup> M. D. L. Tolela and P. Foche, *Planta Med.*, 1979, **35**, 48.

<sup>11</sup> K. Oka and S. Hara, *Yuki Gosei Kagaku Kyokaishi*, 1979, **37**, 25 (*Chem. Abs.*, 1979, **90**, 187 183).

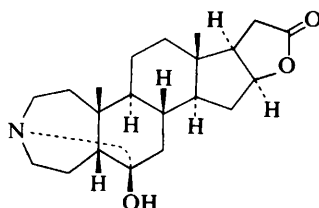
<sup>12</sup> K. Oka and S. Hara, *J. Org. Chem.*, 1978, **43**, 3790.

<sup>13</sup> K. Oka and S. Hara, *J. Am. Chem. Soc.*, 1977, **99**, 3859.





(18)

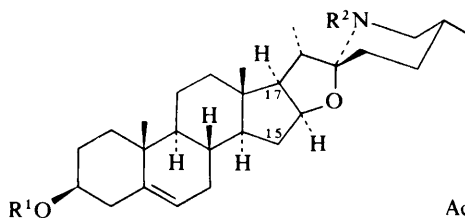


(19)

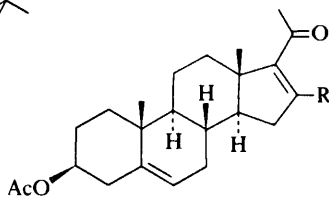
has been suggested for cycloneosamandaridine,<sup>13,14</sup> and methods for the construction of the  $\gamma$ -lactone moiety of the latter have been elaborated.<sup>14</sup>

### 3 Solanum Alkaloids

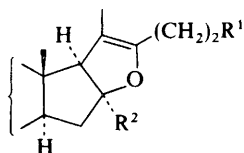
Solasodine (20a) is a useful starting material for the synthesis of pregnane derivatives such as (21a).<sup>15</sup> In an improved version of a known degradation, *O*-acetyl-*N*-nitrososolasodine (20b) was treated sequentially with methanolic toluene-*p*-sulphonic acid and hot acetic acid to give a mixture of dihydrofurans (22a), (22b), and (22c) in good yield. This dihydrofuran mixture was degraded further, to furnish the pregane derivative (21a) in a 60% overall yield from solasodine.<sup>16</sup> The 16-methyl-pregnane derivative (21b) was prepared by oxidative cleavage of the pseudosolasodine derivative (22d). The hydroxy-lactone (23)



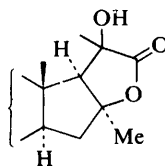
(20) a;  $R^1 = R^2 = H$   
b;  $R^1 = Ac, R^2 = NO$



(21) a;  $R = H$   
b;  $R = Me$



(22) a;  $R^1 = CHMeCH_2OMe, R^2 = H$   
b;  $R^1 = CMe_2OMe, R^2 = H$   
c;  $R^1 = CMe=CH_2, R^2 = H$   
d;  $R^1 = CHMeCH_2NHAc, R^2 = Me$



(23)

<sup>14</sup> K. Oka and S. Hara, *J. Org. Chem.*, 1978, **43**, 4408.

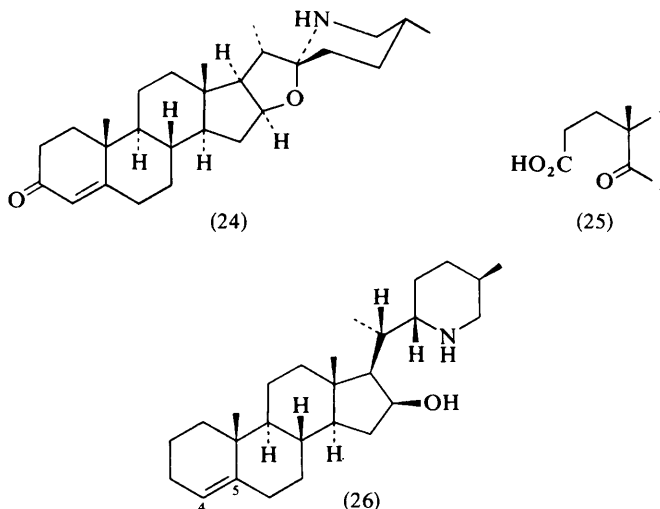
<sup>15</sup> D. M. Harrison, in 'The Alkaloids', ed. M. F. Grondon, (Specialist Periodical Reports), The Chemical Society, London, 1978, Vol. 8, p. 250.

<sup>16</sup> G. G. Bakker and P. Vrijhof, *Tetrahedron Lett.*, 1978, 4699.

<sup>17</sup> E. S. Belenkaya, L. M. Morozovskaya, L. I. Klimova, and G. S. Grinenko, *Khim. Farm. Zh.*, 1978, **12**, 105 (*Chem. Abs.*, 1978, **89**, 215 659).

was a by-product in this reaction.<sup>17</sup> The chemistry of solasodine has been reviewed.<sup>18</sup>

Solasodenone (24) has been oxidized with potassium permanganate–sodium periodate to yield the keto-acid (25).<sup>19</sup> The same starting material gave (26) on Wolff–Kishner reduction of the ketone moiety followed by treatment of the product with lithium aluminium hydride; the corresponding 4,5 $\alpha$ - and 4,5 $\beta$ -dihydro-derivatives of (26) were similarly prepared.<sup>20</sup>



Complete assignments have been made for the carbon resonances in the <sup>13</sup>C n.m.r. spectra of a number of *Solanum* alkaloids and related compounds.<sup>21,22</sup> The assignments for the spectra of solasodine and its derivatives were aided by the availability of [15 $\xi$ , 17 $\alpha$ -<sup>2</sup>H<sub>2</sub>]solasodine, which was prepared from solasodine *via* the keto-amide (27a),<sup>21</sup> and by the paramagnetic broadening of resonances due to carbon atoms of ring F that is induced by [Cu(acac)<sub>2</sub>].<sup>21,22</sup> In the course of these studies, 25-isoverazine (28) and solacongestidine (28a) were synthesized by standard procedures from the piperazine (27b). The latter was prepared in 93% yielded by Wolff–Kishner reduction with concomitant hydrolysis of the keto-amide (27a).<sup>22</sup>

Two novel, isomeric, 3-amino-20-pyridyl-pregnanes (C<sub>27</sub>H<sub>42</sub>N<sub>2</sub>O<sub>2</sub>) have been isolated from *Solanum seaforthianum* and named solaseaforthine (29a) and

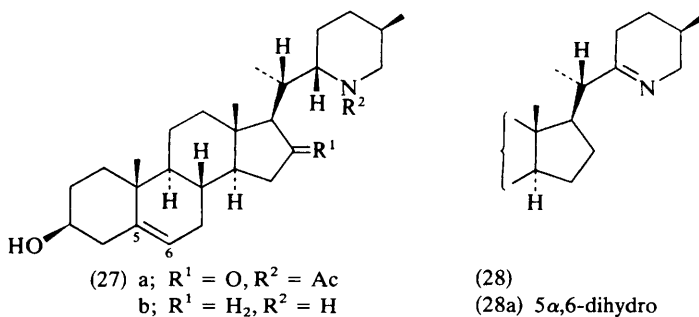
<sup>18</sup> M. I. Goryaev, M. P. Irismetov, H. O. Kim, G. A. Tolstikov, Kh. A. Alibaeva, V. V. Kurilskaya, R. Kh. Gayanov, and L. P. Volgina, *Tr. Inst. Khim. Nauk, Akad. Nauk Kaz. SSR*, 1977, **46**, 42 (*Chem. Abs.*, 1978, **89**, 129 782).

<sup>19</sup> M. P. Irismetov, M. I. Goryaev, and V. V. Kurilskaya, *Izv. Akad. Nauk Kaz. SSR, Ser. Khim.*, 1978, **28**, No. 2, p. 58 (*Chem. Abs.*, 1978, **89**, 163 849).

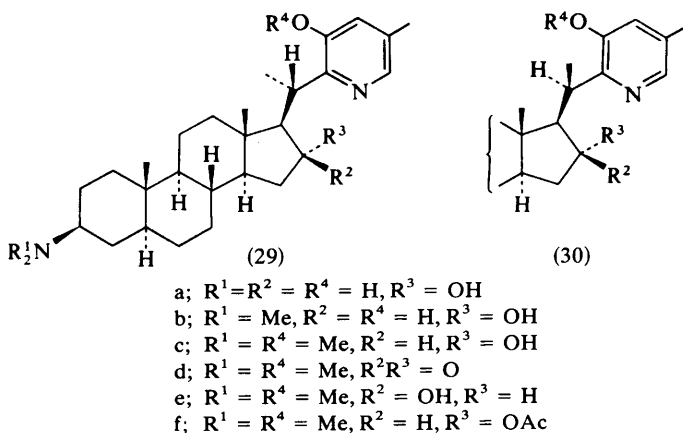
<sup>20</sup> M. P. Irismetov, M. I. Goryaev, V. V. Kurilskaya, and G. D. Tsepochnik, *Vestn. Akad. Nauk Kaz. SSR*, 1978, No. 8, p. 64 (*Chem. Abs.*, 1979, **90**, 39 119).

<sup>21</sup> G. J. Bird, D. J. Collins, F. W. Eastwood, R. H. Exner, M. L. Romanelli, and D. D. Small, *Aust. J. Chem.*, 1979, **32**, 783.

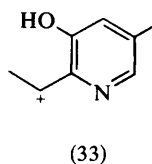
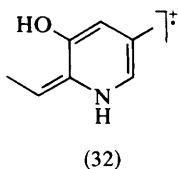
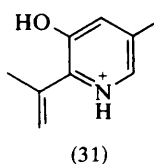
<sup>22</sup> G. J. Bird, D. J. Collins, F. W. Eastwood, and R. H. Exner, *Aust. J. Chem.*, 1979, **32**, 797.



isosolaseaforthine (30a), respectively.<sup>23</sup> These structures were deduced on the basis of spectroscopic studies on a number of derivatives, the most important features of which are summarized below. (a) The stereochemistry of ring A of these alkaloids was deduced from the circular dichroic spectra of their salicylidene derivatives. (b) The mass spectra of the *NN*-dimethyl derivatives (29b) and (30b) showed diagnostically valuable ions with  $m/z$  454 ( $M^+$ ), 150, 137, and 136 [assigned to ions (31), (32), and (33) respectively], and 110 and 84 (characteristic of a 3-dimethylamino-steroid). (c) The n.m.r. and u.v. spectra of (29b) and (30b) were consistent with the 3-hydroxy-5-methylpyridine structures indicated. (d) Oxidation of the 16-hydroxy-23-methoxy-derivatives (29c) and (30c) furnished ketones (29d) and (30d) respectively. The 16-oxo structures that are indicated were assigned on the basis of the mass spectral fragmentation patterns observed. These ketones were reduced with sodium borohydride to give two new alcohols; since these alcohols must be assigned the  $16\beta$ -hydroxy structures (29e) and (30e) respectively, the original alcohols (29c) and (30c) must possess the  $16\alpha$ -hydroxy stereochemistries shown. (e) Circular dichroism studies on derivatives (29f) and (30f) demonstrated that these compounds are epimers at C-20, and permitted the assignment of the  $20S$  stereochemistry to solaseaforthine.<sup>23</sup> Solaseaforthine and

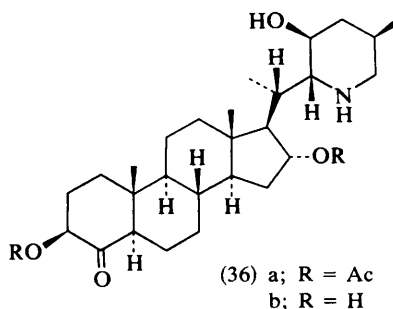
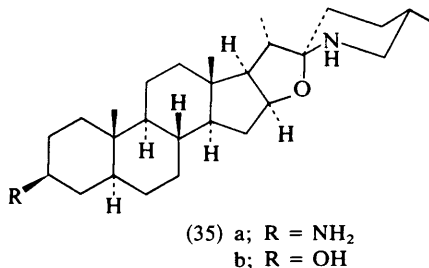
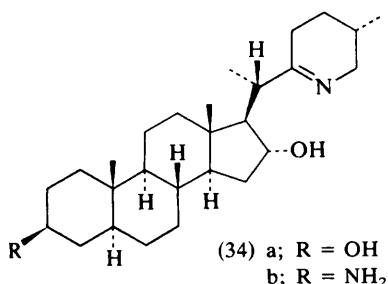


<sup>23</sup> E. Ali, A. K. Chakravarty, T. K. Dhar, and S. C. Pakrashi, *Tetrahedron Lett.*, 1978, 3871.



isosolaseaforthine were each accompanied by their  $\Delta^5$ -analogues, and were purified only after hydrogenation of the crude mixtures.<sup>23</sup>

The structure (34a) of 25-isosolafloridine, isolated from *S. callium*, was earlier assigned in part by an X-ray crystallographic study,<sup>24,25</sup> while that of the accompanying base solacallinidine (34b) was deduced on the basis of spectroscopic comparison with the former alkaloid.<sup>25</sup> A chemical correlation of the two alkaloids, together with details of their isolation and structure determination, have now been published.<sup>26</sup> Details of the isolation from *S. dunalianum* and the structure determination of soladunalinidine (35a) have appeared; tomatidine (35b) was also isolated from the same plant.<sup>27</sup> Solafilidine (36a) and desacetyl-solafilidine (36b) have been isolated in high yield from dried fruits of *S. affin. ecuadorensis*.<sup>28</sup>



<sup>24</sup> B. M. Gatehouse and A. J. Jozsa, *Acta Crystallogr., Sect. B*, 1977, **33**, 3782.

<sup>25</sup> G. J. Bird, D. J. Collins, F. W. Eastwood, B. M. K. C. Gatehouse, A. J. Jozsa, and J. M. Swan, *Tetrahedron Lett.*, 1976, 3653.

<sup>26</sup> G. J. Bird, D. J. Collins, F. W. Eastwood, and J. M. Swan, *Aust. J. Chem.*, 1979, **32**, 597.

<sup>27</sup> G. J. Bird, D. J. Collins, F. W. Eastwood, and J. M. Swan, *Aust. J. Chem.*, 1979, **32**, 611.

<sup>28</sup> P. Martinod, J. Hidalgo, C. Guevara, and M. E. Herrera, *Politecnica*, 1977, **3**, 46 (*Chem. Abs.*, 1979, **90**, 148 439).

The solasodine-based glyco-alkaloids solamargine and solasonine have been isolated from immature fruits of *S. macranthum*,<sup>29</sup> from ripe fruits of *S. viarum*,<sup>30</sup> from Spanish-grown *S. nigrum*,<sup>31</sup> and from *S. affin. nigrum* L. grown in Costa Rica.<sup>31</sup> The same glyco-alkaloids, together with  $\beta$ -solamargine, were isolated from aerial parts of *S. nigrum*. The changes in distribution and concentration of these glyco-alkaloids were studied during growth of the plant.<sup>32</sup> The stems and leaves of 'black nightshade' contained  $\alpha$ -solasonine and  $\alpha$ -solamargine; berries of this plant contained, in addition,  $\beta$ -solamargine.<sup>33</sup> The alkaloids of 'nightshade' (*Solanum* sp.) have been reviewed.<sup>34</sup>

A comprehensive survey of the solasodine content of 85 native Australian *Solanum* species has been published.<sup>35</sup> Several studies have appeared which describe the changes in distribution and concentration of solasodine during the life cycle of *S. laciniatum*.<sup>36</sup> The effects of light colour on the solasodine content of *S. laciniatum*<sup>37</sup> and on the solasodine content of clones of *S. dulcamara*<sup>38</sup> have been studied; the effect of ecological factors on alkaloid production by these two species has also been investigated.<sup>39</sup> The solasodine contents of developing berries,<sup>40</sup> fruits,<sup>41</sup> and seed callus<sup>42</sup> of *S. khasianum* have been reported.

The solanidine glyco-alkaloid solanine has been identified in flowers and leaves of *S. paniculatum*,<sup>43</sup> and the glyco-alkaloid content of a number of *Solanum* species has been reported.<sup>44</sup> Genetic factors governing the glyco-alkaloid composition of *S. chacoense* have been studied.<sup>45</sup> A direct relationship has been established between glyco-alkaloid content and resistance to the potato leaf-hopper, *Empoasca fabae*, in ten wild potato species; the most resistant species studied, *S. polyadenium*, had a total glyco-alkaloid content of 0.69%, while the least resistant species, *S. bulbocastanum*, had a glyco-alkaloid content of only

<sup>29</sup> S. H. Hilal, M. M. Shabana, and M. Y. Haggag, *Egypt. J. Pharm. Sci.*, 1975 (publ. 1977) **16**, 483 (*Chem. Abs.*, 1978, **89**, 143 340).

<sup>30</sup> M. A. Rocca, *Rev. Fac. Farm. Odontol. Araraquara*, 1976, **10**, 329 (*Chem. Abs.*, 1978, **89**, 143 373).

<sup>31</sup> R. Aguilar Lara and C. E. Alfaro Lara, *Rev. Cienc. Farm.*, 1976, 119 (*Chem. Abs.*, 1978, **89**, 20 295).

<sup>32</sup> S. M. Aslanov and E. N. Novruzov, *Izv. Akad. Nauk. Az. SSR, Ser. Biol. Nauk*, 1978, No. 3, p. 15, (*Chem. Abs.*, 1979, **90**, 118 092).

<sup>33</sup> B. T. Ivanchenko and E. A. Tkalalo, *Fitokhim. Izuch. Flory B. SSR, Biofarm. Issled. Lek. Prep.*, 1975, 97 [ed. E. N. Medvedskii, Leningrad Med. Inst. im I. P. Pavlova: Leningrad, USSR] (*Chem. Abs.*, 1978, **89**, 3153).

<sup>34</sup> K. Von der Dunk, *PTA Prakt. Pharm.*, 1979, **8**, 78, 82 (*Chem. Abs.*, 1979, **90**, 183 135).

<sup>35</sup> V. Bradley, D. J. Collins, P. G. Crabbe, F. W. Eastwood, M. C. Irvine, J. M. Swan, and D. E. Symon, *Aust. J. Bot.*, 1978, **26**, 723.

<sup>36</sup> V. V. Kurnosov and L. A. Pikova, *Rastit. Resur.*, 1978, **14**, 225 (*Chem. Abs.*, 1978, **89**, 20 306); L. A. Pikova, V. V. Kurnosov, and E. I. Korneva, *ibid.*, 1978, **14**, 377 (*Chem. Abs.*, 1978, **89**, 126 149); E. N. Abou-Zied, S. A. El-Shafie, and M. Abou-Sekkina, *Pharmazie*, 1978, **33**, 676.

<sup>37</sup> G. K. Kuznetsova, G. P. Pushkina, and S. S. Shain, *Khim. Farm. Zh.*, 1978, **12**, 72 (*Chem. Abs.*, 1978, **89**, 193 969).

<sup>38</sup> J. Bernath, P. Tetenyi, I. Horvath, and I. Zambo, *Herba Hung.*, 1978, **17**, 57 (*Chem. Abs.*, 1978, **89**, 56 438).

<sup>39</sup> J. Bernath and P. Tetenyi, *Acta Bot. Acad. Sci. Hung.*, 1978, **24**, 41 (*Chem. Abs.*, 1979, **90**, 36 463).

<sup>40</sup> N. S. Sharma, S. Varghese, J. Desai, and J. J. Chinoy, *Indian J. Exp. Biol.*, 1979, **17**, 224 (*Chem. Abs.*, 1979, **90**, 148 571).

<sup>41</sup> B. Bhatt and M. R. Heble, *Environ. Exp. Bot.*, 1978, **18**, 127 (*Chem. Abs.*, 1978, **89**, 194 027).

<sup>42</sup> H. C. Chaturvedi, A. R. Chowdhury, and A. Uddin, *Indian J. Exp. Biol.*, 1979, **17**, 107 (*Chem. Abs.*, 1979, **90**, 118 143).

<sup>43</sup> N. S. De Siqueira and A. Macan, *Trib. Farm.*, 1976, **44**, 101 (*Chem. Abs.*, 1978, **89**, 39 412).

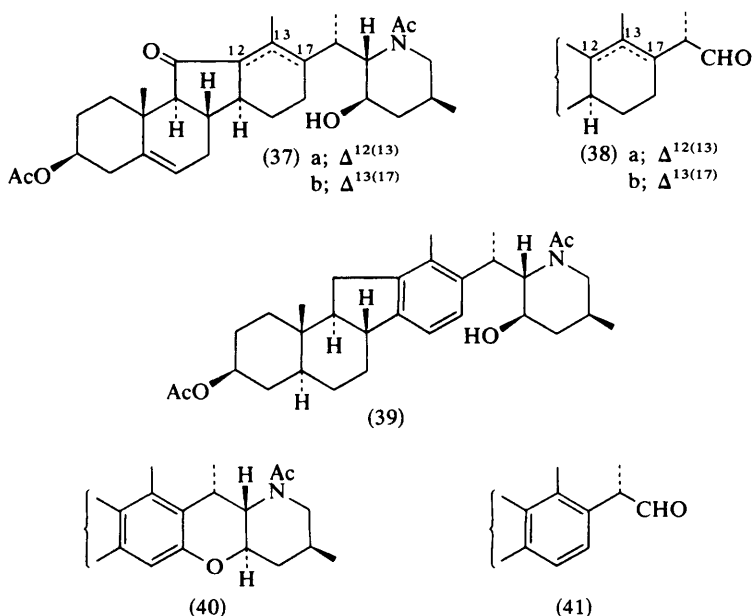
<sup>44</sup> S. F. Osman, S. F. Herb, T. J. Fitzpatrick, and P. Schmiediche, *J. Agric. Food Chem.*, 1978, **26**, 1246 (*Chem. Abs.*, 1978, **89**, 160 082).

<sup>45</sup> G. D. McCollum and S. L. Sinden, *Am. Potato J.*, 1979, **56**, 95 (*Chem. Abs.*, 1979, **90**, 148 587).

0.01%.<sup>46</sup> Glyco-alkaloids are responsible, at least in part, for the resistance of several other species to various agricultural pests.<sup>47</sup> A t.l.c. system for the quantitative determination of potato glyco-alkaloids has been reported.<sup>48</sup> The enzymic hydrolysis of  $\alpha$ -chaconine and  $\alpha$ -solanine<sup>49</sup> and the hydrolysis of solanine by the potato blight fungus, *Phytophthora infestans*,<sup>50</sup> have been studied. Techniques for studying the alkaloids of *Solanum* species have been reviewed.<sup>51</sup>

#### 4 *Veratrum* and *Fritillaria* Alkaloids

Photolysis of the hypoidites derived from alcohols (37a) and (37b) gave the aldehydes (38a) and (38b) respectively. The related alcohol (39) formed the cyclic ether (40) as well as the expected aldehyde (41) when submitted to photolysis in the presence of mercuric oxide and iodine.<sup>52</sup> The synthesis of steroidal alkaloids of the C-nor-D-homo variety has been reviewed.<sup>53</sup>



<sup>46</sup> W. M. Tingey, J. D. Mackenzie, and P. Gregory, *Am. Potato J.*, 1978, **55**, 577 (*Chem. Abs.*, 1979, **90**, 36 413).

<sup>47</sup> Z. Mierzwa and A. Uzarewicz, *Ziemiak*, 1976, 15 (*Chem. Abs.*, 1978, **89**, 212 142); J. M. Dow and J. A. Callow, *Phytopathol. Z.*, 1978, **92**, 211 (*Chem. Abs.*, 1978, **89**, 212 139); S. L. Sinden, J. M. Schalk, and A. K. Stoner, *J. Am. Soc. Hortic. Sci.*, 1978, **103**, 596 (*Chem. Abs.*, 1978, **89**, 176 523).

<sup>48</sup> L. S. Cadle, D. A. Stelzig, K. L. Harper, and R. J. Young, *J. Agric. Food Chem.*, 1978, **26**, 1453 (*Chem. Abs.*, 1978, **89**, 193 829).

<sup>49</sup> A. P. Swain, T. J. Fitzpatrick, E. A. Talley, S. F. Herb, and S. F. Osman, *Phytochemistry*, 1978, **17**, 800.

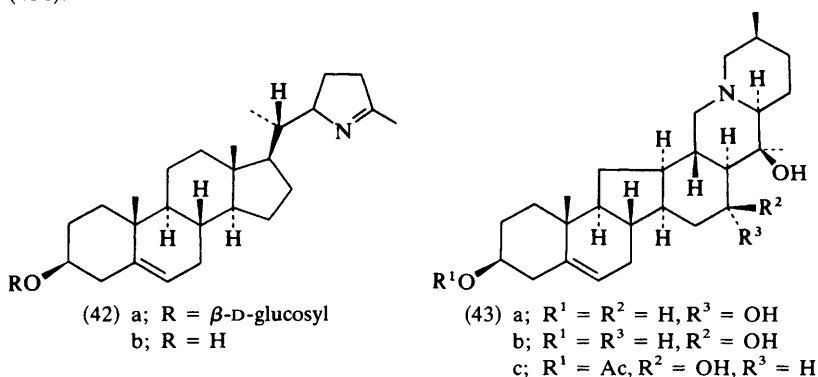
<sup>50</sup> H. L. Holland and G. J. Taylor, *Phytochemistry*, 1979, **18**, 437.

<sup>51</sup> R. Aguilar Lara and C. E. Alfaro Lara, *Rev. Cienc. Farm.*, 1976, 109 (*Chem. Abs.*, 1978, **89**, 48 930); T. Kawasaki, *Method. Chim.*, 1978, **11**, 87 (*Chem. Abs.*, 1978, **89**, 110 081).

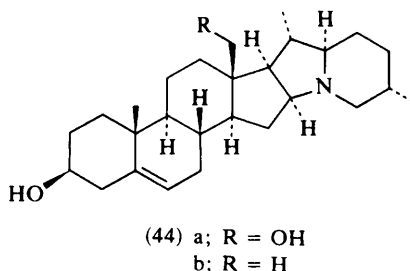
<sup>52</sup> H. Sugimoto, H. Umeda, S. Sugiura, and T. Masamune, *J. Chem. Res.*, 1978, (S) 380; (M) 4523.

<sup>53</sup> E. Brown and M. Ragault, *Tetrahedron*, 1979, **35**, 911.

Above-ground parts of *Veratrum album* subspecies *lobelianum* have yielded a new glyco-alkaloid, glucoveracintine (42a). This structure was deduced by consideration of the spectroscopic evidence, together with the observation that hydrolysis of the glycoside, catalysed by the enzyme emulsin, gave glucose and the known aglycone veracintine (42b).<sup>54</sup> Veramarine, which was also isolated from *V. album* subspecies *lobelianum*, was earlier assigned the cevanine-based structure (43a).<sup>55</sup> Veramarine has now been assigned the revised structure (43b) as a result of a single-crystal X-ray diffraction study performed on the 3-*O*-acetyl derivative (43c).<sup>56</sup>



Isorubijervine (44a) and the new alkaloids procevine (C<sub>27</sub>H<sub>43</sub>NO), shinonomenine (C<sub>27</sub>H<sub>43</sub>NO), and veraflorizine (C<sub>27</sub>H<sub>43</sub>NO<sub>2</sub>) have been isolated from aerial parts of young seedlings of *V. grandiflorum* grown in the light.<sup>57</sup> Procevine was assigned the interesting structure (45) on the basis of spectroscopic studies and biogenetic considerations. This structure was confirmed by treatment of isorubijervine (44a) with toluene-*p*-sulphonyl chloride and pyridine, to yield the tetra-alkylammonium salt (46). The latter was reduced with sodium-ethanol to give solanidine (44b) and procevine (45) in a ratio of 3:7.<sup>57</sup> Procevine<sup>57</sup> (pseudosolanidine)<sup>58</sup> is one of the few alkaloids whose synthesis, by the route



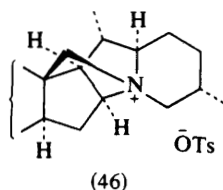
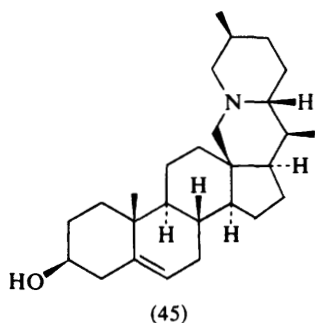
<sup>54</sup> D. Grančai, V. Suchý, J. Tomko, and L. Dolejš, *Chem. Zvesti*, 1978, **32**, 120 (*Chem. Abs.*, 1978, **89**, 39 410).

<sup>55</sup> S. Itô, T. Ogino, and J. Tomko, *Collect. Czech. Chem. Commun.*, 1968, **33**, 4429.

<sup>56</sup> F. Pavelčík and J. Tomko, *Tetrahedron Lett.*, 1979, 887.

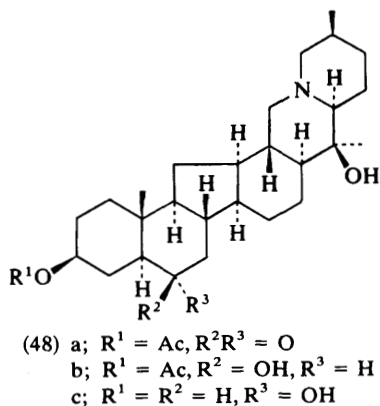
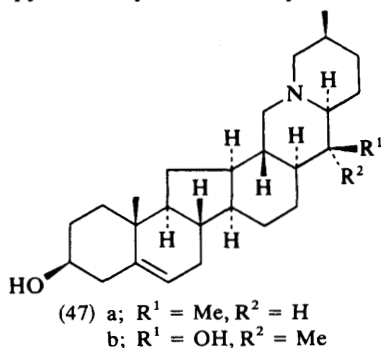
<sup>57</sup> K. Kaneko, N. Kawamura, T. Kuribayashi, M. Tanaka, and H. Mitsunashi, *Tetrahedron Lett.*, 1978, 4801.

<sup>58</sup> S. W. Pelletier and W. A. Jacobs, *J. Am. Chem. Soc.*, 1953, **75**, 4442.



described above, had been performed prior to its isolation as a natural product,<sup>58</sup> and is the first naturally occurring alkaloid with the 'cevanidane'<sup>59</sup> skeleton.

Shinonomenine (47a) was assigned the structure and stereochemistry indicated, following an X-ray crystallographic study of its hydroiodide salt, and is the first naturally occurring cevanine derivative which possesses a 20 $\beta$ -methyl group.<sup>57</sup> The structure of veraflorizine (47b) was assigned on the basis of a spectroscopic study of the free base and its monoacetyl derivative, and was confirmed by the partial synthesis of the latter as follows: verticinone monoacetate (48a) was reduced with sodium borohydride to give the acetoxo-diol (48b), which underwent dehydration on treatment with phosphorus oxychloride in pyridine to yield 3-O-acetylveraflorizine.<sup>57</sup>



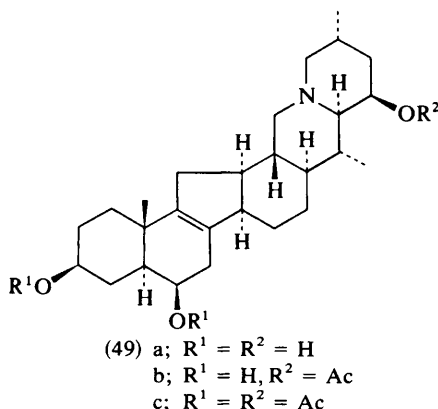
Korsine (49a) and a new alkaloid korsinamine (49b) have been isolated from *Korolkowia sewerzowii*. Korsinamine gave korsine on base-catalysed hydrolysis. The position of the acetyl group in the new alkaloid was deduced from n.m.r. and m.s. comparisons of korsine, korsinamine, and diacetylkorsinamine (i.e. triacetylkorsine) (49c).<sup>60</sup> Korsidine, korseveriline, sevedine, and sevcoridinine have also been isolated from *K. sewerzowii*.<sup>61</sup>

<sup>59</sup> J. C. Sheehan, R. L. Young, and P. A. Cruickshank, *J. Am. Chem. Soc.*, 1960, **82**, 6147.

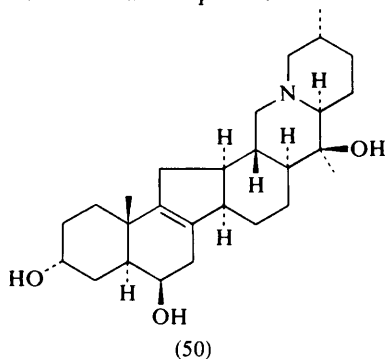
<sup>60</sup> K. Samikov, R. Shakirov, and S. Yu. Yunusov, *Khim. Pri. Soedin.*, 1978, 233 (*Chem. Abs.*, 1978, **89**, 197 759).

<sup>61</sup> D. U. Abdullaeva, K. Samikov, R. Shakirov, and S. Yu. Yunusov, *Khim. Pri. Soedin.*, 1978, 817 (*Chem. Abs.*, 1979, **90**, 20 283).





A new alkaloid, edpetisidine (50), has been isolated from *Petillium eduardi*. The structure indicated was assigned on the basis of spectroscopic studies on edpetisidine, its dihydroderivative, and its diacetyl-dihydro-derivative.<sup>62</sup> Imperialine, verticine (48c), and an unidentified base of formula  $C_{27}H_{41}NO_2$  have been isolated from bulbs of *Fritillaria imperialis*.<sup>63</sup>



Nine unidentified alkaloids were detected in roots and rhizomes of *V. dahuricum*; the variation in their concentrations during growth of the plant was studied.<sup>64</sup> The teratogenic effects of cyclopamine and of other alkaloids of *V. californicum* have been reviewed.<sup>65</sup> A method for the quantitative determination of jervine has been published.<sup>66</sup>

The *Veratrum* alkaloid esters have been reviewed.<sup>67</sup>

<sup>62</sup> R. Shakirov, A. Nabiev, and S. Yu. Yunusov, *Khim. Pri. Soedin.*, 1978, 416 (*Chem. Abs.*, 1979, **90**, 23 341).

<sup>63</sup> I. Masterova and J. Tomko, *Chem. Zvesti*, 1978, **32**, 116 (*Chem. Abs.*, 1978, **89**, 20 324).

<sup>64</sup> G. F. Lozovaya and A. A. Dergacheva, *Vopr. Farm. Dal'nem Vostoke*, 1977, **2**, 45 (*Chem. Abs.*, 1979, **90**, 164 759).

<sup>65</sup> R. F. Keeler, *Lipids*, 1978, **13**, 708.

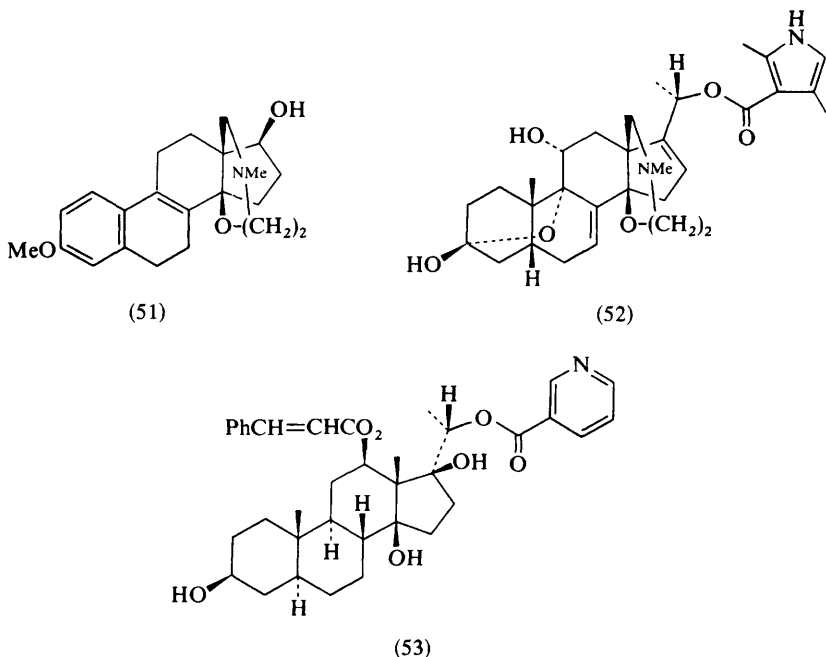
<sup>66</sup> G. F. Lozovaya and O. Ya. Zakharova, *Vopr. Farm. Dal'nem Vostoke*, 1977, **2**, 107 (*Chem. Abs.*, 1979, **90**, 187 184).

<sup>67</sup> N. V. Bondarenko, *Fitokhim. Izuch. Flory B. SSR Biofarm. Issled. Lek. Prep.*, 1975, 84 [ed. E. N. Medvedskii, Leningrad, Med. Inst. im. I. P. Pavlova: Leningrad, USSR] (*Chem. Abs.*, 1978, **89**, 110 064).

### 5 Miscellaneous

The synthesis of the steroidal amine (51) has been reported.<sup>68</sup> Compound (51) is structurally related to the extremely toxic alkaloid batrachotoxin (52), isolated from the skin of the Columbian arrow-poison frog, *Phyllobates aurotaenia*.<sup>69</sup>

The isolation of tomentomin (53) from leaves of *Marsdenia tomentosa* is the subject of a recent patent.<sup>70</sup>



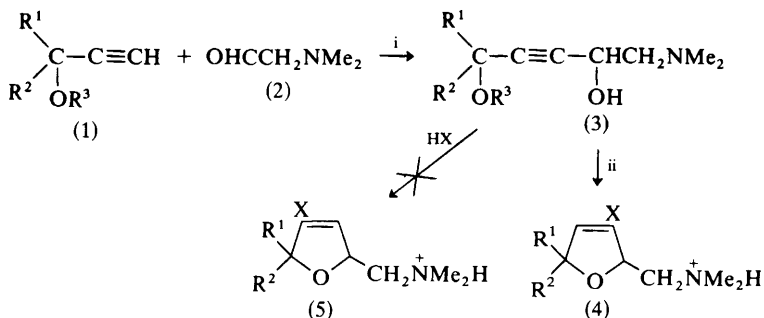
<sup>68</sup> N. K. Levchenko, A. P. Sviridova, G. M. Segal, and I. V. Torgov, *Bioorg. Khim.*, 1978, **4**, 1651 (*Chem. Abs.*, 1979, **90**, 187 205).

<sup>69</sup> T. Tokuyama, J. Daly, and B. Witkop, *J. Am. Chem. Soc.*, 1969, **91**, 3931; cf. R. Imhof, E. Gössinger, W. Graf, H. Berner, L. Berner-Fenz, and H. Wehrli, *Helv. Chim. Acta*, 1972, **55**, 1151; I. L. Karle, *Pure Appl. Chem.*, 1977, **49**, 1291.

<sup>70</sup> H. Mihashi, H. Seto, and K. Hayashi, Japan Kokai 78 46 956 (*Chem. Abs.*, 1978, **89**, 104 093).

### 1 Muscarine Alkaloids

Acetylenic glycols have been shown to cyclize under acidic conditions to give dihydrofurans; in attempts to extend this type of cyclization to give muscarine analogues, only partial success has been achieved. Cyclization of amino-acetylenic glycols only occurred with a sulphonic acid ion-exchange resin that was impregnated with mercuric sulphate, and then only to give the 4-substituted product (see Scheme 1).<sup>1</sup> Simple and functionalized spiro-furans can be



Reagents: i,  $\text{NaNH}_2$ , dioxan; ii, HX, sulphonic acid ion-exchange resin impregnated with  $\text{HgSO}_4$ .

Scheme 1

synthesized, however, by the cyclization of unsaturated  $\beta$ -ketols with phenyl-selenenyl chloride, followed by removal of the selenium and introduction of the amino-group<sup>2</sup> (see Scheme 2).

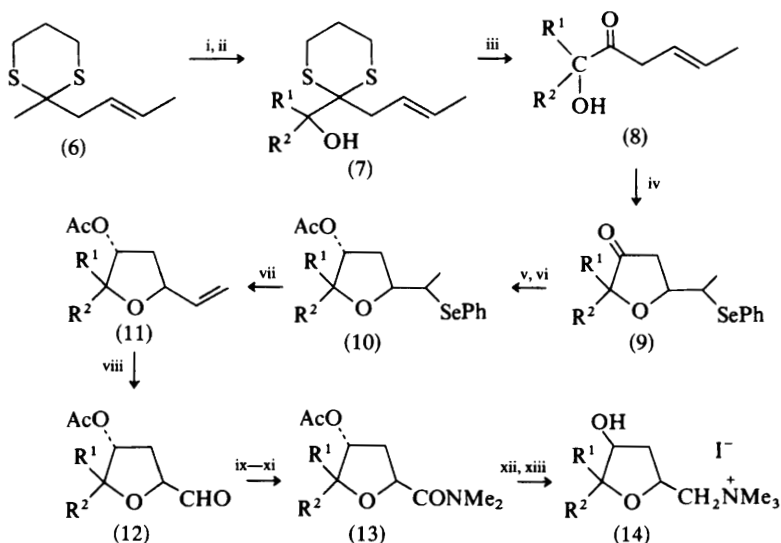
### 2 Imidazole Alkaloids

A new *Pilocarpus* alkaloid, epi-isopiloturine, has been isolated from *Pilocarpus microphyllus*; its structure (15) was elucidated by  $^{13}\text{C}$  n.m.r. spectroscopy and by its conversion into neopilosine and anhydropiloturine.<sup>3</sup> *N*-Methylmurexine (16;  $\text{R} = \text{Me}$ ) has been reported to occur in the marine gastropod mollusc *Nucella*

<sup>1</sup> K. Bowden and B. H. Warrington, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1493.

<sup>2</sup> Z. Lysenko, F. Ricciardi, J. E. Semple, P. C. Wang, and M. M. Joullie, *Tetrahedron Lett.*, 1978, 2679.

<sup>3</sup> H. W. Voigtlaender, G. Balsam, M. Engelhardt, and L. Pohl, *Arch. Pharm. (Weinheim, Ger.)*, 1978, **311**, 927 (*Chem. Abs.*, 1979, **90**, 152 419).

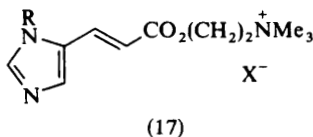
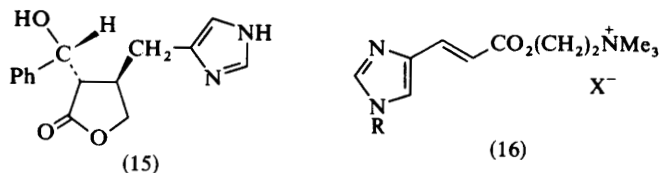


Reagents: i,  $\text{Bu}^n\text{Li}$ , THF, at  $-30^\circ\text{C}$ ; ii,  $\text{R}^1\text{R}^2\text{CO}$ ; iii,  $\text{AgNO}_3$ , *N*-chlorosuccinimide, MeCN,  $\text{H}_2\text{O}$ ,  $0^\circ\text{C}$ ; iv,  $\text{PhSeCl}$ ; v,  $\text{NaBH}_4$ ; vi,  $\text{Ac}_2\text{O}$ , DMAP, py; vii,  $\text{O}_3$ ,  $\text{CH}_2\text{Cl}_2$ , at  $-78^\circ\text{C}$ , then  $\text{NEt}_3$ , heat; viii,  $\text{O}_3$ , MeOH, at  $-78^\circ\text{C}$ ,  $\text{Me}_2\text{S}$ ; ix, Jones reagent; x,  $(\text{ClCO})_2$ ; xi,  $\text{Me}_2\text{NH}$ ; xii,  $\text{LiAlH}_4$ ; xiii, MeI (excess).

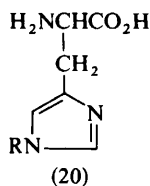
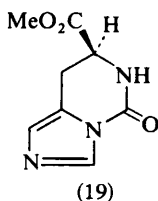
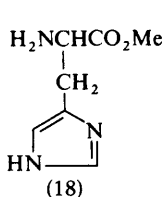
Scheme 2

*emarginata*;<sup>4</sup> however, a recent unambiguous synthesis of the two possible *N*-methyl derivatives of murexine (16;  $\text{R} = \text{H}$ ), *i.e.* (16;  $\text{R} = \text{Me}$ ) and (17;  $\text{R} = \text{Me}$ ), indicates that the natural compound is neither of these;<sup>5</sup> the need for further investigation is indicated.

*L-N*-Methylhistidine (20;  $\text{R} = \text{Me}$ ) or its ethyl counterpart (20;  $\text{R} = \text{Et}$ ) can be prepared<sup>6</sup> by treating *carboxy*-methylhistidine (18) with *NN'*-carbonyldiimidazole to give the imidazo[1,5-*c*]pyrimidine (19); this, upon alkylation (with RI) followed by hydrolysis (with 6M-HCl) gives the *N*-alkyl-histidine (20;  $\text{R} = \text{Me}$  or Et).

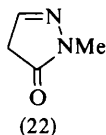
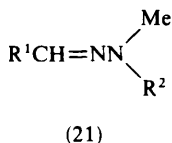


<sup>4</sup> J. A. Bender *et al.*, *Comp. Gen. Pharmacol.*, 1974, **5**, 191.



### 3 Pyrazole Alkaloids

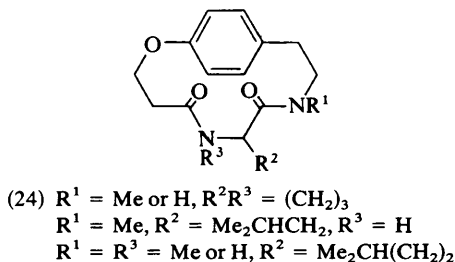
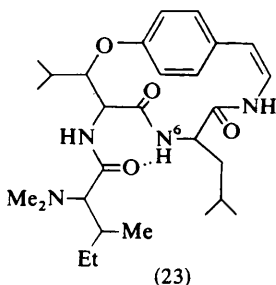
The direct insertion of plant material into the mass spectrometer can give useful information on the constituents present, provided that sufficient data have already been accumulated from synthetic compounds and from conventional phytochemistry. Direct mass spectral analysis (MIKES)<sup>7</sup> of whole freeze-dried mushrooms (*Helvella esculenta*) indicates the presence of gyromitrin (21;  $R^1 = \text{Me}$ ,  $R^2 = \text{CHO}$ ), its isobutyl homologue (21;  $R^1 = \text{Bu}^i$ ,  $R^2 = \text{CHO}$ ), and 4,5-dihydro-1-methyl-5-oxo-1*H*-pyrazole (22). Also present were the hydroxy- and amino-methylacetaldehyde hydrazones (21;  $R^1 = \text{Me}$ ,  $R^2 = \text{CH}_2\text{OH}$ ) and (21;  $R^1 = \text{Me}$ ,  $R^2 = \text{CH}_2\text{NH}_2$ ).



### 4 Peptide Alkaloids

Partial <sup>1</sup>H relaxed spectra of frangulanine (23) have been used to assign the overlapping resonance lines,<sup>8</sup> and the conformation of the alkaloid in CHCl<sub>3</sub> has been deduced by <sup>1</sup>H and <sup>13</sup>C n.m.r., to show that a hydrogen bond exists, in the form of a  $\gamma$  loop, between the isoleucine side-chain and the NH at position 6.<sup>9</sup>

Several examples of fourteen-membered, *para*-bridged ring systems (24) that are related to the peptide alkaloids have been synthesized; all bind univalent ( $\text{Li}^+$ )



<sup>5</sup> C. C. Duke, J. V. Eichholzer, and J. K. MacLeod, *Tetrahedron Lett.*, 1978, 5047.

<sup>6</sup> A. Noordam, L. Maat, and H. C. Beyerman, *Recl. Trav. Chim. Pays-Bas*, 1978, **97**, 293.

<sup>7</sup> G. A. McClusky, R. G. Cooks, and A. M. Knevel, *Tetrahedron Lett.*, 1978, 4471.

<sup>8</sup> E. Haslinger, *Monatsh. Chem.*, 1978, **109**, 523.

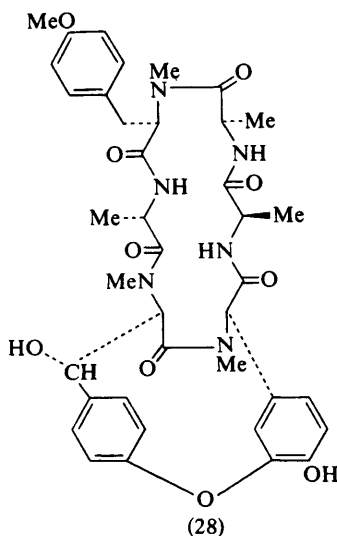
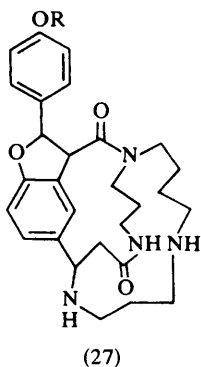
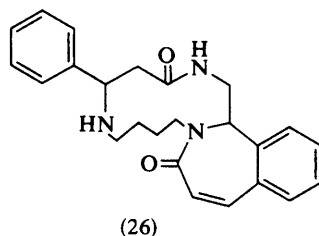
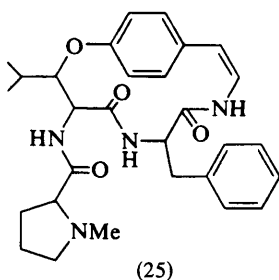
<sup>9</sup> E. Haslinger, *Tetrahedron*, 1978, **34**, 685.

and bivalent ( $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$ ) cations.<sup>10</sup> The naturally occurring alkaloid ceanothine B (25) also shows this type of affinity.

The macrocyclic spermidine alkaloid pleurostyline,<sup>11</sup> isolated from the leaves of *Pleurostylie africana*, has structure (26). Aphelandrine, obtained from the roots of *Aphelandra squarrosa*,<sup>12</sup> has been assigned structure (27;  $\text{R} = \text{H}$ ). It is present in eight other species of *Aphelandra* and also in *Encephalosphaera lasiandra*; its *O*-methyl ether (27;  $\text{R} = \text{Me}$ ) was isolated only from *Aphelandra sinclairiana*,<sup>13</sup> however.

A cyclic hexapeptide, bouvardin (28), isolated from *Bouvardia ternifolia*, shows high cytotoxic properties through inhibiting the division of hamster ovary cells.<sup>14</sup>

The toxin isolated from *Amanita phalloides*,  $\beta$ -amanitin (29), has been shown to have an extensive hydrogen-bonding network. X-Ray crystallographic analysis of a single crystal confirms the presence of two eighteen-membered rings, with all eight peptide groups in the *trans* conformation.<sup>15</sup>



<sup>10</sup> J. C. Lagarias, R. A. Houghton, and H. Rapoport, *J. Am. Chem. Soc.*, 1978, **100**, 8202.

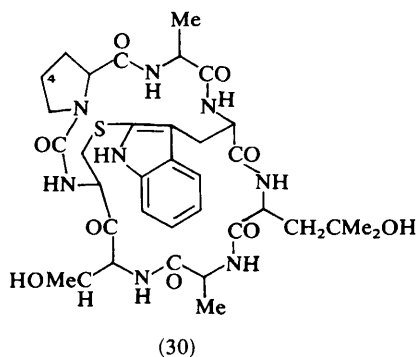
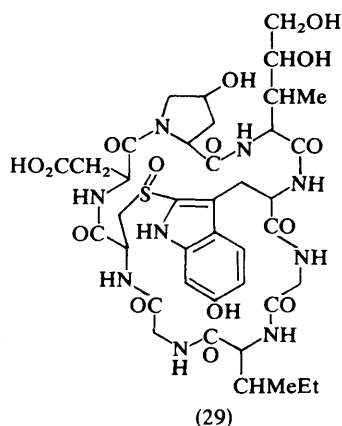
<sup>11</sup> H. Wagner, J. Burghart, and S. Bladt, *Tetrahedron Lett.*, 1978, 781.

<sup>12</sup> P. Daetwyler, H. Bosshardt, H. O. Bernhard, M. Hesse, and S. Johnne, *Helv. Chim. Acta*, 1978, **61**, 2646.

<sup>13</sup> H. Bosshardt, A. Guggisberg, S. Johnne, and M. Hesse, *Pharm. Acta Helv.*, 1978, **53**, 355.

<sup>14</sup> R. A. Tobey, D. J. Orlicky, L. L. Deaven, L. B. Rall, and R. J. Kissane, *Cancer Res.*, 1978, **38**, 4415 (*Chem. Abs.*, 1979, **80**, 80 771).

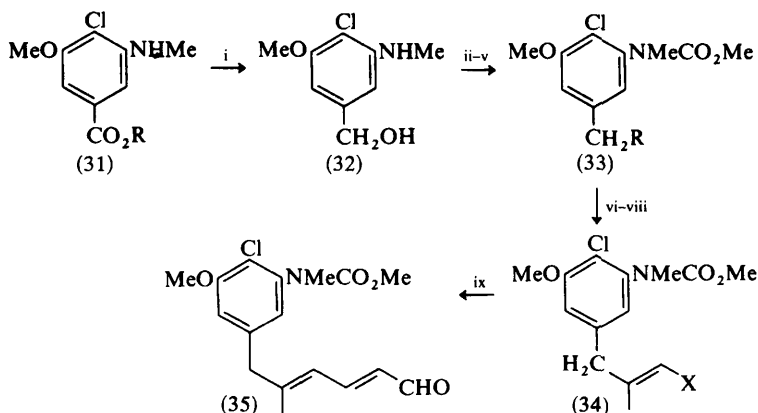
<sup>15</sup> E. C. Kostansek, W. N. Lipscomb, R. R. Yocum, and W. E. Thiessen, *Biochemistry*, 1978, **17**, 3790.



A non-toxic derivative of phalloidin, *i.e.* [Pro<sup>4</sup>]phalloin (30), is also a component of the green deathcap toadstool (*Amanita phalloides*), proline replacing *allo*-hydroxyproline at position 4 of phalloin.<sup>16</sup>

The isoquinoline peptide alkaloid amphibine 1 is discussed in Chapter 7.

A review on maytansine and maytansinoids gives an account of the source plants, biological activity, and structure-activity relationships<sup>17</sup> of this important anti-tumour-active family of compounds. Synthetic studies on the ansa macrocides continue apace. Corey has reported the synthesis of a key intermediate, which incorporates most of the left-hand portion of the ring system, by a simple stereospecific route (Scheme 3).<sup>18</sup> The ester (31) [reported in Vol. 9, p. 258] was



Reagents: i,  $\text{LiAlH}_4$ , THF; ii,  $\text{ClCO}_2\text{Me}$ ,  $\text{K}_2\text{CO}_3$ , acetone; iii, 4%  $\text{MeOH-NaOH}$ , at  $25^\circ\text{C}$ ; iv,  $\text{MeSO}_2\text{Cl}$ ,  $\text{NEt}_3$ , THF, at  $-78^\circ\text{C}$ , then at  $-25^\circ\text{C}$ ; v,  $\text{NaI}$ , DME, at  $-25^\circ\text{C}$ ; vi,  $\text{Me}_2(\text{MeO})\text{CC}\equiv\text{C-Cu}^- \text{Li}^+$ , THF; vii,  $\text{TsOH}$ ,  $\text{MeOH}$ ; viii,  $\text{MnO}_2$ ,  $\text{CH}_2\text{Cl}_2$ ; ix,  $\text{Me}_2\text{SiCHLiCH}=\text{NBU}^t$ .

**Scheme 3**

<sup>16</sup> E. Munekata, H. Faulstich, and T. Wieland, *Justus Liebig's Ann. Chem.*, 1978, 776.

<sup>17</sup> M. Leboeuf, *Plant. Med. Phytother.*, 1978, **21**, 53 (*Chem. Abs.*, 1978, **89**, 193 785).

<sup>18</sup> E. J. Corey, M. G. Bock, A. P. Kozikowski, A. V. R. Rao, D. Floyd, and B. Lipshutz, *Tetrahedron Lett.*, 1978, 1051.

reduced to the alcohol (32), and subsequent treatment with methyl chloroformate followed by 4% methanolic sodium hydroxide gave the urethane (33; R = OH), which on successive mesylation and iodide solvolysis gave (33; R = I); cross-coupling with the cuprate reagent (vi) gave (34; X = CH<sub>2</sub>OTHP). Subsequent removal of the tetrahydropyranyl group and oxidation of the resulting alcohol gave the enol (34; X = CHO), which was finally converted, by known methods,<sup>19</sup> into the dienal (35). The use of the techniques quoted in this and previous reports has culminated in the final synthesis of a maytansenoid, shown in Scheme 4.<sup>20</sup> The macrolide (±)-*N*-methylmaysenine [(±)-4,5-deoxymaysine] (36) was produced by condensation of the aldehyde (35) with dithian [37; R = C(OMe)Me<sub>2</sub>] to give the adduct [38; R<sup>1</sup> = C(OMe)Me<sub>2</sub>, R<sup>2</sup> = H] *via* the cuprate coupling reagent described in Scheme 3 [reagent (vi)]; this was a mixture (55:45) of diastereoisomers at C-10 [by the maytansine numbering; see (42)], and it was used as such to complete the synthesis. Methylation gave the methoxy-alcohols [38; R<sup>1</sup> = C(OMe)Me<sub>2</sub>, R<sup>2</sup> = Me] (which could be separated by h.p.l.c. but not by t.l.c.), which on oxidation gave (39; X = O); following its condensation with the α-trimethylsilyl derivative of propionaldehyde *N*-*t*-butylimine (after prior α-lithiation with *s*-butyl-lithium) to give (39; X = CMeCHO), further chain-extension occurred, to give (39; X = CHMeCH=CHCO<sub>2</sub>Me). Hydrolysis to the acid and *N*-deprotection gave the amino-acid (40). Cyclization of the amino-acid (40) was eventually accomplished by a new lactamization process; its tetra-*n*-butyammonium salt, dissolved in benzene, reacted with mesitylenesulphonyl chloride in di-isopropylethylamine to give the lactam (41). Separation of the two C-10 epimers (by preparative-scale layer chromatography; p.l.c.) and conversion of the less polar epimer, by desilylation, carbonylation, and dithian cleavage, into (±)-*N*-methylmaysenine (36) completed this notable synthesis.

The macrolide character of the maytansanoids originally suggested that they may have been elaborated by fungal or bacterial contaminant sources present in the Maytaneous plants: subsequent investigations did not support this view, but the recent patent<sup>21</sup> describing the isolation of antibiotics C-15003 P-3, C-15003 P-3', and C-15003 P-4 from the fermentation broth of a new species of *Nocardia* strain C-15003, with structural similarities to the maytansanoids, *i.e.* (42; R = COCHMe<sub>2</sub>), (42; R = COPr), and (42; R = COCH<sub>2</sub>CHMe<sub>2</sub>), respectively, re-opens the question of the origin of maytansanoids. Of greater importance is likely to be the easier and cheaper commercial production of these anti-tumour-active compounds.

The horsetail alkaloid palustrine has been assigned<sup>22</sup> the *threo*-*cis*-17-(1-hydroxypropyl)-1,5,10-triazabicyclo[11.4.0]heptadec-15-en-11-one structure (43). The dihydro-alkaloid has been synthesized, confirming the stereochemistry.<sup>23</sup>

<sup>19</sup> E. J. Corey, D. Enders, and M. G. Bock, *Tetrahedron Lett.*, 1976, 7.

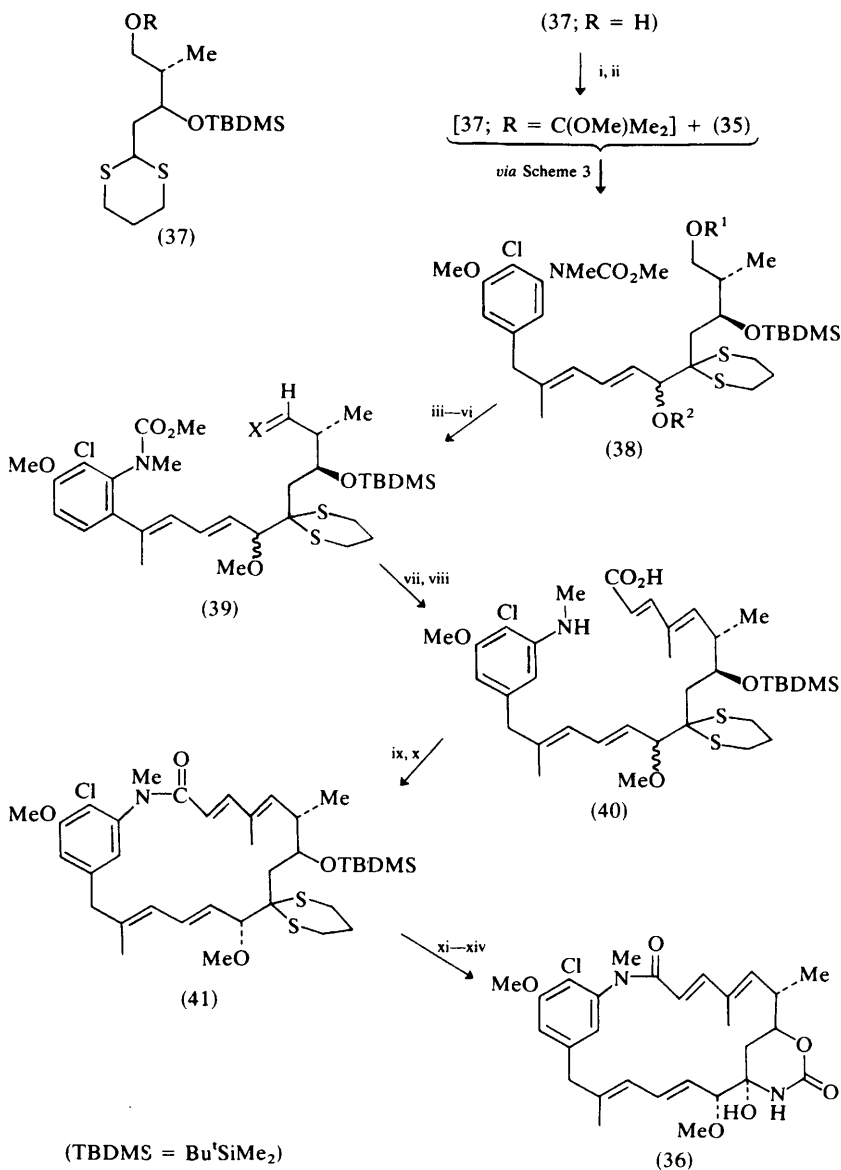
<sup>20</sup> E. J. Corey, L. O. Weigel, D. Floyd, and M. G. Bock, *J. Am. Chem. Soc.*, 1978, **100**, 2916.

<sup>21</sup> E. Higashide, M. Asai, S. Tanida, K. Otsu, and Y. Kozai, Ger Offen. 2 746 252 (*Chem. Abs.*, 1979, **90**, 34 105).

<sup>22</sup> P. Ruedi and C. H. Eugster, *Helv. Chim. Acta*, 1978, **61**, 899.

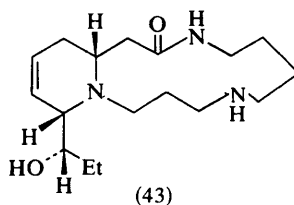
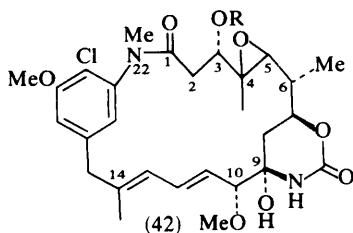
<sup>23</sup> E. Waelchli-Schaer and C. H. Eugster, *Helv. Chim. Acta*, 1978, **61**, 928.





Reagents: i,  $Me(OMe)CH=CH_2$ ,  $POCl_3$ ,  $CH_2Cl_2$ ,  $0^\circ C$ ; ii,  $Bu^tLi$ ,  $NN'$ -tetramethylethylenediamine; iii, HMPT,  $NaH$ ,  $MeI$ ; iv,  $DMSO$ ,  $PhH$ ,  $EtN=C=NEt$ ,  $py$ ,  $CF_3CO_2H$ ; v,  $\alpha$ - $Me_3Si(Me)C(Li)CH=NBu^t$ ; vi, lithiodimethyl methoxycarbonylmethanephosphonate; vii, 5%  $NaOH$ ,  $MeOH$ ,  $H_2O$ ,  $THF$ ; viii,  $Pr^tSLi$ , HMPT,  $0^\circ C$ ; ix,  $Bu^tNOH$ , toluene; x, mesitylenesulphonyl chloride,  $Pr_2NEt$ ,  $PhH$ ; xi,  $Bu^t_4NF$ ,  $THF$ ; xii,  $p$ - $NO_2C_6H_4O_2CCl$ ,  $py$ ; xiii,  $NH_4OH$ ,  $Bu^tOH$ ,  $25^\circ C$ ; xiv,  $Hg_2Cl_2$ ,  $CaCO_3$ ,  $MeCN$ ,  $H_2O$ .

Scheme 4



## 5 Alkaloid-containing Plants and Unclassified Alkaloids

A review on sulphur-containing alkaloids has appeared,<sup>24</sup> as has one on the Lauraceae alkaloids,<sup>25</sup> and the third (and last!) volume of Glasby's encyclopaedic series.<sup>26</sup> The toxicity of alkaloids with respect to their structure and geographical source has been reviewed, and the generalization that has been made from this ecogeographic study is that tropical plants produce more toxic alkaloids than do those from temperate regions.<sup>27</sup>

### *Caulerpa racemosa* and *C. taxifolia*

On the basis of spectral and chemical evidence, the structure of the algal pigment caulerpin has been re-assigned<sup>28</sup> as (44); a synthesis using *N*-methylindol-2-yl acetate and double *cis*-condensation further substantiated the new structure.

### *Croton lechleri*

The alkaloid taspine (45) isolated from this South American plant has a high anti-inflammatory activity.<sup>29</sup>

### *Dicarpellum pronyensis*

Three alkaloids, *i.e.*, dicarprines A, B, and C, isolated from the leaves of this plant,<sup>30</sup> have the aminododecene structures  $\text{CH}_3\text{CH}(\text{NHR}^1)\text{CH}(\text{OR}^2)\text{CH}_2(\text{CH}=\text{CH})_3\text{CH}_2\text{CH}_3$ , where  $\text{R}^1 = \text{R}^2 = \text{Me}$ ,  $\text{R}^1 = \text{Me}$  and  $\text{R}^2 = \text{H}$ , and  $\text{R}^1 = \text{R}^2 = \text{H}$ , respectively.

### *Diptychocarpus strictus*

The seeds and aerial parts of this plant contain 0.13 and 0.10% total alkaloids, two of which are isopropylurea and 6-thiomethyl-*N*-hexylurea.<sup>31</sup>

### *Gyromitra esculenta*

The mycelia (grown from isolated ascospores) of this fungus, as well as its fruiting bodies, contain toxic substances which have been identified as *N*-methyl-

<sup>24</sup> S. F. Aripova and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 1978, 26 (*Chem. Abs.*, 1979, **89**, 6458).

<sup>25</sup> I. R. C. Bick and W. Sinchai, *Heterocycles*, 1978, **9**, 903.

<sup>26</sup> J. S. Glasby, 'Encyclopedia of the Alkaloids', Vol. 3, Plenum, New York, 1977.

<sup>27</sup> D. A. Levin, *Biochem. Syst. Ecol.*, 1978, **6**, 61.

<sup>28</sup> B. C. Maiti, R. H. Thomson, and M. Mahendran, *J. Chem. Res. (S)*, 1978, 126.

<sup>29</sup> G. S. Perdue, R. N. Blomster, D. A. Blake, and R. N. Farnsworth, *J. Pharm. Sci.*, 1979, **68**, 124.

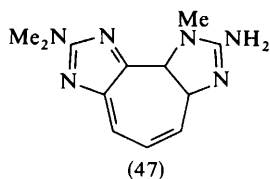
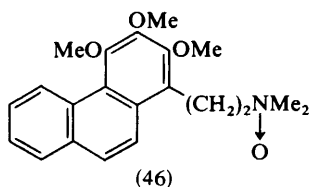
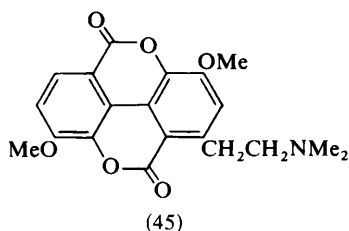
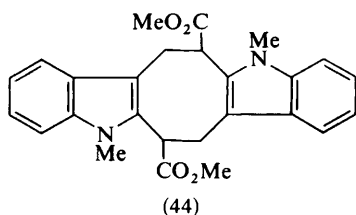
<sup>30</sup> B. Adéoti, T. Sévenet, and M. Pais, *Phytochemistry*, 1978, **17**, 831.

<sup>31</sup> O. Abdjalimov, S. F. Aripova, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 1978, 535 (*Chem. Abs.*, 1978, **89**, 193 849).

*N*-formylhydrazones, the main component being acetaldehyde *N*-methyl-*N*-formylhydrazone.<sup>32</sup>

### *Meiocarpidium lepidotum*

The root and stem bark contain two aminophenanthrene alkaloids, the major component being methoxyatherosperiminine and the minor component its *N*-oxide (46).<sup>33</sup>



### *Parazoanthus* sp.

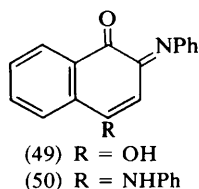
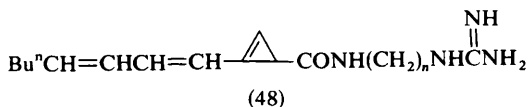
A new zoanthoxanthin, containing the tetra-azacyclopent[*e*]azulene structure (47), has been isolated from this bathyal marine organism.<sup>34</sup>

### *Polyandrocarpa* sp.

This marine tunicate contains two novel compounds, polyandrocarpidines I (48;  $n = 5$ ) and II (48;  $n = 4$ ); both of these related compounds possess anti-bacterial and cytotoxic activity.<sup>35</sup>

### *Reseda luteola*

In addition to resedine, resedinine, phenyl- $\beta$ -naphthylamine, and  $\beta$ -hydroxyphenylethylamine, the above-ground parts of this plant contain two new alkaloids, lutine (49) and lutinine (50).<sup>36</sup>



<sup>32</sup> M. Raudaskoski and H. Pyysalo, *Z. Naturforsch., Teil C*, 1978, **33**, 472.

<sup>33</sup> M. Leboeuf, A. Fournet, A. Bouquet, and A. Cavé, *Plant. Med. Phytother.*, 1977, **11**, 284 (*Chem. Abs.*, 1978, **89**, 103 723).

<sup>34</sup> R. F. Schwartz, M. B. Yunker, and P. J. Scheuer, *Tetrahedron Lett.*, 1978, 2235.

<sup>35</sup> M. T. Cheng and K. L. Rinehart, Jr., *J. Am. Chem. Soc.*, 1978, **100**, 7409.

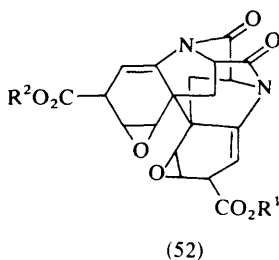
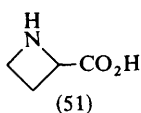
<sup>36</sup> K. L. Lutfullin, M. M. Tadzhibaev, V. M. Malikov, U. A. Abdullaev, and U. Rakhmankulov, *Khim. Prirod. Soedin.*, 1977, 826 (*Chem. Abs.*, 1978, **89**, 75 412).

*Ruscus hypoglossum* and *Urginea maritima*

The leaves of these two plants are highly resistant to the insect *Spodoptera littoralis*, and the active principle has been shown to be azetidine-2-carboxylic acid (51), present in the former plant at a concentration of 0.019% and the latter at 1.7% by weight of their fresh leaves.<sup>37</sup>

*Xanthoparmelia scabrosa*

Four scabrosin derivatives, *i.e.* (52;  $R^1 = R^2 = \text{Me}$ ), (52;  $R^1 = \text{Me}$ ,  $R^2 = \text{Pr}^n$ ), [52;  $R^1 = \text{Me}$ ,  $R^2 = \text{Me}(\text{CH}_2)_4$ ], and (52;  $R^1 = R^2 = \text{Pr}^n$ ), have been characterized by  $^{13}\text{C}$  n.m.r. spectroscopy.<sup>38</sup>



<sup>37</sup> E. Hassid, S. W. Applebaum, and Y. Birk, *Phytoparasitica*, 1976, **4**, 173 (*Chem. Abs.*, 1979, **90**, 118 205).

<sup>38</sup> W. R. Begg, J. A. Elix, and A. J. J. Jones, *Tetrahedron Lett.*, 1978, 1047.

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