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THE SYNTHESIS OF *ASPIDOSPERMA* ALKALOIDS CONTAINING A FUNCTIONAL GROUP AT C-18; THE TOTAL SYNTHESIS OF (±)-N,O-DIACETYLCYLINDROCARPINOL, (±)-CYLINDROCARINE, (±)-CYLINDROCARPINE, (±)-CYLINDROCARPIDINE, AND (±)-20-ALLYL-20-DESETHYL-20-EPIASPIDOSPERMINE†[1a]

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Abstract—The first total synthesis of (±)-N,O-diacetylcylindrocarpinol **49**, (±)-cylindrocarine **51**, (±)-cylindrocarpidine **1**, and (±)-cylindrocarpine **52**, starting from pent-4-enal and proceeding *via* the ketones **12** and **40**, is described. The stereoisomeric ketones **20** and **41** were used as intermediates in a parallel synthesis of (±)-20-allyl-20-desethyl-20-epiaspidospermine **47**.

Although several syntheses of the aspidospermine ring system had been reported none of these, at the outset of the investigations described here, had been applied to the synthesis of alkaloids containing a functionalised two-carbon unit at C-20, e.g. cylindrocarpidine **1**.‡ In developing a synthesis of this group of alkaloids we also hoped, ultimately, to be able to extend it to the synthesis of the kopsinine **2** group; hence, we obviously required a versatile approach which would lead to either the *cis* C/D or the *trans* C/D isomeric series, the former for conversion into cylindrocarpidine, and the latter for conversion into kopsinine, via formation of the 2,16 bond. After exploring several unsuccessful original approaches,[1b] we assessed the published routes to the aspidospermine ring system, and of these it appeared that the one most likely to be applicable was a modification of Stork's original synthesis[2] of aspidospermine.

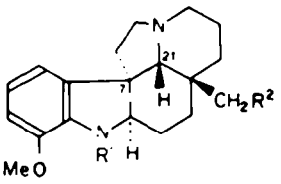
Our initial objective was the synthesis of cylindrocarpidine **1** and N-acetylcylindrocarpinol **3**, and for this purpose we required a tricyclic ketone **4** which contained, by reason of its mode of synthesis, a comparatively inert substituent attached to the future C-20, but one which could be transformed into a hydroxyethyl group or an acetic ester residue, as and when required. It was also evident that a sterically undemanding substituent was required at the angular position. The synthesis[3] of both aspidospermine **5** and a stereoisomer **6** containing a *trans* C/D ring junction from a common intermediate **7** indicates that there is probably little difference in stability between the two stereochemical series; in the aspidospermine series the *cis* C/D isomer is favoured, but in compounds containing a bulky substituent at C-20 the order of stabilities may well be reversed. If then such a pentacyclic system is constructed by a Fischer indole reaction the product will almost certainly be the thermodynamically more stable *trans* C/D isomer since the intermediate indolenines in both the *cis* and *trans* C/D series will have an opportunity to equilibrate, via reverse Mannich fission of the 7,21 bond. An illustration of the reversed order of stabilities in this series appears to be provided by the work of Inoue and Ban,[4] who obtained only the *trans* C/D pentacyclic product **8** by the Fischer indole cyclisation of the *o*-methoxyphenylhydrazone of the tricyclic ketone **9**. This retention of stereochemical integrity was attributed to insufficiently rigorous experimental conditions; it was suggested that prolonged heating of the indolenine (formed by Fischer indole closure) with acetic acid is perhaps necessary to effect the fission and recombination of the 7,21 bond for production of the thermodynamically more stable isomer, assumed to be the *cis* isomer. Alternatively it was suggested that the failure to isolate the *cis* C/D isomer could be ascribed to difficulty of isolation. However, it is our view that with a bulky substituent such as a phenoxyethyl group at the angular position the thermodynamically preferred isomer will probably be the *trans* C/D isomer **8**, and even if reversible Mannich fission and recombination occurs there may well be very little *cis* isomer present at equilibrium.

For these reasons we chose the allyl group as the sterically undemanding angular substituent, and thus our first investigations were directed towards the synthesis of the tricyclic ketone (**4**, R=$CH_2CH{=}CH_2$).

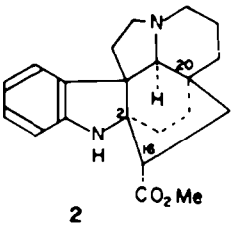
Alkylation of the pyrrolidine enamine of pent-4-enal[5] by means of methyl acrylate afforded the aldehydo-ester **10**, which was converted into its pyrrolidine enamine and alkylated with methyl vinyl ketone to give, after hydrolysis and cyclisation, the desired cyclohexenone derivative **11** in moderate yield. Conversion of this ketone into the bicyclic aminoketone **12** can in principle be achieved in two ways.[2] Thus, reaction of the ethylene ketal of the ketone **11** with ammonia should produce the amide **13** which, on reduction ($LiAlH_4$), acid hydrolysis, and cyclisation should afford the bicyclic ketone **12**, via the enone **14**. Furthermore, the thermodynamically preferred mode of cyclisation of **14**, which presumably involves axial approach of the amino group to the enone system, should ensure that the bicyclic aminoketone has a *cis* ring junction, which is the stereochemistry required for the completion of a synthesis of cylindrocarpidine. That this is in fact the preferred mode of cyclisation is

†Dedicated to Prof. R. B. Woodward on the occasion of his sixtieth birthday.

‡The configurations shown are those of the naturally-occurring alkaloids, all synthetic compounds reported here are racemic, but only one enantiomer is illustrated.



1 R¹ = Ac; R² = CO_2Me
3 R¹ = Ac; R² = CH_2OH
5 R¹ = Ac; R² = Me
48 R¹ = Ac; R² = CHO
49 R¹ = Ac; R² = CH_2OAc
50 R¹ = Ac; R² = CN
51 R¹ = H; R² = CO_2Me
52 R¹ = $COCH{=}CHPh$; R² = CO_2Me



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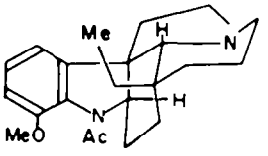

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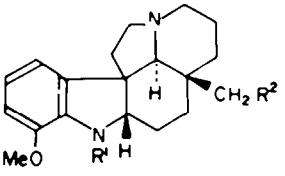
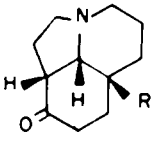


6 R¹ = Ac; R² = Me
8 R¹ = H; R² = CH_2OPh



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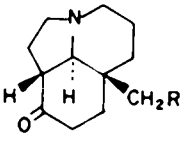


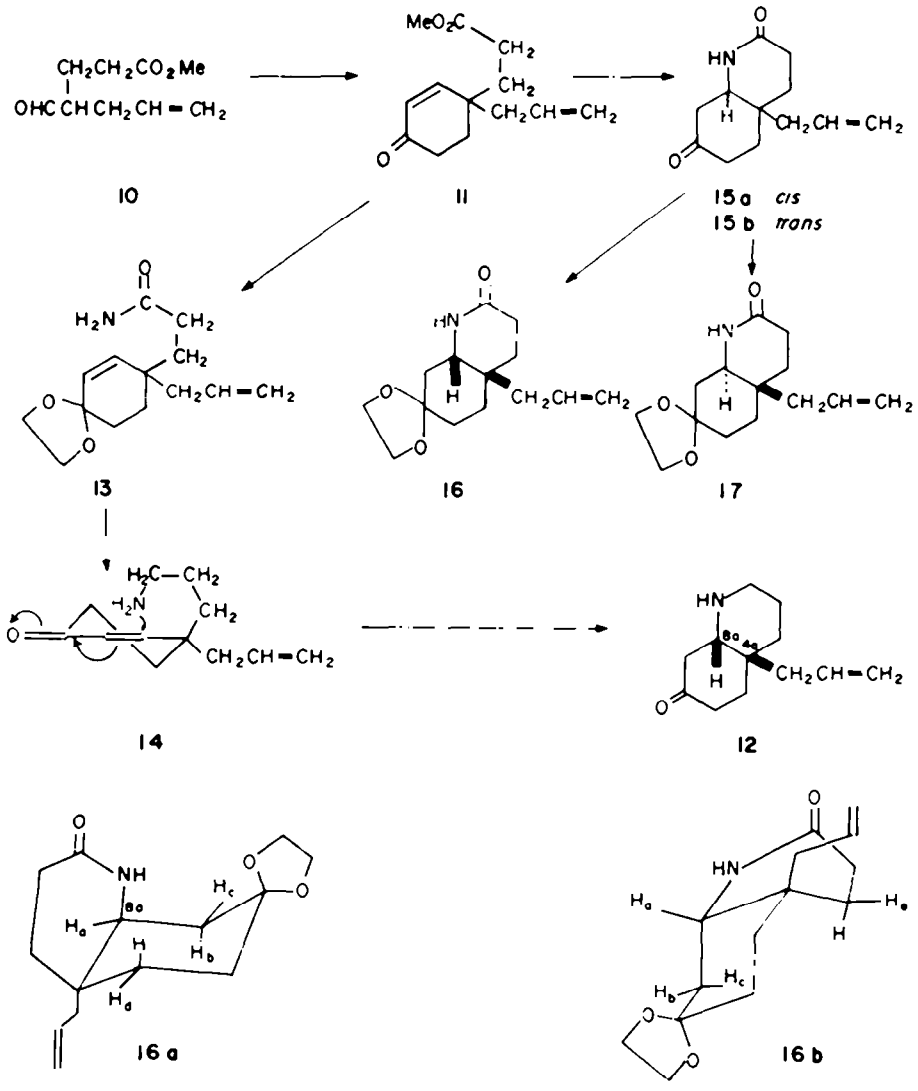
7 R = Me
9 R = CH_2OPh

evident from Stork's synthesis[2] of the analogous ethyl compound, the stereochemistry of which was later unequivocally established by Ban and his collaborators.[6] Since this route was expected to yield one isomer only it was our initial method of choice; however, the ketone **11** unaccountably gave only a low yield of product on attempted ketalisation, and hence this route was abandoned in favour of the alternative pathway, which involved the addition of ammonia to the enone system, followed by cyclisation, the product being a mixture of the *cis* and *trans* bicyclic amidoketones (**15a** and **15b**). Since nucleophilic addition of ammonia can occur on either face of the enone system both *cis* and *trans* isomers of the bicyclic amidoketone can obviously be formed. The crystalline product, however, proved to be an inseparable mixture which gave only one spot on TLC in three solvent systems but the presence of two components was deduced from the doubling of signals in the NMR spectrum, e.g. the signal owing to the proton at C-8a appeared as a doublet of triplets centred on τ6.34, which together accounted for one proton. Conversion of the mixture of ketones into the corresponding ethylene ketals afforded a crystalline product, m.p. 110–112°, which exhibited two closely-running spots on TLC, and the expected duplication of signals in the NMR spectrum, from which it was estimated that the isomers were present in approximately equal amounts. Careful chromatography of this mixture eventually led to the isolation of the two isomeric ketals, of m.p. 126.5–127.5° **16** (46%) and 162–163° **17** (45%). The most significant difference in the NMR spectra of these two ketals was observed in the signal ~6.5τ owing to the proton at C-8a. In the spectrum of the higher melting isomer this signal appeared as a broadened triplet owing to coupling of H_a with H_b and H_c in the *trans* isomer (cf. **17a**); in the spectrum of the lower melting isomer it appeared as a complex multiplet owing to an additional (W) coupling of H_a with H_d in conformation **16a**, or of H_a with H_e in conformation **16b**.

This tentative assignment of the *cis* stereochemistry **16** to the isomer of m.p. 126.5–127.5°, and the *trans* stereochemistry **17** to the isomer of m.p. 162–163° was later confirmed independently from the spectrographic properties of their transformation products, and by an independent synthesis of the aminoketone **12**.

Reduction† of the pure, racemic amidoketals **16** and **17** by means of $LiAlH_4$ smoothly gave the isomeric

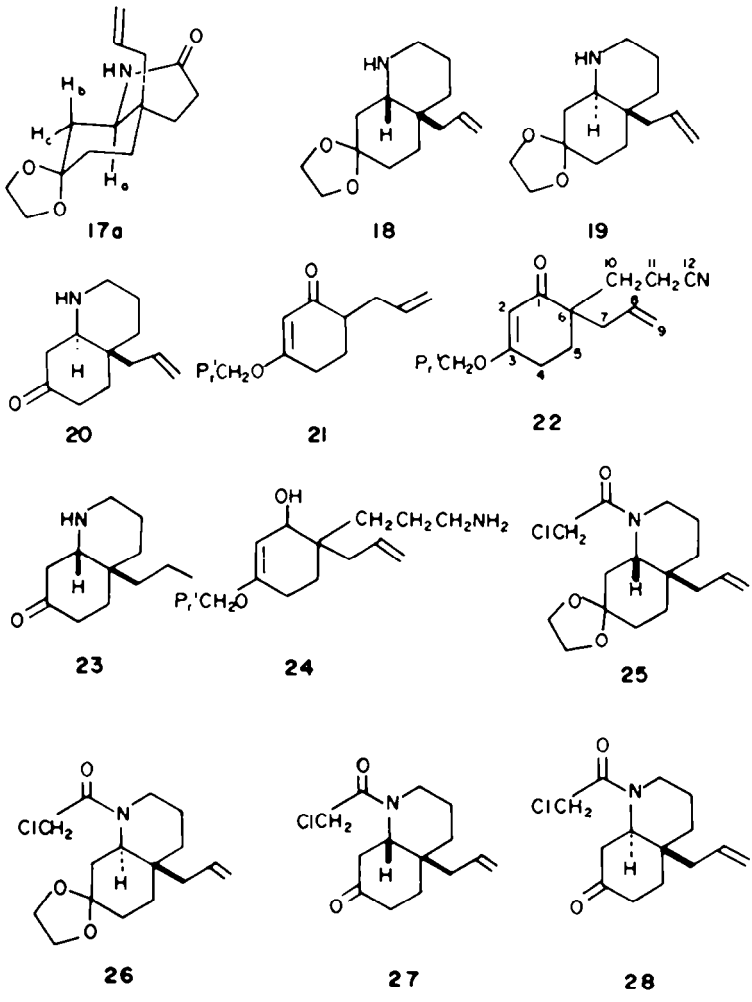
†From this point onwards, as far as the preparation of 20-allyl-20-desethylaspidospermine, three syntheses were executed. In preliminary experiments the mixture of *cis* and *trans* isomers was employed in order to examine the feasibility of the synthesis; subsequently the synthesis was repeated using the pure *cis* and pure *trans* isomers independently. For the sake of conciseness, only the experiments on the purified *cis* and *trans* racemates are discussed in detail.



aminoketals **18** and **19**, from which the aminoketones **12** and **20** were released by dilute acid hydrolysis. All four compounds appeared, from spectral evidence and chromatographic behaviour, to be single substances; unfortunately, the NMR spectra, and particularly the signal owing to the proton at C-8a, did not allow any confirmatory deductions concerning the stereochemistry of these compounds to be made.

In principle the β-aminoketones **12** and **20** should be capable of equilibration via reversible β-elimination and Michael addition under acidic or basic conditions. However, the retention of stereochemical homogeneity in the preparation of **12** and **20** suggests that they are stable to dilute acid, at least under the conditions employed for ketal hydrolysis. Since the preferred Michael addition product has been shown to be the *cis*-decahydroquinoline derivative (cf. Refs. 2 and 6, and **14** → **12**), the equilibration of the aminoketones **12** and **20** in the presence of dilute alkali was studied, under the conditions employed for the epimerisation of lobeline.[7] However, both ketones were unaffected by treatment with very dilute alkali (0.005 M), and were even unchanged after being heated for 10 h at 100° with 0.2 M alkali. Presumably the *cis* isomer can adopt the ideal geometry required for ring-opening and reclosure (**14** ⇌ **12**); the *trans* isomer can not do so, and hence fission of the β-aminoketone system in **20** requires a much higher activation energy, certainly much higher than is required for the isomerisation of lobeline, a monocyclic, conformationally mobile system.

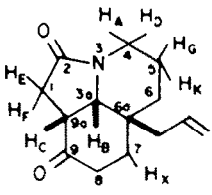
The isolation of the *trans*-aminoketone **20** and its stereochemical stability, are of importance in connection with other aspects of the overall investigation. Nevertheless, for the synthesis of cylindrocarpidine, the failure of **20** to isomerise, and the failure to obtain the *cis* isomer **12** by the stereospecific route (**11** → **13** → **14** → **12**), rendered an independent stereospecific route desirable. Such a route was found in the dialkylation of the enol ether of cyclohexan-1,3-dione, a reaction which has been applied so elegantly in the synthesis of (±)-β-vetivone.[8] Accordingly, 6-allyl-3-isobutoxycyclohexenone[9] **21** was alkylated by means of acrylonitrile in the presence of Triton B to give the nitrile **22** in moderate yield, after allowing for the starting material recovered. As far as we were aware, this was the first example of a second alkylation of an enol ether of this type by an intermolecular process. The previous example, applied in the vetivone synthesis, constituted a spiroannelation by



intramolecular alkylation. It was thus imperative to establish unequivocally that alkylation had indeed occurred at C-6, and not at C-2 or C-4, the possible alternative sites of attack. Alkylation at C-2 was easily eliminated, since the product contained four olefinic protons, and alkylation at C-4 was eliminated by its off-resonance coherent proton spin-decoupled ^{13}C NMR spectrum, which revealed the presence of four singlets owing to fully substituted carbon atoms, i.e. the nitrile carbon (C-12, 120.08 ppm), the carbonyl carbon (C-1, 200.77 ppm), the β-carbon of the enone system (C-3, 176.26 ppm), and the α'-carbon atom (C-6, 45.77 ppm) (chemical shifts refer to downfield shifts from TMS).

Reduction of the enone **22** was initially attempted by means of $NaBH_4$–$CoCl_2$ in methanol,[10] but concomitant reduction of the terminal double bond also occurred, the product after hydrolysis with dilute acid almost certainly being the saturated aminoketone **23** (NMR spectrum). However, reduction of **22** with $LiAlH_4$ smoothly gave the amino-enol ether **24**, which when hydrolysed with dilute acid simultaneously cyclised to give as sole product the bicyclic aminoketone **12**, identical in every respect with the isomer previously deduced to be the *cis* isomer. This at once confirms the earlier, tentative stereochemical assignments for the isomers **12** and **20**, and provides a more direct, higher yielding synthesis of the desired intermediate **12**.

The next phase of the synthesis involved addition of two carbon atoms and closure of the 5-membered ring. Chloroacetyl chloride provided the two-carbon unit, and on the basis of trial experiments chloroacetylation of the ketals **18** and **19** was preferred, rather than chloroacetylation of the aminoketones **12** and **20**. The products, **25** and **26**, as well as the amidoketones **27** and **28** liberated on acid hydrolysis, were all shown to be single racemates, and therefore had retained their stereochemical homogeneity. Cyclisation of **27** and **28** to form the tricyclic amidoketones was achieved by means of potassium t-butoxide in a mixture of benzene and t-butanol at room temperature. Again the products were stereochemically pure, although in principle each amidoketone can give rise to two diastereoisomeric products, i.e. **27** → **31** → **29** ⇄ **30**; similarly, **28** → **32** ⇄ **33**. Fortunately, proof of the stereochemistry of the products was not difficult to obtain. The course of the cyclisation of the *cis* amidoketone **27** will almost certainly be parallel to that of Stork's analogous ethyl compound, the product from which has been rigorously shown[6] to be the all-*cis* compound **34**. In fact, the NMR spectra of the all-*cis* compound **34**[6] and the product of cyclisation of the amidoketone **27** in the region 5.9–7.1τ show a quite remarkable similarity. The protons responsible for these signals are those at positions 3a, 4 and 9a, and the very similar fine structures observed in the two spectra are clearly a reflection of the



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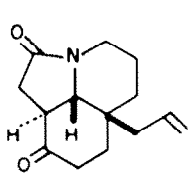

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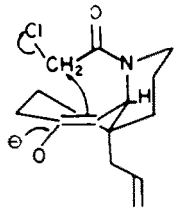

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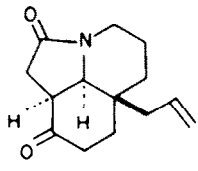

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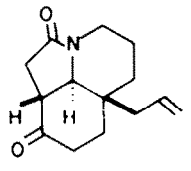

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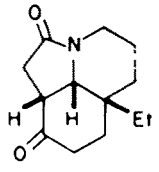

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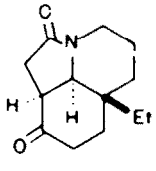

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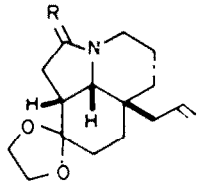
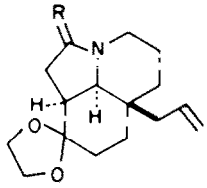
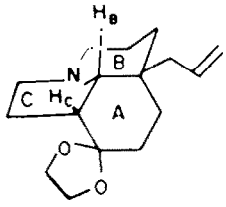


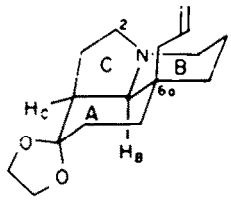
36 R = O
38 R = H_2



37 R = O
39 R = H_2



38a



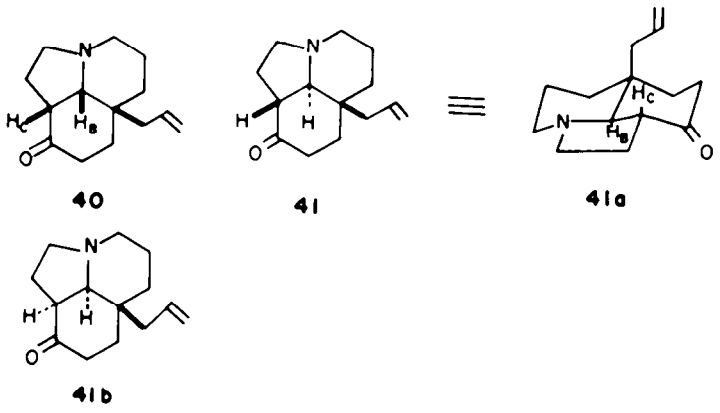
39a

identical stereochemistry of the two compounds. Significantly, the proton at C-3a in **29** gives rise to a clear double doublet centred on 6.5τ (J = 6.5, 1.5 Hz) owing to vicinal coupling with the proton at C-9a and W-coupling with one of the protons at position 7. Such a coupling is only possible in the all-*cis* isomer **29**; models indicate that there is no possibility of W-coupling in the C-9a epimer **30**.

A similar comparison enabled the stereochemistry of the product of cyclisation of the *trans* amidoketone **28** to be established. The NMR spectrum of the product in the region 5.7–7.1τ is virtually identical with that of Ban's ethyl analogue **35**;[3,6] again the signals concerned are those owing to the protons at positions 3a, 4 and 9a. The C-3a proton in **32** gives rise to a doublet at 6.2τ (J = 9.5 Hz) owing to a coupling with H-9a; no W-coupling is observed and none would be expected (models). The C-9a proton (H_C) appears as a clean quartet centred on 6.9τ ($J_{BC} - J_{CD} = J_{CD} = 9.5$ Hz); this coincidence of coupling constants is also consistent with the appropriate dihedral angles deduced from Dreiding models of the *trans* A/B, *cis* B/C isomer **32**.

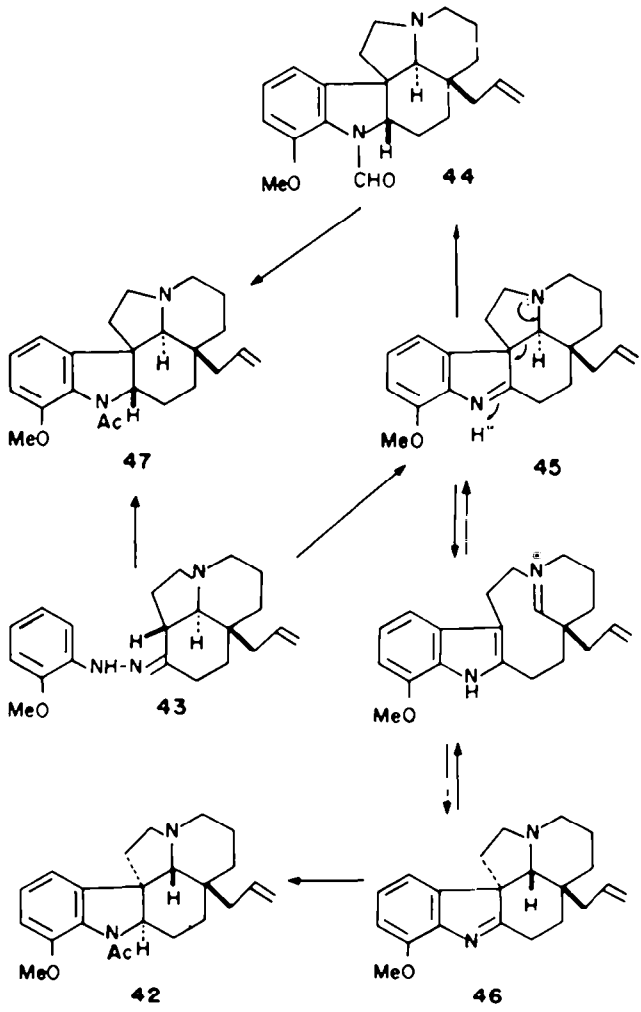
For the synthesis of the crucial tricyclic ketones it was now necessary to remove the amide carbonyl group from **29** and **32**, and this was achieved by the familiar device of protecting the ketone carbonyl group by ketal formation, reduction ($LiAlH_4$) of the amide function, and release of the ketone carbonyl group by acid hydrolysis. The amidoketones **29** and **32** gave rise to crystalline ketals **36** and **37** which, on reduction, afforded the aminoketals **38** and **39** as colourless oils. Of the two, only the all-*cis* isomer **38** exhibited Bohlmann bands in its IR spectrum. Thus it appears that reduction of **36** gives rise to an aminoketal **38** with a *trans* B/C ring junction, the conformation of which (cf. **38a**) is an unstrained one in which both 6-membered rings exist in the chair conformation. The two possible conformations of the isomer with a *cis* B/C ring junction are considerably more strained, and in any case would not be expected to exhibit Bohlmann bands. In contrast the reduction of the amidoketal **37** gives a product **39** with a *cis* B/C ring junction which, in spite of the non-bonded interactions between the newly-formed (axial) methylene group at C-2 and the axial methylene group attached to C-6a (cf. **39a**), appears to be considerably less strained than its *trans* B/C isomer.

The chemical and stereochemical relationships in this tricyclic series thus exactly parallel those observed by Ban *et al.*[6] in the corresponding ethyl series, e.g. **34**, **35** and their transformation products. A further parallel is observed in the products of hydrolysis of the ketals **38** and **39**, to give the important aminoketones **40** and **41**. Both products exhibit strong Bohlmann bands, hence the hydrolysis of the all-*cis* isomer **38** proceeds normally. However, the diaxial interactions in the ketone corresponding to the aminoketal **39a** are such that, once the



carbonyl group at C-9 is liberated these interactions can be relieved by epimerisation of the adjacent centre (C-9a), and concomitant inversion of the nitrogen atom. The product is thus not the aminoketone of structure **41b** but the all-*trans* isomer **41**, which exists in the less strained conformation **41a**.

The most critical stage of the synthesis, namely, the construction of the pentacyclic aspidospermidine (or stereoisomeric) ring system had now been reached, and for this purpose the *o*-methoxyphenylhydrazones of the aminoketones **40** and **41** were prepared. Cyclisation of the *o*-methoxyphenylhydrazone of the all-*cis* ketone **40** by means of acetic acid afforded an indolenine which on reduction ($LiAlH_4$) gave the corresponding indoline as a brown solid, m.p. 93–95°, better characterised as its N-acetyl derivative, m.p. 189.5–190°. Since this product exhibited in its NMR spectrum a quartet centred on 5.45τ owing to the proton at C-20 (the aspidospermine "fingerprint")[11] it was almost certain that it possessed the natural stereochemistry, and was thus 20-allyl-20-desethylaspidospermine **42**. In order to establish this conclusion firmly, the cyclisation of the *o*-methoxyphenylhydrazone **43** of the all-*trans* ketone **41** by means of acetic acid and formic acid was studied. As expected



cyclisation by means of formic acid produced the N-formylindoline (20-allyl-20-desethyl-20-epivallesine) **44**; however, cyclisation by means of acetic acid gave a mixture of products (owing to equilibration of **45** with **46**), from which 20-allyl-20-desethylaspidospermine **42** and its stereoisomer **47** were obtained after reduction and acetylation.† The structure of **47** was unequivocally established by its formation from the N-formylindoline **44** by hydrolysis and acetylation. A notable feature of the NMR spectrum of **47** was the absence of the aspidospermine "fingerprint" in the region of 5.5τ; instead the C-2 proton appeared as triplet at 5.1τ.

For the completion of the synthesis it now remained only to manipulate the allyl group attached to C-20, and of the several naturally-occurring compounds into which 20-allyl-20-desethylaspidospermine could be transformed N-acetylcylindrocarpinol[12] was the most accessible. Accordingly, 20-allyl-20-desethylaspidospermine **42** was oxidised by means of osmium tetroxide and sodium paraperiodate to give an almost quantitative yield of (±)-N-acetylcylindrocarpinal, **48**, m.p. 214–216°, the spectroscopic data for which compared favourably with the published data[11] for the optically active material. Reduction of the aldehyde by $NaBH_4$ in methanol gave (±)-N-acetylcylindrocarpinol, **3**, m.p. 200–201°, which was identical with authentic N-acetylcylindrocarpinol[12,14] in IR spectrum and TLC behaviour in three solvent systems. For final confirmation of identity the synthetic and natural materials were further converted by acetylation into N,O-diacetylcylindrocarpinol **49**. Direct comparison of the synthetic N,O-diacetylcylindrocarpinol, m.p. 193–196°, with the natural material showed that they gave identical IR, UV and mass spectra, and exhibited identical behaviour on TLC in three solvent systems.

Our next objective was the group of ester alkaloids exemplified by cylindrocarpidine **1**, and for this purpose oxidation of the allyl group to an acetic acid residue was required. Owing to the suspected sensitivity of the methoxyaspidospermidine nucleus to vigorous oxidising agents we preferred to utilise the already prepared N-acetylcylindrocarpinal **48**, which was converted into its oxime and thence, by dehydration with acetic anhydride, into the nitrile **50**. Methanolysis of **50** with methanol and sulphuric acid was accompanied by partial deacetylation, which afforded a mixture of (±)-cylindrocarine **51** and (±)-cylindrocarpidine **1**. Chromatographic separation gave pure (±)-cylindrocarine, whose spectroscopic data were identical with those reported[12] for natural (−)-cylindrocarine, as far as could be judged. In subsequent experiments the mixture of (±)-cylindrocarine and (±)-cylindrocarpidine resulting from the methanolysis of the nitrile was reacetylated to give pure (±)-cylindrocarpidine **1**, m.p. 178–179°, identical with natural (−)-cylindrocarpidine[14] in IR, UV, mass and NMR spectra, and in TLC behaviour in three solvent systems.

Finally the isolation of (±)-cylindrocarine allowed us to complete the synthesis of (±)-cylindrocarpine **52**, by acylation with cinnamoyl chloride in pyridine. The (±)-cylindrocarpine so produced was also shown by direct comparison to be identical with authentic (±)-cylindrocarpine[14] in IR, UV, mass, and NMR spectra, and in TLC behaviour in three solvent systems.

†In the preliminary communication[14] in which this work was described the stereochemistry of **44** and **47** was inadvertently given incorrectly

EXPERIMENTAL

M.ps were measured on a Kofler hot-state apparatus. IR spectra were recorded on a Unicam SP 1000 G spectrophotometer. UV spectra were recorded on a Unicam SP 800 A spectrophotometer, using 95% EtOH as solvent. NMR spectra were measured on Varian A 60 A, Perkin Elmer R 12, R 32, or Brüker 90 MHz instruments. Mass spectra were recorded on an A.E.I. MS 902 spectrometer. TLC was carried out using plates coated with Merck Kieselgel G or GF 254. The use of alumina for chromatography refers to Woelm neutral grade III alumina. Light petroleum refers to the fraction b.p. 60–80° unless otherwise stated.

The pyrrolidine enamine of pent-4-enal

Pent-4-enal[7] (42.25 g) was added slowly during 0.5 hr to a vigorously stirred, ice-cold suspension of anhydrous potassium carbonate (29.7 g) in pyrrolidine (92.6 g). Stirring was continued at room temperature for a further 17 hr and then the mixture was filtered (sinter). The residue was washed well with dry ether (500 ml) and then the ether was removed *in vacuo*. The residue was distilled under reduced pressure to give the pyrrolidine enamine of pent-4-enal (51.2 g; 74%), as a colourless oil, b.p. 83–85°/15 mm; $\nu_{max.}$ (film) 1655 (C=C–N) cm^{-1}.

Methyl 4-formylhept-6-enoate **10**

Freshly distilled methyl acrylate (38.2 g) in dry benzene (100 ml) was slowly added to a stirred solution of the pyrrolidine enamine of pent-4-enal (41.2 g) in dry benzene (150 ml), the experiment being carried out in an atmosphere of dry nitrogen. The mixture was stirred at room temperature for 4.5 hr and then refluxed for 38 hr. Glacial acetic acid (22 ml) in water (80 ml) was added dropwise and then refluxing continued for a further 14 hr. When cold, the benzene layer was separated and the aqueous layer washed with ether. The combined organic extracts were washed with dil. HCl (50 ml) and water (80 ml); dried, and evaporated. The residue was fractionally distilled to give methyl 4-formylhept-6-enoate (42.6 g; 84%) as a colourless oil, b.p. 123–125°/18 mm, pure by VPC analysis; $\nu_{max.}$ (film) 2720 (aldehyde C–H), 1740 (ester carbonyl), 1720 (aldehyde carbonyl), 1640 weak (double bond), 1260, 1210 and 1180 (ester C–O) cm^{-1}; τ (in $CDCl_3$) 0.35 (1H, d, J 1.5 Hz, –CHO), 3.88–4.55 (1H, m, –CH=CH_2), 4.70–5.10 (2H, m, –CH=CH_2), 6.32 (3H, s, –$COOCH_3$), 7.40–8.35 (7H, m).

4-(2-*Methoxycarbonylethyl*)-4-*allylcyclohex*-2-*enone* **11**

Pyrrolidine (13.0 g) in dry benzene (200 ml) was added to a solution of methyl 4-formylhept-6-enoate (27.2 g) in dry benzene (100 ml) and the mixture was refluxed in an atmosphere of dry nitrogen, using a water separator, until no more water was collected (2 hr). The crude product exhibited $\nu_{max.}$ 1738 (ester carbonyl), 1655 (C=C–N) cm^{-1}.

The reaction mixture was then concentrated to 150 ml and cooled to allow the addition of a solution of freshly distilled methyl vinyl ketone (16.1 g) in dry benzene (20 ml) during 0.5 hr. After being stirred for 1 hr at room temperature the mixture was refluxed for 18 hr. Glacial acetic acid (10 ml) was then added dropwise and the mixture was refluxed for a further 4 hr. The reaction mixture was allowed to cool and washed successively with water, dil. HCl, and water, dried and evaporated. This produced a thick brown oil which was distilled to give 4-(2-*methoxycarbonylethyl*)-4-*allylcyclohex*-2-*enone* (13.34 g, 37.5%) as a very pale yellow oil, b.p. 154–156°/0.4 mm. (Found: C, 69.95; H, 8.15. $C_{13}H_{18}O_3$ requires: C, 70.2; H, 8.15%); $\nu_{max.}$ (film) 1730 (ester carbonyl), 1680 (enone carbonyl), 1640 weak (double bond), 1260, 1210 and 1180 (ester C–O) cm^{-1}, $\lambda_{max.}$ (ε) 227 (8,500) nm, τ (in $CDCl_3$) 3.28 (1H, d, J = 10 Hz, –CH=CH–C=O), 4.02 (1H, d, J = 10 Hz, –CH=CH–C–O), 4.0–4.5 (1H, m, –CH=CH_2), 4.7–5.1 (2H, m, –CH=CH_2), 6.30 (3H, s, –$COOCH_3$), 7.35–8.35 (10H, m).

4a-*Allyl*-2,7-*dioxo*-*decahydroquinoline* **15**

A mixture of 4-(2-methoxycarbonylethyl)-4-allylcyclohex-2-enone (12.11 g) in EtOH (250 ml) and conc. aq NH_3 (40 ml) was stirred at room temperature for 96 hr. The solution was evaporated to dryness and the resultant yellow oil produced

white crystals on being cooled overnight. Recrystallisation from aqueous ethanol afforded colourless needles, m.p. 109–110°, of 4a-*allyl*-2,7-*dioxo*-*decahydroquinoline* (6.40 g, 56.7%). (Found: C, 69.45; H, 8.2; N, 7.0 $C_{12}H_{17}NO_2$ requires: C, 69.50; H, 8.3; N, 6.8%); ν_{max} (Nujol) 3280 broad (NH), 1715 (ketone carbonyl), 1645 (lactam carbonyl), 1640 weak (double bond) cm^{-1}, τ (in $CDCl_3$) 2.95 (1H, bs, exchanges with D_2O, -NH), 3.80–4.40 (1H, m, $-CH$=CH_2), 4.6–5.0 (2H, m, $-CH$=CH_2), 6.34 (1H, d of t, J = 5 Hz and 0.5 Hz, -N–CH), 7.25–8.50 (12H, m).

4a-*Allyl*-7,7-*ethylenedioxy*-2-*oxo*-*decahydroquinoline* (**16** and **17**)

A mixture of 4a-allyl-2,7-dioxo-decahydroquinoline (1.00 g), dry benzene (150 ml), ethylene glycol (2.45 g), and toluene-*p*-sulphonic acid (30 mg) was refluxed in an atmosphere of dry nitrogen, using a water separator, for 68 hr. Evaporation of the solvents provided an oily residue which was subjected to silica gel chromatography (150 g, elution with 10% MeOH in $CHCl_3$). 4a-*Allyl*-7,7-*ethylenedioxy*-2-*oxo*-*decahydroquinoline* (1.11 g, 91%) was obtained as colourless needles from benzene/light petroleum, m.p. 110–112°. (Found: C, 66.85; H, 8.4; N, 5.5. $C_{14}H_{21}NO_3$ requires: C, 66.9; H, 8.4; N, 5.6%); ν_{max} (Nujol) 3190 (NH), 1660 (amide carbonyl), 1110 (C–O) cm^{-1}, τ (in $CDCl_3$) 3.20 (1H, bs, exchanges with D_2O, N–H), 4.0–5.1 (3H, m, olefinic protons), 6.05 (2H, s, $-O-CH_2-CH_2-O-$), 6.08 (2H, s, $-O-CH_2-CH_2-O-$), 6.2–7.0 (1H, m, CH–N), 7.4–8.8 (12H, m). TLC analysis and the presence of two signals for the ethylenedioxy group indicated the crystalline solid to be an approximately 1:1 mixture of two isomers.

In larger scale procedures, very careful column chromatography on Silica gel M.F.C. and elution with 5% MeOH in $CHCl_3$ yielded, in the first band, 4a-*allyl*-7,7-*ethylenedioxy*-2-*oxo*-trans-*decahydroquinoline* **17** (45%), m.p. 162–163°, recrystallised from benzene/light petroleum. (Found: C, 67.0; H, 8.3; N, 5.5. $C_{14}N_{21}NO_3$ requires: C, 66.9; H, 8.4; N, 5.6%); ν_{max} (Nujol) 3190 (NH), 1660 (amide carbonyl), 1110 (C–O) cm^{-1}, τ (in $CDCl_3$) 2.9 (1H, bs, exchanges with D_2O, NH), 3.9–4.5 (1H, m, $-CH$=CH_2), 4.7–5.1 (2H, m, $-CH$=CH_2), 6.05 (4H, s, $-O-CH_2-CH_2-O-$), 6.53 (1H, bt, J = 9 Hz, $-CH_2-CH$–N, *trans* proton at ring junction), 7.45–9.0 (12H, m), followed by 4a-*allyl*-7,7-*ethylenedioxy*-2-*oxo*-cis-*decahydroquinoline* **16** (46%), m.p. 126.5–127.5°, recrystallised from benzene/light petroleum (Found: C, 66.90; H, 8.4; N, 5.9); ν_{max} (Nujol) 3190 (NH), 1660 (amide carbonyl), 1110 (C–O) cm^{-1}, τ (in $CDCl_3$) 2.85 (1H, bs, exchanges with D_2O, N–H), 3.8–4.5 (1H, m, $-CH$=CH_2), 4.7–5.2 (2H, m, $-CH$=CH_2), 6.08 (4H, s, $-O-CH_2-CH_2-O-$), 6.35–6.90 (1H, m, CH_2-CH–N, *cis* proton at ring junction), 7.4–8.9 (12H, m).

4a-*Allyl*-7,7-*ethylenedioxy*-cis-*decahydroquinoline* **18**

A solution of 4a-allyl-7,7-ethylenedioxy-2-oxo-*cis*-decahydroquinoline (810 mg) in dry THF (25 ml) was slowly added to a suspension of $LiAlH_4$ (820 mg) in dry THF (25 ml) while stirring under nitrogen. The mixture was refluxed for 21 hr, allowed to cool and then the excess of $LiAlH_4$ was destroyed by addition of water (2 ml). The precipitate was removed by filtration and washed well with THF and ether. The filtrates were combined and evaporated to give 4a-*allyl*-7,7-*ethylenedioxy*-cis-*decahydroquinoline* (645 mg, 85%), as white needle-shaped crystals from chloroform, m.p. 170–174°, which then resolidified to remelt at 194–194.5°. (Found: C, 70.9; H, 9.65; N, 5.90. $C_{14}H_{23}NO_2$ requires: C, 70.75, H, 9.75; N, 5.90%); ν_{max} (Nujol) 3420 broad (N–H), 1640 weak (double bond), 1110 (C–O, ketal) cm^{-1}, τ (in $CDCl_3$) 3.75–4.45 (1H, m, $-CH$=CH_2), 4.7–5.2 (2H, m, $-CH$=CH_2), 6.00 (4H, s, $-O-CH_2-CH_2-O-$), 6.7–8.9 (16H, m, decreases to 15H with D_2O, N–H), *m/e* (%) 237 (13), 195 (100), 194 (48), 123 (74), 122 (61), 109 (74), 99 (95).

4a-*Allyl*-7,7-*ethylenedioxy*-trans-*decahydroquinoline* **19**

4a-Allyl-7,7-ethylenedioxy-2-oxo-*trans*-decahydroquinoline (1.00 g) was treated under the same conditions as in the previous paragraph except that boiling under reflux took place during 40 hr. Colourless crystals of 4a-*allyl*-7,7-*ethylenedioxy*-trans-*decahydroquinoline* (850 mg, 90%) were obtained from benzene/ether, m.p. 180–182°, which then resolidified to produce needle-shaped crystals which remelted at 235–237°. (Found: C, 70.8; H, 9.5; N, 5.7. $C_{14}H_{23}NO_2$ requires: C, 70.75; H, 9.75; N, 5.9%), ν_{max} (film) 3325 broad (N–H), 1640 weak (double bond), 1090 (C–O, ketal) cm^{-1}, τ (in $CDCl_3$) 3.8–4.6 (1H, m, $-CH$=CH_2), 4.75–5.20 (2H, m, $-CH$=CH_2), 6.04 (4H, s, $-O-CH_2-CH_2-O-$), 6.75–9.20 (16H, m, decreasing to 15H with D_2O, N–H), *m/e* (%) 237 (20), 195 (100), 194 (55), 123 (72), 122 (60), 109 (70), 99 (95).

4a-*Allyl*-7-*oxo*-cis-*decahydroquinoline* **12**

4a-Allyl-7,7-ethylenedioxy-*cis*-decahydroquinoline (224 mg) was dissolved in absolute EtOH (10 ml) and dil. HCl (8 ml) was added. This solution was heated at 80° for 1.5 hr, allowed to cool and then neutralised by additon of $NaHCO_3$ solution. Extraction with $CHCl_3$ followed by combination of the organic extracts, drying and evaporation *in vacuo* afforded a pale yellow oil (150 mg, 82%) which decomposed on attempted distillation. Purification by PLC (kieselgel; eluted with $CHCl_3$ (90%), MeOH (9%), conc. NH_3 (1%) produced an analytical sample of 4a-*allyl*-7-*oxo*-cis-*decahydroquinoline*. (Found: M$^+$, 193.14642. $C_{12}H_{19}NO$ requires: 193.14666); ν_{max} (film) 3320 broad (N–H), 1710 (ketone carbonyl), 1635 weak (double bond) cm^{-1}, τ (in $CDCl_3$) 3.65–4.45 (1H, m, $-CH$=CH_2), 4.65–5.15 (2H, m, $-CH$=CH_2), 6.70 (1H, bs, exchanges with D_2O, N–H), 6.8–9.2 (15H, m), *m/e* (%) 193 (2), 177 (21), 151 (25), 136 (50), 135 (11), 134 (17), 121 (22), 93 (10), 91 (30), 85 (70), 83 (100).

4a-*Allyl*-7-*oxo*-trans-*decahydroquinoline* **20**

4a-Allyl-7,7-ethylenedioxy-*trans*-decahydroquinoline (332 mg) was treated as above to give a colourless oil (256 mg, 95%) which also decomposed on attempted distillation. Preparative TLC as above afforded an analytical sample of 4a-*allyl*-7-*oxo*-trans-*decahydroquinoline*. (Found: M$^+$, 193.14601. $C_{12}H_{19}NO$ requires 193.14666); ν_{max} 3320 broad (N–H), 1710 (ketone carbonyl) 1640 weak (double bond) cm^{-1} τ (in $CDCl_3$) 3.7–4.5 (1H, m, $-CH$=CH_2), 4.6–5.1 (2H, m, $-CH$=CH_2), 6.75 (1H, bs, exchanges with D_2O, N–H), 6.8–9.4 (15H, m), *m/e* (%) 193 (3), 177 (20), 151 (26), 136 (50), 135 (19), 134 (22), 121 (20), 93 (13), 91 (25), 85 (86), 83 (100).

6-*Allyl*-6-*cyanoethyl*-3-*isobutoxy*-*cyclohexenone* **22**

6-Allyl-3-isobutoxy-cycloxenone (4.16 g)* was dissolved in t-butanol (30 ml) and a 40% aq. solution of "Triton B" (0.5 g) was added with stirring under nitrogen. This solution was then cooled in ice and after 20 mins acrylonitrile (2.1 g) in t-butanol (10 ml) was added. The mixture was then allowed to warm up to room temperature and was stirred for 20 hr. It was then boiled under reflux for 2 hr, allowed to cool and then the solvent removed *in vacuo*. The residue was partitioned between $CHCl_3$ and water and the organic layer evaporated to provide a brown oil. The oil was chromatographed on a silica gel column (300 g, elution with 8% ethyl acetate in benzene) to afford as the first band a mixture of the starting material and the required product. Immediately after this came a band of pure 6-*allyl*-6-*cyanoethyl*-3-*isobutoxy*-*cyclohexenone*. Rechromatography of the first band gave a total yield of product of 1.323 g, 26% (total yield based on recovered starting material was 53%). The product, a very pale yellow oil, was redistilled to provide an analytical sample as a colourless oil, b.p. 150–153°. (Found: C, 73.8; H, 9.0; N, 5.1. $C_{16}H_{25}NO_2$ requires: C, 73.55; H, 8.85; N, 5.3%); ν_{max} (film) 2245 (–CN), 1650 (enone carbonyl), 1610 (enone double bond), 1240, 1190 (C–O, ether) cm^{-1}, τ (in $CDCl_3$) 4.0–4.7 (1H, m, $-CH$=CH_2), 4.7–5.2 (3H, m, $-CH$=CH_2 + enone H), 6.4 (2H, d, J = 7 Hz, $CH-CH_2-O$), 7.4–8.4 (11H, m), 9.02 (6H, d, J = 7 Hz, $(CH_3)_2CH$–), λ_{max} (*e*) 252 (15,000) nm, *m/e* (%) 261 (5), 233 (5), 221 (9), 209 (15), 208 (100), 207 (10), 206 (20), 205 (10), 177 (15), 165 (30), 152 (80), 125 (15).

*^{13}C NMR spectrum (figures refer to a downfield shift from TMS in p.p.m.) 200.77 (s, C-1), 176.26 (s, C-3), 120.08 (s, C-12), 118.98 (t, C-9), 101.68 (d, C-2), 132.96 (d, C-8), 74.96 (t, C-13), 45.77 (s, C-6), 39.07 (t, C-7), 30.68 (t, C-10), 29.19 (t, C-5), 27.76 (d, C-14), 25.55 (t, C-4), 19.05 (q, 2C-15), 12.28 (t, C-11).

6-*Allyl*-6-(3-*aminopropyl*)-3-*isobutoxycyclohexenol* **24**

6-Allyl-6-cyanoethyl-3-isobutoxy-cyclohexenone (690 mg) was dissolved in dry THF (30 ml) and the solution was slowly added to a suspension of $LiAlH_4$ (300 mg) in dry THF (40 ml) with

stirring in an atmosphere of dry nitrogen. The mixture was boiled under reflux for 2 hr, then cooled and the excess of $LiAlH_4$ was destroyed by addition of wet tetrahydrofuran. The solution was filtered and the precipitate washed well with ether. The filtrate was dried and evaporated to give a pale yellow oil (635 mg, 90%) of 6-*allyl*-6-(3-*aminopropyl*)-3-*isobutoxycyclohexenol* (decomp. on distillation). (Found: M⁺, 267.31962. $C_{16}H_{29}NO_2$ requires: M⁺ 267.219817); ν_{max} ($CHCl_3$) 3600 (O–H, unbonded), 3380 (N–H), ν_{max} (film) 3600–3100 broad (NH, OH hydrogen bonded), 1660 (enol double bond), 1640 weak (double bond), 1195 (C–O, ether) cm⁻¹, τ (in $CDCl_3$) 3.9–4.7 (1H, m, $-CH{=}CH_2$), 4.85 (1H, bs, enone H), 5.0–5.5 (2H, m, $-CH{=}CH_2$), 6.0–6.5 (2H, m, CH_2–NH_2), 6.55 (2H, d, J = 6 Hz, CH–CH_2–O), 7.2–9.1 (15H, m, 3H exchange with D_2O, OH + NH_2), 9.10 (6H, d, J = 6 Hz, $(CH_3)_2$–CH), *m/e* (%) 267 (1), 249 (14), 248 (15), 208 (56), 207 (84), 206 (32), 193 (51), 192 (100), 177 (20), 176 (34), 164 (25), 152 (57), 151 (100), 150 (100), 137 (52), 136 (80), 135 (50), 134 (57).

Cyclisation of 6-*allyl*-6-(3-*aminopropyl*)-3-*isobutoxycyclohexenol*

6-Allyl-6-(3-aminopropyl)-3-isobutoxycyclohexenol (630 mg) was dissolved in EtOH (10 ml) and dil. HCl (35 ml) was added. This mixture was stirred at room temperature for 1 hr and then neutralised with $NaHCO_3$ solution. Exaction with $CHCl_3$, drying and evaporation of the organic extract, provided a pale yellow oil (280 mg, 55%), which was shown to be identical (IR, NMR spectra and TLC behaviour) with 4a-allyl-7-oxo-*cis*-decahydroquinoline prepared by the previous route. (Found: M⁺, 193.14639. $C_{12}H_{19}NO$ requires: M⁺, 193.14666).

1-*Chloroacetyl*-4a-*allyl*-7,7-*ethylenedioxy*-cis-*decahydroquinoline* **25**

A solution of 4a-allyl-7,7-ethylenedioxy-*cis*-decahydroquinoline (2.33 g) in $CHCl_3$ (70 ml) was cooled in an ice-bath. A solution of chloroacetyl chloride (1.70 g) in $CHCl_3$ (40 ml) was added simultaneously with dil. NaOH solution (20 ml) during 30 mins. The mixture was stirred for 3 hr at 0° and then the $CHCl_3$ layer was separated and washed successively with dil. HCl, dil. $NaHCO_3$ solution and brine. The $CHCl_3$ layer was then dried and evaporated *in vacuo* to leave a yellow oil which crystallised from ether as white, fluffy, needle-shaped crystals (2.65 g, 87%), m.p. 124–125°, of 1-*chloroacetyl*-4a-*allyl*-7,7-*ethylenedioxy*-cis-*decahydroquinoline*. (Found: C, 61.1; H, 7.65; N, 4.6; Cl, 11.6. $C_{16}H_{24}NO_3Cl$ requires: C, 61.3; H, 7.7; N, 4.45; Cl, 11.35%); ν_{max} (Nujol) 1650 (amide carbonyl), 1095 (C–O, ketal), 790 (C–Cl) cm⁻¹, τ (in $CDCl_3$) 3.8–4.6 (1H, m, $-CH{=}CH_2$), 4.75–5.20 (2H, m, $-CH{=}CH_2$), 5.2–5.7 (1H, m, CH–N, ring junction), 5.90 (2H, s, Cl–CH_2–C=O), 6.03 (4H, s, –O–CH_2–CH_2–O), 6.1–7.0 (2H, m, N–CH_2), 7.1–8.9 (12H, m), *m/e* (%) 315 (2), 313 (5), 278 (46), 192 (19), 134 (13), 122 (18), 99 (100).

1-*Chloracetyl*-4a-*allyl*-7,7-*ethylenedioxy*-trans-*decahydroquinoline* **26**

4a-Allyl-7,7-ethylenedioxy-*trans*-decahydroquinoline (1.28 g) was treated as above to produce 1-*chloroacetyl*-4a-*allyl*-7,7-*ethylenedioxy*-trans-*decahydroquinoline* (1.70 g, 99%) as colourless crystals from ether, m.p. 80–81° (Found: C, 61.3; H, 7.65; N, 4.55; Cl, 11.55. $C_{16}H_{24}NO_3Cl$ requires: C, 61.3; H, 7.7; N, 4.45; Cl, 11.35%); ν_{max} (Nujol) 1665 (amide carbonyl), 1105 (C–O, ketal), 790 (C–Cl) cm⁻¹, τ (in $CDCl_3$) 3.9–4.6 (1H, m, $-CH{=}CH_2$), 4.8–5.2 (2H, m, $-CH{=}CH_2$), 5.97 (2H, s, Cl–CH_2–CO), 6.04 (4H, s, O–CH_2–CH_2–O), 5.7–7.3 (3H, m, CH–N–CH_2), 7.3–9.0 (12H, m), *m/e* (%) 315 (2), 313 (4), 278 (21), 192 (14), 134 (11), 122 (10), 99 (100).

1-*Chloroacetyl*-4a-*allyl*-7-*oxo*-cis-*decahydroquinoline* **27**

A solution of 1-chloroacetyl-4a-allyl-7,7-ethylenedioxy-*cis*-decahydroquinoline (2.66 g) in absolute EtOH (45 ml) was stirred together with dil. HCl (100 ml) at 80° for 2 hr. The mixture was allowed to cool and thoroughly extracted with $CHCl_3$. The organic extracts were washed with dil. $NaHCO_3$ solution followed by brine, then dried and evaporated *in vacuo* to afford a yellow gum (2.16 g, 95%) which could not be crystallised. Preparative TLC (elution with $CHCl_3$ containing 2% MeOH) provided an analytical sample of 1-*chloroacetyl*-4a-*allyl*-7-*oxo*-cis-*decahydroquinoline*. (Found: M⁺, 269.117953, $C_{14}H_{20}NO_2{}^{35}Cl$ requires 269.118248; Found: M⁺, 271.115015, $C_{14}H_{20}NO_2{}^{37}Cl$ requires 271.115298), ν_{max} 1720 (ketone carbonyl), 1650 (amide carbonyl), 790 (C–Cl) cm⁻¹, τ (in $CDCl_3$) 3.9–4.6 (1H, m, $-CH{=}CH_2$), 4.7–5.2 (2H, m, $-CH{=}CH_2$), 5.3–7.1 (3H, diffuse m, $-CH_2$–N–CH), 7.1–9.1 (12H, m), 5.9 (2H, s, $-CH_2Cl$), *m/e* (%) 271 (3), 269 (6), 234 (100), 228 (30), 192 (50), 152 (45), 135 (25), 122 (27), 96 (30).

1-*Chloroacetyl*-4a-*allyl*-7-*oxo*-trans-*decahydroquinoline* **28**

1-Chloroacetyl-4a-allyl-7,7-ethylenedioxy-*trans*-decahydroquinoline (1.44 g) was treated as above to produce long, needle-shaped crystals of 1-*chloroacetyl*-4a-allyl-7-*oxo*-trans-*decahydroquinoline* (1.15 g, 93%), m.p. 135–136°. (Found: C, 62.45; H, 7.45; N, 5.25; Cl, 13.6. $C_{14}H_{20}NO_2Cl$ requires: C, 62.3; H, 7.4; N, 5.2; Cl, 13.25%); ν_{max} 1710 (ketone carbonyl), 1670 (amide carbonyl), 1635 (double bond), 790 weak (C–Cl) cm⁻¹, τ (in $CDCl_3$) 3.8–4.5 (1H, m, $-CH{=}CH_2$), 4.6–5.1 (2H, m, $-CH{=}CH_2$), 5.90 (2H, s, $-CH_2Cl$), 5.6–6.3 (2H, m, $-CH_2$–N), 6.6–9.3 (13H, m), *m/e* (%) 271 (2), 269 (5), 234 (60), 206 (42), 192 (46), 152 (32), 151 (39), 136 (32), 122 (57), 96 (100).

6a-*Allyl*-2,9-*dioxo*-cis *A/B*, cis *A/C*-*decahydro*-4H-*pyrrolo* [3,2,1-ij] *quinoline* **29**

A solution of 1-chloroacetyl-4a-allyl-7-oxo-*cis*-decahydroquinoline (1.70 g) in a 1:1 mixture of benzene and t-butanol (60 ml) was slowly added with stirring to a solution of potassium t-butoxide prepared by dissolving potassium (350 mg) in t-butanol (20 ml). The mixture was stirred at room temp., under dry nitrogen, for 19 hr and then heated to 50° for 1 hr. After the mixture had cooled it was neutralised with dil. HCl and then evaporated to dryness. The residue was partitioned between water and $CHCl_3$ and the aqueous layer extracted numerous times with $CHCl_3$. The organic layers were combined, dried and evaporated *in vacuo* to furnish a yellow oil. Chromatography of this oil on Kieselgel (130 g, elution with 2% MeOH in $CHCl_3$) provided 6a-*allyl*-2,9-*dioxo*-cis-A/B, cis A/C-*decahydro*-4H-*pyrrolo* [3,2,1-ij] *quinoline* (660 mg, 64% based on material consumed) as colourless plates, m.p. 127.5–129° from benzene/ether. (Found: C, 71.7; H, 8.05; N, 6.05. $C_{14}H_{19}NO_2$ requires: C, 72.0; H, 8.10; N, 6.0%); ν_{max} (Nujol) 1710 (ketone carbonyl), 1685 (lactam carbonyl), 1640 weak (double bond) cm⁻¹, τ (in $CDCl_3$) 3.65–4.35 (1H, m, $-CH{=}CH_2$), 4.55–5.0 (2H, M, $-CH{=}CH_2$), 6.00 (1H, broadened doublet, J_{AD} = 13 Hz, H_A), 6.47 (1H, d of d, J_{BC} = 6.5 Hz and J_{BX} = 1.5 Hz, H_B), 6.85–7.28 (2H, m, H_C), 7.3–9.0 (12H, m), *m/e* (%) 233 (7), 204 (20), 192 (89), 191 (100), 190 (89), 176 (72), 163 (49), 162 (38), 150 (42), 149 (100), 148 (29), 138 (40), 135 (61), 121 (28), 120 (29).

It should be noted that a small amount of starting material (300 mg) was also recovered from the column.

6a-*Allyl*-2,9-*dioxo*-trans A/B, cis A/C-*decahydro*-4H-*pyrrolo* [3, 2, 1-ij] *quinoline* **32**

1-Chloroacetyl-4a-allyl-7-oxo-*trans*-decahydroquinoline (1.00 g) was treated as above, except that heating for 2 hr took place. The product was chromatographed on a kieselgel column (60 g, elution with $CHCl_3$/AcOEt/MeOH, 90: 10:2) to afford 6a-*allyl*-2,9-*dioxo*-trans A/B, cis A/C- *decahydro*-4H-*pyrrolo* [3,2,1-ij] *quinoline* (555 mg, 67% based on material consumed) as colourless crystals, m.p. 124–125°, from benzene/ether. (Found: C, 71.9; H, 7.95; N, 5.95. $C_{14}H_{19}NO_2$ requires: C, 72.0; H, 8.10; N, 6.0%); ν_{max} (Nujol) 1700 (ketone carbonyl), 1670 (amide carbonyl), 1640 weak (double bond) cm⁻¹, τ (in $CDCl_3$) 3.9–4.7 (1H, m, $-CH{=}CH_2$), 4.7–5.2 (2H, m, $-CH{=}CH_2$), 5.75 (1H, d of d, J_{AD} = 13 Hz, J_{AO} – J_{AX} = 5 Hz, H_A), 6.22 (1H, doublet, J_{BC} = 9.5 Hz, H_B), 6.83 (1H, q, J_{CB} = J_{CF} = J_{CF} = 9.5 Hz, H_C), 7.25 (1H, m, H_D), 7.3–9.2 (12H, m), *m/e* (%) 233 (32), 205 (30), 191 (25), 190 (14), 176 (15), 163 (36), 162 (12), 150 (11), 149 (44), 138 (23), 135 (15), 121 (17), 120 (10).

A small amount of starting material (100 mg) was recovered from the column.

6a-*Allyl*-9,9-*ethylenedioxy*-2-*oxo*-cis A/B, cis A/C-*decahydro*-4H-*pyrrolo* [3,2,1-ij] *quinoline* **36**

6a-Allyl-2,9-dioxo-*cis* A/B, *cis* A/C-decahydro-4H-pyrrolo [3,

2,1-ij] quinoline (1.55 g) was dissolved in dry benzene (160 ml) and after addition of ethylene glycol (1.5 g) and toluene-*p*-sulphonic acid (30 mg) the mixture was boiled under a Dean–Stark apparatus for 24 hr. The solvent was then removed *in vacuo* and the residue taken up in $CHCl_3$. The solution was washed with dil. $NaHCO_3$ solution and brine, and then dried and evaporated to provide 6a-*allyl*-9,9-*ethylenedioxy*-2-*oxo*-cis A/B, cis A/C-*decahydro*-4H-*pyrrolo* [3,2,1-ij] *quinoline* (1.74 g, 95%) as a pale yellow gum.

Further purification using a silica gel column (200 g, eluted with $CHCl_3$ 80, AcOEt 20, and MeOH 2) produced colourless crystals from $CHCl_3$/light petroleum (1:3), m.p. 100.5–101.5°. (Found: C, 69.6; H, 8.05; N, 5.05. $C_{16}H_{23}NO_3$ requires: C, 69.3; H, 8.3; N, 5.1%); ν_{max} (Nujol) 1695 (lactam carbonyl), 1640 weak (double bond), 1095 (C–O, ketal) cm^{-1}, τ (in $CDCl_3$), 3.75–4.50 (1H, m, $-CH{=}CH_2$), 3.7–5.2 (2H, m, $-CH{=}CH_2$), 6.02 (4H, s, $-O-CH_2-CH_2-O-$), 5.95 (1H, broad d, J_{AD} = 13 Hz, H_A), 6.81 (1H, dd, J_{BC} = 5.5 Hz and J_{BX} 1 Hz, H_B), 7.9–9.1 (14H, m), *m/e* (%) 277 (20), 247 (20), 236 (94), 235 (100), 234 (98), 220 (37), 218 (57), 205 (27), 190 (21), 163 (15), 150 (48), 149 (100), 99 (100).

6a-*Allyl*-9,9-*ethylenedioxy*-2-*oxo*-trans A/B, cis A/C-*decahydro*-4H-*pyrrolo* [3,2,1-ij] *quinoline* **37**

6a-Allyl-2,9-dioxo-*trans* A/B, *cis* A/C-decahydro-4H-pyrrolo [3,2,1-ij] quinoline (500 mg) was treated as above except that boiling under reflux took place over 40 hr. The product was chromatographed on a kieselgel G column (50 g, eluted with 3% MeOH in $CHCl_3$) to give colourless crystals, m.p. 96–98° (from ether), of 6a-*allyl*-9,9-*ethylenedioxy*-2-*oxo*-trans A/B, cis A/C-*decahydro*-4H-*pyrrolo* [3,2,1-ij] *quinoline*. (Found: C, 68.95; H, 8.1; N, 4.9. $C_{16}H_{23}NO_3$ requires: C, 69.3; H, 8.3; N, 5.1%); ν_{max} (Nujol) 1690 (lactam carbonyl), 1640 weak (double bond), 1095 (C–O, ketal) cm^{-1}, τ (in $CDCl_3$) 3.8–4.6 (1H, m, $-CH{=}CH_2$), 4.7–5.2 (2H, m, $-CH{=}CH_2$), 6.05 (4H, s, $-O-CH_2-CH_2-O-$), 6.9–9.1 (14H, m), 6.65 (1H, d, J = 8.5 Hz, H_B), 5.7 (1H, m, H_A), *m/e* (%) 277 (53), 235 (68), 234 (42), 232 (53), 190 (30), 177 (73), 176 (39), 150 (43), 149 (100), 108 (63), 99 (100).

6a-*Allyl*-9,9-*ethylenedioxy*-cis A/B, cis A/C-*decahydro*-4H-*pyrrolo* [3,2,1-ij]-*quinoline* **38**

A solution of 6a-allyl-9,9-ethylenedioxy-2-oxo-*cis* A/B, *cis* A/C-decahydro-4H-pyrrolo [3,2,1-ij] quinoline (1.64 g) in dry THF (40 ml) was slowly added to a suspension of $LiAlH_4$ (1.6 g) in dry THF (60 ml) with stirring under dry nitrogen. This mixture was boiled under reflux for 24 hr, allowed to cool, and the excess of $LiAlH_4$ destroyed by additon of wet THF. The suspension was filtered and the residue washed well with ether. The organic filtrates were then dried and evaporated *in vacuo* to afford a pale yellow oil. Distillation of the oil produced 6a-*allyl*-9,9-*ethylenedioxy*-cis A/B, cis A/C-*decahydro*-4H-*pyrrolo* [3,2,1-ij] *quinoline* as a colourless oil b.p. 215–220°/0.015 mm, (1.38 g, 89%). (Found: M$^+$, 263.188539. $C_{16}H_{25}NO_2$ requires: M$^+$, 263.188518); ν_{max} (film) 2780, 2720, 2670 (Bohlmann bands), 1640 weak (double bond), 1090 (C–O, ketal) cm^{-1}, τ (in $CDCl_3$) 3.75–4.50 (1H, m, $-CH{=}CH_2$), 4.7–5.2 (2H, m, $-CH{=}CH_2$), 6.05 (4H, s, $-O-CH_2-CH_2-O-$), 6.6–7.2 (2H, m, H_B and H_C), 7.3–9.2 (16H, m), *m/e* (%) 263 (9), 262 (7), 222 (25), 221 (100), 220 (58), 204 (26), 136 (19), 135 (63), 99 (46)

6a-*Allyl*-9,9-*ethylenedioxy*-trans A/B, cis A/C-*decahydro*-4H-*pyrrolo* [3,2,1-ij]-*quinoline* **39**

6a-Allyl-9,9-ethylenedioxy-2-oxo-*trans* A/B, *cis* A/C-decahydro-4H-pyrrolo [3,2,1-*ij*] quinoline (380 mg) was treated as above to produce 6a-*allyl*-9,9-*ethylenedioxy*-trans A/B, cis A/C-*decahydro*-4H-*pyrrolo* [3,2,1-ij] *quinoline* (320 mg, 88%) as a colourless gum which decomposed on attempted distillation. (Found: M$^+$, 263.188772. $C_{16}H_{25}NO_2$ requires: M$^+$, 263.188518); ν_{max} (film) 1640 weak (double bond), 1090 (C–O, ketal) cm^{-1}, τ (in $CDCl_3$) 3.8–4.5 (1H, m, $-CH{=}CH_2$), 3.7–5.2 (2H, m, $-CH{=}CH_2$), 6.00 (4H, s, $-O-CH_2-CH_2-O-$), 6.6–7.2 (2H, m, H_B and H_C), 7.2–9.2 (16H, m), *m/e* (%) 263 (10), 262 (10), 221 (18), 220 (12), 136 (21), 135 (19), 102 (100), 99 (65).

6a-*Allyl*-9-*oxo*-cis A/B, cis A/C-*decahydro*-4H-*pyrrolo* [3,2,1-ij] *quinoline* **40**.

6a-Allyl-9,9-ethylenedioxy-*cis* A/B, *cis* A/C-dehydro-4H-pyrrolo [3,2,1-*ij*] quinoline (1.34 g) was dissolved in EtOH (20 ml) and dil. HCl (50 ml) was added with stirring. The mixture was heated at 90° for 1 hr, cooled and then neutralised by the addition of solid $NaHCO_3$. Extraction with $CHCl_3$ was followed by drying and evaporation to afford a yellow oil (1.10 g, 99%). Further distillation gave 6a-*allyl*-9-*oxo*-cis A/B, cis A/C-*decahydro*-4H-*pyrrolo* [3,2,1-ij] *quinoline* as a colourless gum. (Found: M$^+$, 219.162341. $C_{14}H_{21}NO$ requires: M$^+$, 219.162306); ν_{max} (film) 2790, 2720, 2680 (Bohlmann bands), 1710 (ketone carbonyl), 1640 weak (double bond) cm^{-1}; τ (in $CDCl_3$) 3.7–4.4 (1H, m, $-CH{=}CH_2$), 4.7–5.1 (2H, m, $-CH{=}CH_2$), 6.8–7.2 (2H, m, H_B + H_C), 7.2–9.1 (16H, m), *m/e* (%) 219 (10), 218 (12), 190 (18), 178 (49), 177 (100), 176 (64), 162 (20), 149 (20), 135 (57), 134 (25).

6a-*Allyl*-9-*oxo*-trans A/B, trans A/C-*decahydro*-4H-*pyrrolo* [3,2,1-ij] *quinoline* **41**

6a-Allyl-9,9-ethylenedioxy-*trans* A/B, cis A/C-decahydro-4H-pyrrolo [3,2,1-ij] quinoline (320 mg) was treated as above to afford a yellow oil. Purification of this oil on a kieselgel G column (eluted with 3% MeOH in $CHCl_3$) produced a pure sample of 6a-*allyl*-9-*oxo*-trans A/B, trans A/C-*decahydro*-4H-*pyrrolo* [3,2,1-ij] *quinoline* (220 mg, 82%) as a colourless gum. (Found: M$^+$, 219.162371. $C_{14}H_{21}NO$ requires: M$^+$, 219.162306); ν_{max} (film) 2800, 2720 (Bohlmann bands), 1720 (ketone carbonyl), 1640 weak (double bond) cm^{-1}, τ (in $CDCl_3$) 3.7–4.45 (1H, m, $-CH{=}CH_2$), 4.6–5.1 (2H, m, $-CH{=}CH_2$), 6.6–7.0 (1H, m, H_C), 6.85 (1H, d, J = 9.5 Hz, H_B), 7.0–9.5 (16H, m), *m/e* (%) 219 (38), 218 (69), 178 (16), 177 (100), 176 (40), 174 (20), 162 (14), 149 (13), 135 (14), 134 (13).

The o-*methoxyphenylhydrazone of* 6a-*allyl*-9-*oxo*-cis A/B, cis A/C-*decahydro*-4H-*pyrrolo* [3,2,1-ij] *quinoline*

6a-Allyl-9-oxo-*cis* A/B, *cis* A/C-decahydro-4H-pyrrolo [3,2,1-ij] quinoline (1.10 g) was dissolved in EtOH (60 ml) and *o*-methoxyphenylhydrazine hydrochloride (960 mg) and anhydrous sodium carbonate (300 mg) were added. The mixture was boiled under reflux, in an atmosphere of dry nitrogen, for 1 hr and then allowed to cool. Evaporation under reduced pressure was followed by addition of benzene and EtOH and re-evaporation to remove water. The residue was dissolved in benzene/ethyl acetate (1:1) and this solution filtered through a short plug of alumina. The filtrate was evaporated to provide the o-*methoxyphenylhydrazone* of 6a-*allyl*-9-*oxo*-cis A/B, cis A/C-*decahydro*-4H-*pyrrolo* [3,2,1-ij] *quinoline* (1.66 g, 98%) as a red gum. (Found: M$^+$, 339.230256. $C_{21}H_{29}N_3O$ requires: M$^+$, 339.231051); ν_{max} (film) 3380 (N–H), 2780, 2720, 2670 (Bohlmann bands), 1640 weak (double bond), 1600 (C=N) cm^{-1}, τ (in $CDCl_3$) 2.48 (1H, bs, exchanges with D_2O, N–H), 2.85–3.30 (4H, m, aromatic H), 3.8–4.5 (1H, m, $-CH{=}CH_2$), 4.7–5.2 (2H, m, $-CH{=}CH_2$), 6.15 (3H, s, –OMe), 6.7–9.1 (18H, m), λ_{max} (ϵ) (in ethanol) 212 (10,200), 270 (9800), 303 (8100) nm, (in 2NHCl) 213 (9900), 223 (inflection, 9500), 273 (8900), 304 (8000) nm, *m/e* (%) 339 (12), 221 (12), 220 (20), 218 (25), 217 (100), 192 (28), 177 (22), 122 (80), 107 (74).

The o-*methoxyphenylhydrazone of* 6a-*allyl*-9-*oxo*-trans A/B, trans A/C-*decahydro*-4H-*pyrrolo* [3,2,1-ij] *quinoline* **43**

6a-Allyl-9-oxo-*trans* A/B, *trans* A/C-decahydro-4H-pyrrolo [3,2,1-ij] quinoline (155 mg), *o*-methoxyphenylhydrazine hydrochloride (150 mg) and anhydrous sodium carbonate (45 mg) were dissolved in EtOH and boiled under reflux for 1 hr. The solution was then cooled and long needle-shaped crystals appeared, which were collected and recrystallised from EtOH to afford the o-*methoxyphenylhydrazone* of 6a-*allyl*-9-*oxo*-trans A/B, trans A/C-*decahydro*-4H-*pyrrolo* [3,2,1-ij] *quinoline* as white needle-shaped crystals (170 mg, 70%), m.p. 163–165°. (Found: C, 74.85; H, 8.35; N, 12.1. $C_{21}H_{29}N_3O$ requires: C, 74.5; H, 8.55; N, 12.4%); ν_{max} ($CHCl_3$) 3380 (N–H), 2800 (Bohlmann band), 1640 weak (double bond), 1600 (C=N) cm^{-1}, τ (in $CDCl_3$) 2.45 (1H, bs, exchanges with D_2O, N–H), 2.8–3.3 (4H, m, aromatic H), 3.8–4.5 (1H, m, $-CH{=}CH_2$), 4.6–5.2 (2H, m, $-CH{=}CH_2$), 6.14 (3H, s, –OMe), 6.6–9.4 (18H, m), λ_{max} (ϵ) (in

ethanol) 213 (9,300), 268 (7,620), 302 (5,650) nm, (in 2N HCl) 212 (8,700), 227 (inflection, 7,800), 273 (6,250), 305 (5,400) nm.

Further amounts of product could be obtained by evaporation of the filtrate produced on collection of the crystals formed from the original reaction mixture (approximately 25 mg, 10%).

20-Allyl-20-desethyldeacetylaspidospermine

The *o*-methoxyphenylhydrazone of 6a-allyl-9-oxo-*cis* A/B, *cis* A/C-decahydro-4H-pyrrolo [3,2,1-ij] quinoline (1.65 g) was dissolved in glacial acetic acid and heated at 95° for 1 hr under dry nitrogen. The solvent was then evaporated *in vacuo* and the residue partitioned between dil. $NaHCO_3$ solution and CH_2Cl_2. The aqueous layer was further extracted with CH_2Cl_2 and the organic extracts were dried and evaporated to provide a brown oil. $\nu_{max.}$ ($CHCl_3$) 2800, 2720 (Bohlmann bands), 1595 (indolenine) cm^{-1}.

This brown oil was dissolved in dry THF (60 ml) and was slowly added to a suspension of $LiAlH_4$ (1.5 g) in dry THF (70 ml). The mixture was then boiled under reflux for 15 hr with stirring under an atmosphere of dry nitrogen. Cooling of the solution was followed by careful addition of wet THF to decompose the excess of $LiAlH_4$. The precipitate was filtered off and washed well with ether. The organic filtrates were combined, dried and evaporated to furnish a yellow oil. Purification of this oil on an alumina column (125 g, gradient elution with benzene (400 ml) and then 5% MeOH in benzene) provided, after recrystallisation from benzene, *20-allyl-20-desethyldeacetylaspidospermine* (1.41 g, 89%) as a pale brown powder, m.p. 93–95°. (Found: M⁺, 324.220089. $C_{21}H_{28}N_2O$ requires: M⁺, 324.220152); $\nu_{max.}$ (film) 3360 (N–H), 2780, 2720, 2680 (Bohlmann bands), 1640 weak (double bond), 1615, 1595 (indoline), τ (in $CDCl_3$) 3.1–3.5 (3H, m, aromatic H), 3.9–4.7 (1H, m, $-CH{=}CH_2$), 4.9–5.4 (2H, m, $-CH{=}CH_2$), 6.20 (3H, s, –OMe), 6.3–7.3 (4H, m, C-2 H, C-21 H, C-5 2H), 7.3–9.2 (15H, m), $\lambda_{max.}$ (ε) 216 (25,500), 246 (4,500), 290 (2,000) nm, *m/e* (%) 324 (20), 296 (5), 282 (19), 281 (18), 220 (31), 204 (27), 180 (20), 179 (94), 178 (54), 160 (26), 136 (100), 135 (42), 105 (60).

20-Allyl-20-desethylaspidospermine **42**

Acetic anhydride (430 mg) was added to a solution of 20-allyl-desethyldeacetylaspidospermine (380 mg) in pyridine (15 ml) and the mixture was stirred at room temp. for 14 hr. Evaporation of the solvent *in vacuo* left a brown residue which was taken up in $CHCl_3$ and washed successively with dil. HCl, dil. $NaHCO_3$ solution, brine, and then dried and evaporated. The solid product was recrystallised from hexane to afford colourless plates, m.p. 189.5–190°, of *20-allyl-20-desethylaspidospermine* (360 mg, 86%). (Found: C, 75.25; H, 8.35; N, 7.95. $C_{23}H_{30}N_2O_2$ requires: C, 75.5; H, 8.20; N, 7.70%); $\nu_{max.}$ (film) 2780, 2720 (Bohlmann bands), 1640 (amide carbonyl) cm^{-1}, τ (in $CDCl_3$) 2.6–3.3 (3H, m, aromatic H), 4.0–4.7 (1H, m, $-CH{=}CH_2$), 4.8–5.2 (2H, m, $-CH{=}CH_2$), 5.45 (1H, broad q, J ~ 6 Hz, "Aspidosperma fingerprint"[11] C-2 H), 6.1 (3H, s, –OMe), 6.6–7.1 (2H, m, C-5 2H), 7.6–9.2 (15H, m), 7.78 (3H, s, N–Ac), $\lambda_{max.}$ (ε) 218 (33,900), 256 (11,200), 290 sh (2,700) nm, *m/e* (%) 366 (15), 365 (3), 325 (30), 324 (60), 323 (55), 281 (25), 266 (15), 164 (25), 160 (27), 158 (30), 136 (100), 123 (30).

Fischer indole closure on the trans *A/B, trans A/C isomer*

(a) *Using glacial acetic acid.* The *o*-methoxyphenylhydrazone of 6a-allyl-9-oxo-*trans* A/B, *trans* A/C-decahydro-4H-pyrrolo [3,2,1-ij] quinoline (85 mg) was dissolved in glacial acetic acid (20 ml) and heated at 100° for 1.5 hr. The solvent was then evaporated *in vacuo* and the residue partitioned between CH_2Cl_2 and dil. $NaHCO_3$ solution. The organic layer was dried and evaporated to give a brown gum which indicated two products by TLC analysis (kieselgel G plate, eluted with 3% MeOH in $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 1595 (indolenine) cm^{-1}.

The brown gum was dissolved in dry THF (20 ml) and slowly added to a suspension of $LiAlH_4$ (150 mg) in dry THF (20 ml). The mixture was boiled under reflux in an atmosphere of dry nitrogen for 15 hr and then allowed to cool. Wet THF was then added to destroy the excess of $LiAlH_4$ and then the precipitate was filtered off and washed well with ether. The filtrate was evaporated and the residue taken up in dry benzene (20 ml) and stirred with acetic anhydride (100 mg) for 2 days. Removal of the solvents *in vacuo* afforded a brown gum which was purified by the use of a kieselgel G preparative plate (eluted twice with 2% MeOH in $CHCl_3$).

The top band (R_f approximately 0.6) was removed from the plate and washed with $CHCl_3$ to afford (±)-*20-allyl-20-desethyl-20-epiaspidospermine* as a colourless crystalline solid (15 mg, 16% based on the phenylhydrazone), m.p. 121–125°. (Found: M⁺, 366.23063. $C_{23}H_{30}N_2O_2$ requires: M⁺, 366.23072); $\nu_{max.}$ (film) 1640 (amide carbonyl) cm^{-1}, $\lambda_{max.}$ (ε) 222 (30,800), 254 (11,200), 290 sh (2,800) nm, τ (in $CDCl_3$) 2.8–3.2 (3H, m, aromatic H), 4.17–4.43 (1H, m, $-CH{=}CH_2$), 4.8–5.1 (2H, m, $-CH{=}CH_2$), 5.13 [1H, bt, J ~ 5.5 Hz, C-2 H (this proton appears as a quartet in the normal *cis* C/D isomer), 6.13 (3H, s, –OMe), 7.8 (3H, s, N–Ac), 6.5–9.2 (17H, m), *m/e* (%) 366 (11), 365 (10), 338 (8), 325 (8), 324 (18), 323 (17), 281 (8), 160 (10), 149 (16), 136 (52).

The lower band (R_f approximately 0.2) was removed and eluted with $CHCl_3$. Removal of the solvent and crystallisation of the residue from hexane afforded *20-allyl-20-desethylaspidospermine* (13 mg, 14% yield from the phenylhydrazone), identical in every respect with that prepared previously.

(b) *Using formic acid.* The *o*-methoxyphenylhydrazone of 6a-allyl-9-oxo-*trans* A/B, *trans* A/C-decahydro-4H-pyrrolo [3,2,1-ij] quinoline (75 mg) was dissolved in 99% formic acid (5 ml) and the mixture was boiled under reflux for 20 min. The solution was cooled and evaporated *in vacuo* to provide a red gum which was taken up in $CHCl_3$ and washed with dil. $NaHCO_3$ solution. The $CHCl_3$ extracts were dried and evaporated and the residue purified by chromatography on a preparative plate (kieselgel G, eluted twice with $CHCl_3$). This furnished (±)-*20-allyl-20-desethyl-20-epivallesine* **44** (20 mg, 24%) as a red gum. (Found: M⁺, 352.2145. $C_{22}H_{28}N_2O_2$ requires: M⁺, 352.2150); $\nu_{max.}$ (film) 2850 (C–H of CHO), 2780, 2715 (Bohlmann bands), 1650 (amide carbonyl) cm^{-1}; τ (in $CDCl_3$) 0.69 (1H, s, –CHO), 2.9–3.5 (3H, m, aromatic H), 4.2–4.5 (1H, m, $-CH{=}CH_2$) 4.8–5.1 (2H, m, $-CH{=}CH_2$), 5.2 (1H, bt, J ~ 5 Hz, C-2H), 6.12 (3H, s, OMe), 6.3–9.3 (17H, m) $\lambda_{max.}$ (ε) 218 (33,900), 255 (13,200), 290 sh (2240) nm, *m/e* (%) 352 (2), 323 (4), 264 (12), 222 (18), 208 (15), 193 (7), 181 (13), 180 (100), 165 (25), 162 (11).

Hydrolysis and acetylation of 20-*allyl*-20-*desethyl*-20-*epivallesine* **44**

20-Allyl-20-desethyl-21-epivallesine (16 mg) was dissolved in MeOH (15 ml) and dil. HCl (5 ml) was added. The mixture was refluxed for 1 hr and then cooled and made just alkaline with $NaHCO_3$ solution. Extraction with $CHCl_3$, drying and evaporation of the organic extracts gave a pale yellow gum.

This gum was taken up in dry benzene (5 ml) and acetic anhydride (50 mg) was added and the mixture stirred at room temp. for 40 hr. Evaporation of the solvents provided a yellow oil which was chromatographed on a preparative plate (kieselgel G, eluted with $CHCl_3$ containing 1% MeOH). The product appeared at low R_f value and was identical in every respect to 20-allyl-20-desethyl-20-epiaspidospermine.

Cleavage of the allyl group by use of osmium tetroxide

(±)-N-Acetylcylindrocarpinal **48**

20-Allyl-20-desethylaspidospermine (225 mg) was dissolved in 80% acetic acid (20 ml) and osmium tetroxide (10 mg) was added. The mixture was stirred in an atmosphere of dry nitrogen for 20 min, during which time the solution darkened considerably. A solution of sodium paraperiodate in 80% acetic acid was then added and the black solution immediately lightened in colour. The mixture was stirred at room temp. for 20 hr and then the solvents were removed *in vacuo* to produce a yellow oil. This residue was partitioned between $CHCl_3$ and Na_2CO_3 solution and then the organic layer was separated, dried and evaporated to produce a crude, pale yellow solid. Recrystallisation of this crude material from $CHCl_3$ afforded *(±)-N-acetylcylindrocarpinal*[11] as cream-coloured crystals, m.p. 214–216° (decomp.) (206 mg, 92%). (Found: M⁺, 368.20982. $C_{22}H_{28}N_2O_3$ requires: M⁺, 368.20998); $\nu_{max.}$ (in $CHCl_3$) 2830 weak (C–H, aldehyde), 2780, 2720 (Bohlmann bands), 1718 (aldehyde carbonyl), 1635 (amide car-

bonyl), 1490, 1390 (C–H, aldehyde) cm^{-1}, τ (in $CDCl_3$) 0.6 (1H, t, J 2.5 Hz, –CHO), 2.7–3.3 (3H, m, aromatic H), 5.45 (1H, bq, J = 6 Hz, C-2 H), 6.13 (3H, s, –OMe), 6.6–7.2 (2H, m, C-5 H_2), 7.55 (1H, s, C-21 H), 7.8 (3H, s, N–Ac), 7.3–9.2 (14H, m), λ_{max} (ϵ) 219 (33,600), 256 (10,960), 291 sh (2,820) nm, *m/e* (%) 368 (10), 340 (6), 324 (100), 311 (15), 281 (15), 174 (14), 166 (12), 160 (8), 138 (82), 110 (30), 109 (5).

These spectral details compare very favourably with those obtained from the optically active N-acetylcylindrocarpinal prepared by Djerassi and Gebreyesus[11] by oxidation of naturally occurring N-acetylcylindrocarpinol.

(±)-N-Acetylcylindrocarpinol **3**

N-Acetylcylindrocarpinal (65 mg) was dissolved in abs. EtOH (10 ml) and a large excess of $NaBH_4$ (150 mg) was then added. The mixture was then stirred overnight (15 hr) under an atmosphere of dry nitrogen after which dil. acetic acid was added until the precipitate, which initially formed, dissolved. Evaporation of the solvents left a yellow oil which was taken up in $CHCl_3$ and then $NaHCO_3$ solution was added. After separation of the $CHCl_3$ layer it was dried and evaporated to produce a white solid. Recrystallisation from benzene afford *(±)-N-acetylcylindrocarpinol* (50 mg, 77%) as fine, white, needle-shaped crystals, m.p. 200–201°. (Found: M$^+$, 370.225153. $C_{22}H_{30}N_2O_3$ requires: M$^+$, 370.225630); ν_{max} (KBr disc) 3600–3200 broad (O–H), 2770, 2720 (Bohlmann bands), 1630 (amide carbonyl), 1490 cm^{-1}; τ (in $CDCl_3$): 2.85–3.3 (3H, m, aromatic H), 5.5 (1H, bq, J = 5 Hz, "Aspidosperma fingerprint", C-2 H), 6.15 (3H, s, –OMe), 6.47 (2H, bt, J = 7 Hz, $-CH_2-CH_2-OH$), 6.8–7.1 (2H, m, C-5 H_2), 7.75 (1H, s, C-21 H), 7.84 (3H, s, N–$COCH_3$), 7.6–9.2 (15H, m), λ_{max} (ϵ) 217 (33,500), 254 (12,300), 290 sh (3,100) nm, *m/e* (%) 370 (15), 369 (3), 343 (6), 342 (18), 327 (9), 326 (8), 325 (7), 311 (10), 174 (25), 168 (20), 160 (18), 141 (35), 140 (100).

(±)-N,O-Diacetylcylindrocarpinol **49**

(±)-N-Acetylcylindrocarpinol (7.5 mg) was dissolved in benzene (1 ml) and pyridine (0.5 ml) and acetic anhydride (0.5 ml) were added. The mixture was stirred at room temp. in an atmosphere of dry nitrogen for 2 hr and then the solvents were evaporated *in vacuo*. The residue, a pale yellow solid, was recrystallised from a mixture (1:1) of benzene and di-isopropyl ether to afford *(±)-N,O-diacetylcylindrocarpinol* **49** (5 mg) as colourless crystals, m.p. 193–196°. (Found: M$^+$, 412.235805. $C_{24}H_{32}N_2O_4$ requires: M$^+$, 412.236193); ν_{max} (film) 1730 (ester carbonyl), 1630 (amide carbonyl), 1485, 1460, 1380 cm^{-1}, λ_{max} (ϵ) 218 (36,200), 255 (11,900), 290 sh (3,150) nm, *m/e* (%) 412 (35), 411 (6), 384 (25), 326 (12), 325 (15), 324 (15), 236 (12), 210 (15), 182 (100), 174 (18), 160 (17), 122 (45).

Authentic N,O-diacetylcylindrocarpinol **49**

Authentic N-acetylcylindrocarpinol (2 mg) was dissolved in benzene (1 ml) and acetic anhydride (0.1 ml) and pyridine (0.1 ml) were added. The mixture was stirred at room temp. for 1.5 hr and then the solvents evaporated *in vacuo*. The yellow solid produced was taken up in dry benzene and recrystallised to give an off-white solid (about 1 mg).

The IR, UV and mass spectra of synthetic (±)-N,O-diacetylcylindrocarpinol and natural N,O-diacetylcylindrocarpinol were identical. Further proof of the identity of the two samples in all but optical properties was provided by their identical behaviour on TLC on kieselgel G and neutral alumina, using three different solvent systems ($CHCl_3$/3% MeOH; light petroleum:acetone:water = 50:25:2; and benzene/4% MeOH).

N-Acetylcylindrocarpinal oxime

N-Acetylcylindrocarpinal (100 mg) was dissolved in absolute EtOH (5 ml) and an ethanolic solution of hydroxylamine hydrochloride (100 mg in 5 ml) was added with stirring. Sodium carbonate solution (5 ml) was then added and the mixture stirred at room temp. for 2 hr. The solvents were removed *in vacuo* to provide a yellow paste which was taken up in $CHCl_3$ and water. The organic layer was separated, dried and evaporated to provide a yellow foam. This was purified by chromatography on a preparative plate (kieselgel G, eluted with 2% MeOH in $CHCl_3$) to afford the *oxime* of N-*acetylcylindrocarpinal* (65 mg, 63%) as a colourless solid, m.p. 230–232°. (Found: M$^+$, 383.21983. $C_{22}H_{29}N_3O_3$ requires: M$^+$, 383.220879); ν_{max} 3600–3150 broad (N–OH), 2790, 2720 (Bohlmann bands), 1630 (amide carbonyl), 1590 (C=N) cm^{-1}, τ (in $CDCl_3$) 2.5–3.3 (4H, m, 1H exchanges with D_2O, 3H aromatic and OH), 5.45 (1H, bq, J = 6 Hz, C-2 H), 6.15 (3H, s, –OMe), 6.7–7.2 (2H, m, C-5 H_2), 7.82 (3H, s, –$NCOCH_3$), 7.4–9.2 (16H, m), λ_{max} (ϵ) 219 (29,500), 255 (13,300), 291 sh (2,250) nm, *m/e* (%) 383 (6), 366 (41), 365 (21), 325 (16), 324 (28), 323 (23), 174 (15), 161 (15), 160 (47), 153 (25), 137 (16), 136 (16), 135 (100).

20-Cyanomethyl-20-desethylaspidospermine **50**

The oxime of N-acetylcylindrocarpinal (60 mg) was dissolved in acetic anhydride (10 ml) and the mixture boiled under reflux for 0.5 hr. The solvent was then evaporated with the aid of a stream of dry nitrogen and the residue chromatographed on a preparative plate (kieselgel G, eluted with 2% MeOH in $CHCl_3$). The major band (at R_f 0.4) was extracted with $CHCl_3$ to afford a colourless gum which was taken up in dry MeOH and evaporated in a stream of dry nitrogen. This produced *20-cyanomethyl-20-desethylaspidospermine* **50** (35 mg, 60%) as a colourless solid, m.p. 245–247°. (Found: M$^+$, 365.20989. $C_{22}H_{27}N_3O_2$ requires: M$^+$, 365.21032); ν_{max} (film) 2780, 2725 (Bohlmann bands), 2240 weak (nitrile), 1650 (amide carbonyl) cm^{-1}, τ (in $CDCl_3$) 2.8–3.3 (3H, m, aromatic H), 5.45 (1H, bq, J = 6 Hz, C-2 H), 6.10 (3H, s, –OMe), 6.7–7.1 (2H, m, C-5 H_2), 7.83 (3H, s, N–$COCH_3$), 7.3–9.1 (15H, m), λ_{max} (ϵ) 221 (27,400), 256 (13,400), 291 sh (2200) nm, *m/e* (%) 365 (29), 364 (8), 325 (14), 324 (9), 323 (26), 295 (8), 174 (9), 163 (21), 160 (16), 136 (15), 135 (100).

(±)-Cylindrocarpidine **1**

20-Cyanomethyl-20-desethylaspidospermine (20 mg) was dissolved in absolute MeOH (5 ml) and conc. H_2SO_4 (2 ml) was added slowly. The mixture was then boiled under reflux for 15 hr, cooled and neutralised with $NaHCO_3$ solution. The neutral solution was then extracted with $CHCl_3$ and the extracts were dried and evaporated to produce a light brown oil. An IR spectrum of this crude oil showed the presence of an ester (1730, 1210 and 1275 cm^{-1}) and an absence of a nitrile peak.

Thus this crude product was dissolved in pyridine (1.5 ml) and acetic anhydride (0.5 ml) was added. The mixture was then heated at 40° for 2 hr and then the solvents were removed *in vacuo* to leave a brown gum. The gum was subjected to chromatography on a kieselgel G column (25 g, eluted with 2% methanol in chloroform). The major product was recrystallised from EtOH to produce white rosettes, m.p. 178–179°, of *(±)-cyclindrocarpidine* (13 mg, 51%). (Found: M$^+$, 398.21872. $C_{23}H_{30}N_2O_4$ requires: M$^+$, 398.22054); ν_{max} (film) 2800, 2720 (Bohlmann bands), 1735 (ester carbonyl), 1650 (amide carbonyl) cm^{-1}, τ (in $CDCl_3$) 2.8–3.2 (3H, m, aromatic H), 5.4 (1H, diffuse multiplet, C-2 H), 6.13 (3H, s, –OMe), 6.44 (3H, s, –COOMe), 6.5–7.0 (2H, m, C-5 H_2), 7.57 (1H, s, C-21 H), 7.80 (3H, s, $COCH_3$), 7.5–9.1 (14H, m), λ_{max} (ϵ) 216 (38,000), 255 (12,100), 290 sh (3,600), *m/e* (%) 398 (45), 397 (8), 370 (10), 367 (8), 356 (9), 355 (10), 339 (7), 325 (40), 324 (100), 281 (11), 266 (9), 168 (90).

The IR, UV and mass spectra of (±)-cylindrocarpidine were shown by direct comparison to be identical with the corresponding spectra of natural cylindrocarpidine; the NMR spectrum of the synthetic material also appeared to be identical with the published spectrum of natural cylindrocarpidine, as far as could be judged. Identity of the two samples was further established by TLC comparison in three solvent systems (benzene/4% MeOH and $CHCl_3$/2% MeOH on kieselgel G, and light petroleum b.p. 60–80°/acetone/water = 50, 25, 2 on neutral alumina).

(±)-Cylindrocarine **51**

20-Cyanomethyl-20-desethylaspidospermine (10 mg) was treated as in the previous method except that the crude product was not treated with pyridine and acetic anhydride. This crude product was chromatographed on a preparative plate (Alumina, eluted with mixture of light petroleum 50, acetone 25 and water 2) and the major band at 0.75 R_f was then extracted with $CHCl_3$

and evaporated to provide a colourless gum (5 mg, 55%) of (±)-*cylindrocarine*. (Found: M⁺, 356.20939. $C_{21}H_{28}N_2O_3$ requires: M⁺, 356.209980); ν_{max} (film) 3380 (N–H), 2810, 2720 (Bohlmann bands), 1730 (ester carbonyl), 1615, 1595 (indoline), 1255, 1210, 1185 (ester, C–O) cm⁻¹, τ (in $CDCl_3$) 3.2–3.4 (3H, m, aromatic H), 6.18 (3H, s, Ph–OMe), 6.44 (3H, s, –COOMe), 6.70–6.95 (5H, m, C-5 H_2, C-2 H and 2 unidentified), 7.4–8.9 (14H, m), λ_{max} (ε) (in methanol) 216 (25,100), 244 (3,500), 288 (1,740) nm, (in ethanol), 216.5 (26,500), 248 (3,800), 292 (1,950) nm, *m/e* (%) 356 (27), 328 (12), 283 (14), 282 (41), 196 (10), 194 (12), 169 (17), 168 (100), 163 (98).

These spectral data closely resemble those cited in the literature for cylindrocarine.[12] However absolute confirmation was not obtainable as natural cylindrocarine was not available for comparison. Conversion of this product into the known cylindrocarpine provided full confirmation of the synthesis of cylindrocarine.

(±)-*Cylindrocarpine* **52**

Cylindrocarine (6 mg) was dissolved in pyridine (2 ml) and cinnamoyl chloride (3 mg) was added with stirring. The mixture was stirred under dry conditions at room temp. for 90 hr and then the solvent was evaporated using a stream of dry nitrogen to leave a red solid. This crude solid was chromatographed (alumina, elution with a mixture of light petroleum 50, acetone 25 and water 2) and the major band (R_f 0.5) was extracted with CH_2Cl_2 to provide a colourless gum (4 mg, 50%) of (±)-*cylindrocarpine*. (Found: M⁺, 486.25203. $C_{30}H_{34}N_2O_4$ requires: M⁺, 486.25184); ν_{max} (film) 2780, 2720 (Bohlmann bands), 1730 (ester carbonyl), 1650 (amide carbonyl), 1610 (double bond) cm⁻¹, λ_{max} (ε) 218 (34,000), 248 (11,000), 285 (21,000) nm, *m/e* (%) 486 (50), 413 (25), 412 (50), 356 (30), 328 (12), 282 (25), 281 (22), 168 (100), 131 (80), 103 (70).

Comparison of the spectra of the synthetic material and those obtained from the natural material showed the IR, UV and mass spectra to be superimposable. Also the TLC analysis, in three separate solvent systems (2% MeOH in benzene, 2% MeOH in $CHCl_3$ on kieselgel G and light petroleum 50, acetone 25 and water 2 on alumina) showed the two materials to be identical.

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