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ANCISTROCLADINE, A NEW TYPE OF ISOQUINOLINE ALKALOID FROM *ANCISTROCLADUS HEYNEANUS**

T. R. GOVINDACHARI† and P. C. PARTHASARATHY

CIBA Research Centre, Goregaon, Bombay 63, India

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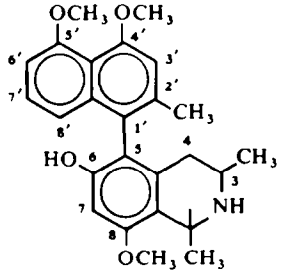
Abstract—A new alkaloid, ancistrocladine, isolated from *Ancistrocladus heyneanus* wall., has been assigned the structure 1 based on spectral and synthetic evidence of the degradation products.

THE genus *Ancistrocladus*[1] belonging to the family Ancistrocladaceae has nearly 20 species[2] of which there are about 10 species in Asia[3]. Although the presence of alkaloids has been reported[3a] in one of the Asian species, *Ancistrocladus tectorius* (Lour.) Merr, not a single representative of the genus has hitherto been examined in detail chemically. The floral anatomy of the Indian species, *Ancistrocladus heyneanus* Wall., has recently been studied.[2]

From the roots of *Ancistrocladus heyneanus* Wall., the only representative[2] of the genus *Ancistrocladus* in India, we have isolated a new optically-active cryptophenolic alkaloid named ancistrocladine, $C_{25}H_{29}O_4N$ (Mol. Wt. 407 from mass spectrum), m.p. 265–267°, for which we had previously[4] assigned a part structure without establishing the position of the third OMe group at C-7 or C-8 of the tetrahydroisoquinoline ring. This paper describes in detail our arguments in the assignment of structure **1** for ancistrocladine. Ancistrocladine formed readily a diacetyl, $C_{29}H_{33}O_6N$, IR, ν_{max} 1628



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(N—Ac) and 1760 cm^{-1} (OAc) and dibenzoyl, $C_{39}H_{37}O_6N$, IR ν_{max} 1630 (N—COC_6H_5) and 1738 cm^{-1} (O CO C_6H_5) derivatives. The former on mild alkaline hydrolysis gave N-acetylancistrocladine, $C_{27}H_{31}O_5N$, M^+ 449, IR, ν_{max} 1635 (N—Ac) and 3430 cm^{-1} (OH) clearly indicating the presence of OH and NH groups in ancistrocladine, and in agreement the alkaloid showed bands in the infrared at 3330 and 3440 cm^{-1} for NH and OH groups, respectively. Ancistrocladine, which has a poor solubility in most of the organic solvents, gave a crystalline hydrochloride, $C_{25}H_{29}O_4N$ HCl, whose NMR spectrum in DMSO-d_6 exhibited the presence of 2 secondary Me's,

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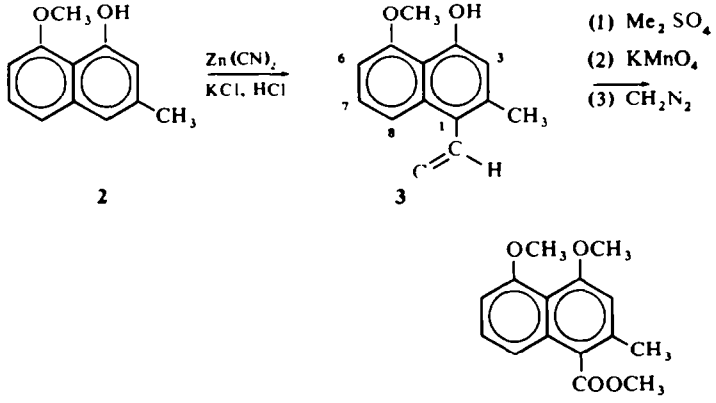
three OMe's and one aromatic Me group thus accounting for all the hetero atoms present in the alkaloid. The UV spectra of ancistrocladine and several of its degradation products described in the sequel are reminiscent of 1,8-dimethoxy-3-methylnaphthalene.[5]

Evidence for the presence of a 1-substituted 4,5-dimethoxy-2-methylnaphthalene ring in ancistrocladine

Mild oxidation of the hydrochloride of the alkaloid with $KMnO_4$ in aqueous acetone at room temperature gave an acidic mixture which with ethereal CH_2N_2 followed by exhaustive column chromatography over silica furnished a crystalline compound, $C_{15}H_{16}O_4$, M^+ 260, m.p. 102–103°, UV λ_{max} 230, 306, 318 and 332 mμ (log ε 4·69, 3·95, 3·95 and 3·92) and λ_{shl} 292 mμ (log ε 3·83) with a close resemblance to 1,8-dimethoxy-3-methylnaphthalene, IR ν_{max} 1720 cm^{-1} (COOMe) and its NMR spectrum revealed the presence of one aromatic Me (s, 2·42), two $OC\underline{H}_3$, one $COOC\underline{H}_3$ (s, 3·87, 3·90 and 3·95) and four aromatic protons of which one was a singlet at 6·62. Since the NMR spectrum of ancistrocladine hydrochloride showed only one shielded aromatic $C\underline{H}_3$ group (s, 2·05), we thought that the oxidation product should be the hitherto unknown methyl 2-methyl-4,5-dimethoxy-1-naphthoate (**4**), which was confirmed by a direct comparison with an authentic specimen synthesised by two unambiguous methods.

Synthesis of methyl 2-methyl-4,5-dimethoxy-1-naphthoate (**4**)

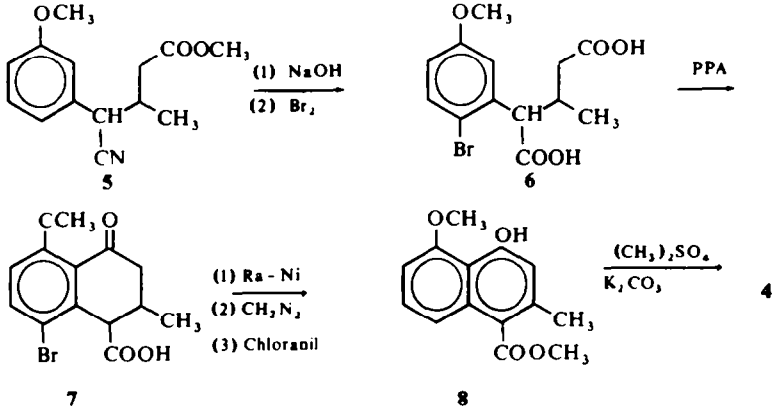
Method A. 1-Hydroxy-8-methoxy-3-methylnaphthalene[6] (**2**), on formylation by the Gattermann procedure gave 2-methyl-4-hydroxy-5-methoxy-1-naphthaldehyde (**3**), $C_{13}H_{12}O_3$, m.p. 112–113°, which in the NMR spectrum showed the following signals: 10·50 (m, C$\underline{H}$O), 6·63 (s, C-3$\underline{H}$), 6·77 (q, J = 1·5 and 8 Hz, C-6 $\underline{H}$), 7·42 (q, J = 8 Hz, C-7$\underline{H}$) and 8·80 (q, J = 1·5 and 8 Hz, C-8$\underline{H}$), the C-8 $\underline{H}$ appeared at a lower field than the C-6 or C-7 $\underline{H}$, presumably due to the deshielding effect of the aldehyde group at C-1. On



2 **3** **4**

methylation with Me_2SO_4 and K_2CO_3 in dry acetone, it gave 2-methyl-4,5-dimethoxy-1-naphthaldehyde, which on oxidation with $KMnO_4$ gave the corresponding acid, whose methyl ester **4**, $C_{15}H_{16}O_4$, m.p. 101–103°, prepared by treatment with ethereal CH_2N_2, was identical in all respects with the oxidation product from ancistrocladine.

Method B. A second method for the synthesis of methyl 2-methyl-4,5-dimethoxy-1-naphthoate (**4**) involved a Michael addition[7] of m-methoxyphenyl acetonitrile to methyl crotonate to yield the cyano ester 5. Alkaline hydrolysis furnished a dicarboxylic acid which when brominated gave the bromo dicarboxylic acid **6**. Cyclisation with PPA yielded 5-bromo-1-keto-8-methoxy-3-methyltetralin-4-carboxylic acid (**7**). Catalytic



debromination followed by esterification with CH_2N_2 and dehydrogenation with chloranil in refluxing xylene furnished methyl 2-methyl-4-hydroxy-5-methoxy-1-naphthoate (**8**). The methyl ether of **8**, made by refluxing with Me_2SO_4 in acetone containing K_2CO_3, m.p. 100–102°, was identical in all respects with the earlier specimen of methyl 2-methyl-4,5-dimethoxy-1-naphthoate (**4**).

Evidence for the presence of a 1,3-*dimethyltetrahydroisoquinoline ring and the naphthalene moiety linked at* C-5 *in ancistrocladine*

N-Formylancistrocladine (**9**), $C_{26}H_{29}O_5N$, prepared by heating the alkaloid with ethyl formate in a sealed tube followed by mild alkaline hydrolysis, on reduction with LAH gave N-methylancistrocladine (**10**), $C_{26}H_{31}O_4N$. Its NMR spectrum disclosed the presence of 2 secondary Me groups at 0·92 and 1·37 ($J = 6{\cdot}5$ Hz), each as a doublet and an unresolved doublet at 1·85 for a benzylic methylene group. A quartet at 4·12 ($J = 6{\cdot}5$ Hz) was also discernible in the NMR spectrum and its position suggested that it should be benzylic and also vicinal to nitrogen. A multiplet at 3·08 was ascribed to the C-3 proton vicinal to nitrogen. On methylation with CH_2N_2, N-formylancistrocladine (**9**) gave N-formyl-O-methylancistrocladine (**11**), $C_{27}H_{31}O_5N$, which with LAH furnished O,N-dimethylancistrocladine (**12**), $C_{27}H_{33}O_4N$. The 100 MHz NMR spectrum* of (**12**) is reproduced in Fig. 1.

The methine **13**, $C_{28}H_{35}O_4N$, formed from the first step of Hofmann exhaustive methylation of O,N-dimethylancistrocladine (**12**) showed IR bands at 975 and 1680 cm^{-1} characteristic of a propenyl group. Its NMR spectrum further confirmed the presence of this grouping and also an α-dimethylaminoethyl side chain; 1·28 (q, olefinic

* By double irradiation it was shown that the multiplet at 3·05 is coupled to the unresolved doublet at 1·86 and to the doublet at 0·93. Therefore the quartet at 4·10 is due to the proton attached to the benzylic carbon at C-1.

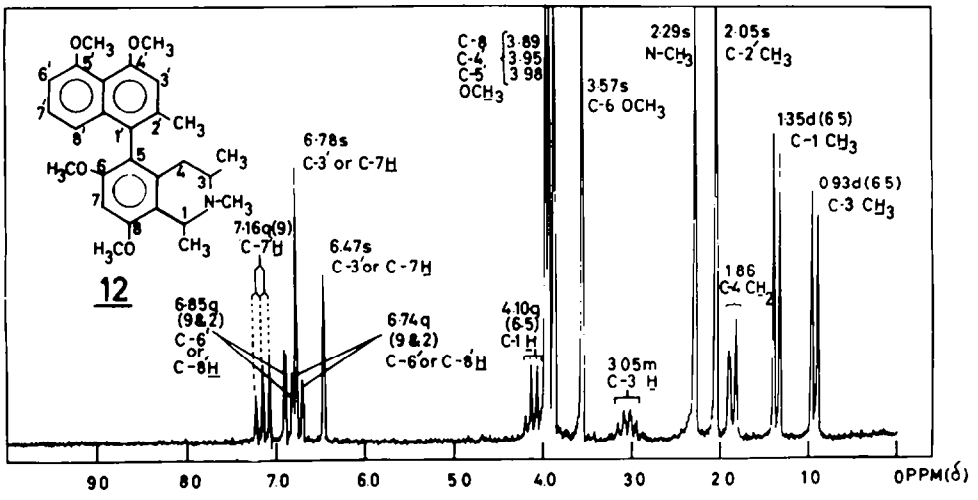
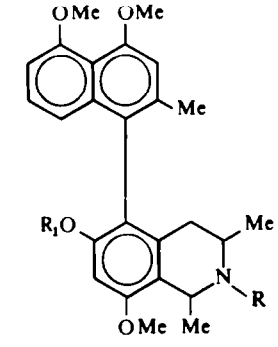
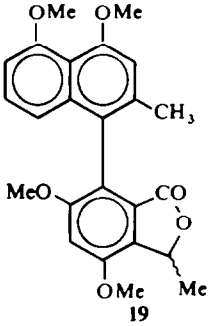


FIG 1. 100 MHz NMR spectrum of O,N-dimethylancistrocladine (**12**) in $CDCl_3$.



9: R = CHO; R_1 = H
10: R = Me; R_1 = H
11: R = CHO; R_1 = Me
12: R = R_1 = Me
21: R = H; R_1 = Me



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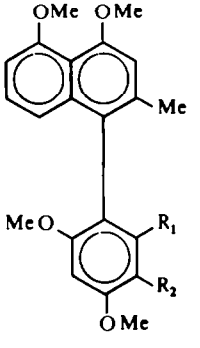


13: R_1 = —CH=CH . Me; R_2 = —CH(Me) . NMe_2
14: R_1 = —CH_2 . CH_2 . Me; R_2 = —CH(Me) . NMe_2
15: R_1 = —CH = CH . Me; R_2 = —CH = CH_2
16: R_1 = —CH_2 . CH_2 . Me; R_2 = —CH = CH_2
17: R_1 = —CH_2 . CH_2 . Me; R_2 = —CH(OH) . Me
18: R_1 = —CH = CH . Me; R_2 = —CH(OH) . Me
20: R_1 = —CH_2 . CH_2 . Me; R_2 = —Et

$C\underline{H}_3$, J=2 and 7 Hz), 4·95 (Oct, vinylic $\underline{H}$, J=7 and 16 Hz), 6·13 (Oct, both benzylic and vinylic $\underline{H}$, J = 2 and 16 Hz) due to a propenyl (*trans*) group and 1·38 (d, —$C\underline{H}$. $C\underline{H}_3$, J=7 Hz), 2·20 (s, $N(C\underline{H}_3)_2$) and 3·83 (q, —$C\underline{H}$-CH_3, J=7 Hz) due to an α-dimethylaminoethyl group. On hydrogenation the methine **13** gave a dihydro derivative, (**14**), $C_{28}H_{37}O_4N$, which showed the absence of bands at 975 and 1680 cm^{-1} in the IR and exhibited in the NMR spectrum a triplet (J = 7 Hz) at 0·53 for the Me group of the n-propyl chain. The unusual shielding* of the olefinic methyl in the methine **13** and the Me group in its dihydro derivative **14** necessitated the placement of the naphthalene ring at C-5 as in structures **13** and **14** thereby bringing the Me's of the propenyl and propyl chains within the shielding zone of the naphthalene ring.

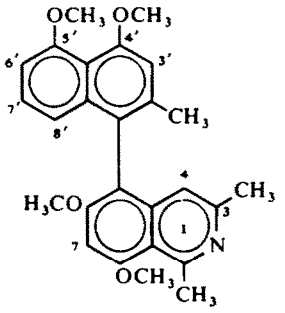
A second Hofmann elimination on the methine **13** led to an optically active, nitrogen-free bismethine (**15**), $C_{26}H_{28}O_4$, which revealed the presence of a vinyl group besides the propenyl chain. The dihydromethine **14** likewise yielded a product, $C_{26}H_{30}O_4$, formulated as **16**, which showed in the IR a band at 905 cm^{-1} for a terminal vinyl group and in the NMR spectrum the vinyl protons displayed a characteristic ABX resonance pattern; δ H_A 5·43 (q, J_{AB} 2·5 Hz and J_{AX} 10 Hz); δ H_B 5·73 (q, J_{AB} 2·5 Hz and J_{BX} 16 Hz) and H_X being both vinylic and benzylic was lost under the aromatic signals. A small amount of the hydroxy compound **17** was also formed in the Hofmann degradation.

In the second-step Hofmann degradation of O,N-dimethylancistrocladine (**12**), besides the bismethine **15**, a small amount of a second product, $C_{26}H_{30}O_5$, was obtained which showed in the IR a band at 3540 cm^{-1} for the presence of a OH group. This compound was shown to contain an α-hydroxyethyl chain as in **18** besides the propenyl group, since on dehydration this gave the bismethine **15**. Ozonolysis of **18** gave an amorphous aldehyde which on oxidation followed by acid treatment gave a gummy lactone, **19**, $C_{24}H_{24}O_6$. This lactone exhibited an intense band in the infrared at 1765 cm^{-1}, indicating that it was 5-membered. The formation of a 5-membered lactone would be expected only when the propenyl and the α-hydroxyethyl side chains are *ortho* to each other as in structure **18** and hence proved the presence of a 1,3-dimethyltetrahydroisoquinoline ring in ancistrocladine. It is of interest to note that in compound **20**, $C_{26}H_{32}O_4$, formed by hydrogenolysis of **18**, the Me group of the Et chain on the NMR spectrum appeared in the normal region (1·15) as a triplet (J = 7 Hz) while the Me group of the n-propyl chain showed up at a higher field (0·53) as a triplet (J = 7 Hz), being shielded by the naphthalene ring. In consonance with the presence of a 1,3-dimethyltetrahydroisoquinoline ring in ancistrocladine, its O-Me derivative **21**, prepared from N-formyl-O-methylancistrocladine (**11**) by drastic hydrolysis with KOH in refluxing ethylene glycol, on dehydrogenation with 10% Pd/c in refluxing decalin gave in 20% yield the isoquinoline **22**, $C_{26}H_{27}O_4N$, $[\alpha]_D$ + 58·87° (c = 1·6) which showed in the NMR spectrum the following signals: 2·02 (s, C-2′ $C\underline{H}_3$), 2·33 (s, C-3 $C\underline{H}_3$), 3·10 (s, C-1 $C\underline{H}_3$), 3·70 (s, C-6 $OC\underline{H}_3$), 3·95, 4·0 (s, 3 $OC\underline{H}_3$ at C-4′, C-5′ and C-8), 6·43 (s, C-3′ or C-7 $\underline{H}$) and the signal due to C-4 $\underline{H}$ was lost under the signals due to 6′, 7′ and 8′ protons.

Evidence for the phenolic hydroxyl group at C-6 in ancistrocladine

A phenolic OH group at C-4′ or C-5′ position in the naphthalene moiety would be

* It is pertinent to note that in isofrol and n-propylbenzene, the Me groups appear at 1·80 (d, J = 7 Hz) and 1·25 (t, J = 6·5 Hz), respectively.



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expected[8] to appear downfield* in the NMR spectrum since this would be H-bonded with the *peri*-OMe group. In N-formylancistrocladine (**9**), N-methylancistrocladine (**10**) and N-acetylancistrocladine, the phenolic OH groups appeared as singlets at 5·27, 4·90 and 5·25, respectively, indicating that the phenolic OH group in ancistrocladine should be present in the tetrahydroisoquinoline ring. The significant shielding of the OMe (s, 3·57) and acetate (s, 1·72) groups in O-methylancistrocladine (**21**) and O,N-diacetylancistrocladine necessitated the placement of the phenolic OH group at C-6 on the tetrahydroisoquinoline ring thereby bringing both the OMe and acetate Me protons at C-6 within the shielding zone of the naphthalene ring.

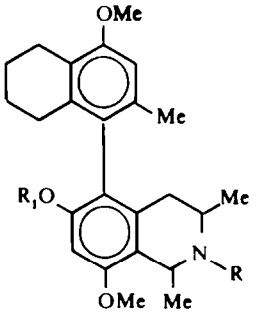
Evidence for the third methoxyl group at C-8 *in ancistrocladine*

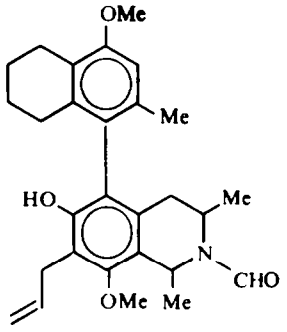
The hydrochloride of ancistrocladine took up 3 moles of H_2 in the presence of Pd/C in alcohol containing $HClO_4$ to furnish, after basification, desmethoxytetrahydroancistrocladine, $C_{24}H_{31}O_3N$, M^+ 381. Spectral studies indicated the loss of a OMe group at C-5′ by hydrogenolysis, followed by the uptake of 2 moles of H_2 to form the product, formulated as **23**. Formylation of **23** by heating with ethyl formate, followed by mild hydrolysis with alkali gave N-formyldesmethoxytetrahydroancistrocladine (**24**). Its NMR spectrum showed the following signals: 0·93 and 1·13 (2 sets of doublets, $J = 6·5$ Hz, C-3 $C\underline{H}_3$), 1·38 and 1·40 (2 sets of doublets, $J = 6·5$ Hz, C-1 $C\underline{H}_3$), 1·97 and 2·02 (2 singlets, C-2′ $C\underline{H}_3$), 5·57 (s, O$\underline{H}$, collapsible with D_2O), 6·53, 6·57 (2 singlets, C-3′ or C-7 $\underline{H}$), 6·68 (s, C-3′ or C-7 $\underline{H}$), 8·20 and 8·30 (2 singlets, N-C$\underline{H}$O). The appearance of two sets of signals for the Me groups at C_1, C_3 and C-2′ and for the formyl and C-7 or C-3′ protons in the NMR spectrum is presumably due to the existence of two species of rotamers which results owing to the restricted rotation† of the amide bond. This phenomenon has been observed in all compounds derived from ancistrocladine, which bear the N—CHO group.

The placement of the third OMe group at C-8 in ancistrocladine rests on the following evidence: Treatment of N-formyldesmethoxytetrahydroancistrocladine (**24**) with allyl

* In the NMR spectra of 1-hydroxy-8-methoxy-3-methylnaphthalene (**2**) and methyl 2-methyl 4-hydroxy-5-methoxy-1-naphthoate (**8**), the hydroxyl protons appeared as singlets at 9·20 and 9·53, respectively.

† The phenomenon of restricted rotation in a few 1-substituted N-acyltetrahydroisoquinolines has been studied in detail in which NMR spectroscopy has found extensive application: *cf.* D. L. Dalton, K. C. Ramey, H. J. Gisler, Jr., L. J. Lendvay and A. Abraham, *J. Am. Chem. Soc.* **91**, 6367 (1969) and papers cited.





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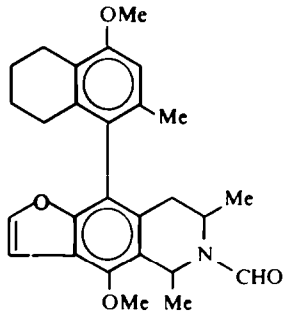

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23: R = R_1 = H
24: R = CHO; R_1 = H
25: R = CHO; R_1 = —CH_2—CH=CH_2
25: R = Me; R_1 = —CH_2 . CH=CH_2

bromide in refluxing acetone containing K_2CO_3 gave O-allyl-N-formyldesmethoxytetrahydroancistrocladine as a froth (**25**), $C_{28}H_{35}O_4N$. Its IR spectrum showed the absence of an OH group and the NMR spectrum disclosed the presence of an O-allyl group: 4·42 (m,—O—C<u>H</u>$_2$—CH=CH_2), and 5·1 m, 3 vinyl <u>H</u>, —O—CH_2—C<u>H</u>=C<u>H</u>$_2$). LAH reduction of **25** gave O-allyl-N-methyldesmethoxytetrahydroancistrocladine **26**, as a gum which was converted to a crystalline hydrochloride, $C_{28}H_{37}O_3N$ HCl, m.p. 295–297° (d). Compound **25** underwent a smooth claisen rearrangement on refluxing with $C_6H_5N(CH_3)_2$ to yield a product, $C_{28}H_{35}O_4N$, M^+ 443, m.p. 170–172°, formulated as **27**. Its IR spectrum revealed the presence of an OH group (ν_{max} 3520 cm^{-1}) and in the NMR spectrum signals reminiscent of a C-allyl group attached to an aromatic ring were present: 3·47 (m, both benzylic and allylic) and 5·0 (m, 3 vinyl <u>H</u>). A singlet at 6·67 (C-3′ <u>H</u>) and the disappearance of the signal due to C-7 <u>H</u> further confirmed the presence of an allyl group at C-7 in compound **27**. Hence the third OMe group in ancistrocladine should be placed at C-8 as in 1. In consonance with structure **27**, C-allyl-N-formyldesmethoxytetrahydroancistrocladine, on ozonolysis followed by cyclisation[9] with hot *o*-phosphoric acid gave the furano compound **28**, $C_{27}H_{31}O_4N$, which in the UV spectrum exhibited maxima at λ 252, 259 and 284 mμ (log ε 4·19, 4·17 and 3·62), reminiscent of a benzofuran.[10] The disappearance of signals due to the C-allyl group and the emergence of 2 sets of doublets for both the α and β-protons of the furan ring in the NMR spectrum were in agreement with structure **28**.

Ancistrocladine represents the first isoquinoline alkaloid to possess a methyl group at C-3 as in **1** and its biogenetic origin, which is under investigation, from "polyketide units" by cyclisation accompanied by oxidative coupling is obvious. It is of interest to note that compounds **15**, **20** and the isoquinoline **22** are optically active and we are currently studying the absolute stereochemistry at C-1 and C-3 and the chirality of the naphthalene ring at C-5 in ancistrocladine.

EXPERIMENTAL

General experimental procedure. M.ps. and b.ps. are uncorrected. UV spectra were determined in 95% EtOH on a Beckman DK 2A spectrophotometer. Rotations were taken in $CHCl_3$ at 25° unless otherwise noted. IR spectra were taken on a Perkin-Elmer Model 421 spectrophotometer. NMR measurements were

made for $CDCl_3$ solns, unless otherwise noted, on a Varian A-60 or HA-100-D spectrometers with TMS as an internal standard, and all the signals are reported in ppm as δ values. The following abbreviations are used to express the multiplicity of the signals; s = Singlet, d = Doublet, q = Quartet, Oct = Octet and m = Multiplet. Merck silica-gel was used for TLC and column chromatography and for visualization, the developed thin-layer chromatoplates were sprayed with a 1% solution of vanillin in aq. H_2SO_4 (1:1) and heated to 110° for 5 min.

Isolation of ancistrocladine (1) *from* Ancistrocladus heyneanus *Wall.* 10 Kg of the pwdered roots was extracted in the cold 5 times with alcohol for 2 days. The dark brown combined alcoholic extract was concentrated to dryness and the residue treated with warm water (2 1) and filtered. To the filtrate, solid $NaHCO_3$ (20 g) was added and the gelatinous mass separated was quickly filtered. The crude alkaloid separated out as a lemon-yellow coloured solid from the filtrate. This was extracted with $CHCl_3$ and the residue, obtained by evaporation of the combined $CHCl_3$ extract, was treated with conc HCl (50 ml) and H_2O (25 ml) at 10°. The crude hydrochloride that had separated was extracted with $CHCl_3$ and the residue, obtained by evaporation of the combined $CHCl_3$ extract, was dissolved in acetone (200 ml) and allowed to stand. White needles (20 g) separated out and was recrystallised from MeOH—MeCOMe, m.p. 220–224° (d), $[\alpha]_D$ 25·51° (c = 2·29 in MeOH). (Found: C, 67·61; H, 6·87; N, 3·29. $C_{25}H_{29}O_4N$ HCl requires: C, 67·56; H, 6·76; N, 3·15%); IR: ^{Nujol} 2440, 2650 and 2720 cm^{-1} (—$\overset{|}{\underset{|}{N}}$+H); $^{CD}3$ $^{SOCD}3$ 1·08 (d, J = 6 Hz, C-3 CH_3), 1·50 (d, J = 6 Hz, C-1 CH_3), 2·05 (s, C-2′ CH_3), 3·85, 3·87, 3·90 (three OCH_3 singlets), 6·63 (s, C-3′ or C-7 H) and 6·88 (s, C-3′ or C-7 H).

The hydrobromide, made by the usual manner, was crystallised from MeOH, white needles, m.p. 229–231° (d). (Found: C, 61·03; H, 6·33. $C_{25}H_{29}O_4N$ HBr requires: C, 61·47; H, 6·19%).

The free base was obtained by treating a methanolic soln of the hydrochloride with $NaHCO_3$ aq. Ancistrocladine was sparingly soluble in all organic solvents. However, an analytical sample was prepared by crystallisation from a large volume of MeOH, white heavy cubes, m.p. 265–267° (d); UV: λ_{max} 230, 290, 305, 320 and 335 mμ (log ε 4·79, 4·00, 4·04, 3·95 and 3·87), spectrum unchanged with either acid or alkali; IR: ^{Nujol} 3330 and 3440 cm^{-1} (NH and OH). (Found: C, 73.80; H, 7·38. $C_{25}H_{29}O_4N$ requires: C, 73·68; H, 7·17%).

O,N-*Diacetylancistrocladine.* This was made by treating the hydrochloride (1 g) with Ac_2O (5 ml) and dry pyridine (5 ml) at room temp for 12 hr. Work-up in the usual manner gave a froth which was purified by passage through a column of silica and eluted with C_6H_6 and C_6H_6 containing 1% MeOH. The latter eluted the diacetyl compound (800 mg) as a colourless gum; UV: λ_{max} 229, 307, 321 and 335 mμ (log ε 4·83, 4·01, 3·94 and 3·88), λ_{sh} 286 mμ (log ε 3·89); IR: $\nu_{max}^{CH_2Cl_2}$ 1760 (OAc) and 1628 cm^{-1} (NAc); NMR: $^{CDCl}3$ 0·90 (d, broad, J = 6·5 Hz, C-3 CH_3), 1·40 (d, broad, J = 6·5 Hz, C-1 CH_3), 1·72 (s, C-6 $OCOCH_3$) and 2·17 (s, C-2′ CH_3).

N-*Acetylancistrocladine.* The above diacetyl compound (90 mg) in MeOH (5 ml) was treated in the cold with methanolic NaOH (5%, 2 ml) and left overnight. Next morning MeOH was removed *in vacuo* and water (10 ml) was added and the aqueous soln was made faintly acidic. After extraction with $CHCl_3$ and removal of the solvent *in vacuo*, a pale yellow froth was obtained. This was dissolved in ether and allowed to stand when colourless crystals of the N-acetyl derivative (50 mg) was obtained, m.p. 277–279°, λ_{max} 230, 305, 321 and 335 mμ (log ε 4·81, 4·05, 4·07, 3·97 and 3·89); IR: ^{CHCl_3} 3430 cm^{-1} (OH) and 1635 cm^{-1} (N-Ac). NMR: ^{CDCl_3} 0·88 (d, broad, J = 6 Hz, C-3 CH). 1·37 (d, broad, J = 6 Hz, C-1 CH_3) 2·22 (s $NCOCH_3$), 5·25 (s, OH, disappears on addn of D_2O), 6·62 (s, C-3′ or C-7 H) and 6·78 (s, C-3′ or C-7 H). (Found: C, 72·11; H, 7·18; N, 3·19. $C_{27}H_{31}O_5N$ requires: C, 72·14; H, 6·95; N, 3·12%).

O,N-*Dibenzoylancistrocladine.* The hydrochloride (400 mg) dissolved in pyridine (3 ml) and benzoyl chloride (2 ml) at room temp for 2 days gave the dibenzoyl derivative (300 mg), colourless cubes from MeOH, m.p. 228–230°; IR: ^{Nujol} 1738 (—$OCOC_6H_5$) and 1630 cm^{-1} ($NCOC_6H_5$). (Found: C, 75·96; H, 6·35; N, 2·25. $C_{39}H_{37}O_6N$ requires: C, 76·08; H, 6·06; N, 2.28%).

Desmethoxytetrahydroancistrocladine (**23**). Ancistrocladine hydrochloride (5 g) dissolved in alcohol (300 ml) containing $HClO_4$ (60%, 1 ml) was shaken in the presence of H_2 at room temp and press over Pd/C (10%, 1 g added 5 times) for 4 days until 3 molar equiv of H_2 was absorbed. After removal of the catalyst, the solvent was evaporated *in vacuo* and the residue treated with $NaHCO_3$aq and extracted with $CHCl_3$. The combined $CHCl_3$ extract was washed with H_2O and dried over anhyd Na_2SO_4. Removal of the solvent gave the required compound as a colourless gum which crystallised from ether, white needles (2·8 g), m.p. 214–217°. M⁺ 381, $[\alpha]_D$ −33·99° (C = 1·30); UV: λ_{max} 284 mμ (log t 3·72), IR: $_{Nujol}$ 3260 and 3540 cm^{-1} (NH

and OH); NMR: $^{CDCl}3$ 1·01 (d, J=7 Hz, C-3 C$\underline{H}_3$), 1·33 (d, J=7 Hz, C-1 C$\underline{H}_3$), 1·71 (m, C-6′, and C-7′ C$\underline{H}_3$ protons), 1·97 (s, C-2′ C$\underline{H}_3$), 2·15 (m, C-8′ C$\underline{H}_2$), 6·37 (s, C-3′ or C-7 $\underline{H}$) and 6·63 (s, C-3′ or C-7$\underline{H}$). (Found: C, 75·23; H, 8·34. $C_{24}H_{31}O_3N$ requires: C, 75·56; H, 8·19%).

N-Acetyldesmethoxytetrahydroancistrocladine. Treatment of desmethoxytetrahydroancistrocladine (0·5 g) with Ac_2O (1 ml) and dry pyridine (1 ml) at room temp followed by mild hydrolysis with aq methanolic alkali (5%, 1 ml) gave the title compd (0·4 g) as needles from ether, m.p. 118–120°; UV: λ_{max} 284 mμ (log ε 3·73). (Found: C, 73·21; H, 8·21; N, 3·15. $C_{26}H_{33}O_4N$ requires: C, 73.73; H, 7·85; N, 3·31%).

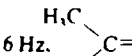
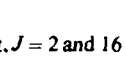
N-Formylancistrocladine (**9**). Ancistrocladine (3·15 g) suspended in freshly distilled $HCOOC_2H_5$ (30 ml) was heated at 100° in a sealed glass tube for 10 hr. At the end of this period, excess HCOOEt was removed *in vacuo* and the residue was dissolved in MeOH (25 ml) and treated in the cold with 2N NaOH (10 ml) for 6 hr. Water was added and the aqueous extract was acidified and extracted with $CHCl_3$. The combined $CHCl_3$ extract was washed with water and dried. Removal of the solvent gave N-formylancistrocladine (2·1 g) which crystallised from acetone, white needles, m.p. 232–234°, $[\alpha]_D$ −126·8° (c = 1·57); UV: λ_{max} 230, 292, 306, 321 and 325 mμ (log ε 4·79, 4·04, 4·06, 3·95 and 3·88); IR: ^{Nujol}3540 (OH), 1660 and 1670 cm^{-1} (N—CHO); NMR: $^{CDCl}3$ 0·88, 1·05 (2 sets of doublets, J = 6·5 Hz, C-3 C$\underline{H}_3$), 1·38, 1·40 (2 sets of doublets, J = 6·5 Hz, C-1 C$\underline{H}_3$), 2·13, 2·20 (2 singlets, C-2′ C$\underline{H}_3$), 4·90 (s, broad, O$\underline{H}$, disappears with D_2O), 5·20, 5·63 (q, 2 sets, J = 6·5 Hz, C-1$\underline{H}$) and 8·13, 8·30 (s, broad, 2 sets, N−C$\underline{H}$O). (Found: C, 71·10; H, 7·15. $C_{26}H_{29}O_5N$ requires: C, 71·70; H, 6·71%).

N-Methylancistrocladine (**10**). The foregoing compd (1 g) was reduced with LAH (1 g) in dry ether. Work-up as usual gave the title compd (700 mg), colourless prisms from ether, m.p. 98–101°, $[\alpha]_D$ −41·10° (C = 2·37), UV: λ_{max} 231, 293, 305, 321 and 335 mμ (log ε 4·75, 3·98, 4·01, 3·91 and 3·84); IR: ^{Nujol} 2702 (N—CH_3) and 3470 cm^{-1} (OH); NMR: $^{CDCl}3$ 1·37 (d, J = 6·5 Hz, C-3 C$\underline{H}_3$), 0·92 (d, J = 6·5 Hz, C-1 C$\underline{H}_3$), 1·85 (d, unresolved, C-4 C$\underline{H}_2$), 2·12 (s, C-2′ C$\underline{H}_3$), 2·28 (s, NC$\underline{H}_3$), 3·08 (m, unresolved, C 3 $\underline{H}$), 3·83, 3·92 (OMe, 3), 4·12 (q, J = 6·5 Hz, C-1 $\underline{H}$), 5·27 (s, $W_{\frac{1}{2}}$ 3·5 Hz, O$\underline{H}$, disappears with D_2O), 6·52 (s, C-3′ or C-7 $\underline{H}$) and 6·75 (s, C-3′ or C-7 $\underline{H}$). (Found: C, 73·89; H, 7·85; N, 3·38. $C_{26}H_{31}O_4N$ requires: C, 74·08; H, 7·41; N, 3·32%).

N-*Formyl*-O-*methylancistrocladine* (**11**). N-Formylancistrocladine (380 mg) dissolved in MeOH (10 ml) was cooled to 0° and treated with excess ethereal CH_2N_2 (from 5 g nitrosomethylurea). Work-up by the usual procedure gave a white froth which was dissolved in ether and allowed to stand. White fluffy needles of the title compd (200 mg) was obtained, recrystallised from ether, m.p. 210–215°, $[\alpha]_D$ −91·79° (C = 3·24); UV: λ_{max} 228, 291, 306, 321 and 335 mμ (log ε 4·86, 4·03, 4·05, 3·96 and 3·89); IR: 1670 cm^{-1} (N-CHO); NMR: $^{CDCl}3$ 0·88, 1·05 (d, 2 sets, J = 6·5 Hz, C-3 C$\underline{H}_3$), 1·43 (d, broad, J = 6·5 Hz, C-1 C$\underline{H}_3$), 208, 2·12 (2 singlets, C-2′ C$\underline{H}_3$), 3·63 (s, broad, $W_{\frac{1}{2}}$ 2·5 Hz, C-6 OC$\underline{H}_3$, 6·53, 6·80 (s, C-3′ or C-7$\underline{H}$), 8·23 and 8·38 (s, broad, 2 sets, N-C$\underline{H}$O). (Found: C, 72·40; H, 7·18. $C_{27}H_{31}O_5N$ requires: C, 72·14; H, 6·95%).

O,N-*Dimethylancistrocladine* (**12**). The foregoing compd (1 g) dissolved in dry THF (20 ml) was reduced with LAH (0·5 g) suspended in dry ether (30 ml). After refluxing gently with vigorous stirring for 6 hr, the reaction mixture was left overnight. Work-up as usual gave O,N-dimethylancistrocladine (800 mg) which crystallised as white prisms from ether, m.p. 183–185°, $[\alpha]_D$ −21·02° (c = 2·55); UV: λ_{max} 231, 291, 305, 320 and 335 mμ (log ε 4·79, 4·02, 4·05, 3·96 and 3·90); NMR: $^{CDCl}3$ 100 MHz, 0·93 (d, J = 6·5 Hz, C-1 C$\underline{H}_3$), 1·35 (J = 6·5 Hz, C-1 C$\underline{H}_3$), 1·86 (d, unresolved, C-4 C$\underline{H}_2$), 2·05 (s, C-2′, C$\underline{H}_3$), 2·29 (s, NC$\underline{H}_3$), 3·05, (m, C-3 $\underline{H}$), 3·57 (s, C-6 OC$\underline{H}_3$), 3·89, 3·95, 3·98 (s, 3 OC$\underline{H}_3$s), 4·10 (q J = 6·5 Hz, C-1 $\underline{H}$), 6·47 (s, C-3, or C-7$\underline{H}$), 6·74 (q J = 9 and 2 Hz, C-6′ or C-8′ $\underline{H}$), 6·78 (s, C-3′ or C-7$\underline{H}$), 6·85 (q J = 9 and 2 Hz, C-6′ or C-8′ $\underline{H}$) and 7·16 (q J = 9 Hz C-7′ $\underline{H}$). (Found: C, 74·34; H, 7·98; N, 3·31. $C_{27}H_{33}O_4N$ requires: C, 74·45; H, 7·64, N, 3·22%).

Methine **13** *from* O,N-*dimethylancistrocladine.* The methiodide (2·8 g), prepared from O,N-dimethylancistrocladine (2·55 g) by treatment with excess MeI in ether, was suspended in H_2O (50 ml) and stirred vigorously with freshly prepared Ag_2O (10 g) for 6 hr. The filtrate, after removal of excess Ag_2O, was evaporated to dryness *in vacuo* at 65°. The residue which had a strong basic smell was extracted with ether, washed with water and dried. Removal of ether gave a colourless gum which crystallised from ether as stout needles, (1·5 g), m.p. 148–149°, M$^+$ 449, $[\alpha]_D$ −148·1° (c = 2·58), UV: λ_{max} 228, 306, 321 and 335 mμ (log ε 4·86, 3·67, 3·56 and 3·49); λ_{sh} 295 mμ (log ε 3·63); IR: ^{Nujol}975 and 1680 cm^{-1} (propenyl group); NMR: $^{CDCl}3$ 100 MHz: 1·28 (q, J = 2 and 7 Hz, C$\underline{H}_3$ of the propenyl), 1·38 (d, J = 7 Hz, —C$\underline{H}$—(CH$_3$) N(C$\underline{H}_3$)$_2$), 2·01 (s, C-2′ C$\underline{H}_3$), 2·20 (s, N(C$\underline{H}_3$)$_2$), 3·55 (s, C-6 OC$\underline{H}_3$), 3·83 (q J = 7 Hz, —C$\underline{H}$—CH$_3$)

4·95 (Oct, J = 7 and 16 Hz, ), 6·13 (Oct, J = 2 and 16 Hz, ), 6·51 (s, C-3′ or C-7 H) and 6·72 (s, C-3′ or C-7 H). (Found: C, 74·81; H, 7·97; N, 3·31. $C_{28}H_{35}O_4N$ requires: C, 74·80; H, 7·85; N, 3·12%).

Dihydromethine **14** *from* **13**. The foregoing methine (112 mg) in alcohol (15 ml) was hydrogenated with Pd/C at atm press for 4 hr to yield the dihydromethine (102 mg), crystallising as cubes from hexane, m.p. 160–162°, UV: λ_{max} 231, 291, 306, 321 and 335 mμ (log ε 4·82, 4·02, 4·04, 3·95 and 3·89); NMR: ^{CDCl_3} 0·53 (t, J = 7 Hz, —CH_2—CH_2—CH_3), 1·55 (d, J = 7 Hz, C-1 CH_3), 2·12 (s, C-2′ CH_3), 2·28 (s, $N(CH_3)_2$), 3·70 (q J = 6·5 Hz, —$CH.CH_3N(CH_3)_2$), 3·55 (s, C-6 OCH_3), 3·92, 3·95, 3·98 (OCH_3s at C-8, C-4′, C-5′), 6·52, 6·80 (s, C-3′ H and C-7 H). (Found: C, 74·41; H, 8·40. $C_{28}H_{37}O_4N$ requires: C, 74·47; H, 8·26%).

Bismethine **15** *and hydroxy compd* **18** *from the methine* **13**. The methiodide (5 g) of the methine **13**, (m.p. 200–205° d), suspended in H_2O (100 ml) was stirred with Ag_2O (12 g) for 6 hr and filtered. The filtrate was evaporated to dryness at 80° and the residue was heated *in vacuo* at 160°/0·5 mm for 1 hr, cooled and extracted with ether. Removal of the solvent and chromatography of the residue (3·1 g) over neutral alumina and elution with C_6H_6 gave the bismethine **15** as white needles (1·8 g), m.p. 197–198°, $[\alpha]_D$ −52·52° (c = 1·49), UV: λ_{max} 231, 307, 321 and 335 mμ (log ε 4·89, 4·15, 4·08 and 3·94); λ_{sh} 265 and 295 mμ (log ε 4·14 and 4·05); IR: ^{Nujol} 920, 970 and 980 cm^{-1} (vinyl and propenyl groups); NMR: ^{CDCl_3} 1·33 (q, J = 1·5 and 6·5 Hz, —C(H)=C(H)CH_3) and 3·58 (s, C-6 OCH_3). (Found: C, 77·15; H, 7·09. $C_{26}H_{28}O_4$ requires: C, 77·20; H, 6·98%).

Elution of the column with C_6H_6 containing MeOH (1%) gave **18**, (420 mg) as white needles, m.p. 139–142°, $[\alpha]_D$ −58·81 (c = 1·35), UV: λ_{max} 229, 306, 321 and 336 mμ (log ε 4·85, 4·09, 3·97 and 3·89); λ_{sh} 295 mμ (log ε 4·04); IR: ^{Nujol} 3540 cm^{-1} (OH). (Found: C, 74·13; H, 7·32. $C_{26}H_{30}O_5$ requires: C, 73·91; H, 7·16%).

Hofmann degradation of dihydromethine **14**. The dihydromethine **14** was transformed to the methiodide by the usual procedure and the resulting methiodide (2 g) was suspended in water and stirred with Ag_2O (5 g), and filtered after 4 hr. The filtrate, on evaporation *in vacuo*, gave a gum which was heated to 180° *in vacuo* (1 mm). The resulting product (1·4 g) was chromatographed over neutral alumina. The fractions eluted with C_6H_6 gave the methine **16** (620 mg), m.p. 184–185°, IR: 905 cm^{-1} (terminal vinyl); NMR: ^{CDCl_3} 0·50 (t, J = 7 Hz, —CH_2—CH_2—CH_3), 2·08 (s, C-2′ CH_3), 3·58 (s, C-6 OCH_3), —C(H_X)=C(H_B)(H_A), δ H_A 5·73 (q, J_{AB} 2·5 Hz, J_{AX} 10 Hz), δ H_B 5·43 (q, J_{AB} 2·5 Hz, J_{BX} 16 Hz), 6·52 (s, C-3′ or C-7 H) and 6·80 (s, C-3′ or C-7 H). (Found: C, 76·70; H, 7·66. $C_{26}H_{30}O_4$ requires: C, 76·82; H, 7·44%).

The fractions eluted by benzene containing 0·5% MeOH, which were found to be homogeneous on TLC, on evaporation *in vacuo* gave **17**, crystallising as white needles (180 mg) from ether, m.p. 168–170°; UV: λ_{max} 230, 291, 305, 320 and 335 mμ (log ε 4·79, 3·99, 4·02, 3·93 and 3·87); IR: 3540 cm^{-1} (OH). (Found: C, 73·83; H, 7·95. $C_{26}H_{32}O_5$ requires: C, 73·56; H, 7·60%).

Lactone **19** *from the hydroxy compd* **18**. Compd **18** (150 mg) dissolved in dry EtOAc was ozonised at 0° for 2 hr. At the end of this period, EtOAc was removed *in vacuo* and the gum was dissolved in acetone (15 ml) and treated with aq $KMnO_4$ (50 mg in H_2O 5 ml). After 1 hr, the reaction mixture was filtered to remove MnO_2, acetone was removed *in vacuo* and the residue was treated with aq $NaHSO_3$ and acid and extracted with $CHCl_3$. The combined $CHCl_3$ extract, on removal of the solvent, gave the title compd as a gum; IR: CH_2Cl_2 1765 cm^{-1} (5-membered lactone).

Catalytic hydrogenation of the hydroxy compd **18**. The foregoing hydroxy compd (225 mg) dissolved in EtOH (150 ml) was hydrogenated over PtO_2 (100 mg) at atm press for 40 hr. After removal of the catalyst, the solvent was evaporated *in vacuo* and the residue (**20**) was crystallised from hexane, m.p. 169–170°, $[\alpha]_D$ −5·30° (C = 1·9); NMR: ^{CDCl_3} 0·53 (t, J = 7 Hz, —CH_2—CH_2—CH_3), 1·15 (t, J = 7 Hz, —CH_2—CH_3), 2·08 (s, C-2′ CH_3), 2·68 (q, J = 7 Hz, —CH_2—CH_3), 3·53 (s, C-6 OCH_3), 6·50 (s, C-3′ or C-7 H) and 6·80 (s, C-3′ or C-7 H). (Found: C, 76·79; H, 8·09. $C_{26}H_{32}O_4$ requires: C, 76·44; H, 7·90%).

Oxidation of ancistrocladine hydrochloride with $KMnO_4$. The hydrochloride (4·4 g) suspended in

water (100 ml) was treated with $KMnO_4$ aq (4 g in 100 ml H_2O) slowly with vigorous stirring. After 4 hr, MnO_2 was filtered off and washed repeatedly with hot water. The combined filtrate which was pale yellow in colour was acidified with 2N HCl and extracted several times with $CHCl_3$. The combined $CHCl_3$ extract was washed with H_2O and the residue (2·8 g) obtained by evaporation of the solvent was methylated with ethereal CH_2N_2 (prepared from 10 g nitrosomethylurea). After usual work-up, the semisolid was disolved in C_6H_6 and chromatographed over silica (100 g) and the column was eluted with C_6H_6. 20 ml fractions were collected and monitored on TLC. Fractions 14 to 21, which were found to be homogeneous on TLC, were combined and crystallised from hexane. Pale yellow needles of methyl 2-methyl-4,5-dimethoxy-1-naphthoate (20 mg; **4**) were formed. This was crystallised several times from hexane, m.p. 102–103°, identical in all respects (TLC, mmp and IR) with authentic specimens described below. M^+ 260, UV: λ_{max} 230, 306, 318 and 332 mμ (log ε 4·69, 3·95, 3·95 and 3·92); λ_{shl} 292 mμ (log ε 3·83), IR: ^{KBr} 1720 cm^{-1} (COOMe), (Found: C, 69·60; H, 6·33. $C_{15}H_{16}O_4$ requires C, 69·21; H, 6·20%).

Synthesis of methyl 2-methyl-4,5-dimethoxy-1-naphthoate (**4**)*:2-Methyl-4,5-dimethoxy-1-naphthaldehyde.* 1-Hydroxy-8-methoxy-3-methyl-naphthalene (**2**, 250 mg) dissolved in dry ether (35 ml) was cooled to 0° and treated with KCl (100 mg) and Zn $(CN)_2$ (300 mg). Dry HCl gas was bubbled in slowly until saturation (2 hr) and the reaction mixture which turned dark yellow was left overnight. After usual work-up, the crude aldehyde (**3**) was obtained as an yellow solid (228 mg). Recrystallisation from ether gave yellow needles, m.p. 112–113°, UV: λ_{max} 233, 257, 395 and 410 mμ (log ε 4·33, 4·39, 4·09, 4·17]; λ_{shl} 333 mμ (log ε 3·90); NMR: ^{CDCl_3} 2·67 (s, C-2 CH_3), 4·00 (s, C-5 OCH_3), 6·63 (s, C-3 H), 6·77 (q, J = 1·5 and 8 Hz, C-6 H), 7·42 (q, J = 8 Hz, C-7 H), 8·80 (q, J = 1·5 and 8 Hz, C-8 H), 10·50 (m, —C(H)=O)) and 10·67 (s, OH). (Found: C, 72·60; H, 5·72. $C_{13}H_{12}O_3$ requires: C, 72·21; H, 5·59%).

The methyl ether, prepared by use of MeI, K_2CO_3 in refluxing acetone, formed pale yellow prisms, m.p. 135–136°. (Found: C, 73·22; H, 6·33. $C_{14}H_{14}O_3$ requires: C, 73·02; H, 6·13%).

Methyl 2-methyl-4,5-dimethoxy-1-naphthoate (**4**). The above aldehyde (80 mg), dissolved in acetone (10 ml) (distilled over $KMnO_4$) was treated at room temp with aq $KMnO_4$ (50 mg in 5 ml H_2O). After usual work-up, the crude acid which was a yellow solid (40 mg) was methylated with ethereal CH_2N_2. Methyl 2-methyl-4,5-dimethoxy-1-naphthoate (32 mg) formed white needles from ether, m.p. 101–103°. (Found: C, 69·52; H, 6·62. $C_{15}H_{16}O_4$ requires: C, 69·21; H, 6·20%).

Michael addition of m-*methoxyphenyl acetonitrile to methyl crotonate.* To a stirred soln of Na (2·6 g) in abs EtOH (50 ml) was added a mixture of *m*-methoxyphenyl acetonitrile (14·7 g) and methyl crotonate (10 g). After refluxing for 3 hr in N_2 atm, alcohol was removed *in vacuo* and the residue was treated with H_2O and extracted with ether. The aq layer was cooled to 10° and acidified with 2N HCl and the separated gum was extracted with ether. The brown residue, obtained on evaporation of the solvent, was distilled *in vacuo*, pale yellow viscous oil (9·3 g), b.p. 179–182°/0·5 mm; IR: CH_2Cl_2 2240 (C≡N) and 1730 cm^{-1} ($COOCH_3$). (Found: C, 67·66; H, 6·46. $C_{14}H_{17}O_3N$ requires: C, 67·99; H, 6·93%).

The above cyanoester (**5**, 9·3 g) was hydrolysed with aq KOH (10%; 50 ml) in an oil-bath at 130° for 24 hr to give a crude dicarboxylic acid (8 g) which was directly brominated without purification. The diacid (8 g) dissolved in dry $CHCl_3$ (50 ml) was treated in the cold (10°) with Br_2 (5 g) dissolved in $CHCl_3$ (20 ml) with stirring. After 2 hr, water was added and the residue was extracted with ether. Removal of the solvent gave a gum (7·2 g) which slowly crystallised from benzene, m.p. 195–200°. (Found: C, 47·49; H, 4·73. $C_{13}H_{15}O_5Br$ requires: C, 47·13; H, 4·53%).

5-Bromo-1-keto-8-methoxy-3-methyltetralin-4-carboxylic acid. The above bromo compd (**6**, 11·6 g) was mixed intimately with PPA (58·9 g) and the mixture was heated to 90–95° for 1 hr. Water was cautiously added and the crude acid (**7**, 5·3 g) was filtered, washed with H_2O and dried. This was crystallised from ether containing a few drops of MeOH, white needles, m.p. 226–228°(d); IR: ^{Nujol} 1640 (CO) and 1730 cm^{-1} (COOH); NMR: ^{CDCl_3} 1·22 (diffuse signal, C-3 CH_3), 2·52 (m, C-2 CH_2), 3·83 (s, C-8 OCH_3), 4·13 (m, C-4 H), 6·88 (d, J = 9 Hz, C-6 H), 7·65 (d, J = 9 Hz, C-7 H) and 10·0 (s, broad, COOH, disappears with D_2O). (Found: C, 50·03; H, 4·34. $C_{13}H_{13}O_4Br$ requires: C, 49·86; H, 4·18%).

Treatment with ethereal CH_2N_2 gave the corresponding methyl ester, m.p. 155–156°; IR: ^{Nujol} 1680 (CO) and 1725 cm^{-1} (COOMe). (Found: C, 51·68; H, 4·75. $C_{14}H_{15}O_4Br$ requires: C, 51·39; H, 4·62%).

1-Keto-8-methoxy-3-methyltetralin-4-carboxylic acid. The foregoing acid (3 g) dissolved in alcohol

(120 ml) containing 2N NaOH (8 ml) was shaken in an atm of H_2 with Ra-Ni (3 g) at room temp for 12 hr. Work-up gave the title compd (1·8 g), colourless needles from acetone, m.p. 195–198° (d); IR: ^{Nujol} 1660 (CO) and 1730 cm^{-1} (COOH), NMR: $CDCl_3+CD_3SOCD_3$ 1·08 (d, J=6·5 Hz, C-3 $C\underline{H}_3$), 3·63 (d, broad, J = 6 Hz, C-4 $\underline{H}$), 6·95 (q, J = 8 and 1·5 Hz, C-7 $\underline{H}$), 7·47 (q, J = 8 Hz, C-6 $\underline{H}$) and 10·62 (s, broad, $W_{\frac{1}{2}}$ 8 Hz, COO$\underline{H}$). (Found: C, 66·83; H, 6·31. $C_{13}H_{14}O_4$ requires: C, 66·65; H, 6·02%).

Methyl 2-methyl-4-hydroxy-5-methoxy-1-naphthoate (**8**). The above acid (0·6 g), anhyd K_2CO_3 (8 g), CH_3I (5 ml) and acetone (75 ml) were refluxed gently on a water-bath for 12 hr. Removal of K_2CO_3 and acetone gave a gum which was passed through a column of neutral alumina and eluted with C_6H_6. The fractions eluted by C_6H_6, which were found to be homogeneous on TLC, were combined and the solvent was removed *in vacuo*. The colourless gum (0·518 g) so obtained was dissolved in dry xylene (20 ml) containing chloranil (0·503 g) and refluxed in N_2 atm in an oil-bath at 150° for 12 hr. Xylene was then removed *in vacuo* and the product was dissolved in ether and washed with dil NaOH aq and then with water. Removal of the solvent and crystallisation of the residue (0·25 g) from hexane gave **8**, pink flaky crystals, m.p. 120–121°: UV: λ_{max} 232, 306, 319 and 334 mμ (log ε 4·71, 3·96, 3·98, 3·97) and λ_{shl} 293 mμ (log ε 3·82); IR: 3350 (OH) and 1725 cm^{-1} (COOMe); NMR: $CDCl_3$ 2·42 (s, C-2 $C\underline{H}_3$), 3·95, 3·97 (s, $OC\underline{H}_3$ and $COOC\underline{H}_3$), 6·67 (q J = 2 and 8Hz, C-6 $\underline{H}$), 6·73 (s, C-3 $\underline{H}$), 7·27 (q, J = 8 Hz, C-7 $\underline{H}$), 7·47 (q, J = 2 and 8 Hz, C-8 $\underline{H}$) and 9·53 (s, O$\underline{H}$, disappears on addn of D_2O). (Found: C, 68·51; H, 5·93. $C_{14}H_{14}O_4$ requires: C, 68·28; H, 5·73%).

Methyl 2-methyl-4,5-dimethoxy-1-naphthoate (**4**). The above ester (120 mg) dissolved in dry acetone (25 ml) was refluxed with anhyd K_2CO_3 (1 g) and MeI (2 ml) for 2 days. After work-up in the usual manner, the required compd (110 mg) was obtained as white needles, m.p. 100–102°, from hexane. (Found: C, 69·52; H, 6·43. $C_{15}H_{16}O_4$ requires: C, 69·21; H, 6·20%).

O-*Methylancistrocladine* (**21**). N-Formyl-O-methylancistrocladine (**11**; 3 g), ethylene glycol (75 ml), water (3 ml) and KOH pellets (20 g) were refluxed gently at 160–165° in an oil-bath for 10 hr in N_2 atm. Water was added and the white solid that separated was filtered and washed with water. The ppt was dried and dissolved in $CHCl_3$ and treated with HCl gas. The hydrochloride, that separated on removal of $CHCl_3$ *in vacuo*, was crystallised from acetone as white needles (1·8 g), m.p. 315–317° (d), $[\alpha]_D$–56·1° (c = 1·9); IR: ^{Nujol} 2450 and 2630 cm^{-1} (N$\dot{H}$). (Found: C, 67·79; H, 7·42. $C_{26}H_{31}O_4N$ HCl requires: C, 68·18; H, 7·04%).

O-Methylancistrocladine (**21**) regenerated from the above hydrochloride cyrstallised slowly from MeOH as white fluffy needles, m.p. 200–202°, UV: λ_{max} 231, 292, 306, 321 and 335 mμ (log ε 4·86, 4·07, 4·11, 4·02 and 3·96); NMR: $CDCl_3$ 0·93 (d, J = 7 Hz, C-3 $C\underline{H}_3$), 1·45 (d, J = 7 Hz, C-1 $C\underline{H}_3$), 2·05 (s, C-2′ $C\underline{H}_3$), 3·57 (s, C-6 $OC\underline{H}_3$), 3·88, 3·95, 3·97 (OMe at C-4′, C-5′ and C-8), 6·45 and 6·80 (s for C-3′ and C-7 $\underline{H}$). (Found: C, 73·75; H, 7·72. $C_{26}H_{31}O_4N$ requires: C, 74·08; H, 7·41%).

Dehydrogenation of O-*methylancistrocladine* (**21**). The title compd (175 mg) dissolved in freshly distilled *cis*-decalin (9 ml) was heated under gentle reflux with Pd/c (10%; 200 mg) in CO_2 stream for 4 hr. At the end of this period C_6H_6 was added and the solvents removed *in vacuo*. Chromatography of the residue over basic alumina and elution of the column first with hexane and then with C_6H_6 containing MeOH (1%) gave a solid (35 mg), which crystallised from ether to give **22**, m.p. 240–242°, $[\alpha]_D$ +58·87° (c = 1·6); UV: λ_{max} 232, 262, 308, 322 and 336 mμ (log ε 4·92, 4·43, 4·16, 4·18 and 4·16), λ_{shl} 245, 293 and 330 mμ (log ε 4·72, 4·04 and 4·15). (Found: C, 74·65; H, 6·90. $C_{26}H_{27}O_4N$ requires: C, 74·80; H, 6·52%).

N-*Formyldesmethoxytetrahydroancistrocladine* (**24**). Desmethoxytetrahydroancistrocladine (4 g) dissolved in freshly distilled HCOOEt (35 ml) was heated in a sealed tube at 100° for 10 hr. The product, after removal of HCOOEt *in vacuo*, was dissolved in MeOH (50 ml) and allowed to stand at room temp with 2N NaOH (10 ml) for 4 hr. Water was added followed by 2N HCl (50 ml) and the crude product was filtered and washed with water. Crystallisation from acetone gave white needles (3 g) of the N-formyl derivative, m.p. 235–237°, $[\alpha]_D$–80·01° (c=1·09); UV λ_{max} 284 and 300 mμ (log ε 3·76 and 3·80); IR: ^{Nujol} 3260 (OH) and 1638 cm^{-1} (N—CHO); NMR: $CDCl_3$ 0·93 and 1·13 (2 sets of doublets, J = 6·5 Hz, C-3 $C\underline{H}_3$), 1·38 and 1·40 (2 sets of doublets, J = 6·5 Hz, C-1 $C\underline{H}_3$), 1·97 and 2·02 (2 singlets, C-2′ $C\underline{H}_3$), 5·57 (s, O$\underline{H}$, collapsible with D_2O), 6·57 (s, C-3′ or C-7 $\underline{H}$), 6·68 (s, C-3′ or C-7 $\underline{H}$), 8·20 and 8·30 (2 singlets, N—C$\underline{H}$O). (Found: C, 73·21; H, 7·75. $C_{25}H_{31}O_4N$ requires: C, 73·32; H, 7·63%).

The O-methyl ether of the above compd made by treatment with ethereal CH_2N_2 formed a white froth which when reduced with LAH in ether gave O,N-dimethyldesmethoxytetrahydroancistrocladine, m.p. 174–175°, $[\alpha]_D$–32·09° (c=2·22); UV: λ_{max} 284 mμ (log ε 3·71); NMR: $CDCl_3$ 100 MHz, 1·05 (*d*, J = 6·5 Hz, C-3 $C\underline{H}_3$), 1·33 (d, J = 6·5 Hz, C-1 $C\underline{H}_3$), 1·65 (m, C-6′ and C-7′ $C\underline{H}_2$), 1·87 (s, C-2′ $C\underline{H}_3$),

1·95 (d, unresolved, C-4 CH_3), 2·15 (m, C-8 CH_2), 2·28 (s, N—CH_3), 2·70 (m, C-5′ H), 3·16 (m, C-3 H), 4·06 (q, J=6·5 Hz, C-1 H), 6·45 (s, C-7 H) and 6·62 (s, C-3′ H). (Found: C, 76·57; H, 8·74. $C_{26}H_{33}O_3N$ requires: C, 76·24; H, 8·61%).

O-*Allyl*-N-*formyldesmethoxytetrahydroancistrocladine* (**25**). Compound **24** (4 g), freshly distilled allyl bromide (10 ml), dry K_2CO_3 (15 g) and acetone (150 ml) were refluxed gently in an oil-bath maintained at 80° for 50 hr. At the end of this period, the reaction mixture was filtered and the residue washed several times with acetone. The combined filtrate was concentrated to dryness and the residue was dissolved in ether, washed with water and dried. The crude gum, dissolved in benzene, was chromatographed over silica and eluted with benzene and then with C_6H_6: $CHCl_3$. The fractions eluted by C_6H_6: $CHCl_3$ (1:1) which was found to be homogeneous on TLC were combined to give the allyl ether **25** as a white froth (2·75 g). $[\alpha]_D$−64·82° (c=1·23); UV: λ_{max} 284 mμ (log ε 3·77); IR: CH_2Cl_2 1660 cm^{-1} (N—CHO). NMR: $CDCl_3$ 0·92 and 1·13 (2 sets of doublets, J=7 Hz, C-3 CH_3), 1·38 (d, J=7 Hz, C-1 CH_3), 1·90 and 1·95 (2 singlets, C-2′ CH_3), 4·45 (m, —O—CH_2—), 5·1 (m, 3 vinyl H), 6·45 (s, C-3′ or C-7 H), 6·58 (s, C-3′ or C-7 H), 8·25 and 8·37 (2 broad singlets, N—CHO). (Found: C, 74·22; H, 8·34. $C_{28}H_{35}O_4N$ requires: C, 74·80; N, 7·85%).

Reduction of the above compd with LAH at room temp gave **26** as a colourless gum; NMR: $CDCl_3$ 1·03 (d, J=6·5 Hz, C-3 CH_3), 1·32 (d, J=6·5 Hz, C-1 CH_3), 1·87 (s, C-2′, CH_3), 2·28 (s, N—CH_3), 3·12 (m, C-3 H), 3·80 (s, C-4′ and C-8 OCH_3), 4·03 (q, J=6·5 Hz, C-1 H), 4·42 (d, unresolved, J=6 Hz, —OCH_2—), 5·05 (m, 3 vinyl H), 6·40 (s, C-3′ or C-7 H) and 6·57 (s, C-3′ or C-7 H).

The hydrochloride of the above base crystallised from acetone as white needles, m.p. 295–297° (d), $[\alpha]_D$−8·6° (c=2·39 in MeOH). (Found: C, 71·30; H, 8·47. $C_{28}H_{38}O_3N$ Cl requires: C, 71·24; H, 8·11%).

Claisen rearrangement of O-*allyl*-N-*formyldesmethoxytetrahydroancistrocladine* (**25**). The title compd (2·75 g) was dissolved in $C_6H_5NMe_2$ (75 ml) and heated under reflux at 230° in an oil-bath for 4 hr in an atmosphere of dry N_2. At the end of this period ether (250 ml) was added, cooled to 0° and then treated with 2N HCl. The ether extract was washed with water and dried. Removal of the solvent gave a gummy residue which showed 2 spots on TLC of which one was found to be the starting material. The crude gum (2·45 g) was dissolved in C_6H_6 and chromatographed over a column of silica and eluted with C_6H_6. 25 ml fractions were collected and monitored on TLC. Fractions 1–45 gave oily impurities. Further elution of the column with C_6H_6: $CHCl_3$ (3:2) gave a colourless gum (611 mg), which when left in CH_3OH overnight formed white plates of **27**, m.p. 170–172°, $[\alpha]_D$−81·08° (C=3·52); UV: λ_{sh} 277 mμ (log ε 3·65) and λ_{max} 283 mμ (log ε 3·68); IR: CH_2Cl_2 3520 (OH) and 1660 cm^{-1} (N—CHO). NMR: $CDCl_3$ 0·93 and 1·13 (2 sets of doublets, J=6·5 Hz, C-3 CH_3), 1·42 and 1·45 (2 sets of doublets, J=6·5 Hz, C-1 CH_3), 1·97 and 2·00 (singlets, C-2′ CH_3), 3·47 (m, CH_2, both benzylic and allylic), 4·80 (s, OH, disappears with D_2O), 5·0 (m, 3 vinyl hydrogens), 6·67 (s, C-3′ H), 8·23 and 8·33 (2 broad singlets, N—CHO). (Found: C, 74·49; H, 7·84. $C_{28}H_{35}O_4N$ requires: C, 74·80; H, 7·85%).

Ozonolysis of 7-C-*allyl*-N-*formyldesmethoxytetrahydroancistrocladine* (**27**). The above compd (350 mg) dissolved in freshly distilled EtOAc (30 ml) was cooled to 0° and treated with O_3 for 3 hr. The ozonide was decomposed by hydrogenation over Pd/c in EtOAc and the colourless gum was heated at 90° for ¼ hr with *o*-phosphoric acid (2 ml). Water was added and the gum that had separated was extracted with ether and washed with water. Removal of the solvent gave a colourless gum which showed one intense spot on TLC. This was chromatographed over silica and the column was eluted with C_6H_6 and then with C_6H_6: $CHCl_3$ (3:2). The latter eluted a gum (75 mg) which when dissolved in CH_3OH gave needles, m.p. 283–285° (d); UV: λ_{max} 252, 259 and 284 mμ (log ε 4·19, 4·17, and 3·62); λ_{sh} 296 mμ (log ε 3·32); IR: ^{KBr}3120 (furan) and 1655 cm^{-1} (N—CHO); NMR: $CDCl_3$ 0·93 and 1·08 (d, J = 7 Hz, C-3CH_3), 1·43 and 1·47 (d, J=7 Hz, C-1 CH_3), 3·87 (s, C-4′ OCH_3), 4·17 and 4·20 (2 sets for C-8 OCH_3), 6·95 (2 sets of doublets, J=2·5 Hz, β-proton of furan), 7·45 (2 sets of doublets, J=2·5 Hz, α-proton of furan), 6·67 (s, C-3′ H) and 8·33 (m, N—CHO). (Found: C, 74·62; H, 7·35. $C_{27}H_{31}O_4N$ requires: C, 74·80; H, 7·21%). The compd gave a positive Ehrlich test.

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