ALKALOIDS OF ANCISTROCLADACEAE†

Tuticorin R. Govindachari* and Papagudi C. Parthasarathy

CIBA-GEIGY Research Centre, Goregaon, Bombay 400 063, India

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

The chemistry of the various isoquinoline alkaloids isolated from species of Ancistrocladus, the only genus of the plant family Ancistrocladaceae, has been reviewed.

Table of contents

---

†Contribution No. 490 from CIBA-GEIGY Research Centre

5. Alkaloids of Ancistrocladus ealaensis - ancistrocladonine, ancistroealaensine, ancistrine, ancistine and ancistrocladeine
6. Alkaloids of Ancistrocladus congolensis - (+)-ancistrocladine, O-methylancistrocladine, ancistrocongine and ancistrocongolansine
7. Conclusion
8. References

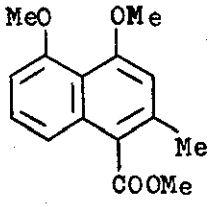
Introduction

ANCISTROCLADUS, the only genus of the plant family Ancistrocladaceae comprising nearly twenty species, is distributed in tropical Asia, the Malay Archipelago and West Africa.[1] Of these, nearly ten species occur in Asia. The only species that grows in India, which was the first to be studied in detail in our laboratories, is Ancistrocladus heyneanus Wall., a woody climber. In 1970 this plant was investigated by us which led to the discovery of ancistrocladine, a new type of isoquinoline alkaloid. In later years more compounds related to ancistrocladine were isolated by us and also by French workers.

Ancistrocladine from Ancistrocladus heyneanus Wall. - absolute stereochemistry

Ancistrocladine, $C_{25}H_{29}O_4N$, m.p. 265-267°, $[\alpha]_D$ - 32.4° (pyridine) is a cryptophenolic secondary base incorporating

three methoxyls, one aromatic methyl and two secondary methyl groups and was isolated in nearly 1% yield from the roots of Ancistrocladus heyneanus. The uv spectrum, λ_{max} 230, 290, 305, 320 and 335 nm, log ε (4.79, 4.00, 4.04, 3.95 and 3.87) denoted a highly aromatic system and had a close resemblance to the uv spectrum of 1,8-dimethoxy-3-methylnaphthalene. The ir spectrum showed absorptions at 3440 and 3330 cm^{-1} due to the -OH and NH functions. Mild permanganate oxidation of the hydrochloride salt of the alkaloid generated an acid whose methyl ester was shown[2,3] to be methyl 4,5-dimethoxy-2-methyl-1-naphthoate (1). This readily accounted for nearly half the number of carbon atoms and also two methoxyl and one aromatic methyl groups present in the molecule.

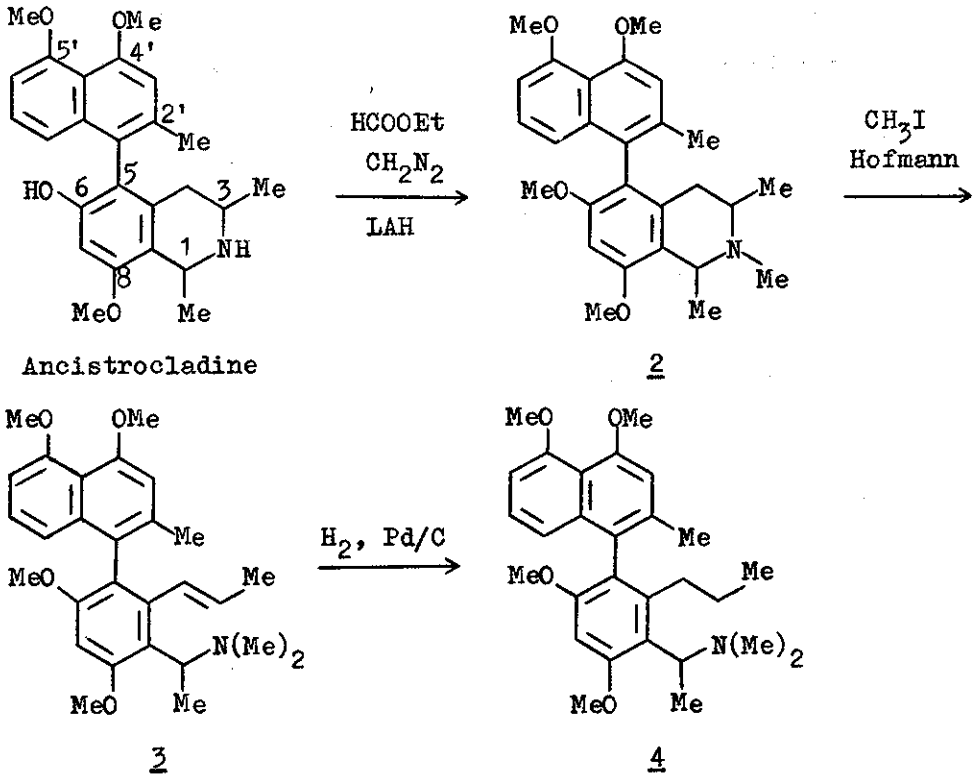


1

The main line of the extensive degradative work involving Hofmann degradation experiments on O,N-dimethylancistrocladine (2) is presented in Scheme 1. The spectroscopic studies of the derived methines obtained in the degradative work unambiguously showed the presence of a 1,3-dimethyltetrahydroisoquinoline ring linked at C-5 to the naphthalene ring in ancistrocladine. On submitting O,N-dimethylancistrocladine (2) to the Hofmann degradation, the methine 3 was formed which showed ir bands at

975 and 1680 cm^{-1} characteristic of a propenyl group. The nmr spectrum of 3 confirmed the presence of this grouping and also an α-dimethylaminoethyl side chain. On hydrogenation the methine 3 gave a dihydro derivative 4 in which the propenyl group was reduced. In the nmr spectrum of 4 a triplet at δ 0.53 (J = 7 Hz) for the methyl group of n-propyl chain was observed. The abnormal shielding of the methyl group in 4 had necessitated the placement of the naphthalene ring at C-5 in ancistrocladine, thereby bringing the methyl group of the n-propyl chain in 4

Scheme 1

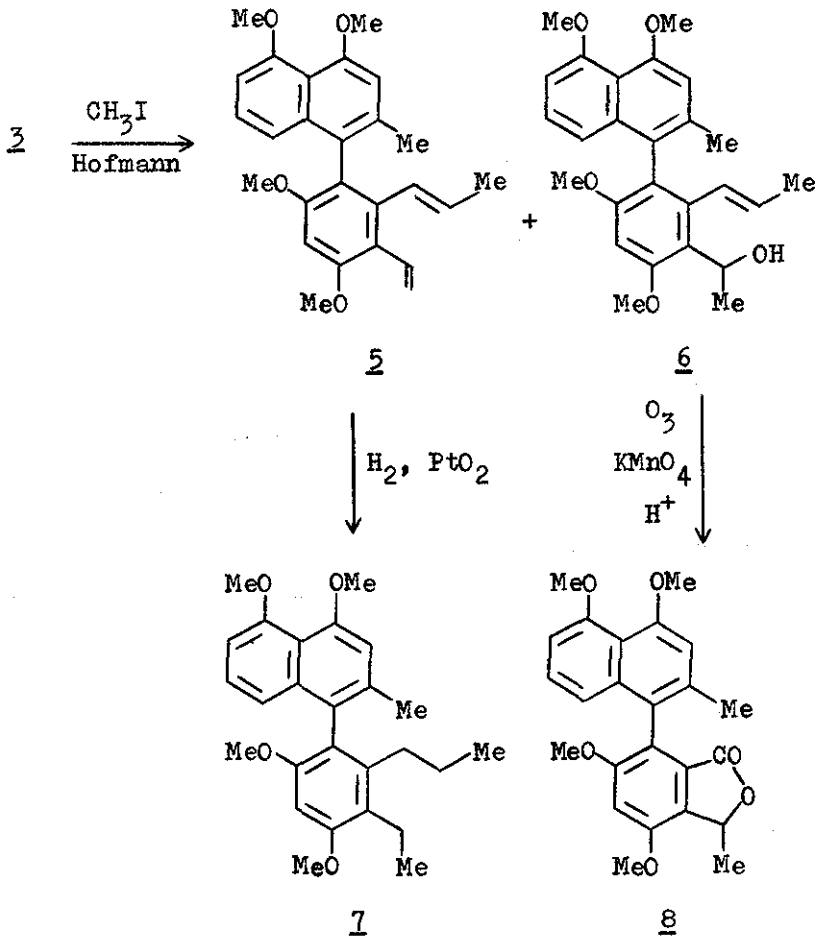


Ancistrocladine

2

3

4



within the shielding zone of the naphthalene ring. A further Hofmann sequence on the methine 3 led to an optically active nitrogen-free bismethine 5 which had a vinyl group besides the propenyl chain. A small amount of the hydroxy compound 6 was formed as a result of the replacement of the dimethylamino group in 3 by a hydroxyl group. Also, this gave 5 on dehydration. Ozonolysis of 6, accompanied by oxidation and acid treatment of the derived product gave a lactone 8. This exhibited an intense

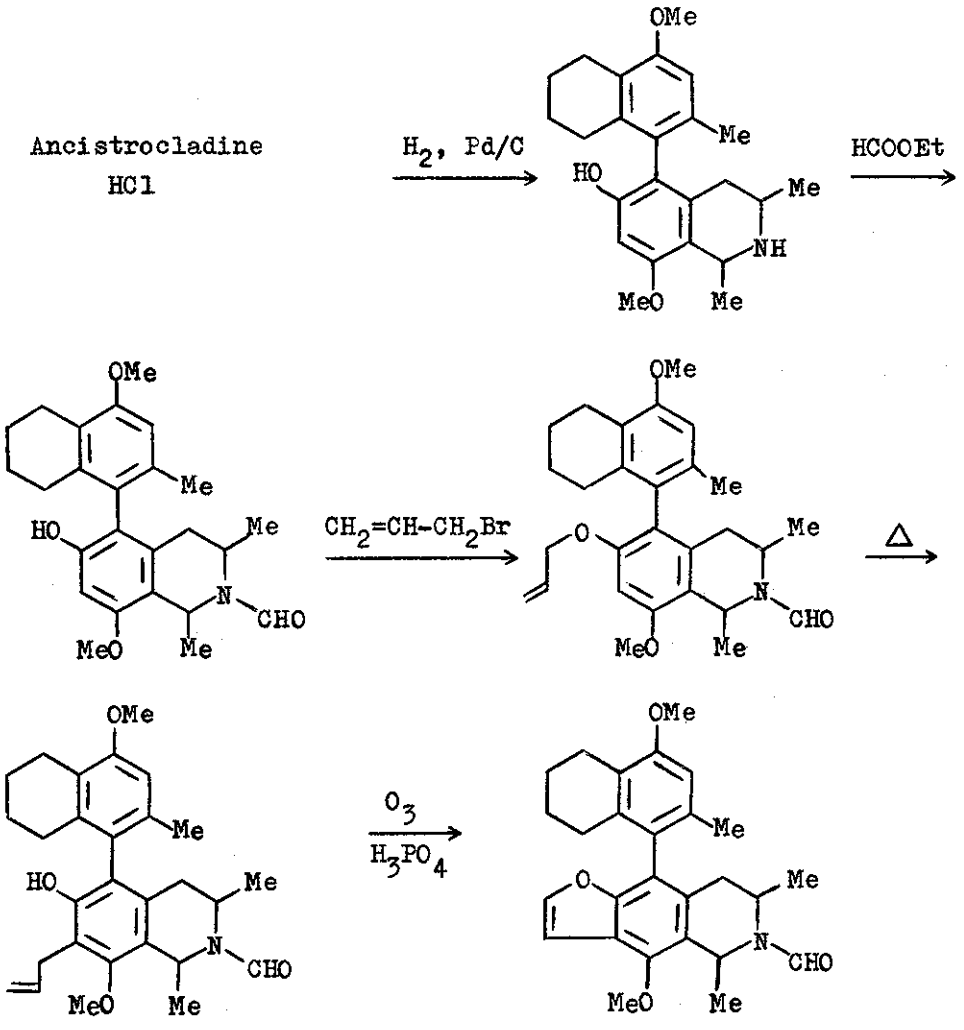
band in the infrared at 1765 cm^{-1} indicating that it was 5-membered. The formation of this lactone would be expected only when the propenyl and the α-hydroxyethyl side chains in 6 are ortho to each other and hence firmly proved the presence of a 1,3-dimethyltetrahydroisoquinoline ring in ancistrocladine.

A phenolic hydroxyl group at C-4' or C-5' position in the naphthalene moiety of ancistrocladine would be anticipated to appear downfield in the nmr spectrum (~δ 9.2-9.5) since this would be hydrogen bonded with the peri-OMe group. In all the derivatives of ancistrocladine in which the hydroxyl group was free, the OH group appeared as singlet in the nmr spectrum between δ 4.9 and 5.3 suggesting that the tetrahydroisoquinoline ring should bear the phenolic hydroxyl group. The significant shielding of the methoxyl and acetate groups (δ 3.57 and 1.72, respectively) in the methyl ether and the O,N-diacetate of the base clearly favoured the placement of the phenolic hydroxyl group at C-6.

A further degradative sequence depicted in Scheme 2 involving a Claisen rearrangement of the allyl ether eventually resulted in the formation of the benzofuran 9. This enabled the assignment of the third methoxyl group at C-8 in ancistrocladine. This was also considered as the most logical position from the biogenetic viewpoint.

In a later paper[4] further evidence, conclusively proving the earlier findings, was presented. This involved Hofmann degradation study on N-methyl-O-benzylancistrocladine and

Scheme 2



9

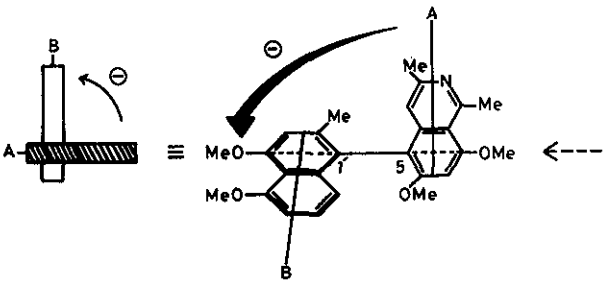
comparison of the nmr spectra of the derived methines with those derived from N-methyl-6-benzyloxy-7-methoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline.

The relative stereochemistry of the methyl substituents at

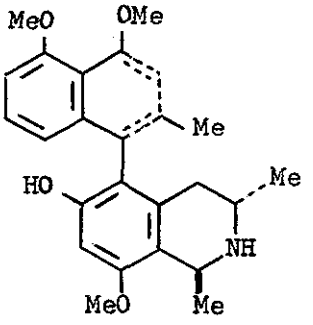
C-1 and C-3 in ancistrocladine was shown[5] to be trans by comparison of the 100 MHz nmr spectrum of O-methylancistrocladine with model compounds which also involved some spin-decoupling experiments. In connection with this work, it was observed that the axial hydrogen at C-1 would be ideally placed for homoallylic coupling with the axial proton at C-4 on the tetrahydroisoquinoline ring. After conclusion of our exhaustive study, the gross structure as well as the relative position of the methyl substituents at C-2' and C-3, shown to be on the same side of the general plane of the isoquinoline ring, were established[5] by Dr. Kartha by an X-ray study of the hydrobromide salt of ancistrocladine. Application of the exciton chirality method[6] led to the derivation of the absolute configuration of ancistrocladine in respect of the disymmetry arising from the restricted rotation around the C(5)-C(1') bond. In the uv spectrum of tetradehydro-O-methylancistrocladine, wherein the asymmetric centres at C-1 and C-3 were destroyed, the intense shorter wavelength absorptions at 232 and 245 nm with transition moments along the long axes of the nuclei ($^1A \rightarrow {}^1B_b$) interacted to give an exciton-split cd spectrum. In the cd spectrum, the sign of the first Cotton effect was positive indicating that the chirality of the long axes should be positive. If the chirality has to be positive, then the molecule should be represented by the absolute configuration as indicated in figure 1. Coupled with the X-ray and chemical studies, ancistrocladine should be depicted by structure 10. This was confirmed by exhaustive ozonolysis of ancistrocladine to yield L(+)-β-amino-n-butyric

acid (11), of known absolute configuration.

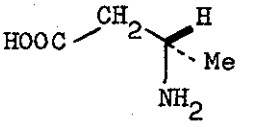
Figure 1



Chirality should be viewed from the direction of the dotted arrow



10

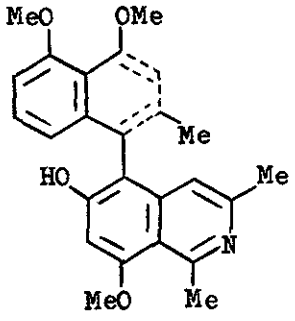


11

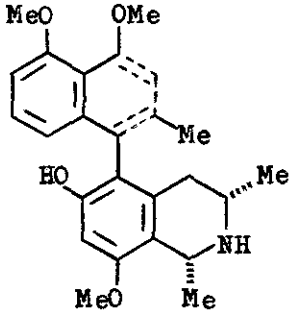
Minor alkaloids of Ancistrocladus heyneanus

Ancistrocladinine

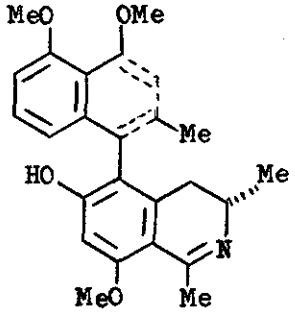
Ancistrocladinine, $C_{25}H_{27}O_4N$, mp 235-238°, was isolated[7] in very low yield (~0.001%) from the roots of Ancistrocladus heyneanus. Its uv spectrum was very similar to ancistrocladine. The conspicuous feature in the nmr spectrum was the presence of only one secondary methyl group (doublet, J = 7 Hz at δ 1.01). The chemical shift due to the secondary methyl protons clearly indicated that it should be located at C-3. Dehydrogenation of ancistrocladinine gave an isoquinoline 12, which was obtained earlier from ancistrocladine (10). On reduction with zinc and aqueous sulphuric acid ancistrocladinine furnished ancistrocladine (10) together with isoancistrocladine, formulated as 13. Therefore ancistrocladinine should possess the structure 14.



12



13



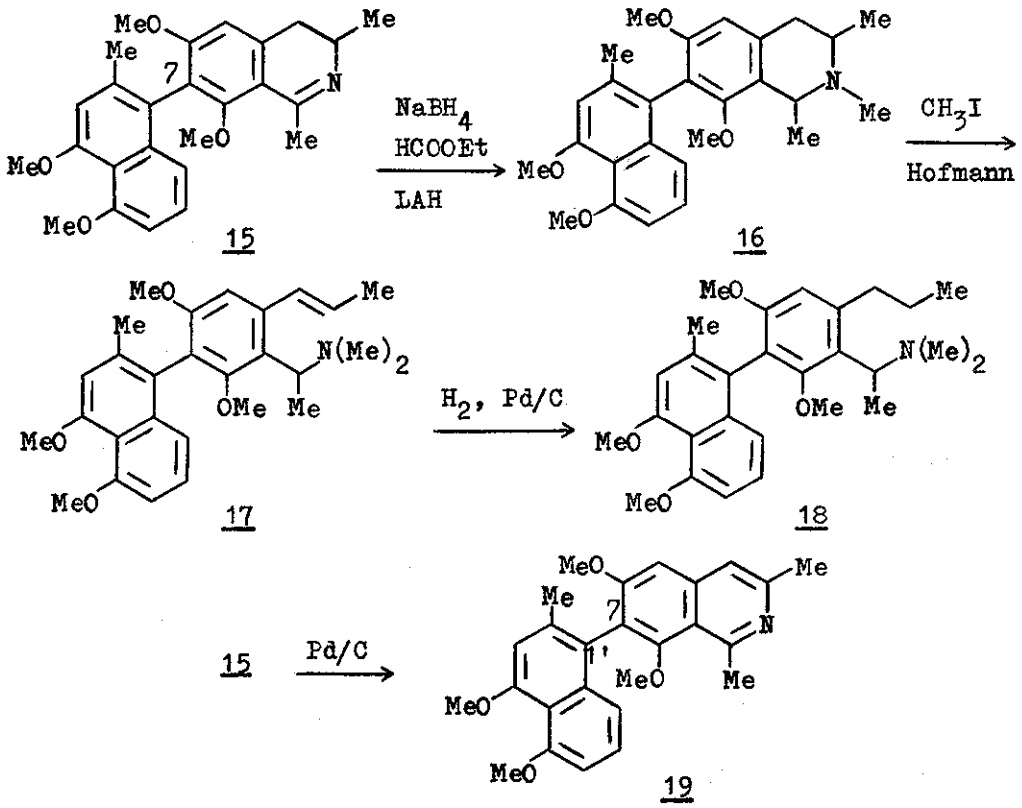
14

Ancistrocladisine

The alkaloid ancistrocladisine, $C_{26}H_{29}O_4N$, mp 178-180° $[\alpha]_D$ -16.13°, was isolated[8] by us from the roots of Ancistrocladus heyneanus in 1972 and its structure was elucidated[8]

without much difficulty. The uv spectrum of the alkaloid showed a strong resemblance to ancistrocladine, ancistrocladinine and 1,8-dimethoxy-3-methylnaphthalene. Like ancistrocladinine, the nmr spectrum of ancistrocladisine displayed only one secondary methyl group at C-3. Extensive degradative and spectroscopic studies (Scheme 3) based essentially on the same line of approach as described for ancistrocladine led to the assignment of structure 15 for ancistrocladisine.

Scheme 3

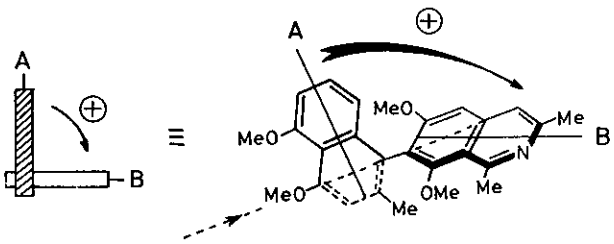


Hofmann degradation of N-methyldihydroancistrocladisine (16) gave the methine base 17 which was particularly amenable

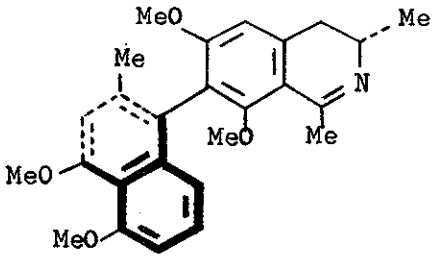
to nmr spectral analysis. Peaks characteristic of both propenyl and α-dimethylaminoethyl side chains were present in the nmr spectrum. The signals of the olefinic methyl group in 17 and the corresponding methyl group in its dihydro derivative 18 (δ 1.93, q, J = 2 and 6.5 Hz, olefinic methyl protons in 17, δ 1.08, t, J = 7 Hz, methyl group of the n-propyl chain in 18) appeared in the normal region, unlike the methines 3 and 4 derived from ancistrocladine. Hence it was concluded that the naphthalene ring should be at C-7 as in structure 15. In agreement with this structure, ancistrocladisine showed two shielded methoxyl groups in the nmr spectrum and also underwent smooth dehydrogenation to furnish the isoquinoline 19. As in ancistrocladine, the use of the exciton chirality method[6] led[9] to the establishment of the absolute configuration of ancistrocladisine. The uv spectrum of 19 was similar to that of the isoquinoline from O-methyl-ancistrocladine. Restricted rotation around the C(7)-C(1') bond linking the naphthalene and isoquinoline chromophores led to a coupled interaction between the two long axis transitions which gave rise to an exciton-split cd spectrum. The sign of the first Cotton effect was positive suggesting that the chirality should be indicated as in figure 2.

The formation of L-β-amino-n-butyric acid by extensive ozonolysis of ancistrocladisine, coupled with the findings of the exciton chirality method, resulted in the elucidation of the absolute stereochemistry as depicted in structure 20.

Figure 2



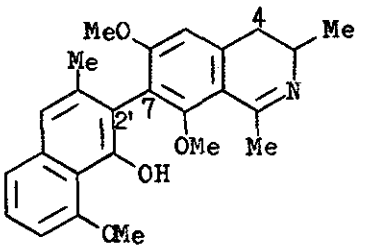
Chirality should be viewed from the direction of the dotted arrow



20

Ancistrocladidine

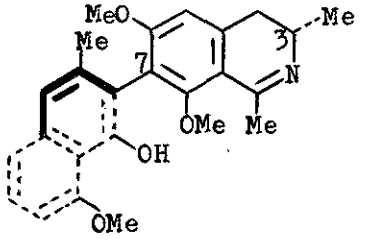
Ancistrocladidine, $C_{25}H_{27}O_4N$, mp 245-47°, $[\alpha]_D$ -149.73°, isomeric with ancistrocladinine, was another unusual isoquinoline alkaloid isolated from the roots of Ancistrocladus heyneanus. In view of its presence in the plant in extremely low yield chemical degradation work could not be undertaken, However, spectral data were sufficient to postulate[10] the structure of the molecule. The ir spectrum showed a pronounced band at 3360 cm^{-1} (OH) and its uv spectrum was strikingly similar to 1-hydroxy-8-methoxy-3-methylnaphthalene. The nmr spectrum of ancistrocladidine was particularly informative revealing the presence of a 1,3-dimethyl-3,4-dihydroisoquinoline and 1-hydroxy-8-methoxy-3-methylnaphthalene rings, the C-2 position of the latter linked to C-7 of the former. Thus in the nmr spectrum the multiplet due to C-4 methylene group at δ 2.55 was in the normal region indicating that the substituted naphthalene must be at C-7 of the isoquinoline ring. Two methoxyl groups were assigned the positions at C-6 and C-8 because of their shielding (nmr signals at δ 3.39 and 3.75). The chemical shift of the hydroxyl proton (δ 9.58) coupled with its resistance to acetylation indicated that it should be bonded to a methoxyl group as in 1-hydroxy-8-methoxy-3-methylnaphthalene. Dihydroancistrocladidine, in which the isoquinoline ring was reduced, gave a O,N-diacetate which showed a shielded (δ 1.98) acetoxyl group in the nmr spectrum. The data outlined above would fit in admirably with structure 21 for ancistrocladidine.



21

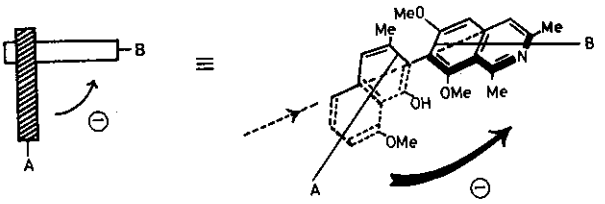
Application of the exciton chirality method had led[9] to the determination of the absolute configuration in respect of the disymmetry arising from restricted rotation around the C(7)-C(2') bond. A Davydov splitting was observed in the allowed transitions for the isoquinoline derived from ancistrocladidine and the first Cotton effect was negative so that the two aromatic chromophores should interact as depicted in figure 3, thus establishing the absolute configuration at the chiral site.

Following the procedure[11] of Corrodi and Hardegger, extensive ozonolysis of ancistrocladidine accompanied by purification of the derived oxidation products gave[9] L-β-amino-n-butyric acid. Thus the absolute stereochemistry of ancistrocladidine was firmly established as 22, the absolute configurations at C-3 and C-7 being S and R, respectively.



22

Figure 3



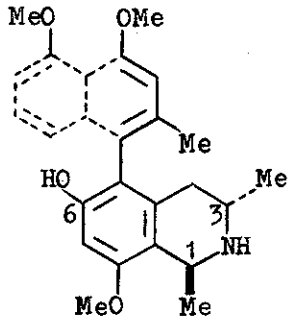
Chirality should be viewed from the direction of the dotted arrow

Hamatine from Ancistrocladus hamatus

Ancistrocladus hamatus, which grows in Sri Lanka, was the second species of the genus Ancistrocladus, recently examined by us. This study led to the isolation[12] of ancistrocladine and yet another new alkaloid name hamatine.

Hamatine, $C_{25}H_{29}O_4N$, m.p. 250-252°, $[\alpha]_D$ + 77.4°, was isomeric with ancistrocladine. The following functional groups, as indicated by uv, ir and nmr spectra, were present in the molecule:

NH and OH groups, 2 secondary methyl and three methoxyl groups of which one was shielded as in ancistrocladine, one aromatic methyl group and a 1,8-dimethoxy-3-methylnaphthalene ring. Dehydrogenation of O-methylhamatine gave an isoquinoline which was found to be an enantiomer of the isoquinoline obtained by dehydrogenation of O-methylancistrocladine. The cd spectrum also corroborated this finding (positive first Cotton effect). The NMR spectra of hamatine and its O-methyl ether showed the trans disposition of the substituents at C-1 and C-3, based on the absence of a long-range coupling and the presence of a phenolic hydroxyl group at C-6 as in ancistrocladine. Since hamatine was not an enantiomer of ancistrocladine, structure 23 was put forth by us.

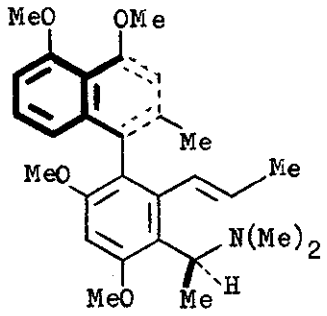


23

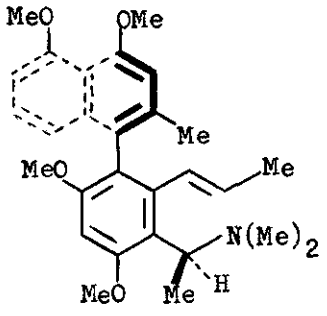
In agreement with the structure 23, hamatine furnished L-β-amino-n-butyric acid confirming the S configuration at C-3.

More recently, we had firmly established[13] the absolute configuration of hamatine at C-1, the only structural feature which was not resolved unambiguously by us earlier. Our earlier study[12] rested on the absence of a long-range coupling for the

C-1 proton in the nmr spectrum of hamatine. Hofmann degradation of O,N-dimethylhamatine, prepared in the same manner as O,N-dimethylancistrocladine (16), gave a methine, different from the isomeric methine 24a derived from O,N-dimethylancistrocladine. Hence it became possible to assign unequivocally structure 24b for the methine from O,N-dimethylhamatine. If position C-1 in hamatine were to possess the R-configuration, the enantiomer of the methine 24a would have resulted on Hofmann degradation.



24a

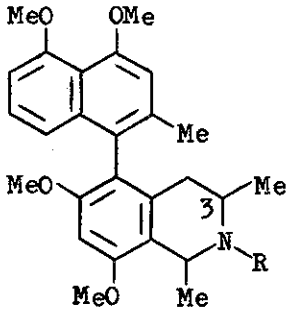


24b

Alkaloids of Ancistrocladus ealaensis - ancistrocladonine, ancistroealaensine, ancistrine, ancistine and ancistrocladeine

From the roots of yet another species of the genus Ancistrocladus, named Ancistrocladus ealaensis, Pousset and his co-workers in France, had isolated[14,15] two new alkaloids, designated as ancistrocladonine, $C_{27}H_{33}O_4N$, mp 82°, $[\alpha]_D$ +20° and ancistroealaensine, $C_{26}H_{31}O_4N$, mp 84°, $[\alpha]_D$ -26°. They observed[14,15] that both ancistrocladonine and N-methylancistroealaensine gave the same methine, different from the methine 24a obtained from

O,N-dimethylancistrocladine (2). Based on nmr spectral comparison of the two methines and their corresponding dihydro derivatives, gross structures 25 and 26 were advanced for these



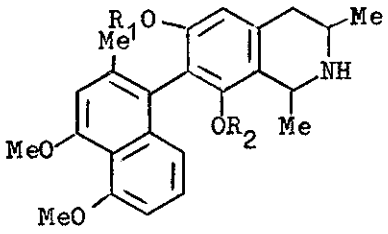
25 R = Me

26 R = H

bases, the two differing from each other in their stereochemistry at C-3. Subsequently when our attention was drawn to this work, we had occasion to prepare the methine 24b from hamatine (23). If structures 25 and 26 represent the correct structures for the alkaloids ancistrocladonine and ancistroealaensine, then the derived methine should be identical or enantiomeric with either of the methines 24a or 24b. However, we had found them to be entirely different. The nmr spectra of the two alkaloids, kindly provided by Dr. Foucher, later revealed[13] that they are probably stereoisomeric mixtures.

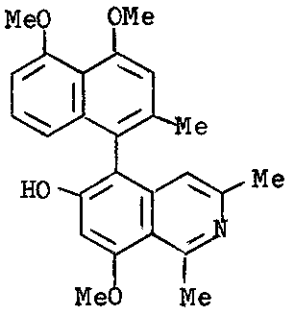
In a subsequent publication[16], the same authors had reported the isolation of three new isoquinoline alkaloids named as ancistrine, $C_{25}H_{29}O_4N$, mp 230-231°, $[\alpha]_D$ -35°, ancistine, $C_{25}H_{29}O_4N$, mp 275°, $[\alpha]_D$ -34° and ancistrocladeine, $C_{25}H_{25}O_4N$, mp 275-277°, $[\alpha]_D$ 0°. Solely on the basis of nmr spectral comparison of these bases with ancistrocladine (10) and ancistrocladisine (15), gross structures 27, 28 and 29 were assigned[17]

for ancistrine, ancistine and ancistrocladeine, respectively.



27 R_1 = H; R_2 = Me

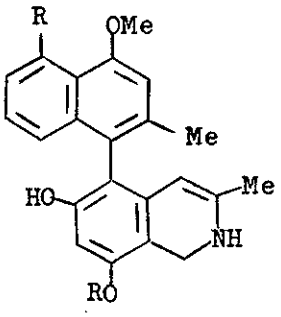
28 R_1 = Me; R_2 = H



29

Alkaloids of Ancistrocladus congolensis - (+)-ancistrocladine, o-methylancistrocladine, ancistrocongine and ancistrocongolensine

From the root and stem-bark of Ancistrocladus congolensis, five alkaloids were isolated.[18] The major component was found to be (-)-ancistrocladine (10). (+)-Ancistrocladine, O-methylancistrocladine, ancistrocongine and ancistrocongolensine were also isolated. The last two bases were tentatively assigned the gross structures 30 and 31, respectively.



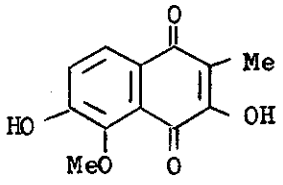
30 R = H

31 R = Me

Conclusion

Recently[19] ancistrocladine and ancistrocladisine were isolated from Ancistrocladus hamatus and the extract of Ancistrocladus heyneanus was found to contain o-methyl-ancistrocladine.

All the bases so far discussed are found to possess a methyl group at C-3 and their biogenetic origin must be quite different from that of other isoquinoline alkaloids. It is conceivable that the alkaloids of Ancistrocladus are formed by phenolic oxidative coupling of the cyclised polyketide units. The pattern of methoxyl and methyl substitution in ancistrocladine and its congeners fits in remarkably with the biogenetic origin from "polyketide" units. It is pertinent to mention here of the occurrence[20] of a new naphthoquinone named ancistroquinone in Ancistrocladus heyneanus. Ancistroquinone was unequivocally assigned the structure 32, whose biogenetic origin from polyketide unit was obvious.



32

REFERENCES

1. H. Santapau, 'The Flora of Khandala on the Western Ghats of India', Records of the Botanical Survey of India, 1960, 16(1), 15; 'The Wealth of India', C.S.I.R. (New Delhi), 1948, 1, 77; Theodore Cooke, 'The Flora of the Presidency of Bombay', Botanical Survey of India (Calcutta), 1958, 1, 93; D. Brandis, 'Indian Trees' Bishen Singh Mahendra Pal Singh, 1971, p. 73.

2. T.R. Govindachari and P.C. Parthasarathy, Indian J. Chem., 1970, 8, 567.

3. T.R. Govindachari and P.C. Parthasarathy, Tetrahedron, 1971, 27, 1013.

4. T.R. Govindachari, P.C. Parthasarathy and H.K. Desai, Indian J. Chem., 1971, 9, 931.

5. Tuticorin R. Govindachari, Kuppuswamy Nagarajan, Papagudi C. Parthasarathy, Tuticorin G. Rajagopalan, Haridutt K. Desai, Gopinath Kartha, Sow-mei Lai Chen and Koji Nakanishi, J. Chem. Soc., Perkin I, 1974, 1413.

6. N. Harada and K. Nakanishi, Accounts Chem. Res., 1972, 5, 257.

7. T.R. Govindachari, P.C. Parthasarathy and H.K. Desai, Indian J. Chem., 1971, 9, 1421.

8. T.R. Govindachari, P.C. Parthasarathy and H.K. Desai, Indian J. Chem., 1972, 10, 1117.

9. Tuticorin R. Govindachari, Papagudi C. Parthasarathy, Tuticorin G. Rajagopalan, Haridutt K. Desai, Kalpathi S. Ramachandran and Eun Lee, J. Chem. Soc., Perkin I, 1975, 2134.

10. T.R. Govindachari, P.C. Parthasarathy and H.K. Desai, Indian J. Chem., 1973, 11, 1190.

11. H. Corrodi and E. Hardegger, Helv. Chim. Acta, 1956, 39, 889.

12. T.R. Govindachari, P.C. Parthasarathy, T.G. Rajagopalan, H.K. Desai, K.S. Ramachandran and Eun Lee, Indian J. Chem., 1975, 13, 641.

13. T.R. Govindachari, P.C. Parthasarathy, H.K. Desai and M.T. Saindane, Indian J. Chem., 1977 (in press).

14. J.P. Foucher, J.L. Pousset, A. Cave, A. Bouquet and R. Paris, Plantes méd. Phytothér, 1971, 5, 16.

15. J.P. Foucher, J.L. Pousset, Adrien Cavé and Andre Cavé, Phytochemistry, 1974, 13, 1253.

16. J.P. Foucher, J.L. Pousset, A. Cavé and R.R. Paris, Plantes méd. Phytothér., 1975, 9, 26.

17. J.P. Foucher, J.L. Pousset and A. Cavé, Phytochemistry, 1975, 14, 2699.

18. J.P. Foucher, J.L. Pousset, A. Cavé, A. Bouquet and R. Paris, Plantes méd. Phytother., 1975, 9, 87.

19. H.K. Desai *et al.*, *Indian J. Chem.*, 1976, **14B**, 473.

20. T.R. Govindachari, P.C. Parthasarathy and J.D. Modi, *Indian J. Chem.*, 1971, **9**, 1042.

Received, 9th July, 1977