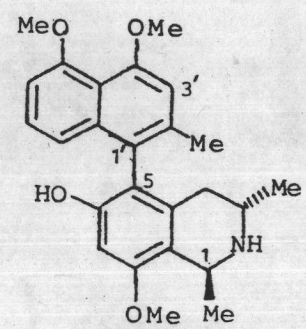
CHAPTER II

HISTORICAL

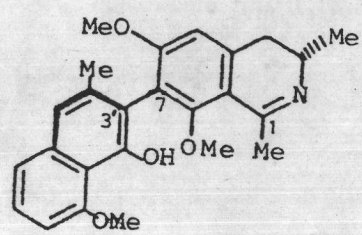
1. Chemistry of *Ancistrocladus* Alkaloids :

One of the novel groups of alkaloids to be discovered in the past 10 years is the naphthalene-isoquinoline group. These compounds have been isolated mainly from the genus *Ancistrocladus* of the family Ancistrocladaceae, although there are a few reports on the isolations from *Triphyophyllum peltatum* of the family Dionchophyllaceae[38,42]

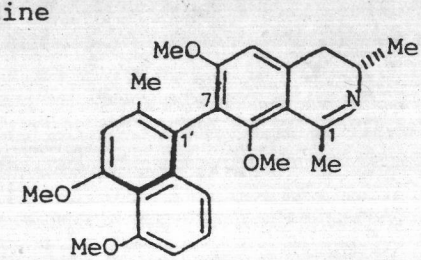
Three skeletal types have been isolated, and are based on the point of linkage of the 1-oxynaphthalene to the isoquinoline unit. Respectively, the linkages are 5-1' (e.g. ancistrocladine), 7-1' (e.g. ancistrocladisine) and 7-3' (e.g. ancistrocladidine).[37]



ancistrocladine



ancistrocladidine

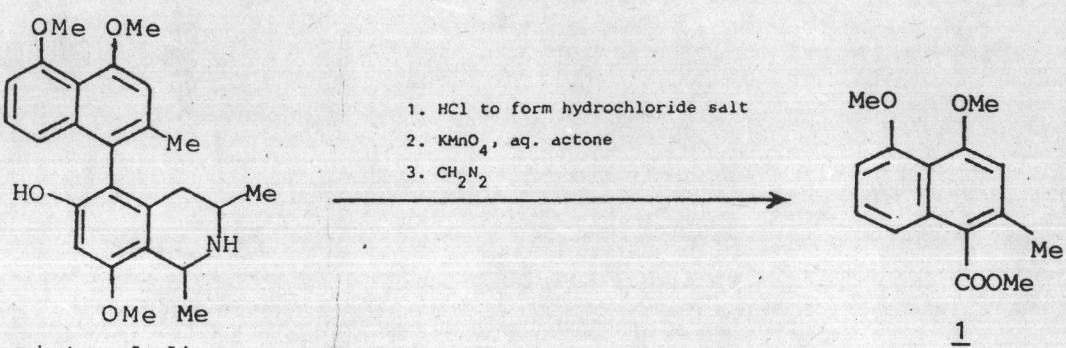


ancistrocladisine

1.1 Stereochemistry of 5-1' linkage naphthalene-isoquinoline

Ancistrocladine

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* Wallich. 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[18,19] 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.



ancistrocladine

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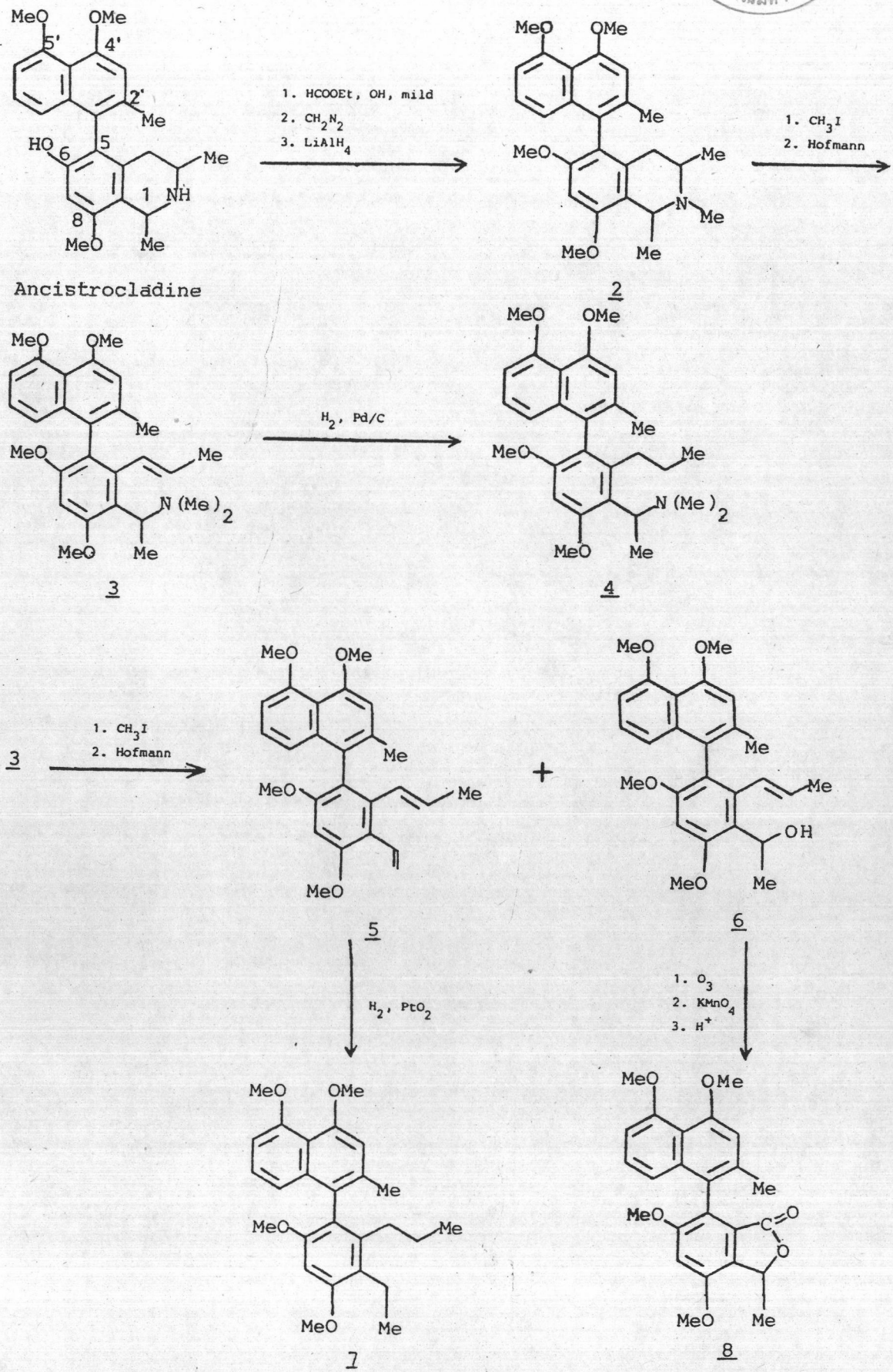
The main line of the extensive degradative work involving Hofmann degradation experiments on O,N-dimethylancistrocladine (2) is presented in Scheme 1.

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-dimethyl-ancistrocladine (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 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

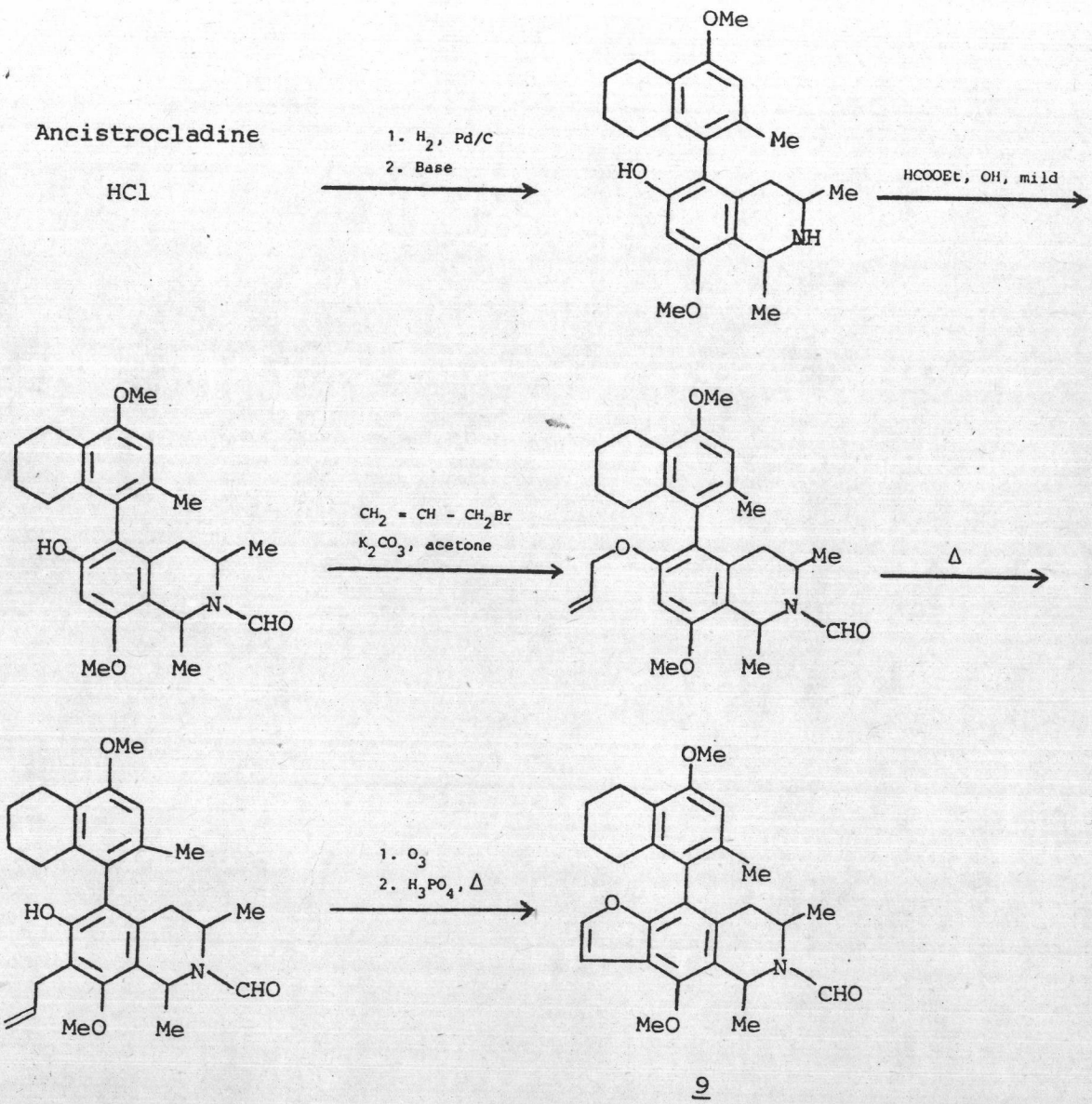
and the α-hydroxyethyl side chains in 6 are *ortho* to each other and hence firmly proved the presence of a 1,3-dimethyltetrahydroisoquinoline ring in ancistrocladine.

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 group (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[20] further evidence, conclusively proving the earlier findings, was presented. This involved Hofmann degradation study on N-methyl-O-benzylancistrocladine and 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.

Scheme 2



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The relative stereochemistry of the methyl substituents at C-1 and C-3 in ancistrocladine was shown[21] 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 their 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[21] by Dr. Kartha by an X-ray study of the hydrobromide salt of ancistrocladine. Application of the exciton chirality method[22] 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 4. Coupled with the X-ray and chemical studies, ancistrocladine should be depicted by structure 10. This was confirmed by exhaustive ozonalysis of ancistrocladine to yield L(+)-β-amino-n-butyric acid (11), of known absolute configuration.

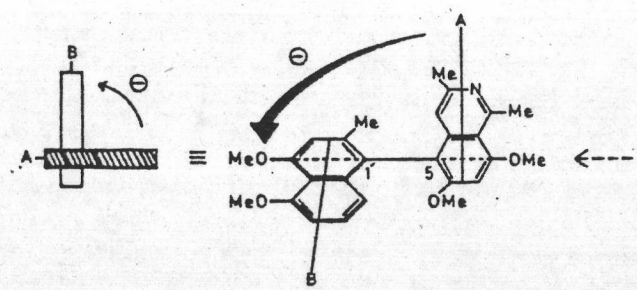
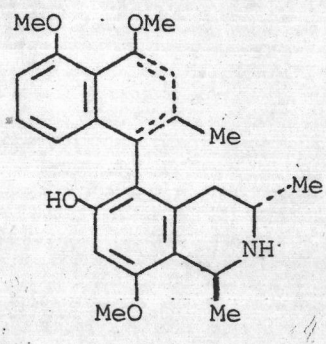


Figure 4. Chirality should be viewed from the direction of the dotted arrow



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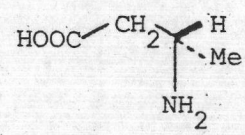
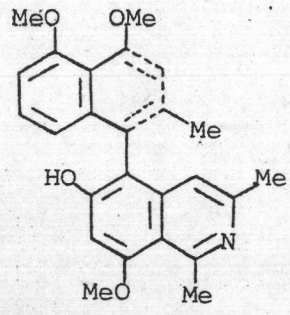


11

Ancistrocladinine

Ancistrocladinine, $C_{25}H_{27}O_4N$, mp 235-238°, was isolated [23] 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.



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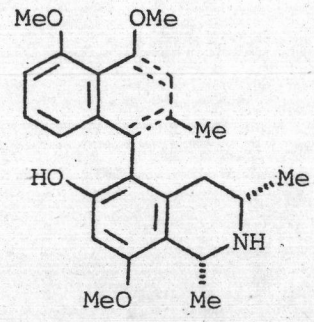

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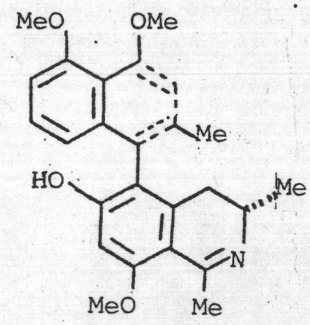


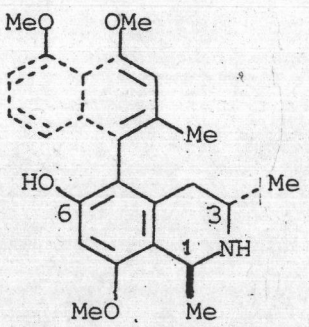
14

Hamatine

Ancistrocladus hamatus which grows in Sri Lanka, was the second species of the genus *Ancistrocladus* to be recently examined. The study led to the isolation[24] of ancistrocladine and another new alkaloid named 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-methylhematine 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 15 was put forth by Govindachari *et al.*[24]

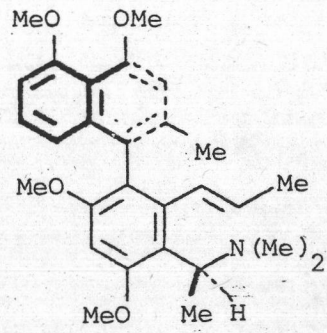


15

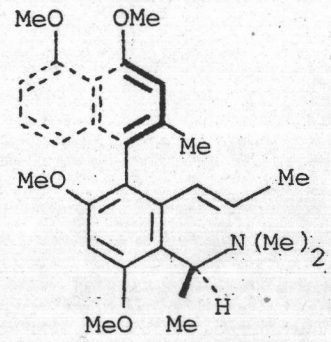
In agreement with the structure 15, hamatine furnished L-β-amino-n-butyric acid confirming the S configuration at C-3.

More recently, it was firmly established[25] the absolute configuration of hamatine at C-1, the only structural feature which was not resolved unambiguously earlier. The earlier study[24] rested on the absence of a long-range coupling degradation of O,N-dimethylhamatine, prepared in the same manner as O,N-dimethylancistrocladine[32], gave a methine, different from the isomeric methine 16a derived from O,N-dimethylancistrocladine. Hence it became possible to assign unequivocally structure 16b for the methine from O,N-dimethylhamatine. If position C-1 in hamatine were to possess the R-configuration, the enantiomer of the methine 16a would

have resulted on Hofmann degradation.



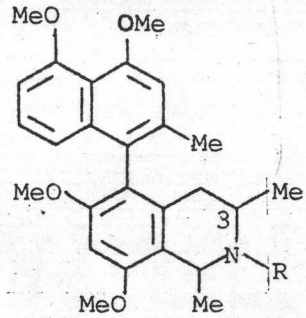
16a



16b

Ancistrocladonine, ancistroealaensine 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[26,27] 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[26,27] that both ancistrocladonine and N-methylancistroealaensine gave the same methine, different from the methine 16a obtained from O,N-dimethylancistrocladine(2). Based on nmr spectral comparison of the two methines and their corresponding dihydro derivatives, gross structures 17 and 18 were advanced for these bases, the two differing from each other in their stereochemistry at C-3. Subsequently when attention was drawn to this work, the methine 16b was prepared from hamatine (15). If structures 17 and 18 represent the correct structures for the alkaloids ancistrocladonine and ancistroealaensine, then the derived methine should be identical or enantiomeric with either of

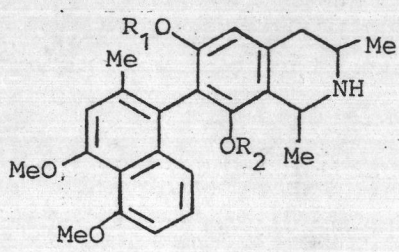


17 R = Me

18 R = H

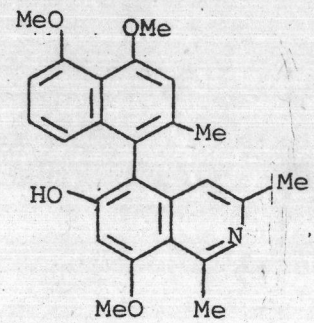
the methines 16a or 16b. However, it was found to be entirely different, later revealed[25] that they are probably stereoisomeric mixtures.

In a subsequent publication[28], 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 (24), gross structures 19, 20 and 21 were assigned[29] for ancistrine, ancistine and ancistrocladeine, respectively.



19 R_1 = H; R_2 = Me

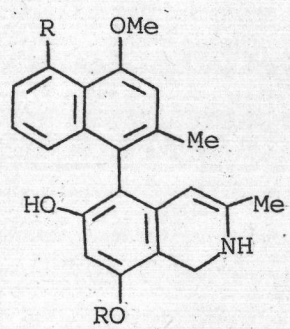
20 R_1 = Me; R_2 = H



21

(+)-Ancistrocladine, O-methylancistrocladine, ancistrocongine and ancistrocongolensine

From the root and stem-bark of *Ancistrocladus congolensis*, five alkaloids were isolated.[30] The major component was found to be (-)-ancistrocladine (10). (+)-Ancistrocladine, O-methyl-ancistrocladine, ancistrocongine and ancistrocongolensine were also isolated. The last two bases were tentatively assigned the gross structures 22 and 23, respectively.



22 R = H

23 R = Me

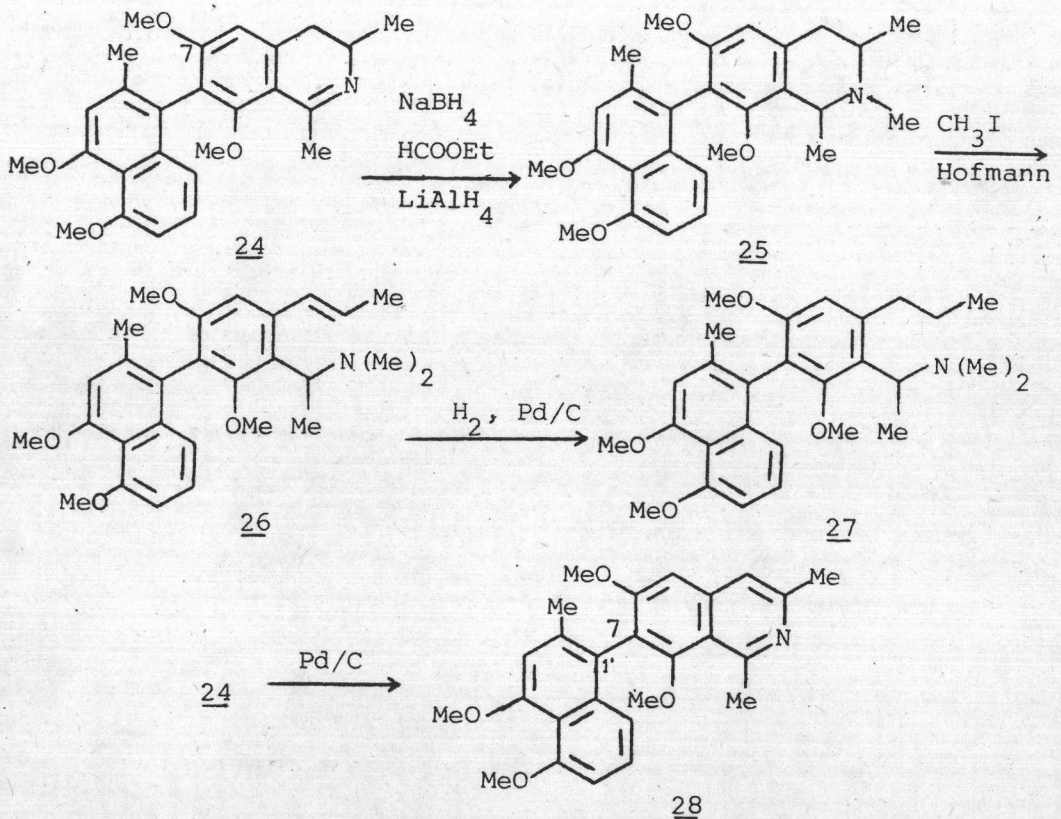
1.2 Stereochemistry of 7-1′ linkage naphthalene-isoquinoline

Ancistrocladisine

The alkaloid ancistrocladisine, $C_{26}H_{29}O_4N$, mp 178-180° $[\alpha]_D$ -16.13°, was isolated[31] from the roots of *Ancistrocladus heyneanus* Wall. in 1972 and its structure was elucidated[31] 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 24 for ancistrocladisine.

Scheme 3



24 25 26 27 28

Hofmann degradation of N-methyldihydroancistrocladisine (25) gave the methine base 26 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 26 and the corresponding methyl group in its dihydro derivative 28 (δ 1.93, q, J = 2 and 6.5 Hz, olefinic methyl protons in 26, δ 1.08, t, J = 7 Hz, methyl group of the n-propyl chain in 27) 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 24. In agreement with this structure, ancistrocladisine showed two shielded methoxyl groups in the nmr spectrum and also underwent smooth dehydrogenation to furnish the isoquinoline 28. As in ancistrocladine, the use of the exciton chirality method[22] led[32] to the establishment of the absolute configuration of ancistrocladisine. The uv spectrum of 28 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 5.

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 29.

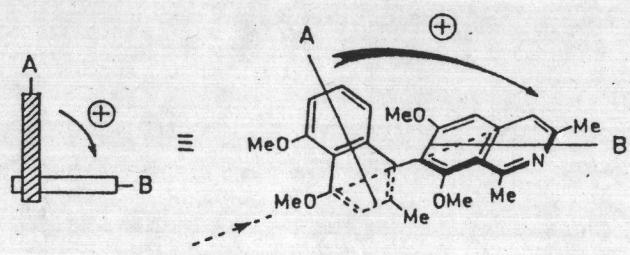
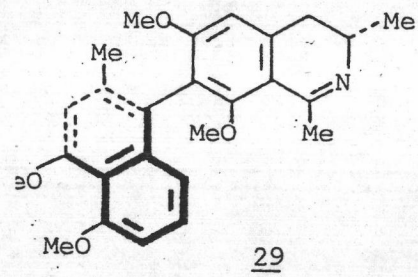


Figure 5 Chirality should be viewed from the direction of the dotted arrow.



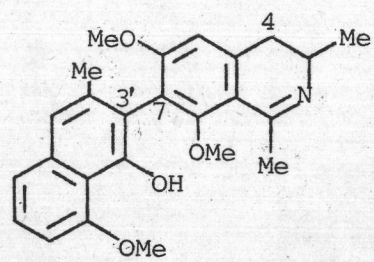
29

1.3 Stereochemistry of 7-3′ linkage naphthalene-isoquinoline

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* Wall.[33] In wiew of its presence in the plant in extremely low yield chemical degradation work could not be undertaken However, spectral data were sufficient to postulate[33] 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-methyl-naphthalene. The nmr spectrum of ancistrocladidine was particularly informative revealing the presence of a 1,3-dimethyl-3,4-dihydroiso-quinoline and 1-hydroxy-8-methoxy-3-methylnaphthalene rings, the C-3′ 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

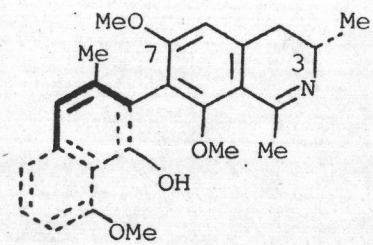
it should be bonded to a methoxyl group as in 1-hydroxy-8-methoxy-3-methylnaphthalene. Dihydroancistrocladidine, in which the isoquinoline ring was reduced, gave a O,N-diacetate which showed a shielded (δ 1.98) acetoxyl group in the nmr spectrum. The data outlined above would fit in admirably with structure 30 for ancistrocladidine.



31

Application of the exciton chirality method had led[32] to the determination of the absolute configuration in respect of the disymmetry arising from restricted rotation around the C(7)-C(3') 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 6, thus establishing the absolute configuration at the chiral site.

Following the procedure[34] of Corrodi and Hardegger, extensive ozonolysis of ancistrocladidine accompanied by purification of the derived oxidation products gave[32] L-β-amino-n-butyric acid. Thus the absolute stereochemistry of ancistrocladidine was firmly established as 31, the absolute configurations at C-3 and C-7 being S and R, respectively.



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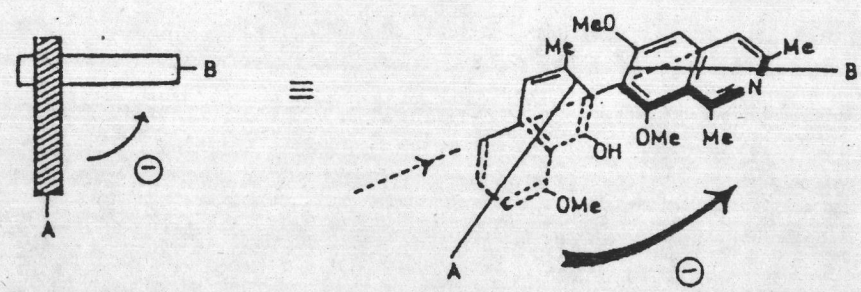


Figure 6 Chirality should be viewed from the direction of the dotted arrow

2. Distribution of Naphthalene-Isoquinoline Alkaloids.

There are seventeen naphthalene-isoquinoline alkaloids obtained from various sources as shown in Table 1.

Table 1. Distribution of Naphthalene-Isoquinoline Alkaloids

A. 5-1' linkage

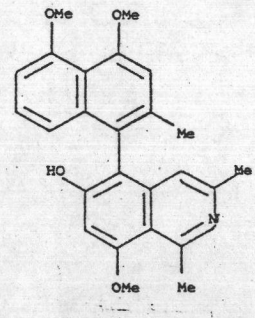
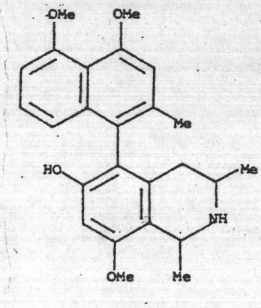
Alkaloid	Source	Reference
Ancistrocladeine	*Ancistrocladus ealaensis*	29
$C_{25}H_{25}O_4N$	*A. tectorius* (Lour.)Merr.	28,29
MW. 403, m.p. 275-7°C		
		
Ancistrocladine	*A. congolensis*	30
$C_{25}H_{29}O_4N$	*A. hamatus* (Vahl.)Gilg.	40
MW. 407,	*A. heyneanus* Wall.	18,19,20
m.p. 265-7°C (dec.)		21,39
	*A. tectorius* (Lour.)Merr.	36

Table 1. (continued)

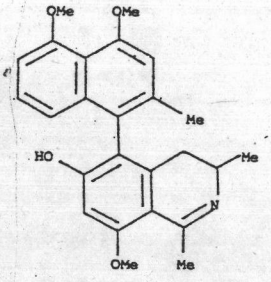
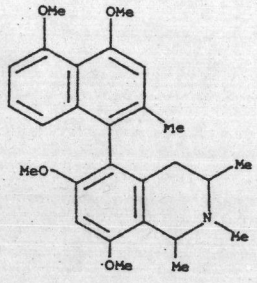
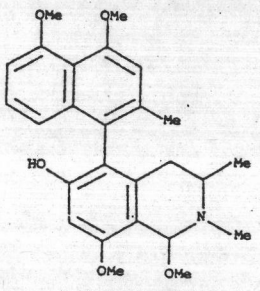
Alkaloid	Source	Reference
Ancistrocladinine $C_{25}H_{27}O_4N$ MW. 405, m.p. 235-8°C (dec.) 	*Ancistrocladus heyneanus* Wall.	21,23,39
Ancistrocladonine $C_{27}H_{33}O_4N$ MW. 435, m.p. 82°C 	*A. ealaënsis*	26,27
Ancistrocline $C_{26}H_{31}O_4N$ MW. 421, m.p. 227-8°C 	*A. tectorius* (Lour.) Merr.	36

Table 1. (coutinued)

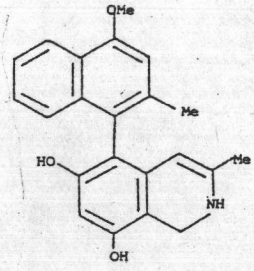
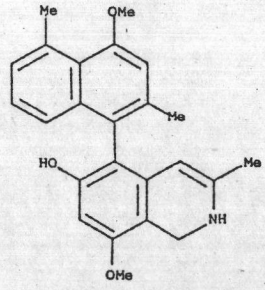
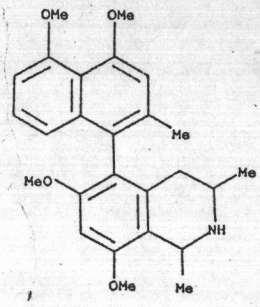
Alkaloid	Source	Reference
Ancistrocongine $C_{22}H_{21}O_3N$ MW. 347, m.p. 298-9°C 	*Ancistrocladus congolensis*	30
Ancistrocongolensine 	*A.congolensis*	30
Ancistroealaensine $C_{26}H_{31}O_4N$ MW. 421, m.p.indefinite (Soften at 84°C) 	*A.ealaënsis*	26,27

Table 1. (continued)

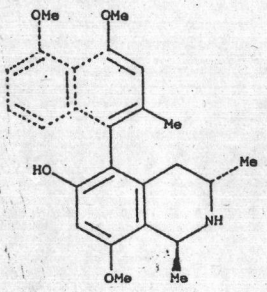
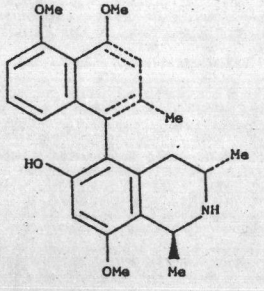
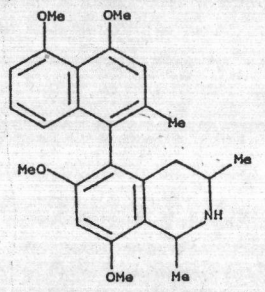
Alkaloid	Source	Reference
Hamatine $C_{25}H_{29}O_4N$ MW. 407, m.p. 250-2°C (an isomer of ancistrocladine) 	*Ancistrocladus hamatus* (Vahl.) Gilg. *A. tectorius* (Lour.) Merr.	24,25 36
 ancistrocladine		
O-Methylancistrocladine $C_{26}H_{31}O_4N$ m.p. 200-2°C 	*A. congolensis* *A. heyneanus* Wall.	30 40

Table 1. (continued)

B. 7-1' linkage

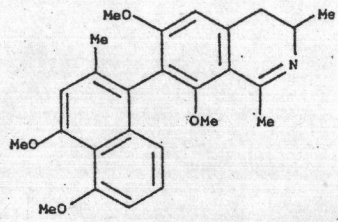
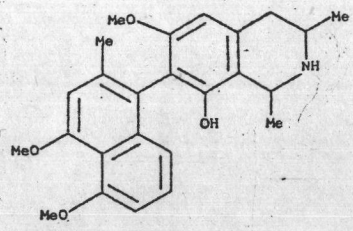
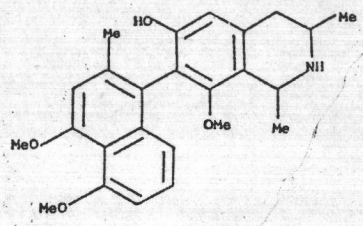
Alkaloid	Source	Reference
Ancistrocladisine $C_{26}H_{29}O_4N$ MW 419, m.p.178-80°C 	*Ancistrocladus hamatus* (Vahl.) Gilg. *A. heyneanus* Wall.	40 31,32,39,41
Ancistine $C_{25}H_{29}O_4N$ MW. 407, m.p.275-6°C 	*A. ealaënsis*	29
Ancistrine $C_{25}H_{29}O_4N$ MW. 407, m.p.230-1°C 	*A. ealaënsis*	29

Table 1. (continued)

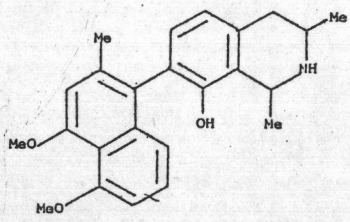
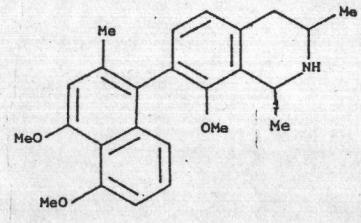
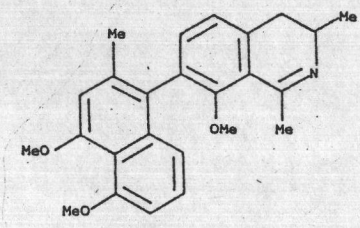
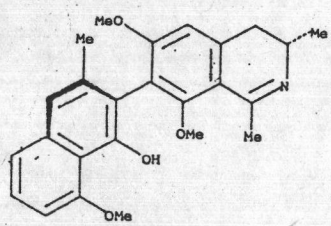
Alkaloid	Sourse	Reference
Triphyophylline $C_{24}H_{27}O_3N$ MW. 377, m.p. 215°C 	*Triphyophyllum peltatum* (Dionchophyllaceae)	38
O-Methyltriphyophylline 	*T. peltatum*	42
O-Methyl-1,2-dehydro triphyophylline 	*T. peltatum*	42

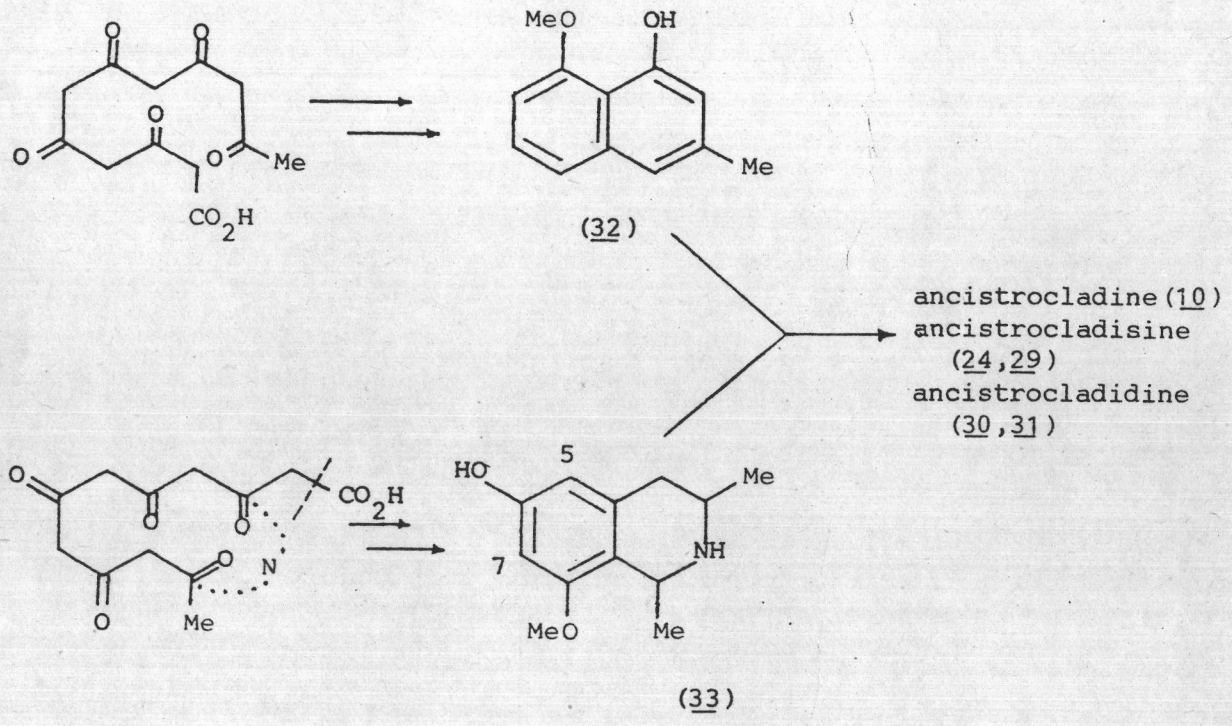
Table 1. (coutinued)

C. 7-3′ linkage

Alkaloid	Source	Reference
Ancistrocladidine $C_{25}H_{27}O_4N$ MW. 405, m.p.245-7℃ (dec.) (an isomer of ancistrocladinine  	*Ancistrocladus heyneanus* Wall.	32,33,39,41

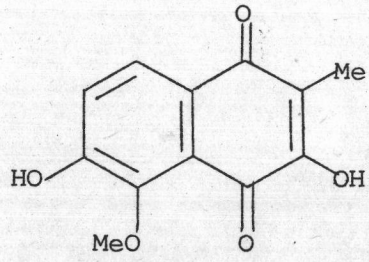
3. Biogenesis

The *Ancistrocladus* alkaloids are of interest for the reason that they are a novel skeletal type which is the most unusual of all the isoquinoline alkaloids. 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 the other isoquinoline alkaloids. No synthetic or biosynthetic data have been reported for these alkaloids, but it is conceivable that they are formed by phenolic oxidative coupling of the cyclised polyketide units,[37,43,44] a naphthalene (32) and a 6,8-dioxygenated tetrahydroisoquinoline (33), as shown in Scheme 4.[37]



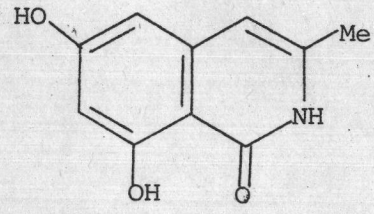
Scheme 4. Biogenesis of naphthalene-isoquinoline alkaloids in plants.

The pattern of methoxyl and methyl substitution in ancistrocladine (10) and its congeners fit in remarkably with the biogenetic origin form polyketide units. It is pertinent to mention of the occurrence of a new naphthoquinone named ancistroquinone in *Ancistrocladus heyneanus* Wall. Ancistroquinone was unequivocally assigned the structure 34, whose biogenetic origin from polyketide unit was obvious.(44)

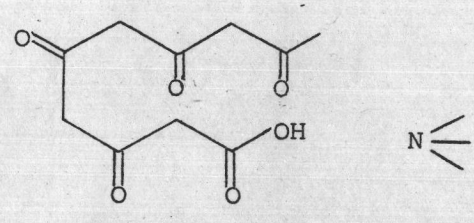


34

One of the simple monomeric isoquinoline alkalois which appears to be closely related to the naphthalene isoquinoline alkaloids is siamine (35), and isoquinolone from *Cassia siamea* Lam. (Leguminosae). Biogenetically this compound could be derived as shown in 36(37)



35



36