Absolute Configuration of Ancistrocladisine and Ancistrocladidine

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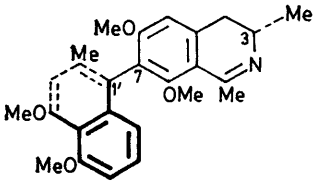
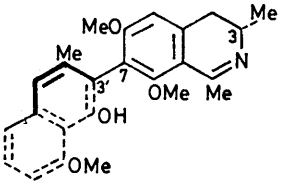
Evidence for the absolute configuration of ancistrocladisine[(3*S*,7*R*)-7-(4,5-dimethoxy-2-methyl-1-naphthyl)-3,4-dihydro-6,8-dimethoxy-1,3-dimethylisoquinoline] (1) and ancistrocladidine [(3*S*,7*R*)-3,4-dihydro-7-(4-hydroxy-5-methoxy-2-methyl-3-naphthyl)-6,8-dimethoxy-1,3-dimethylisoquinoline] (2), based on a study of c.d. and chemical data, is presented.

RECENTLY we have reported [1,2] the isolation and structure elucidation of two novel isoquinoline alkaloids from the roots of *Ancistrocladus heyneanus* Wall. (Ancistrocladaceae). A characteristic feature of these alkaloids is the presence of a substituted naphthalene ring at C-7 of a 3,4-dihydro-6,8-dimethoxyisoquinoline. We now present evidence for the illustrated absolute configurations of ancistrocladisine (1) and ancistrocladidine (2).

The exciton chirality method,[3] a versatile method for determining absolute configurations of natural products by use of split-type Cotton effects, was employed [4] in

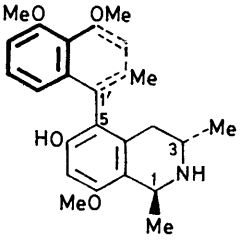


(1)



(2)

elucidating the absolute configuration of ancistrocladine (3), isolated from the same plant. The correctness of the method for derivation of the absolute configuration of ancistrocladine in respect of the dissymmetry arising from restricted rotation around the C(5)–C(1′) bond was



(3)

unequivocally established by a combination of *X*-ray and chemical methods. We have made use of the exciton chirality method coupled with the results of chemical degradation for establishing the absolute configuration of ancistrocladisine and ancistrocladidine.

Ancistrocladisine.—The u.v. spectrum (Figure 1) of didehydroancistrocladisine [$\lambda_{max.}$ 238, 307, 320, and 334 nm (log ε 4.92, 4.13, 4.10, and 4.18)], derived from ancistrocladisine by dehydrogenation, is similar to that of the

[1] T. R. Govindachari, P. C. Parthasarathy, and H. K. Desai, *Indian J. Chem.*, 1972, **10**, 1117.
[2] T. R. Govindachari, P. C. Parthasarathy, and H. K. Desai, *Indian J. Chem.*, 1973, **11**, 1190.
[3] N. Harada and K. Nakanishi, *Accounts Chem. Res.*, 1972, **5**, 257.
[4] T. R. Govindachari, K. Nagarajan, P. C. Parthasarathy, T. G. Rajagopalan, H. K. Desai, G. Kartha, Sow-mei Lai Chen, and K. Nakanishi, *J.C.S. Perkin I*, 1974, 1413.

isoquinoline from *O*-methylancistrocladine. Restricted

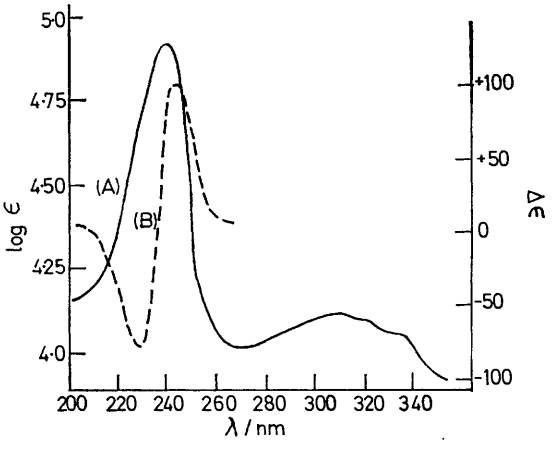


FIGURE 1

rotation around the C(7)—C(1′) bond joining the naphthalene and isoquinoline chromophores leads to a coupled interaction between the two long axis transitions centred at 235 nm, and gives rise (Figure 1) to split c.d. extrema: $\Delta\varepsilon_{243}$ + 95; $\Delta\varepsilon_{228}$ — 86.4 (EtOH). These signs (positive first Cotton effect) show that the chirality is positive as shown in Figure 2.

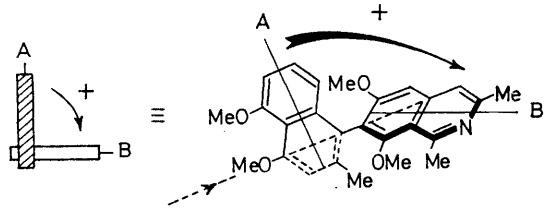
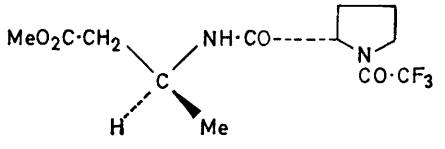


FIGURE 2

The absolute configuration at C-3 in ancistrocladisine was deduced as follows. Extensive ozonolysis of dihydroancistrocladisine in aqueous 10% formic acid followed by ion-exchange chromatography gave (+)-L-β-aminobutyric acid, characterized by conversion into the *N*-trifluoroacetyl-L-prolyl peptide methyl ester (4). Since the absolute configuration of (+)-L-β-aminobutyric acid has been firmly established [5] as *S*, it follows that ancistrocladisine has the *S*-configuration at C-3. Hence structure (1) represents the absolute configuration of ancistrocladisine.



(4)

Ancistrocladidine.—The shape and amplitude of the u.v. spectrum [$\lambda_{max.}$ 227, 244, 290, 307, 322, and 335 nm (log ε 4.73, 4.96, 3.99, 3.99, 3.99, and 3.99)] of didehydroancistrocladidine, made from ancistrocladidine by dehydrogenation over palladium—charcoal, indicate that the molecule contains overlapping naphthalene and isoquinoline chromophores. The intense shorter wavelength absorptions at 227 and 244 nm with transition moments along the long axes of the nuclei interact to give an exciton-split c.d. spectrum with extrema of $\Delta\varepsilon_{244}$ — 96.1 and $\Delta\varepsilon_{227}$ + 125.8 (in EtOH). The negative first Cotton effect sign indicates that the chirality of the long axes is negative.

Extensive ozonolysis of dihydroancistrocladidine, formed by reduction of ancistrocladidine with sodium borohydride, gave L-β-aminobutyric acid, enabling the assignment of the absolute configuration at C-3 as *S* in ancistrocladidine. Thus structure (2) depicts the absolute configuration of ancistrocladidine.

EXPERIMENTAL

U.v. spectra were taken for solutions in 95% ethanol with a Beckman DK 2A spectrophotometer. I.r. spectra were recorded with a Perkin-Elmer 421 spectrophotometer. G.l.c. analyses were carried out on a 183 × 0.2 cm (i.d.) glass column with a Varian Aerograph 2 740 instrument equipped with a flame ionisation detector and with nitrogen as carrier gas. The stationary phase was 3% OV-17 with a column support of GasChrom Q (80—100 mesh). C.d. spectra were obtained with a JASCO J-40 automatic recording spectropolarimeter calibrated with aqueous (+)-camphor-10-sulphonic acid, $\Delta\varepsilon_{290}$ + 2.2.

Ozonolysis of Dihydroancistrocladisine.—A solution of dihydroancistrocladisine (1.044 g) in aqueous formic acid (10%; 40 ml) was cooled in ice and treated with ozone for 12 h. The solution was heated with hydrogen peroxide (30%; 8 ml) and formic acid (85%; 8 ml) for 3 h on a boiling water bath. Platinum black (0.3 g) was then added and the solution was heated at 60 °C for 1 h to remove the excess of peroxy-acid, filtered, and extracted with chloroform to remove neutral impurities. The aqueous solution was evaporated to dryness *in vacuo*, the final traces of formic acid being removed by repeated additions of water (3 × 5 ml) and evaporation. The residue was subjected to ion-exchange column chromatography [1 × 110 cm of Dowex 50-X8 (200—400 mesh) (H^+)]. The column was maintained at 50 °C and eluted with 1N-HCl at 25 ml h^{-1}. The eluates were monitored by t.l.c. [phenol–water (3 : 1 w/w)] followed by spraying with ninhydrin. Fractions which were homogeneous on t.l.c. and had the same R_F value as authentic β-aminobutyric acid were combined and lyophilised to dryness. The residue (33 mg) was partly crystalline and was used for the subsequent reaction.

N-Trifluoroacetyl-L-prolyl-L-β-aminobutyric Acid Methyl Ester.—Thionyl chloride (0.2 ml) was cooled to —5 °C and treated with absolute methanol (2 ml) added in portions. After cooling the mixture for 10 min at —5 °C, the foregoing residue from ozonolysis dissolved in absolute methanol (1 ml) was added slowly. The mixture was left at room temperature overnight. Methanol was then removed under reduced pressure and the residue was treated with a solution of *N*-trifluoroacetyl-L-prolyl chloride (80 mg) in dry methylene chloride (2 ml) at 10 °C. Triethylamine (1 ml) was added and the mixture was left at room temperature overnight. Removal of the solvent under reduced pressure and extraction of the residue after addition of water with methylene chloride gave the *dipeptide* as white needles, m.p. 92—93° (Found: C, 46.8; H, 5.75. $C_{12}H_{17}F_3N_2O_4$ requires

[5] K. Balenović, D. Cerar, and Z. Fuks, *J. Chem. Soc.*, 1952, 3316.

C, 46.45; H, 5.5%), identical (m.p., mixed m.p., i.r. spectrum) with a specimen prepared from L-β-aminobutyric acid. The dipeptide gave a single peak in g.l.c., t_R 20.1 min; the product made from (±)-β-aminobutyric acid showed two peaks at 17.1 and 20.1 min for the (−)-D- and (+)-L-isomers, respectively.

Didehydroancistrocladidine.—A mixture of ancistrocladidine (0.1 g), diphenyl ether (7 ml), and palladium–charcoal (10%; 0.1 g) was heated at 200 °C in a gentle stream of CO_2 for 2h. The product was cooled and filtered and the filtrate passed over a column of alumina, eluted first with hexane to remove the diphenyl ether and then with benzene to give a solid which crystallised from ether as pale yellow *needles*, m.p. 210—211°, M^+ 403 (Found: C, 74.5; H, 6.55. $C_{25}H_{25}NO_4$ requires C, 74.4; H, 6.25%).

Ozonolysis of Dihydroancistrocladidine.—Ozonolysis of dihydroancistrocladidine (prepared by reduction of ancistrocladidine with sodium borohydride) by the method described for dihydroancistrocladisine, followed by ion-exchange chromatography, gave L-β-aminobutyric acid. This was transformed into the *N*-trifluoroacetyl dipeptide methyl ester, m.p. 92°, identical (m.p., mixed m.p., g.l.c., and i.r, spectrum) with an authentic sample.

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