THALIBRINE AND NORTHALIBRINE, NEW BISBENZYLISOQUINOLINE ALKALOIDS FROM THALICTRUM ROCHEBRUNIANUM

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Thalibrine and northalibrine, new alkaloids from Thalictrum rochebrunianum, have been assigned the mono-ether-bridged tail-to-tail bisbenzylisoquinoline structures 1 and 2.

The genus Thalictrum (Ranunculaceae) has proven to be a rich source of benzylisoquinoline-derived alkaloids.[1] As part of a continuing phytochemical study of Thalictrum rochebrunianum,[2] we now report the isolation and structure determination of the new bisbenzylisoquinoline alkaloids thalibrine (1) and northalibrine (2).[3]

Thalibrine (1) was obtained as an amorphous solid, $[\alpha]_D = +110^\circ$ (c = 0.135 $CHCl_3$), uv λ_{max}^{EtOH} (ε): 284 nm (8000). Its infrared spectrum (KBr)

showed no carbonyl absorption, but a band at 3400 cm^{-1}, attributable to a non-associated phenolic hydroxyl, was observed.

The nmr spectrum of thalibrine ($CDCl_3$) showed the presence of four aromatic methoxyls at δ 3.60, 3.75 (6 H), and 3.77, as well as two superimposed N-methyls at 2.45. Of the eleven aromatic protons present, eight were readily discernible, four as singlets at δ 6.15, 6.31 (H-8 and H-8'), 6.50 and 6.53 (H-5 and H-5'), and four as pairs of doublets centered at δ 6.80 (2 H, J = 8.5 Hz) and 7.03 (2 H, J = 8.5 Hz).

Treatment of thalibrine with excess diazomethane afforded the amorphous O-methylthalibrine (3), $[\alpha]_D = +82^\circ$ (c = 0.36 $CHCl_3$); nmr ($CDCl_3$) δ 2.49 and 2.51 (s, 3 H each, 2 x NMe), 3.58, 3.61, 3.78, 3.79 and 3.80 (s, 3 H each, 5 x OMe), 6.10, 6.15 (s, 1 H each, H-8 and H-8'), 6.55, 6.58 (s, 1 H each, H-5 and H-5'), 6.80 (d, 2 H, J = 8.5 Hz), 7.06 (d, 2 H, J = 8.5 Hz), 6.75—7.01 (m, 3 H). Except for the opposite sign of its rotation, these data are virtually those recorded for O-methyldauricine, strongly suggesting that 3 is the S, S-enantiomer of O-methyldauricine. The corresponding reaction of thalibrine with CD_2N_2 in dioxane-D_2O [4] gave O-trideuteriomethylthalibrine (4). A comparison of the nmr spectra of 3 and 4 proved the new methyl group of methyl ether 3 to be the shielded methyl at δ 3.58. In a dauricine-type alkaloid,[5] this corresponds to a methoxyl at C-7 or C-7', thus suggesting the original phenolic hydroxyl of thalibrine to be at one of these positions.

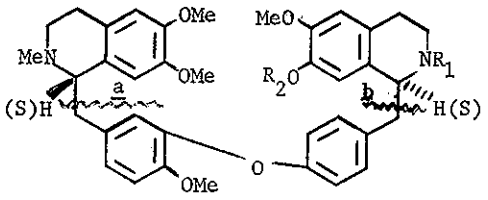
The mass spectra [6] of thalibrine (1) and its derivatives 3 and 4 are characteristic of those of bisbenzylisoquinolines containing only a tail-to-tail ether bridge. None of the above gave detectible molecular ions. High resolution spectra for 1, 3 and 4 all gave base peaks (100%) corresponding to

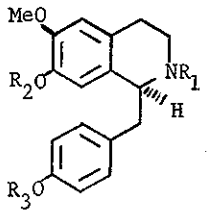
the exact masses for the fragments a and b. All three compounds also give very small (ca. 1%) but significant peaks corresponding to the larger fragments M-1-a and M-1-b. The presence of the phenolic hydroxyl of 1 in one of the two isoquinoline head units is thus firmly established.

Treatment of methyl ether 3 with sodium in liquid ammonia cleanly cleaved the molecule into phenolic and non-phenolic portions, identified as S-armepavine (8) and S-O-methylarmepavine (5) by comparison with authentic samples. Similar cleavage of the trideuteriomethyl ether 4 afforded S-O-methylarmepavine (5) and S-7-trideuteriomethyl-N-methylcoclaurine (6). Proof of the position of the CD_3O group in the isoquinoline portion of 6 was obtained by deuteriomethylation of 6 to give S-O, O-bis(trideuteriomethyl)-N-methylcoclaurine (7), identical with a sample synthesized from authentic S-N-methylcoclaurine.

Northalibrine (2) was obtained as an amorphous solid, $[\alpha]_D = +47^\circ$ (c = 0.2 $CHCl_3$), uv λ_{max}^{EtOH} (ε): 284 nm (5000). Its nmr spectrum ($CDCl_3$) showed the presence of four aromatic methoxyls at δ 3.60, 3.71 and 3.73 (6 H), and only one N-methyl (3 H) at 2.46. N-Methylation (formalin-borohydride) afforded a product identical (ir, nmr, tlc, rotation) with thalibrine (1).

The mass spectrum of northalibrine (2) shows a base peak (100%) for fragment a (m/e 206) and a fairly strong peak (23%) for fragment b (m/e 178). Both the OH and the NH of 2 must therefore be located in the same isoquinoline unit. The relation of the two heads (a and b) of 2 to the lower part of the molecule is revealed by sodium-ammonia cleavage of northalibrine, which affords S-O-methylarmepavine (5) and S-coclaurine (9) as the non-phenolic and phenolic products, respectively.





1, R_1 = Me, R_2 = H

2, R_1 = R_2 = H

3, R_1 = R_2 = Me

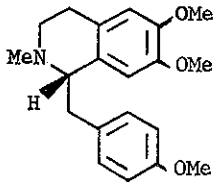
4, R_1 = Me, R_2 = CD_3

6, R_1 = Me, R_2 = CD_3, R_3 = H

7, R_1 = Me, R_2 = R_3 = CD_3

8, R_1 = R_2 = Me, R_3 = H

9, R_1 = R_2 = R_3 = H



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