HETEROCYCLES, Vol. 4, No. 4, 1976

THALIBRINE AND NORTHALIBRINE, NEW BISBENZYLISOQUINOLINE ALKALOIDS FROM THALICTRUM ROCHEBRUNIANUM

José M. Saá, Michael J. Mitchell, and Michael P. Cava*

Department of Chemistry, University of Pennsylvania
Philadelphia, Pennsylvania 19174, U. S. A.

and

Jack L. Beal

College of Pharmacy, The Ohio State University
Columbus, Ohio 43210, U. S. A.

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).

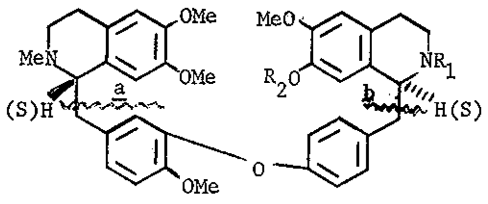
Treatment of thalibrine with excess diazomethane afforded the amorphous O-methylthalibrine (**3**), $[\alpha]_D = +82^{\circ}$ (c = 0.36 $CHCl_3$); nmr ($CDCl_3$) δ 2.49 and 2.51 (s, 3 H each, 2 x NMe), 3.58, 3.61, 3.78, 3.79 and 3.80 (s, 3 H each, 5 x OMe), 6.10, 6.15 (s, 1 H each, H-8 and H-8'), 6.55, 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.

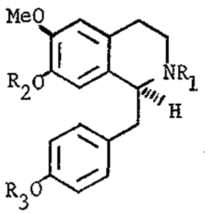


1, R_1 = Me, R_2 = H

2, R_1 = R_2 = H

3, R_1 = R_2 = Me

4, R_1 = Me, R_2 = CD_3

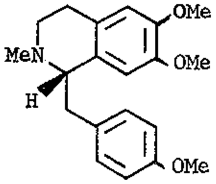


6, R_1 = Me, R_2 = CD_3, R_3 = H

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



5

ACKNOWLEDGEMENT We thank the National Institutes of Health for grants (CA 11445 and HL 07502) in support of this work, and also the Fundacion Juan March for a supporting fellowship to one of us (J. M. Saá). We also thank Dr. C. Costello (Massachusetts Institute of Technology) for the determination of high resolution mass spectra.

REFERENCES

1. P. L. Schiff and R. W. Doskotch, Lloydia, 1970, 33, 403.

2. a) H. H. S. Fong, J. L. Beal and M. P. Cava, Lloydia, 1966, 29, 94;
b) M. P. Cava, J. M. Saá, M. V. Lakshmikantham, M. J. Mitchell, J. L. Beal, R. W. Doskotch, A. Ray, D. C. DeJongh and S. R. Shrader, Tetrahedron Lett., 1974, 4259.
c) J. M. Saá, M. J. Mitchell, M. V. Lakshmikantham and M. P. Cava, Tetrahedron Lett., in press.

3. From root bases by extraction, followed by repeated countercurrent distribution. Details to be published elsewhere.

4. K. J. Van der Merwe, P. S. Steyn and S. H. Eggers, Tetrahedron Lett., 1965, 3293.

5. I. R. C. Bick, J. Harley-Mason, N. Sheppard and M. J. Vernengo, J. Chem. Soc., 1961, 1896.

6. For some general references concerning the mass spectra of bisbenzylisoquinoline alkaloids, see the following: a) J. Baldas, Q. N. Porter, I. R. C. Bick and M. J. Vernengo, Tetrahedron Lett., 1966, 2059;
b) M. Tomita, T. Kikuchi, K. Fujitani, A. Kato, H. Furukawa, Y. Aoyagi, M. Kitano and T. Ibuka, Tetrahedron Lett., 1966, 857;
c) D. C. DeJongh, S. R. Shrader and M. P. Cava, J. Amer. Chem. Soc., 1966, 88, 1052; d) J. Baldas, I. R. C. Bick, T. Ibuka, R. S. Kapil and Q. N. Porter, J. Chem. Soc. Perkin I, 1972, 592; e) J. Baldas I. R. C. Bick, M. R. Falco, J. X. deVries and Q. N. Porter, ibid., 1972, 597; f) J. Baldas, I. R. C. Bick, T. Ibuka, R. S. Kapil and Q. N. Porter, ibid., 1972, 599.

Received, 14th January, 1976