LEUCOXYLONINE AND OCOXYLONINE - HEXAOXYGENATED APORPHINES FROM OCOTEA LEUCOXYLON

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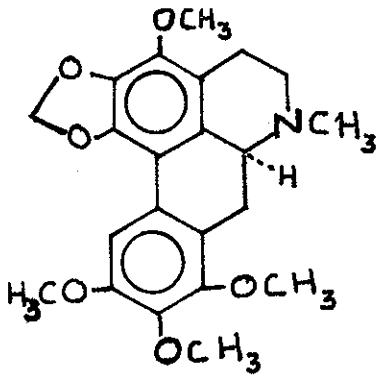
Leucoxylonine and ocoxylonine, two aporphine alkaloids isolated from Ocotea leucoxylon (Lauraceae) have been assigned structures 1 and 2, respectively. They are the first examples of aporphine bases in which all but one of the aromatic positions are oxygenated.

In 1960, a preliminary phytochemical investigation of the leaf and stem alkaloids of Ocotea leucoxylon resulted in the isolation of the known dicentrine (5), and the two new alkaloids leucoxine and leucoxylonine.[1] Subsequently, the structure and absolute configuration of leucoxine were established as shown in 4 by X-ray crystallography;[2] this result has escaped general recognition in the chemical literature.[3] We have now reinvestigated the leaf alkaloids of O. leucoxylon, resulting in the isolation of the known ocoteine (6), and the new aporphine ocoxylonine as well as the three above-mentioned alkaloids. Structures 1 and 2 are proposed for leucoxylonine and ocoxylonine, respectively, making these the first examples of hexaoxygenated aporphines.



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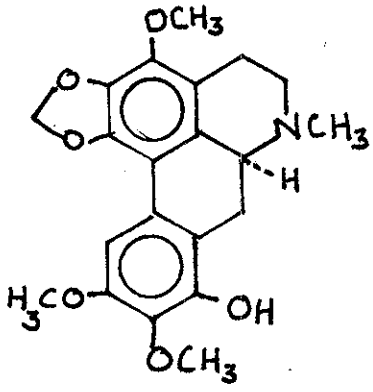

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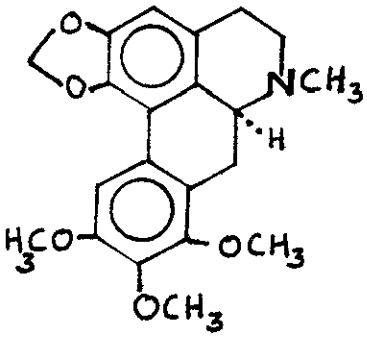

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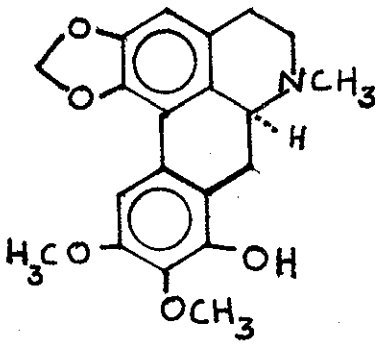

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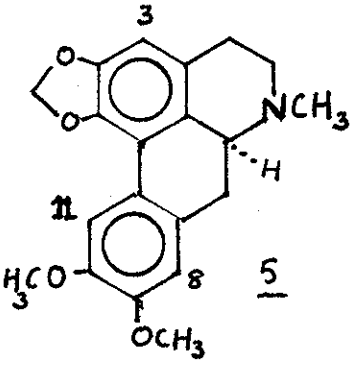

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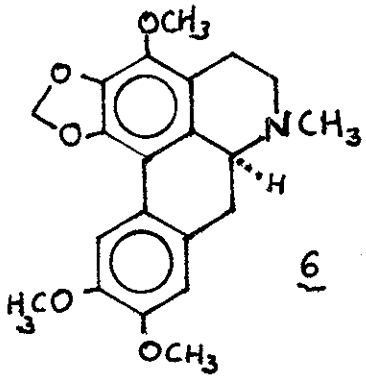

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Leucoxylonine (1) was obtained as an amorphous solid $[\alpha]_D$ = +54° (MeOH). The mass spectrum of 1 indicated the composition $C_{22}H_{25}NO_6$, and showed a strong molecular ion at m/e 399 (65%), and significant fragment ions at m/e 398 (90), 386 (30), 385 (50), 384 (90), 383 (100), 382 (20) and 356 (21). The nmr spectrum of 1 ($CDCl_3$) showed one N-methyl at δ 2.56 (3 H), four methoxyls at 3.86, 3.90, 3.91 and 4.01 (3 H each), and a diasteriotopic methylenedioxy group as a pair of doublets centered at 5.98 and 5.96 (J = 10 cps). In addition, only one aromatic proton was observed at 7.48 as a singlet. The uv absorption spectrum of 1 (EtOH) showed a maximum at 283 nm (ε = 20,860). Leucoxylonine formed a crystalline methiodide, mp 228-230° (decomp.), $[\alpha]_D$ = +32° (MeOH). This sample was identical (ir, mixture mp) with a sample of the original preparation[1] of leucoxylonine methiodide.

Ocoxylonine (2) crystallized from methanol as colorless needles, mp 161-162°, $[\alpha]_D$ = +45° ($CHCl_3$). The mass spectrum of 2 indicated the composition $C_{21}H_{23}NO_6$, and showed a molecular ion at m/e 385 (78%) and significant fragment ions at 384 (100), 370 (15), 354 (20), 342 (34), 327 (9) and 311 (10). The nmr spectrum of 2 ($CDCl_3$) shows one N-methyl at δ 2.36 (3 H), three methoxyls at 3.90, 3.93 and 4.01 (3 H each) and a methylenedioxy group as a pair of doublets centered at 5.98 and 5.96 (J = 10 cps). In addition a single aromatic proton was observed at 7.30 as a singlet. The uv absorption spectrum of 2 (EtOH) showed maxima (ε) at 224 (35,280), 284 (23,760), and 305 sh (12,000); an alkaline bathochromic shift of the maxima to 294 nm indicated the presence of a phenolic function. O-Methylation of 2 with diazomethane afforded leucoxylonine (1), indicating the latter to be a monomethyl ether of ocoxylonine. Conversely, benzyl-

selenolate demethylation[4] of leucoxylonine (1) occurred regiospecifically to give ocoxylonine (2) in 68% isolated yield.

The assignment of structures 1 and 2 to leucoxylonine and ocoxylonine rests upon a comparison of their spectral and chemical properties with those of the corresponding 3-desmethoxy aporphines ocopodine (3)[5] and leucoxine (4)[6]. The nmr spectrum of leucoxylonine (1) is virtually identical with that reported for ocopodine (3)[5] except that it shows an additional methoxyl at δ 4.01 in place of the C-3 proton at δ 6.48 in the ocopodine spectrum. Like leucoxine (4), ocoxylonine (2) gives a positive Gibbs test,[7] indicating that the sole aromatic proton of 2 must be para to the phenolic function. In ocoxylonine (2) this condition can only be met by a C-8 hydroxyl and an unsubstituted C-11 position; the only alternative structure containing a C-11 hydroxyl and C-8 proton is excluded, since its O-methylation product, leucoxylonine (1) does not show a characteristic high-field C-11 methoxyl[8] in its nmr spectrum. The selective benzylselenolate demethylation of leucoxylonine (1) to ocoxylonine (2) parallels the corresponding selective conversion[4] of ocopodine (3) to leucoxine (4).

All of the aporphines found so far in O. leucoxylon (1, 2, 4, 5 and 6) may be viewed as derivatives of dicentrine (5) in which further oxygenation has taken place at C-3 and or C-8.

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comparison samples of leucoxine and leucoxylonine methiodide. We also thank Dr. C. Costello (Massachusetts Institute of Technology) for the determination of high-resolution mass spectra.

REFERENCES

1 S. Goodwin, A. F. Smith and E. C. Horning, Chem. Ind. (London), 1960, 691.

2 G. M. Brown, Chemical Division Annual Progress Report, Sept. 1966, ORNL-3994, p. 114.

3 See however, M. P. Cava and A. Venkateswarlu, "Advances in Aporphine Chemistry," Academic Press Inc., New York (1969), p. 331-340.

4 R. Ahmad, J. M. Saá and M. P. Cava, J. Org. Chem., 1977, 42, 1228.

5 M. P. Cava, Y. Watanabe, K. Bessho, M. J. Mitchell and A. I. DaRocha, Tetrahedron Lett., 1968, 2407.

6 The following properties for leucoxine (4) have been recorded in our laboratory: mp 208-210°; $[\alpha]_D$ +84° (EtOH); mass spectrum: M^+, m/e 355; nmr spectrum: 2.46 (s, 3 H, N-methyl), 3.76, 3.83 (s, 3 H each, methoxyl) 6.07, 6.09 (d, 1 H each, J = 12 c/s), 6.65, 7.28 (s, 1 H each, Ar).

7 H. D. Gibbs, J. Biol. Chem., 1927, 72, 649.

8 M. Shamma, "The Isoquinoline Alkaloids: Chemistry and Pharmacology," Academic Press, New York (1972), p. 220.

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