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OCOTEA ALKALOIDS: VARIABILINE, A NOVEL AMINOAPORPHINE

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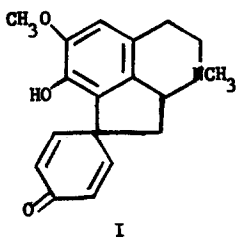
As part of a continuing study of the alkaloids of the genus Ocotea (Lauraceae),[2,3] we have now examined the Brazilian species Ocotea variabilis. Separation of the bases of O. variabilis by a combination of gradient countercurrent distribution and plc afforded (+)-glaziovine (I), (+)-apoglaziovine (II),[4] and (+)-nantenine (III) in addition to a new base, variabiline (IV), which proved to be the first example of an amino-substituted benzylisoquinoline-derived alkaloid.

Variabiline (IV), $C_{32}H_{32}N_2O_2$, forms white crystals, m.p. 116-117°, and is optically inactive; it forms a dihydrochloride, m.p. 185-187° dec. and a monohydrochloride, m.p. 230-232° dec.

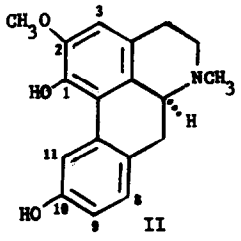
The following spectral data for variabiline are consistent with a 1,2,10-trisubstituted phenolic aporphine structure: ir (KBr) 3.0 μ (OH); uv_{max}^{EtOH} 213 nm (log ε 4.55), 233 (4.45), 265 (4.44), 280 sh (4.26) and 318 (3.74); $\lambda_{max}^{EtOH-NaOH}$ 220 nm (log ε 4.53), 250 (4.49), 283 sh (4.12), and 350 (3.88); nmr ($CDCl_3$) δ 7.95 (1 H, d, J = 2.5 Hz, C_{11}-H), 7.02 (1 H, d, J = 8 Hz, C_8-H), 6.57 (1 H, d of d, J = 2.5 and J = 8 Hz, C_9-H), 6.50 (1 H, s, C_3-H), 7.24 (10 H, s, 2 x C_6H_5), 4.68 (4 H, s, 2 x benzylic CH_2), 3.82 (3 H, s, OCH_3), 2.50 (3 H, s, NCH_3), and 5.90 (1 H, s, OH, disappearing in presence of D_2O). In addition to the molecular ion at m/e 476, the most revealing peaks in the mass spectrum were those at M-91 and M-182, consistent with the loss of one and two benzyl groups, respectively.

In view of the presence of glaziovine and apoglaziovine in O. variabilis, structure IV appeared likely for variabiline. Confirmation of this structure was obtained synthetically. Thus, (+)-glaziovine (I, 1.0 g) was heated to 200-210° for 2 hours with a mixture of dibenzylamine (4.0 g) and dibenzylamine hydrochloride (1.0 g) to give (40%) variabiline, identical (ir, uv, nmr) with the natural base.

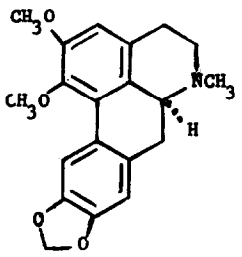
The simple base benzylmethylamine has been long known as a natural product.[5] It seemed possible, therefore, that O. variabilis might have contained dibenzylamine which could have reacted with glaziovine to form variabiline during extraction of the plant. However, no dibenzylamine was detectable in the crude alkaloid mixture; furthermore, no variabiline was produced when a methanolic solution of glaziovine, dibenzylamine, and dibenzylamine hydrochloride was heated under the conditions used in the plant extraction (55-60° for 20 hours). We suggest that variabiline may arise in the plant by rearrangement of the N-unsubstituted imine of glaziovine, followed by reductive benzylation, benzaldehyde serving as the source of the benzyl groups.[6]



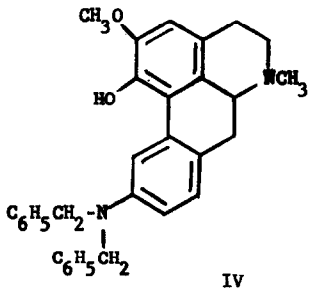
I



II



III



IV

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4. Our (+)-apoglaziovine had $[\alpha]_D^{25}$ = +165° ($CHCl_3$) and m.p. 249-252° dec; its ir ($CHCl_3$) and nmr ($CDCl_3$) spectra were identical with those of the racemic base prepared by HCl rearrangement of (±)-glaziovine. The previously reported (-)-apoglaziovine of m.p. 149-152° dec (249-252° ?) and $[\alpha]_D$ = -35° must be a mixture of (-) and racemic material: B. Gilbert, M. E. A. Gilbert, M. M. de Oliveira, O. Ribeiro, E. Wenkert, B. Wickberg, U. Hollstein, and H. Rapoport, J. Am. Chem. Soc., 86, 694 (1964).

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