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OCOBOTRINE AND 14-EPISINOMENINE. NEW TRANS-MORPHINANE ALKALOIDS OF OCOTEA BRACHYBOTRA

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The plants belonging to the family Lauraceae are a rich source of alkaloids, particularly those of the proaporphine and aporphine types[1].

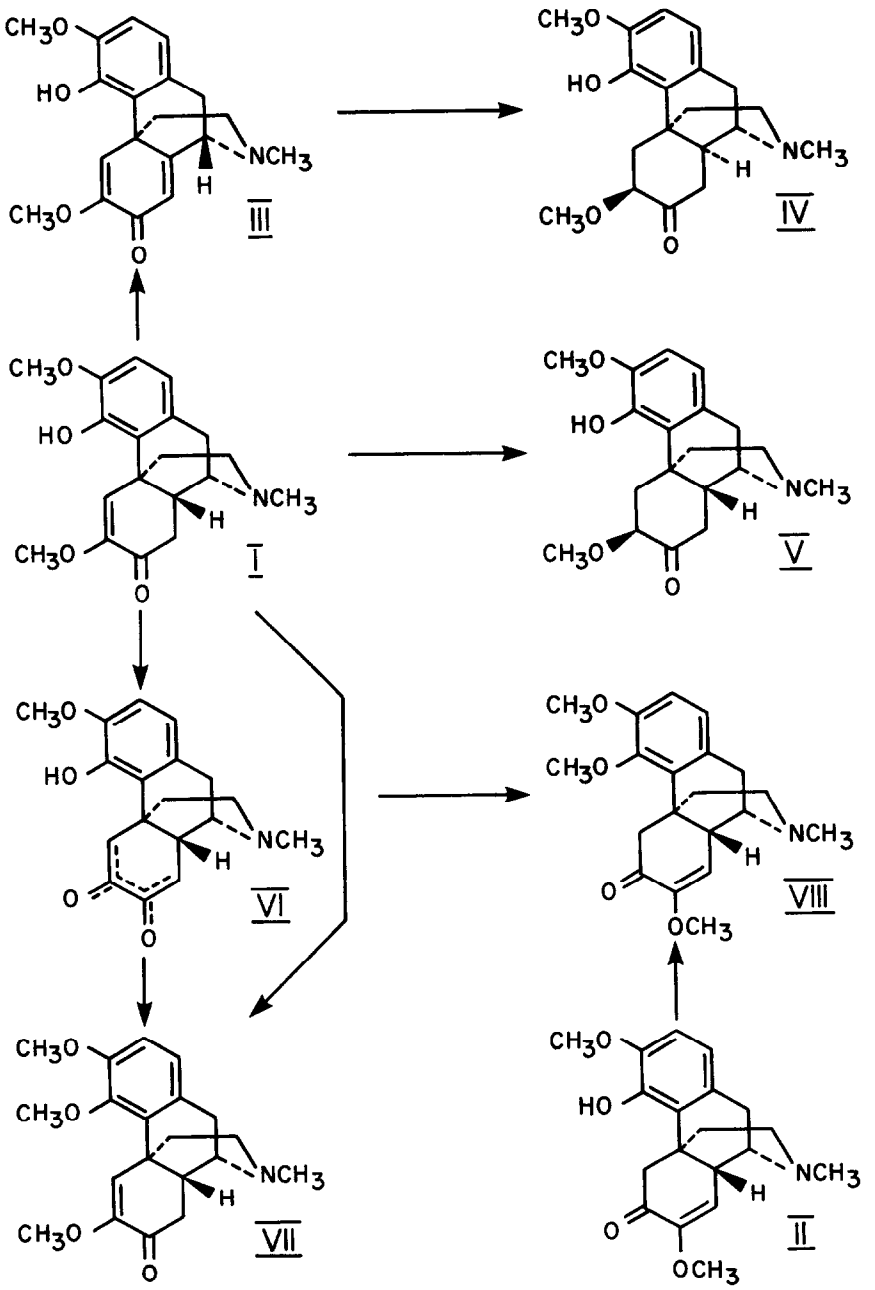
On the other hand, the alkaloids of the morphinane type are not usually found in this family. Only in the genus Cassytha[2] a morphinandienone, i.e. sinacutine III, was observed.

In a Brazilian lauracea, [Ocotea brachybotra (Meiss.) Mez] we have found four morphinane-alkaloids, including two already known, sinacutine and pallidine, and two new ones, ocobotrine I and 14-episinomenine II to which we have ascribed the unusual trans-B/C morphinane-structures.

I-Ocobotrine, m.p. 97-99°C (AcOEt/Et_2O) $C_{19}H_{23}NO_4 \cdot \frac{1}{2} CH_3COOC_2H_5$; the solvent of crystallization was removed by drying in vacuo with heating to yield an amorphous product: $[\alpha]_D^{20}$ -93° (c = 1 in $CHCl_3$); λ_{max}^{MeOH} 264 (log ε 4.01) 210 (log ε 4.52); IR ($CHCl_3$) 3500, 1680, 1620; δ NMR ($CDCl_3$) 7.76 (1H, s, 5-H), 6.75 and 6.73 (1H each, s, 1-H and 2-H) 6.35 (1H, br.s; exchange with D_2O, 4-OH) 3.90 (3H, s, OCH_3) 3.65 (3H, s, OCH_3), 2.35 (3H, s, NCH_3); m/e 329 (M^+, 55%) 314 (100) 286 (24) 271 (4) 192 (25) 189 (10) 157 (8) 115 (10). I.HCl m.p. 296-7°C (MeOH).

These data suggest a 8,14-dihydromorphinandienone structure.

The data reported for similar structures (8,14-dihydrosalutaridine[3] and isosinomenine[4]) are very similar, excepting the c.s. value of the C-5 vinyl proton (δ 6.76). A similar value of the vinyl proton at C-5 (δ 7.56) is found only in the related dienones (sinacutine and salutaridine)[5].


CH3O
HO
NCH3
H
O
III
IV
I
V
VI
VII
VIII
II
OCH3

In the molecular models of these dienones, a marked interaction between 5-H and 4-OH is observable, which accounts for the downfield shift. With 8,14-dihydro structures this interaction is possible only in B/C-trans structures. Furthermore, the mass spectrum of I in comparison with those reported for 8,14-dihydrosalutaridine[3] and isosinomenine[6] shows two important features, i.e. the lack of the fragment at m/59 and the strong intensity of M^+, which is 55% of the parent peak. Both these properties are characteristic of trans-morphinane structures[7].

Chemical correlations further confirmed the suggested structure. Ocobotrine--O-acetate was selectively brominated at C-8 with Br_2 in a mixture of CF_3COOH and CH_3COOH containing dry HBr, and the bromoketone [m.p. 166-168°C (ethyl ether); 8-H, δ 5.64, d, J 12 Hz] was simultaneously dehydrohalogenated and deacetylated with DBU yielding sinacutine III, identical to the natural product (m.p., t.l.c., $[\alpha]_D$ and NMR). Furthermore, I was hydrogenated with Pd in ethyl acetate to a mixture of two dihydroderivatives epimer at C-6, which after equilibration with methanolic KOH gave the more stable isomer V, having equatorial 6-OCH_3 group[8]. Compound V [m.p. 210-212°C; $[\alpha]_D^{20}$ -19.6° (c = 1 in $CHCl_3$)] proved different from tetrahydrosinacutine IV [m.p. 189-191°C; $[\alpha]_D^{20}$ +68.8° (c = 1 in $CHCl_3$)] obtained from sinacutine by similar hydrogenation and equilibration. As hydrogenation of morphinandienones is known[9] to occur on the less indereded side of the C ring giving products having B/C cis-configuration, V and IV should differ only in the C-14 configuration. Moreover, the mass spectra confirmed the proposed structures, the fragment at m/e 59 being present in IV with a relative abundance higher (27%) than in V (0.7%).

II-14-episinomenine; m.p. 118-120°C (benzene), $C_{19}H_{23}NO_4 \cdot \frac{1}{2} C_6H_6$; after drying in vacuo: $[\alpha]_D^{20}$ -40° (c = 1 in $CHCl_3$); λ_{max}^{MeOH} 272 (log ε 3.87) 211 (log ε 4.41); IR (KBr) 3500, 1675, 1625. II. HCl . 2 H_2O m.p. 200-210°C (MeOH).

The mass spectrum was almost indistinguishable from that of sinomenine[6] as was the NMR from that of 14-episinomenine, prepared[4] by alkaline isomerization of sinomenine. I is hydrolyzed at C-6 with 5% HCl, yielding VI as a mixture of enols; these are then methylated with $(CH_3)_2SO_4$ and t-BuOK[10], giving VII and VIII. The main product VIII [(m.p. 133-134°C; $[\alpha]_D^{20}$ -33.3° (c = 0.35 in $CHCl_3$)] proved identical (m.p., t.l.c., $[\alpha]_D$) to O-methyl-14-episinomenine obtained from II with CH_2N_2, whilst the minor product VII (m.p. 123-124°C; $[\alpha]_D^{20}$ -86° (c = 0.5 in $CHCl_3$) was identical (m.p., t.l.c., $[\alpha]_D$) to O-methyl-ocobotrine obtained from I with $(CH_3)_2SO_4$ and t-BuOK.

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