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3ξ-HYDROXYVOBTUSINE, A KEY-LINK BETWEEN VOBTUSINE AND AMATAINE

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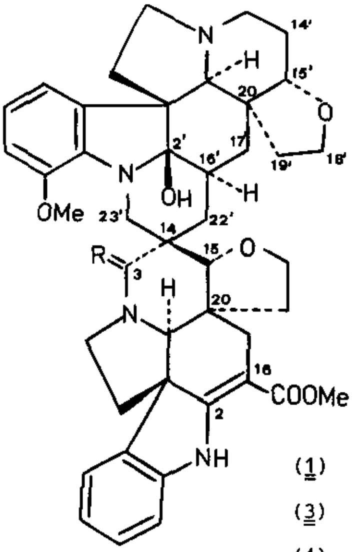
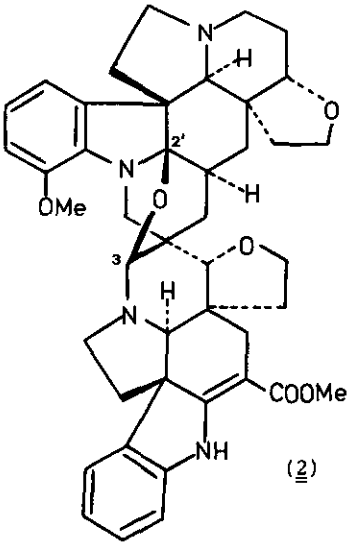
Abstract - The title compound, a 'bisindoline' alkaloid from the root bark of *Voacanga chalotiana* (Apocynaceae) has structure (4) proved by correlation with vobtusine (1) and amataine (2).

A characteristic of the genera *Callichilia* (*Hedranthera*), *Conopharyngia*, *Rejoua* and *Voacanga* of the Apocynaceae family is the occurrence of 'dimer' alkaloids of the vobtusine type, the prototype of this being vobtusine (1) itself. The intriguing structure of vobtusine was proposed on the basis of chemical and spectroscopic studies[1a,b] and fully elucidated by X-ray analysis of its dibromo derivative.[2] Much of these alkaloids belong to the vobtusine series (*i.e.*, with 14*S*-configuration) [vobtusine, demethyl-



(1) R:H_2
(3) R:O
(4) R:H,OH



(2)

vobtusine[3], 18'-oxovobtusine[4], 2'-deoxy-18'-oxovobtusine[4], 3-oxovobtusine (3)[5], 3-oxovobtusine N-oxide[5], 2'-deoxy-3-oxovobtusine[5]], whereas only few naturally occurring related alkaloids belong to the stereoisomeric series (14R)[*i.e.*, amataine (2, subsessiline, grandifoline)[6], folicangine[1b,7], 18'-oxosubsessiline[5], owerreine[3] and isovoafolidine[1b,7]].

The large scale extraction of the root bark of *Voacanga chalotiana* Pierre ex Stapf gave in addition to vobtusine, amataine and other reported alkaloids[8], a new 'bisindoline' alkaloid[9] to which structure of 3ξ-hydroxyvobtusine (4) was assigned on chemical and spectroscopic grounds. The new alkaloid is a colourless amorphous solid, insoluble in all the apolar solvents, sparingly soluble in aprotic and protic polar solvents and exhibits UV spectrum [λ_{max}(MeOH) 221,263,299 and 325 nm] and IR spectrum [ν_{max}(nujol) 3450-3300,1680,1610 cm^{-1}] compatible with the same functionality and chromophores as in vobtusine and amataine. The ^1H-NMR spectrum shows a singlet at δ($CDCl_3$) 8.95(1H, N*H*), two multiplets at δ 7.05-7.25 and 6.60-6.95(total seven aromatic protons), two doublets at δ 5.09 [1H, ^2J 14Hz, C(23')-*H*] and 4.53 [1H, ^3J 10 Hz, C(3)-*H*; singlet after D_2O exchange] and two methyl singlets at δ 3.80 and 3.73. The chemical shift of C(23')-H as well as the Cotton effect amplitudes in CD spectrum [λ_{max}(MeOH) 238 nm ($\Delta\varepsilon$ +8.6), 264(-9.2), 288(+6.0) and 323(-25.2)] for (4) are indicative of (14S) configuration[10]. The presence of the carbinolamine group N-C(3)-OH and the configuration at C(14) are confirmed by quantitative $NaBH_4$ reduction to vobtusine and by dehydratio to amataine[11], the last transformation being accompained by configurational inversion at the spiro center C(14).

The EI-MS spectrum (70 eV) does not exhibit a peak at 734 due to $M^{\cdot +}$ and it is not reproducible owing to the thermal-induced dehydration to amataine. However at 200°, along with ions at m/e 716(13%), 658(10), 502(4), 391(5), 363(24), 331(21), 168(12) and 138(100) characteristic of amataine[6], it displays peaks at m/e 717(8), 698(5) and 640 (5) corresponding to $(M\text{-}OH)^+$, $(M\text{-}2H_2O)^{\cdot +}$ and $(M\text{-}2H_2O\text{-}C_2H_2O_2)^{\cdot +}$ indicative of the presence of two hydroxy groups in the molecule.

All these evidences support the proposed structure of 3ξ-hydroxyvobtusine for (4) and this was found identical to 'hydratoamataine' obtained on acidic treatment (dioxane, 0.01N HCl, 2 hr at 80°) of amataine[6]. A convincing mechanism for the transformation 3ξ-hydroxyvobtusine $\rightleftharpoons$ amataine has been precedently formulated by Hesse[6], the inversion of configuration at the spiro center C(14) being strictly required by C(2')-C(3) ether bridge formation.

(**4**) represent the obvious precursor of 3-oxovobtusine (**3**) and its intermediacy in the formation of amataine is suggested on the basis of the reported chemical behaviour. Although 3ξ-hydroxyvobtusine and 3-oxovobtusine have been formed (t.l.c.) in the iodine-promoted oxidation[12] of vobtusine, we have not evidenced traces of these compounds when vobtusine was stored under oxygen even in the presence of adsorbents such as silica or alumina.

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9 3ξ-hydroxyvobtusine gives a blue spot with Ce(IV) sulfate on silica gel plate with R_f 0.18 (hexane-CH_2Cl_2-AcOEt-MeOH, 25:5:20:10) in comparison with amataine (R_f 0.54) and vobtusine (R_f 0.27). It was isolated in 0.001% yield by silica gel chromatography (hexane-AcOEt-MeOH, 48:48:4) followed by rechromatography ($CHCl_3$-MeOH, 95:5).

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11 A solution of (**4**) in anhydrous DMSO is completely converted into amataine by heating at 80° for 1 hr or on long standing (c.a. 1 month) at r.t..

12 For a related oxidation of voacangine into 19-hydroxyvoacangine and 19-oxovoacangine, see V.C.Agwada, Y.Morita, U.Renner, M.Hesse, and H.Schmid, *Helv. Chim. Acta*, 1975,**58**,1001.

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