Voacinol: a New Bisindole Alkaloid from *Voacanga Grandifolia* (Miq) Rolfe

Tuticorin R. Govindachari,* Gopalan Sandhya, Sundaram Chandrasekharan, and Krishnamoorthy Rajagopalan

Department of Organic Chemistry, University of Madras, A. C. College Campus, Madras 600 025, India

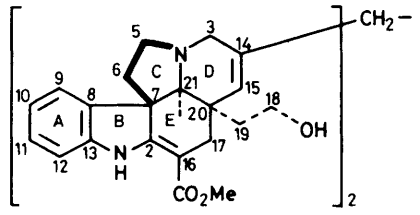
Voacinol, a new bisindole alkaloid from *Voacanga grandifolia* has been assigned a 14,14'-methylene-bis-18-hydroxytabersonine structure (**1**), on the basis of spectral data.

In a reinvestigation of *Voacanga grandifolia* (Miq) Rolfe, powdered leaves were extracted with 90% ethanol (at 30 °C) and processed for alkaloids by gradient pH extraction,[1] initially using aqueous sulphuric acid (1.5%), the bases isolated at pH 8 being submitted to a second passage through aqueous citric acid (1%). The alkaloids obtained at pH 4.5 from the latter extract on chromatography yielded vobtusine,[2] deoxyvobtusine,[3] amataine[4] (already reported from this source), desacetylvindoline (not earlier reported from *V. grandifolia*), and a new bisindole alkaloid which we named voacinol and assigned structure (**1**), on the basis of spectral data.

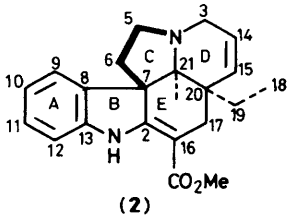
Voacinol was obtained in a low yield of about 0.002% as a yellow amorphous solid, $[\alpha]_D^{25}$ − 105.5° ($CHCl_3$), whose purity was established by h.p.l.c. analysis. The u.v. [λ_{max} (EtOH) (log ε) 226(4.44), 298(4.40), 328(4.54)] and i.r. [γ_{max}($CHCl_3$) 3420, 3395, 1675, and 1610 cm^{-1}] spectra indicated the presence of a β-anilinoacrylic ester system as in tabersonine.[5]

The ^{13}C n.m.r. shifts δ(Me_4Si), of voacinol (**1**) and tabersonine[6] (**2**), are respectively: Ring A: 137.4, 137.8 (C-8); 121.6, 121.4 (C-9); 120.8, 120.5 (C-10); 127.8, 127.6 (C-11); 109.4, 109.2 (C-12); 143.1, 143.1 (C-13); Ring B: 166.0, 166.7 (C-2); 55.1, 55.0 (C-7); Ring C: 50.9, 50.8 (C-5); 44.4, 44.3 (C-6); 69.5, 69.9 (C-21); Ring D: 52.7, 50.3 (C-3); 129.7, 124.8 (C-14); 133.7, 132.9 (C-15); 41.0, 41.2 (C-20); Ring E: 91.9, 92.2 (C-16); 30.5, 26.7 (C-17); 58.8, 7.3 (C-18); 37.9, 28.4 (C-19); 39.0, nil (C-22), 168.6, 168.8 (C=O); 50.9, 50.8 (-OMe). It can be seen that the chemical shifts of all the carbons present in rings A, B, and C of (**1**) and (**2**) are nearly identical. The olefinic carbon C-14 of ring D in (**1**) has a shift of δ 129.7, downfield by about 5 p.p.m. from the corresponding carbon in (**2**), due to the attachment of a further carbon atom instead of hydrogen. C-14 is clearly the point of attachment of the methylene bridge linking the two units. The modification of the ethyl side chain in (**2**) to an 18-hydroxyethyl side chain in (**1**) is seen by the shift of the C-18 carbon from δ 7.3 in (**2**) to 58.8 in (**1**). The resonance at δ 39 is ascribed to the methylene carbon linking two identical 18-hydroxytabersonine units, consistent with its doubly allylic nature.

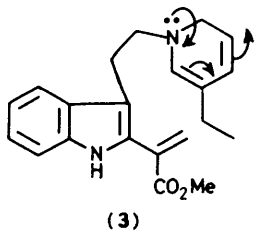
The most significant feature of the ^1H n.m.r. spectrum of (**1**) is the presence of only one olefinic proton at δ 5.5 as



(**1**)



(**2**)



(**3**)

compared to two olefinic protons in the spectrum of (**2**).[7] The single olefinic proton signal is seen as a slightly broadened singlet due to allylic coupling with the protons at C-22. If the linkage between the two monoindole units had been through the C-15 carbon atoms, the olefinic proton would have shown up as a triplet, split by the methylene protons at C-3. ^{1}H n.m.r. ($CDCl_3$): δ (Me_4Si), 8.9 (1H, s, D_2O exchangeable, NH), 7.3—6.65 (4H, m, aromatic H), 5.5 (1H, br. s, olefinic H), 3.75 (3H, s, OMe), 3.45 (2H, t, H_2C-18), 3.25 (2H, d, H_2CC-3), 2.65—2.7 (3H, H_2C-5, HC-21), 2.45 (2H, H_2C-22), 2.4—1.8 (4H, H_2C-6, H_2C-17), 1.66 (1H, m, D_2O exchangeable, OH), and 1.2 (2H, m, H_2C-19). The proton at C-21 appears at δ 2.65 in agreement with the chemical shifts of the protons at C-21 in vindoline,[8] tabersonine (**2**), and 11-methoxy tabersonine[9] which have an α-hydrogen at C-21. A β-hydrogen at C-21 usually appears around δ 2.9—3 as in (20*R*)-18,19-dihydroxypseudovincadifformine, pandoline, and 20-epipandoline.[10] All alkaloids of the vindoline group which have an α-hydrogen at C-21, also have the C-7–C-6 bond β and the ethyl side chain at C-20 in the α configuration Taken together with the identical chemical shifts at C-7, C-20, and C-21, it can be safely assumed that voacinol has the same stereochemistry as tabersonine.

The fast atom bombardment mass spectrum (f.a.b.-m.s.) showed an $(MH)^{\cdot+}$ ion at *m/z* 717, indicating the molecular ion at *m/z* 716, corresponding to the molecular formula $C_{43}H_{48}N_4O_6$. There are strong peaks at *m/z* 365 (90%) and 351 which should correspond to two 18-hydroxytabersonine units, one with the linking methylene unit and the other without it, respectively. This structure may arise from nucleophilic attack of two dienamine units (**3**), on an electrophilic formaldehyde equivalent. The hypothesis that a molecule of structure (**3**) (14,21-dehydrosecodine) is an intermediate in the principal indole alkaloid skeletal rearrangement and formation is widely accepted.[11] After the two units are linked by a methylene bridge, further transformations would lead to the ultimate structure of voacinol. It is needless to speculate about the hydroxylation of the ethyl side chain since this could take place at any stage in the biogenetic progression from strictosidine onwards. We are not aware of any other bisindole alkaloid with a methylene linking two identical monoindole units as in voacinol.

We thank Professor P. C. Srinivasan of the Department of Organic Chemistry, University of Madras and Dr. K. Nagarajan, Searle India Limited, Bombay, for valuable discussions, the Department of Science and Technology for a grant, Dr. B. C. Das, C.N.R.S., Gif-Sur-Yvette, France, for the mass spectrum, Dr. N. Chandrakumar, C.L.R.I., Madras for the ^{13}C-n.m.r. spectrum. Amrutanjan Limited for providing facilities, and Professor A. N. Namboodiri, Tropical Botanical Gardens and Research Institute, Trivandrum, for the supply of plant material.

Received, 19th January 1987; Com. 058

References

1 S. W. Pelletier, B. S. Joshi, and H. K. Desai, 'Advances in medicinal plant research,' Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, 1985, p. 153.
2 J. Poisson, M. Plat, H. Budzikiewicz, L. J. Durham, and C. Djerassi, *Tetrahedron*, 1966, **22**, 1075.
3 P. C. Majumdar, T. K. Chanda, and B. N. Dinda, *Phytochemistry*, 1974, **11**, 1261.
4 V. C. Agwada, J. Naranjo, M. Hesse, H. Schmid, Y. Rolland, N. Kunesch, J. Poisson, and A. Chatterjee, *Helv. Chim. Acta*, 1977, **60**, 2838.
5 M. M. Janot, J. Le Men, and C. Fan., *C. R. Acad. Sci., Paris*, 1959, **248**, 3005.
6 M. Shamma and D. M. Hindenlang, 'Carbon 13 n.m.r. Shift assignments of amines and alkaloids,' Plenum Press, New York and London, 1979, p. 226.
7 M. Plat, J. Le Men, and M. M. Janot, *Tetrahedron Lett.*, 1962, 271.
8 A. De Bruyn, L. De Taeye, R. Simonds, and C. De Pauw, *Bull. Soc. Chim. Belg.*, 1981, **90**, 185.
9 M. Lounasmaa and S. K. Kan, *Acta Chem. Scand., Ser. B*, 1980, **34**, 379.
10 C. Kan, H-P. Husson, S. K. Kan, and M. Lounasmaa, *Planta Med.*, 1981, **41**, 195.
11 R. T. Brown, G. F. Smith, K. S. J. Stapleford, and D. A. Taylor, *Chem. Commun.*, 1970, 190; and reference 1 therein.