Structure, Synthesis, and Stereochemistry of Deoxytubulosine

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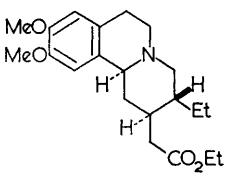
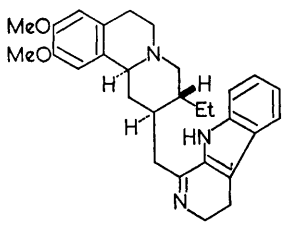
THE fruits of *Alangium lamarckii* (Thwaites) have afforded a new alkaloid, $C_{29}H_{37}N_3O_2$, showing ultraviolet absorption in agreement with the sum of isolated indole and veratrole chromophores; the indolic nitrogen is unsubstituted (infrared). The alkaloid contains two *O*-methyl groups (Zeisel) and

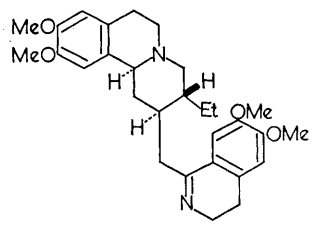
one *C*-methyl group (Kuhn–Roth) and these were confirmed by the integrated n.m.r. spectrum which further reveals that the *C*-methyl group is part of an ethyl residue. Two aromatic protons appear as singlets (τ 3·42 and 3·30) and a multiplet in the τ 3·0—2·6 region corresponds to four additional aromatic protons. Dr. H. Budzikiewicz (Stanford) kindly determined the mass spectrum and on the basis of his interpretation of the results he suggested to one of us (J.R.M.) that the new alkaloid is the deoxy-relative of tubulosine which had been isolated from *Pogonopus tubulosus*[1]; largely by n.m.r. and mass spectrometry,[1] this had been assigned the gross structure (IV; R=H, with a phenolic hydroxyl group in the β-carboline residue). The parent peak for deoxytubulosine occurs at *m/e* 459 which confirms the molecular formula and the fragmentation pattern with peaks at *m/e* 244, 246, 272—275, 286, and 288 is characteristic[2,3] of a dimethoxybenzoquinolizidine moiety. The strong peaks at *m/e* 171 and 185 correspond to a tetrahydro-β-carboline system[1] and the whole spectrum matches that reported[1] for the synthetic base[4] (as IV; R=H). These results strongly support the gross structure (as IV; R=H) but give no information concerning its stereochemistry for two reasons. (*a*) Mass spectrometry is commonly insensitive to stereochemistry and (*b*) the complete stereochemistry of the synthetic base (as IV; R=H) was not known. Proof of the structure and stereochemistry of deoxytubulosine was obtained in the following way.



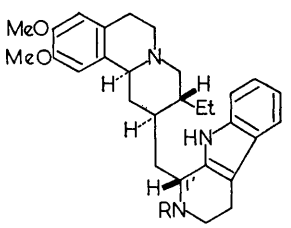
(I)



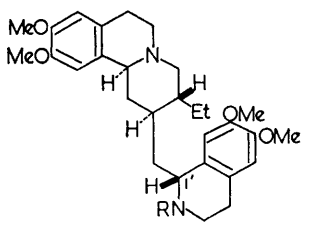
(II)



(III)



(IV)



(V)

The earlier synthesis[4] from the (±)-ester[5] (as I) was repeated and the intermediate (as II) was reduced with borohydride to afford two crystalline diastereoisomers (as IV; R=H; epimeric at C-1′) one of which was identical, apart from its racemic nature, with deoxytubulosine. This establishes the structure of the alkaloid save for the absolute stereochemistry and the configuration at C-1′. The optically-active ester[6] (I) of proved absolute configuration[7] has recently been made available by

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[2] H. Budzikiewicz, S. C. Pakrashi, and H. Vorbruggen, *Tetrahedron*, 1964, **20**, 399.
[3] G. Spiteller and M. Spiteller-Friedman, *Tetrahedron Letters*, 1963, 153.
[4] A. R. Battersby, G. C. Davidson, and J. C. Turner, *J. Chem. Soc.*, 1961, 3899.
[5] A. R. Battersby and J. C. Turner, *J. Chem. Soc.*, 1960, 717.
[6] A. R. Battersby and B. J. T. Harper, *J. Chem. Soc.*, 1959, 1748.
[7] A. R. Battersby and S. Garratt, *J. Chem. Soc.*, 1959, 3512; E. E. van Tamelen, P. E. Aldrich, and J. B. Hester, *J. Amer. Chem. Soc.*, 1959, **91**, 6214; Y. Ban, M. Terashima, and O. Yonemitsu, *Chem. and Ind.*, 1959, 568; A. R. Battersby and S. Garratt, *Proc. Chem. Soc.*, 1959, 86.

synthesis[8] and material generously provided by Dr. H. T. Openshaw (Wellcome Research Laboratories) was converted[4] into its amide with tryptamine. Reduction of the derived base (II) as above afforded deoxytubulosine (IV; R=H), $[\alpha]_D -24 \pm 1°$ ($CHCl_3$) identical with the natural product $[\alpha]_D -24 \pm 1°$ ($CHCl_3$).

The absolute configuration at C-1′ of deoxytubulosine was shown to correspond to that in emetine (V; R=H) since the molecular rotation difference of (IV; R=H) and (IV; R=Ac), $\Delta[M]$ $-17°$, corresponds to that of emetine (V; R=H) and *N*-acetylemetine $\Delta[M] -74°$. Isoemetine (V; R=H, epimeric at 1′) shows a positive $\Delta[M]$, $+460°$, on acetylation. These results prove that structure (IV; R=H) is a complete expression for deoxytubulosine; emetine (V; R=H) and its isoquinoline relatives also occur in *A. lamarckii*.[1]

Recently, Djerassi and his colleagues[9] have converted tubulosine into its deoxy-derivative and have shown this to be identical with our alkaloid. The combined information thus establishes rigorously the absolute stereochemistry and skeletal structure of tubulosine.

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[8] H. T. Openshaw and N. Whittaker, *J. Chem. Soc.*, **1963**, 1461.
[9] H. Monteiro, H. Budzikiewicz, C. Djerassi, R. R. Arndt, and W. H. Baarschers, following paper.