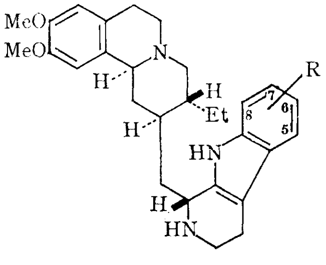
The Synthesis of Tubulosine

By H. T. OPENSHAW and NORMAN WHITTAKER

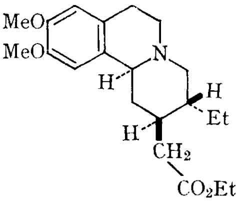
(*The Wellcome Research Laboratories, Beckenham, Kent*)

THE alkaloid tubulosine, isolated from *Pogonopus tubulosus* (DC) Schumann[1] and from *Alangium lamarckii* Thw.,[2] has been assigned the structure (I; R = OH) on the basis of its conversion[3] into deoxytubulosine (I; R = H), the structure and stereochemistry of which have been proved by synthesis.[4] A study of the published[5] absorption spectra of tubulosine by Dr. A. J. Everett of these laboratories led to the conclusion that the phenolic hydroxyl group is in the 6-position of the β-carboline ring system. The intensities and frequencies of infrared absorption in the C–H deformation region are not characteristic of a system of three vicinal aromatic hydrogen atoms, thus excluding positions 5 and 8 for the hydroxyl group. Further, the ultraviolet absorption of the β-carboline fragment of tubulosine, obtained by subtraction of the absorption of the veratrole chromophore from the spectrum of tubulosine, favoured a 6- rather than a 7-hydroxy-substituent. In support of this, the ultraviolet absorption of an equimolecular mixture of 3-ethyl-1,2,3,4,6,7-hexahydro-9,10-dimethoxy-2-oxo-11b*H*-benzo[*a*]quinolizine with 1,2,3,4-tetrahydro-6-hydroxy-β-carboline proved very similar to that of tubulosine. Independent evidence for the placing of the hydroxyl group in the 6-position derives from the ultraviolet absorption of a dehydrogenation product of the alkaloid.[3]

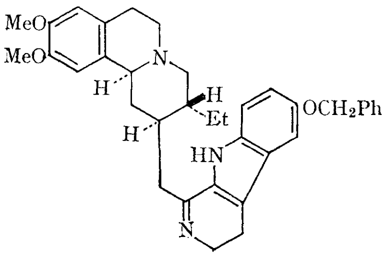
We have confirmed the assigned constitution (I; R = 6-OH) by total synthesis of tubulosine. The *lævo*-rotatory ester[6] (II) was converted[7] into its 5-benzyloxytryptamide (m.p. 186—187·5°) which on cyclisation with phosphoryl chloride gave the dihydro-β-carboline (III) [dihydrobromide, m.p. 242—243°, $[\alpha]_D^{22}$ + 86·4° (*c* 1 in MeOH)]. Reduction with borohydride gave a crystalline {m.p. 194—196° (evac. cap.), $[\alpha]_D^{25}$ − 18·5° (*c* 1 in $CHCl_3$)} and an amorphous benzyloxytetrahydro-β-carboline. On catalytic debenzylation over palladised alumina, the former gave hydrated isotubulosine {m.p. 163—164° (evac. cap.), $[\alpha]_D^{26}$ − 78·7° (*c* 2 in pyridine)} whilst the latter afforded tubulosine {m.p. 282—283° (evac. cap.), $[\alpha]_D^{26}$ − 62·7° (*c* 2 in pyridine)}. The infrared and ultraviolet spectra of the synthetic tubulosine were identical with those of the natural alkaloid [m.p. 282—283° (evac. cap.), undepressed in admixture] kindly supplied by Professor V. Deulofeu, who has independently confirmed the identity of the two compounds by thin-layer chromatography.[8]



(I)



(II)



(III)

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[7] H. T. Openshaw and N. Whittaker, Belgian Patent **661,294**.

[8] Performed by Mr. S. Gerszberg (Buenos Aires).