# A SYNTHESIS OF (±)-9-DEMETHYLTUBULOSINE

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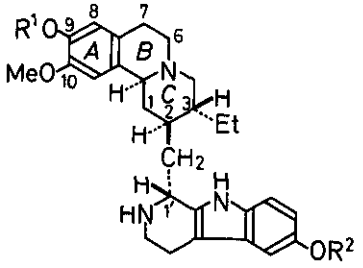
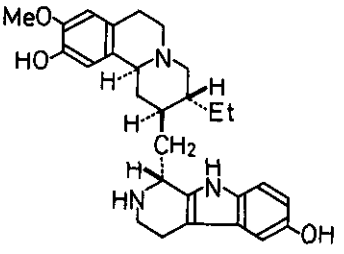
Abstract —— (±)-9-Demethyltubulosine (I) has been synthesized from the tricyclic amino acid VII through the intermediates VIII, IX, and IV. Nonconformity of synthetic (±)-I with demethyltubulosine indicated the alternative 10-demethyl structure (V) to be the correct expression for this Alangium alkaloid.

Among a number of benzoquinolizidine alkaloids isolated from Alangium lamarckii Thw. (Alangiaceae) is a phenolic base designated as demethyltubulosine.[1,2] On the basis of its two-step methylation to O-methyltubulosine (III) through tubulosine (II) and on the mass spectral evidence, Popelak and co-workers[1] reported that the structure of demethyltubulosine had to be expressed by either the formula I or V, but a differentiation was not possible at that time. In the present work we selected (±)-9-demethyltubulosine (I) as a target for synthesis with a view to elucidating the exact location of the phenolic hydroxyl group in ring A of the natural base. This selection was based on our recent finding[3,4] that desmethylpsychotrine, a co-occurring alkaloid,[2] has the 9-demethyl structure (VI), and the synthesis of (±)-I was accomplished as follows.

The key intermediate generated in the synthetic plan was the racemic tricyclic amino acid VII, which was prepared in eight steps from ethyl (±)-trans-5-ethyl-2-oxo-4-piperidineacetate[5] according to the recently reported procedure[3] ("lactim ether method"[6]). Condensation of VII with 5-benzyloxytryptamine[7] using the coupling reagent diethyl phosphorocyanidate[8] ($Et_3N$, $HCONMe_2$, room temp., 6 h) furnished the amide VIII (mp 92.5–94°C)[9,10] in 93% yield. On cyclization with $POCl_3$ (boiling toluene, 2.5 h), the amide VIII was converted into the dihydro-β-carboline IX (69% yield; mp 105–106°C),[11] which was then hydrogenated over Adams catalyst (dioxane, 1 atm, 29°C, 40 min). Chromatographic separation (silica gel, $CHCl_3$–EtOH) of the hydrogenation products afforded (±)-O,O-dibenzyl-9-demethyltubulosine (IV) [29% yield; $^1$H nmr ($CDCl_3$) δ:[12] 3.83 (3H, s, MeO); $^{13}$C nmr ($CDCl_3$) δ:[12] 36.5 (C-2), 36.9 (C-1), 49.4 (C-1′)] and its 1′-epimer (XII) [54% yield; $^1$H nmr ($CDCl_3$) δ: 3.54 (3H, s, MeO); $^{13}$C nmr ($CDCl_3$) δ: 37.9 (C-2), 38.3 or 38.6 (C-1), 52.3 (C-1′)] as glassy materials. Debenzylation [Pd-C/$H_2$, MeOH–AcOH (1 : 1, v/v), 1 atm, 27°C, 3 h] of IV gave the desired phenolic base I



I: $R^1 = H$; $R^2 = H$
II: $R^1 = Me$; $R^2 = H$
III: $R^1 = Me$; $R^2 = Me$
IV: $R^1 = PhCH_2$; $R^2 = PhCH_2$



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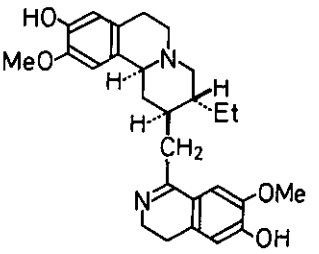
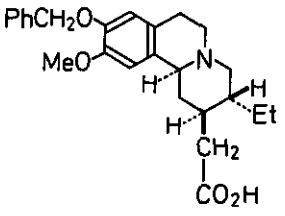
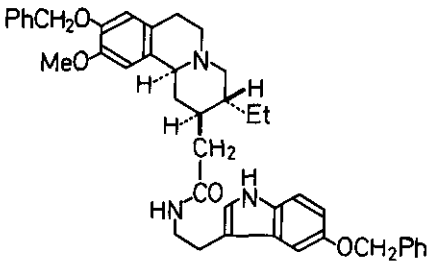


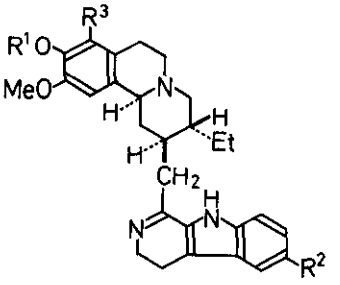
VI



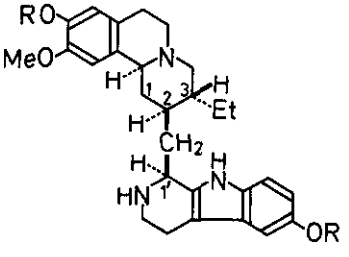
VII



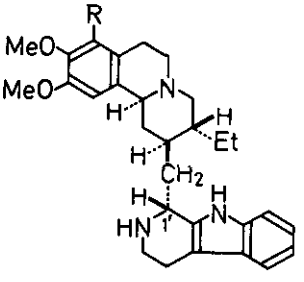
VIII



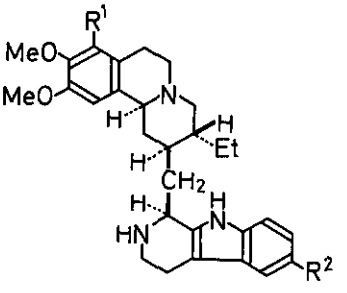
IX: $R^1 = PhCH_2$; $R^2 = PhCH_2O$; $R^3 = H$
X: $R^1 = Me$; $R^2 = H$; $R^3 = H$
XI: $R^1 = Me$; $R^2 = H$; $R^3 = PhCH_2O$



XII: R = $PhCH_2$
XIII: R = H



XIV: R = H
XV: R = $PhCH_2O$
XVI: R = OH



XVII: $R^1 = H$; $R^2 = H$
XVIII: $R^1 = H$; $R^2 = OH$
XIX: $R^1 = PhCH_2O$; $R^2 = H$
XX: $R^1 = OH$; $R^2 = H$

(81% yield), which was characterized as a dihydrate [mp 213–214°C (dec.); $^1$H nmr ($Me_2SO$-$d_6$) δ: 3.71 (3H, s, MeO)]. The epimeric base XII was similarly debenzylated to produce the corresponding phenolic base XIII [mp 235–236.5°C (dec.); $^1$H nmr ($Me_2SO$-$d_6$) δ: 3.49 (3H, s, MeO)] in 86% yield.

Proof of the correctness of the assigned configuration at C-1′ of IV, XII, I, and XIII was provided by the following findings. The formation of a 1 : 1.9 mixture of IV and XII in the above catalytic hydrogenation of IX corresponded to that[13] of a 1 : 2 mixture of deoxytubulosine (XIV) and isodeoxytubulosine (XVII) or to that[14] of a 1 : 1.9 mixture of O-benzylalangimarckine (XV) and its 1′-epimer (XIX) in a similar hydrogenation of the dihydro-β-carboline X or XI. On tlc (silica gel, $CHCl_3$–EtOH or $CHCl_3$–MeOH) analysis, IV and I showed higher Rf values than did their 1′-epimers XII and XIII, and this chromatographic behavior corresponded to that[15] observed for a pair of tubulosine (II)[13,15–17] and isotubulosine (XVIII)[13,15,17] and to that[14,18] found for a pair of XV and XIX or of alangimarckine (XVI) and its 1′-epimer (XX). In the $^1$H nmr spectra of IV and XII in $CDCl_3$ or of I and XIII in $Me_2SO$-$d_6$ (see above), the methoxyl protons of XII or XIII resonated at higher field than did those of IV or I by 0.29 or 0.22 ppm. Such a relationship has been found[15,18] to hold for a pair of tubulosine (II) and isotubulosine (VIII) and of alangimarckine (XVI) and its 1′-epimer (XX). The fourth criterion employed for the stereochemical assignment was the $^{13}$C nmr spectral data described above. Each of the C-1, C-2, and C-1′ carbon signals of IV appeared upfield from the corresponding carbon signal of XII by 1.4–2.9 ppm. These trends are similar to those found by Wenkert *et al.*[19] for ochrolifuanine A and ochrolifuanine B, a 1′-epimeric pair of the indoloquinolizidine-type congeners, and to those[18] found by us for a pair of alangimarckine (XVI) and its 1′-epimer (XX).

Although the uv (in MeOH, 0.1 N aq. HCl, or 0.1 N aq. NaOH) and mass spectra of (±)-I were virtually identical with those of natural (–)-demethyltubulosine,[1] the $^1$H nmr spectra and tlc behavior of the two samples were not identical. Thus, the results reported above definitely exclude the structure I, contrary to our expectation, and have led us to propose the alternative 10-demethyl structure (V) for demethyltubulosine.

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9. Recrystallized from AcOEt. This sample was found to contain 0.5 equivalent mole of AcOEt of crystallization.

10. Satisfactory spectral data and/or elemental analyses were obtained for all the new compounds described.

11. The analysis pointed to the formula $C_{42}H_{45}N_3O_3 \cdot 2H_2O \cdot EtOH$.

12. In ppm downfield from tetramethylsilane.

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