(-)-9-DEMETHYLTUBULOSINE, AN ALKALOID FROM ALANGIUM VITIENSE (A. GRAY) BAILLON (ALANGIACEAE)

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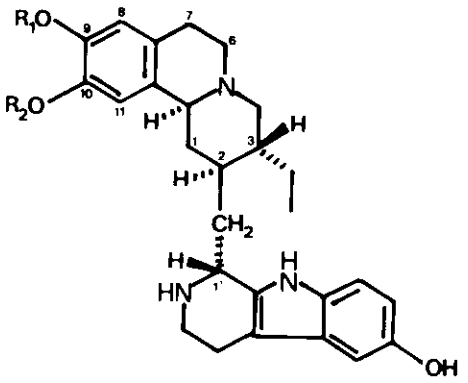
Abstract - The structure of (-)-9-demethyltubulosine, isolated from the trunk bark of Alangium vitiense (Alangiaceae), was determined from an analysis of its MS, ^{1}H and ^{13}C nmr data and by a direct comparison with the synthetic racemic alkaloid.

Several species of the genus Alangium have been studied chemically [1-4]. Previously we have reported the oncostatic effect on lymphoid murine tumors of alkaloids from the trunk bark of A. vitiense [5]. Further work in the studies of these alkaloids has resulted in the isolation of tubulosine 1 (yield 0.5 g/kg) and a new alkaloid 2 (yield 0.3 g/kg) whose structure is now shown to correspond to (-)-9-demethyltubulosine.

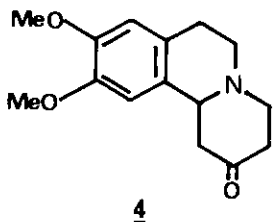
Alkaloid 2 isolated in crystalline form [mp 200°C ($CHCl_3$) ; $[\alpha]_D^{20}$-40° (c = 1, pyridine)] possessed the molecular formula $C_{28}H_{35}N_3O_3$ on the basis of the microanalytical data. Signals for 28 carbon atoms were also observed in the ^{13}C nmr spectrum (Me_2SO-d_6) of this molecule. The uv spectrum [λ_{max} nm (log ε) : 278 (4.1) in EtOH and 284 (4.1), 306 (sh, 3.92), 326 (sh, 3.60) in EtOH + NaOH] indicated a tubulosine structure 1 bearing a phenolic group in the benzoquinolizidine ring system[6]. This feature was confirmed by the observation of peaks at m/e 461 ($M^{+\cdot}$), 258 (benzoquinolizidine moiety) and 187 (β-carboline moiety) in the mass spectrum of 2. It thus appeared that alkaloid 2 was related or identical to demethyltubulosine 3 previously isolated from A. lamarckii[6]. However, at that time it was not possible to determine whether the phenolic OH group in alkaloid 3 was situated at the position C-9 or C-10. Total synthesis of the



Tubulosine **1** : $R_1 = R_2 = Me$

Demethyltubulosines **2** : $R_1 = H$, $R_2 = Me$

3 : $R_1 = Me$, $R_2 = H$



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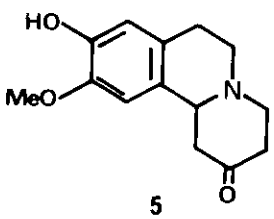

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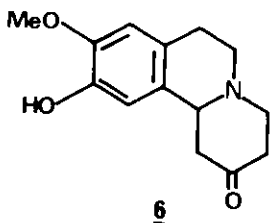

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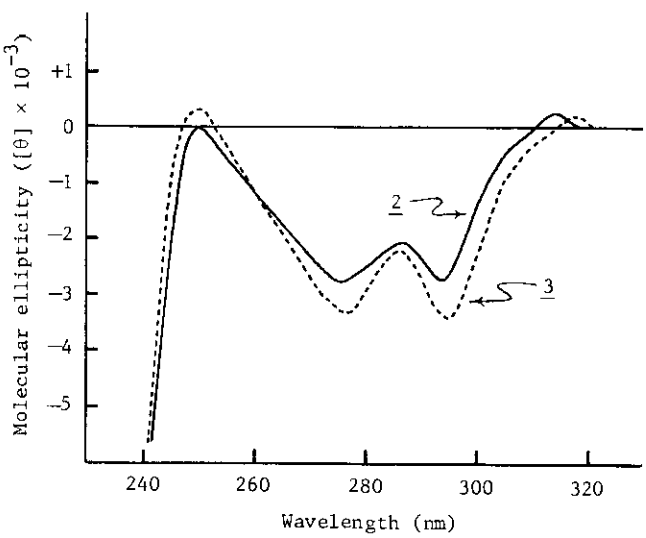

Fig. 1. CD Curves of 9-Demethyltubulosine (2) and 10-Demethyltubulosine (3) in Ethanol at 18°C

racemic alkaloid subsequently established the structure of the natural product as 10-demethyltubulosine 3[7].

Although ^{13}C nmr has been used to determine the position of one or more methoxy or hydroxy groups in the aromatic ring of a number of different alkaloid types, the existing data do not permit the determination of the substitution pattern in molecules where these two functionalities co-occur (i.e. as in 2 or 3). For this reason we have prepared the model compounds 4-6 [8] and studied their ^{13}C nmr spectra.

We observed that with respect to compound 4 the phenolic OH in compounds 5 and 6 produces a deshielding of ca. 3-4ppm in the C-8 and C-11 resonances, respectively (see Table 1). The same differences were also found in the positions of C-8 and C-11 resonances in the natural compounds 1-3 which enabled us to suggest that alkaloid 2 possesses the 9-demethyl structure.

Definite proof for the structure 2 was obtained by a direct comparison of the natural product with synthetic (±)-9-demethyltubulosine[9] and its C-1' epimer. A part from the chiroptical property, alkaloid 2 was identical in all respects to synthetic (±)-9-demethyltubulosine.

Tentative assignment of the absolute configuration of 2, as depicted in the formula, was made by a comparison of CD curves of 2 and 3 [10] (Fig. 1).

The isolation of only 9-demethyltubulosine 2 as one of the major alkaloid from A. vitiense is interesting in view of the fact that its 10-demethyl isomer occurs in another species of the same genus [6].

TABLE 1. ^{13}C NMR CHEMICAL SHIFT VALUES (δ)

Carbon	1[a)]	(±) 4[a)]	2[b)]	(±)-5[a)]	(±)-3[b)]	(±)-6[a)]
C-8	111.8	111.6	115.2	115.1	111.9[g)]	112.2[i)]
C-9	147.1[c)]	147.9[d)]	144.8[e)]	145.0[f)]	144.2[h)]	146.1[j)]
C-10	146.9[c)]	147.6[d)]	145.8[e)]	146.0[f)]	145.7[h)]	144.3[j)]
C-11	109.3	108.1	109.7	107.9	112.1[g)]	111.2[i)]

a) Run in $CDCl_3$ at 22.63 MHz with TMS as an internal standard.

b) Run in DMSO-d_6 at 25.00 MHz with TMS as an internal standard.

c-i) Assignments indicated by a given superscript may be reversed.

REFERENCES

1. S. C. Pakrashi, R. Mukhopadhyay, P. G. Dastidar, A. Bhattacharjya and E. Ali, Tetrahedron Lett., 1983, 24, 291, and references cited therein.

2. D. Shi, Z. Wang, Z. Bi, X. Zeng and D. Shi, Zhongcaoyao, 1983, 14, 165 ; Chem. Abstr, 1983, 99, 19662h.

3. L. Hou, M. Chen and H. Zhu, Zhongcaoyao, 1981, 12, 352 ; Chem. Abstr., 1982, 96, 139646r.

4. M. J. Chen, L. L. Hou and H. Zhu, Chih Wu Hsueh Pao, 1980, 22, 257 ; Chem. Abstr., 1981, 94, 12818b.

5. a) G. Mathé, M. Hayat, E. Chenu, H.-P. Husson, T. Sévenet, C. Kan and P. Potier, Cancer Res., 1978, 38, 1465 ; b) Plant collected in Vanuatu (New Hebrides) by T. Sévenet whom we thank.

6. A. Popelak, E. Haack and H. Spingler, Tetrahedron Lett., 1966, 1081.

7. T. Fujii, M. Ohba, A. Popelak, S. C. Pakrashi and E. Ali, Heterocycles, 1980, 14, 971.

8. Compound 4 has been previously synthesized by F. D. Popp and R. F. Watts, J. Pharm. Sci., 1978, 67, 871. Synthesis of compounds 5 and 6 will be published later.

9. M. Ohba, M. Hayashi and T. Fujii, Heterocycles, 1980, 14, 299.

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