

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

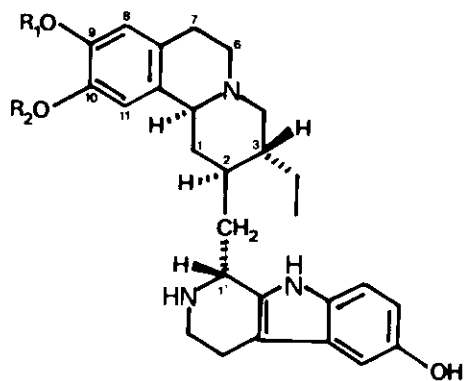
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Abstract - The structure of (-)-9-demethyltubulosine, isolated from the trunk bark of Alangium vitiense (Alangiaceae), was determined from an analysis of its MS,  $^1\text{H}$  and  $^{13}\text{C}$  nmr data and by a direct comparison with the synthetic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

Several species of the genus Alangium have been studied chemically <sup>1-4</sup>. Previously we have reported the oncostatic effect on lymphoid murine tumors of alkaloids from the trunk bark of A. vitiense <sup>5</sup>. 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<sub>3</sub>) ;  $[\alpha]^{20}_{-40}$  ( $c = 1$ , pyridine)] possessed the molecular formula C<sub>28</sub>H<sub>35</sub>N<sub>3</sub>O<sub>3</sub> on the basis of the microanalytical data. Signals for 28 carbon atoms were also observed in the  $^{13}\text{C}$  nmr spectrum (Me<sub>2</sub>SO-d<sub>6</sub>) of this molecule. The uv spectrum [ $\lambda_{\text{max}}$  nm (log  $\epsilon$ ) : 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 <sup>6</sup>. This feature was confirmed by the observation of peaks at  $m/e$  461 (M<sup>+</sup>), 258 (benzoquinolizidine moiety) and 187 ( $\beta$ -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 <sup>6</sup>. 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<sub>1</sub> = R<sub>2</sub> = Me  
 Demethyltubulosines { 2 : R<sub>1</sub> = H, R<sub>2</sub> = Me  
                               3 : R<sub>1</sub> = Me, R<sub>2</sub> = H

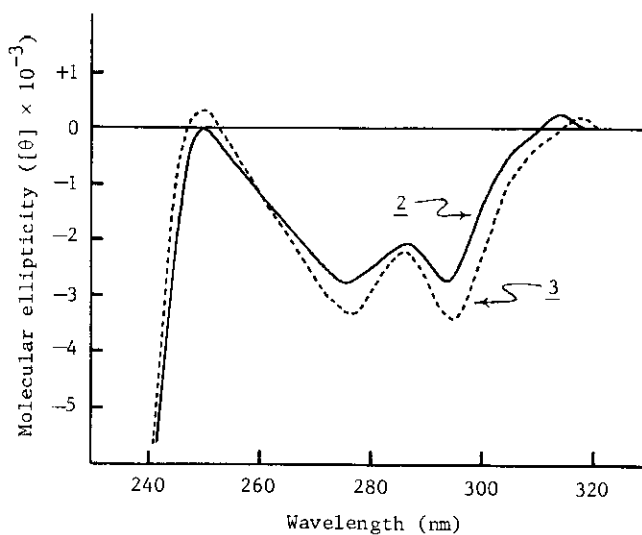
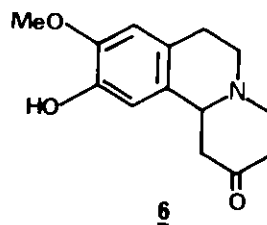
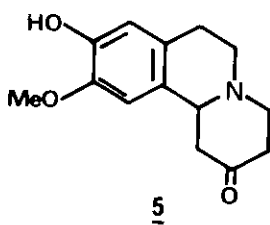
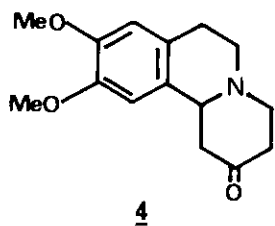


Fig. 1. CD Curves of 9-Demethyltubulosine (2) and 10-Demethyltubulosine (3) in Ethanol at 18°C

racemic alkaloid subsequently established the structure of the natural product as 10-demethyl-tubulosine 3<sup>7</sup>.

Although <sup>13</sup>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<sup>8</sup> and studied their <sup>13</sup>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<sup>9</sup> 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<sup>10</sup> (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 <sup>6</sup>.

TABLE 1. <sup>13</sup>C NMR CHEMICAL SHIFT VALUES (δ)

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

a) Run in CDCl<sub>3</sub> at 22.63 MHz with TMS as an internal standard.

b) Run in DMSO-d<sub>6</sub> at 25.00 MHz with TMS as an internal standard.

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

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- 10 We are grateful to Dr. A. Popelak, Boehringer Mannheim GmbH, Mannheim, Germany, for the generous gift of a natural sample<sup>6</sup> of 3.

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