(-)-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 $^{1-6}$. 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$_3$); [$a$]$^20$-$40^\circ$ (c = 1, pyridine)]
possessed the molecular formula C$_{28}$H$_{35}$N$_3$O$_3$ on the basis of the microanalytical data. Signals for
28 carbon atoms were also observed in the $^{13}$C nmr spectrum (Me$_2$SO-$d_6$) of this molecule. The uv
spectrum [$\lambda_{\max}$ nm (log e) : 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
benzoquinolinizidine ring system $^6$. This feature was confirmed by the observation of peaks at m/e
461 (M$^+$), 258 (benzoquinolinizidine 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. lamarcki* $^6$. 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
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 \textsuperscript{3}.

Although \textsuperscript{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 \textsuperscript{2} or \textsuperscript{3}). For this reason we have prepared the model
compounds 4-\textsuperscript{6} \textsuperscript{8} and studied their \textsuperscript{13}C nmr spectra.

We observed that with respect to compound \textsuperscript{4} the phenolic OH in compounds \textsuperscript{5} and \textsuperscript{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 \textsuperscript{2} possesses the 9-demethyl structure.

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

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

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

\begin{table}
<table>
<thead>
<tr>
<th>Carbon</th>
<th>\textsuperscript{1}a)</th>
<th>(\pm) \textsuperscript{4}a)</th>
<th>\textsuperscript{2}b)</th>
<th>(\pm) \textsuperscript{5}a)</th>
<th>(\pm) \textsuperscript{6}b)</th>
<th>(\pm) \textsuperscript{6}a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-8</td>
<td>111.8</td>
<td>111.6</td>
<td>115.2</td>
<td>115.1</td>
<td>111.9\textsuperscript{g)}</td>
<td>112.2\textsuperscript{f)}</td>
</tr>
<tr>
<td>C-9</td>
<td>147.1\textsuperscript{c)}</td>
<td>147.9\textsuperscript{d)}</td>
<td>144.8\textsuperscript{e)}</td>
<td>145.0\textsuperscript{f)}</td>
<td>144.2\textsuperscript{h)}</td>
<td>146.1\textsuperscript{i)}</td>
</tr>
<tr>
<td>C-10</td>
<td>146.9\textsuperscript{c)}</td>
<td>147.6\textsuperscript{d)}</td>
<td>145.8\textsuperscript{e)}</td>
<td>146.0\textsuperscript{f)}</td>
<td>145.7\textsuperscript{h)}</td>
<td>144.3\textsuperscript{i)}</td>
</tr>
<tr>
<td>C-11</td>
<td>109.3</td>
<td>108.1</td>
<td>109.7</td>
<td>107.9</td>
<td>112.1\textsuperscript{g)}</td>
<td>111.2\textsuperscript{i)}</td>
</tr>
</tbody>
</table>

a) Run in CDCl\textsubscript{3} at 22.63 MHz with TMS as an internal standard.
b) Run in DMSO-\textsubscript{d\textsubscript{6}} at 25.00 MHz with TMS as an internal standard.
c-i) Assignments indicated by a given superscript may be reversed.
REFERENCES


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