

STRUCTURE OF DEMETHYLTUBULOSINE: A TOTAL SYNTHESIS OF (±)-10-DEMETHYLTUBULOSINE

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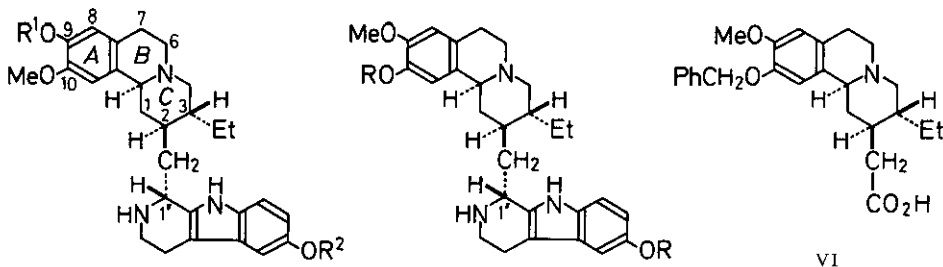
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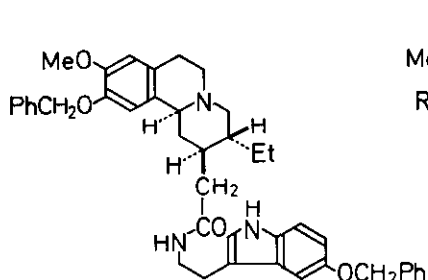
**Abstract** — (±)-10-Demethyltubulosine (IV) has been synthesized from the tricyclic amino acid VI through the intermediates VII, VIII, and V. Identity of synthetic (±)-IV with natural (-)-demethyltubulosine unequivocally established the structure of this *Alangium* alkaloid.

Demethyltubulosine is a phenolic alkaloid isolated from *Alangium lamarckii* Thw. (*Alangiaceae*).<sup>1,2</sup> Popelak and co-workers<sup>1</sup> proposed the structure I or IV for this compound on the basis of its two-step methylation to O-methyltubulosine (III) through tubulosine (II) and on the mass spectral evidence. Quite recently, Fujii and co-workers<sup>3</sup> synthesized (±)-9-demethyltubulosine (I) and found that it was not identical with natural demethyltubulosine. This indicated the alternative 10-demethyl structure (IV) to be the correct expression for this *Alangium* alkaloid. Now we wish to report the results of our further efforts directed toward the synthesis of (±)-IV, which have confirmed the structure of demethyltubulosine.

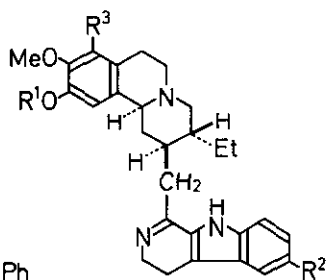
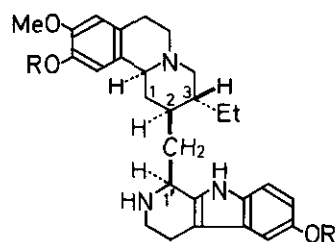


I: R<sup>1</sup> = H; R<sup>2</sup> = H  
 II: R<sup>1</sup> = Me; R<sup>2</sup> = H  
 III: R<sup>1</sup> = Me; R<sup>2</sup> = Me

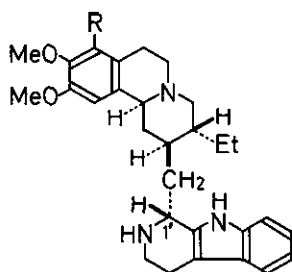
IV: R = H  
 V: R = PhCH<sub>2</sub>



VII

VIII: R<sup>1</sup> = PhCH<sub>2</sub>; R<sup>2</sup> = PhCH<sub>2</sub>O;  
R<sup>3</sup> = HIX: R<sup>1</sup> = Me; R<sup>2</sup> = H; R<sup>3</sup> = HX: R<sup>1</sup> = Me; R<sup>2</sup> = H; R<sup>3</sup> = PhCH<sub>2</sub>OXI: R = PhCH<sub>2</sub>

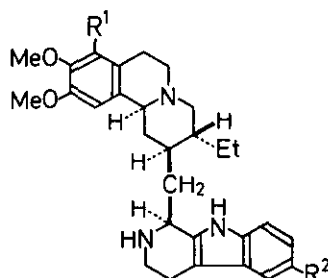
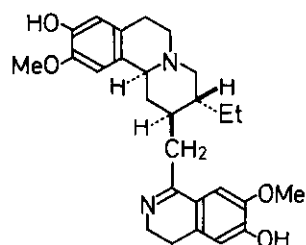
XII: R = H



XIII: R = H

XIV: R = PhCH<sub>2</sub>O

XV: R = OH

XVI: R<sup>1</sup> = H; R<sup>2</sup> = HXVII: R<sup>1</sup> = H; R<sup>2</sup> = OHXVIII: R<sup>1</sup> = PhCH<sub>2</sub>O; R<sup>2</sup> = HXIX: R<sup>1</sup> = OH; R<sup>2</sup> = H

XX

The key intermediate selected for the synthesis of the target molecule [(±)-IV] was the racemic tricyclic amino acid VI, and it was prepared in eight steps from ethyl (±)-*trans*-5-ethyl-2-oxo-4-piperidineacetate<sup>4</sup> according to the recently reported procedure<sup>5</sup> ("lactim ether method"<sup>6</sup>). Condensation of VI with 5-benzyloxytryptamine<sup>7</sup> using the coupling reagent diethyl phosphorocyanidate<sup>8</sup> (Et<sub>3</sub>N, HCONMe<sub>2</sub>, room temp., 6 h) produced the amide VII (mp 150.5–152°C)<sup>9</sup> in 96% yield. The amide VII was then subjected to dehydracyclization with POCl<sub>3</sub> in boiling toluene for 2.5 h to give the dihydro-β-carboline VIII (59% yield) as a yellow glass, which was hydrogenated with hydrogen and Adams catalyst (dioxane, 1 atm, 19°C, 1.5 h). Chromatographic separation (silica gel, CHCl<sub>3</sub>-EtOH) of the hydrogenation products furnished (±)-0,0-dibenzyl-10-demethyltubulosine (V) [25% yield; <sup>1</sup>H nmr (CDCl<sub>3</sub>) δ:<sup>10</sup> 3.83 (3H, s, OMe), 5.08 (4H, s, C(10)-OCH<sub>2</sub>Ph and C(6')-OCH<sub>2</sub>Ph); <sup>13</sup>C nmr (CDCl<sub>3</sub>) δ:<sup>10</sup> 36.3 (C-2), 36.8 (C-1), 49.3 (C-1')]<sup>11</sup> and its 1'-epimer (XI) [54% yield; <sup>1</sup>H nmr (CDCl<sub>3</sub>) δ: 3.80 (3H, s, OMe), 4.92 (2H, s, C(10)-OCH<sub>2</sub>Ph), 5.01 (2H, s, C(6')-OCH<sub>2</sub>Ph); <sup>13</sup>C nmr (CDCl<sub>3</sub>) δ: 38.4 (C-2), 38.9 or 39.2 (C-1), 52.3 (C-1')] as glassy substances.

In line with our studies<sup>3</sup> on ( $\pm$ )-I and its 1'-epimer as well as their O,O-dibenzyl derivatives, the assignments of the relative configuration at C-1' of V and XI were based on the following evidence. The formation of V and XI in a 1:2.2 molar ratio on hydrogenation of VIII was comparable to that of deoxytubulosine (XIII) and isodeoxytubulosine (XVI) in a 1:2 molar ratio<sup>12</sup> or to that of O-benzylalanganimarckine (XIV) and its 1'-epimer (XVIII) in a 1:1.9 molar ratio<sup>13</sup> in a similar hydrogenation of the dihydro- $\beta$ -carboline IX or X. On thin-layer chromatography [silica gel, CHCl<sub>3</sub>-EtOH (10:1, v/v)], V moved faster than its 1'-epimer XI, and this behavior corresponded to that<sup>14</sup> found for a pair of tubulosine (II)<sup>12,14-16</sup> and isotubulosine (XVII)<sup>12,14,16</sup> and to that<sup>13,17</sup> observed for a pair of XIV and XVIII or of alanganimarckine (XV) and its 1'-epimer (XIX). In the <sup>1</sup>H nmr spectra of V and XI in CDCl<sub>3</sub> (*vide supra*), the methylene protons of the C(10)-benzyloxy group in XI were more shielded than those in V by 0.16 ppm. Such an upfield shift observed for the 1'-epimer has also been found<sup>14,17</sup> for the C(10)-methoxyl protons of isotubulosine (XVII) or XIX and not for those of tubulosine (II) or alanganimarckine (XV). The <sup>13</sup>C nmr data also fulfilled a reliable criterion upon which to test the stereochemical relationship. The C-1, C-2, and C-1' carbon signals of V resonated at higher field than the corresponding ones of XI by 2.1-3.0 ppm. This feature was similar to that found by Wenkert *et al.*<sup>18</sup> for ochrolifuanine A and ochrolifuanine B, a 1'-epimeric pair of indoloquinolizidine-type analogues, and to that<sup>17</sup> observed by us for a pair of alanganimarckine (XV) and its 1'-epimer (XIX).

On catalytic hydrogenolysis [Pd-C/H<sub>2</sub>, MeOH-AcOH (1:1, v/v), 1 atm, 18°C, 3 h], V afforded the desired phenolic base ( $\pm$ )-IV (79% yield), which was characterized as a dihydrate [mp 199-201°C (dec.); <sup>1</sup>H nmr (Me<sub>2</sub>SO-d<sub>6</sub>)  $\delta$ :<sup>10</sup> 3.72 (3H, s, OMe)]. A similar debenzoylation of the epimeric base XI gave the corresponding phenolic base ( $\pm$ )-XII [mp 215-217°C (dec.);<sup>19</sup> <sup>1</sup>H nmr (Me<sub>2</sub>SO-d<sub>6</sub>)  $\delta$ : 3.71 (3H, s, OMe)] in 88% yield. It was found that the uv (MeOH, 0.1 N aq. HCl, or 0.1 N aq. NaOH), ir (Nujol), <sup>1</sup>H nmr (Me<sub>2</sub>SO-d<sub>6</sub>), and mass spectra and chromatographic behavior of the synthetic ( $\pm$ )-IV were identical with those of natural (-)-demethyltubulosine dihydrate<sup>1</sup> [mp 198-200°C (dec.)].

Thus, the above results establish the structure of the Alangium alkaloid demethyltubulosine as 10-demethyltubulosine [IV (absolute configuration shown)]. It is of interest to note that the positions of the methoxyl and the hydroxyl groups in ring A of this base are just the reverse of those of desmethylpsychotrine (XX),<sup>2,5,20</sup> a co-occurring alkaloid.<sup>2</sup>

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10. In ppm downfield from internal tetramethylsilane.
11. Crystallized from EtOH in colorless needles, mp 89–91°C, which were found to contain 0.5 equivalent mole of EtOH of crystallization.
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19. The analysis pointed to the formula  $C_{28}H_{35}N_3O_3 \cdot 2/3 H_2O$ .
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