

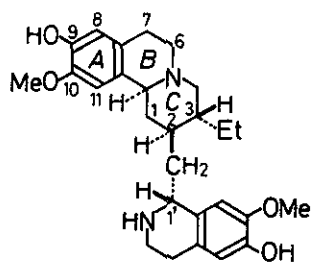
## SYNTHESES OF (-)-9-DEMETHYLCEPHAELINE AND (-)-10-DEMETHYL-CEPHAELINE

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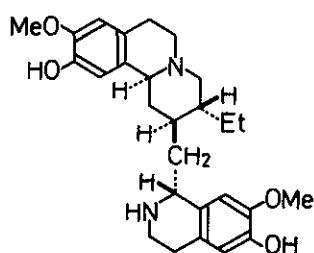
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**Abstract** — The synthesis of (-)-9-demethylcephaeline (I) has been accomplished by reduction of (+)-O,O-dibenzyl-9-demethylpsychotrine (XIa) followed by debenzylation of the resulting (-)-tetrahydroisoquinoline derivative XIIa. A parallel synthesis starting with (+)-O,O-dibenzyl-10-demethylpsychotrine (XIb), prepared from the (-)-tricyclic amino ester VIIIb through the (-)-amino acid IXb and the (-)-amide Xb, gave (-)-10-demethylcephaeline (II).

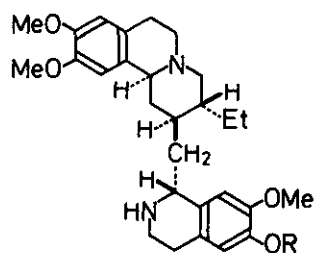
(-)-Demethylcephaeline is a phenolic base among a number of benzoquinolizidine alkaloids in Alangium lamarckii Thw. (family Alangiaceae).<sup>1</sup> Based on its chemical correlation with the ipecac alkaloids cephaeline (III) and emetine (IV) and on the uv, ir, and mass spectral evidence, Pakrashi and Achari<sup>1</sup> have assigned the alternative structure I (absolute configuration shown) or II to this alkaloid, but a discrimination between the 9- and the 10-demethyl structures remains to be settled. We have recently shown that (+)-desmethylpsychotrine, another Alangium alkaloid,<sup>2</sup> has the 9-demethyl structure (V),<sup>3</sup> whereas (-)-demethyltubulosine, yet another phenolic Alangium alkaloid,<sup>2,4</sup> is not a 9-demethylated base,<sup>5</sup> but 10-demethyltubulosine (VI).<sup>6</sup> In the present study, therefore, both 9-demethylcephaeline (I) and 10-demethylcephaeline (II) were selected as the synthetic chiral targets with a view to elucidating the exact location of the phenolic function in ring A of natural (-)-demethylcephaeline. We first tried to synthesize the 9-demethyl structure I from (+)-O,O-dibenzyl-9-demethylpsychotrine (XIa), an intermediate prepared from (+)-ethyl cincholoiponate (VII) through (-)-VIIIa, IXa, and (-)-Xa and utilized in our recent synthesis<sup>3</sup> of (+)-9-demethylpsychotrine (V). On catalytic reduction (Pt/H<sub>2</sub>, EtOH, 1 atm, 18°C, 1 h) and chromatographic separation (silica gel, CHCl<sub>3</sub>-MeOH) of the hydrogenation products, (+)-XIa provided the (-)-base XIIa [47% yield;  $[\alpha]_D^{26} -18.7^\circ$  (c 0.82, EtOH); <sup>13</sup>C nmr (CDCl<sub>3</sub>)  $\delta$ :<sup>7</sup> 36.9 (C-2), 36.9 (C-1), 51.9 (C-1')]<sup>8</sup> and its 1'-epimer (-)-XIIIa [30% yield;  $[\alpha]_D^{26} -25.6^\circ$  (c 0.66, EtOH); <sup>13</sup>C nmr (CDCl<sub>3</sub>)  $\delta$ :<sup>7</sup> 38.9 (C-2), 39.4 (C-1), 55.3 (C-1')] as glassy materials. The above formation of (-)-XIIa and (-)-XIIIa in a 1.6:1 molar ratio was comparable to



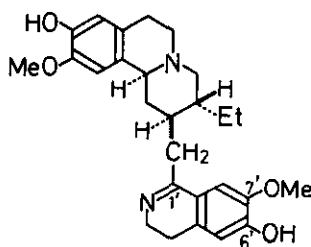
I



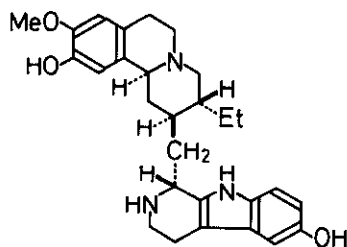
II



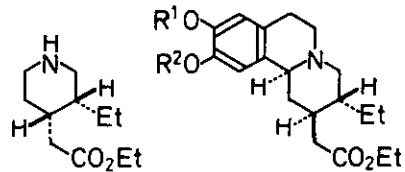
III: R = H  
IV: R = Me



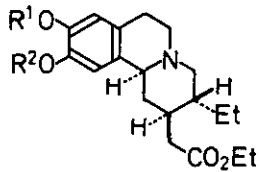
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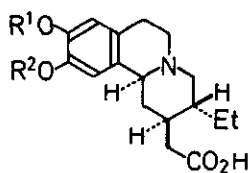
VI



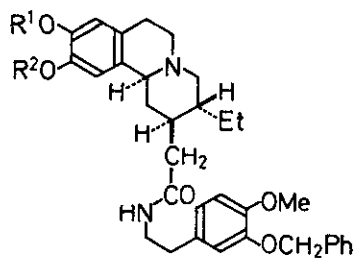
VII



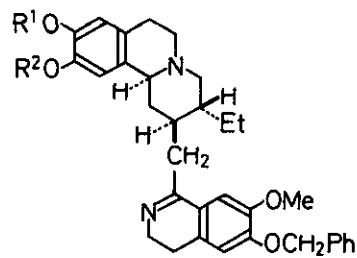
VIIIa,b



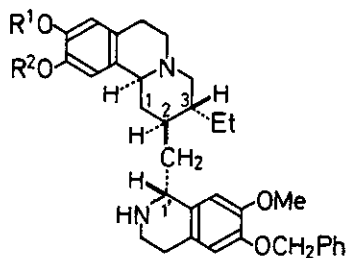
IXa,b



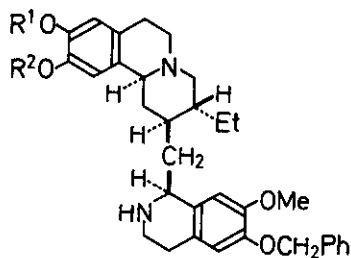
Xa,b



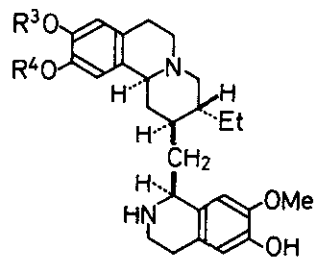
XIa,b



XIIa,b



XIIIa,b



XIV: R<sup>3</sup> = H; R<sup>4</sup> = Me  
XV: R<sup>3</sup> = Me; R<sup>4</sup> = H

a: R<sup>1</sup> = PhCH<sub>2</sub>; R<sup>2</sup> = Me  
b: R<sup>1</sup> = Me; R<sup>2</sup> = PhCH<sub>2</sub>

that of emetine (IV) and its 1'-epimer (isoemetine) in a 1.7 : 1 molar ratio in a similar hydrogenation of O-methylpsychotrine (V, MeO for OH at C-9 and C-6').<sup>9</sup> On tlc analysis (silica gel, CHCl<sub>3</sub>-EtOH), (-)-XIIa moved faster than (-)-XIIIa, and this difference in mobility corresponded to that observed for a pair of emetine (IV) and isoemetine. In the <sup>13</sup>C nmr spectra in CDCl<sub>3</sub>, the C-1, C-2, and C-1' carbon signals of (-)-XIIa resonated at higher field than the corresponding signals of (-)-XIIIa by 2.0-3.4 ppm (vide supra). These findings permitted us to assign the configuration at C-1' of (-)-XIIa and (-)-XIIIa by the analogy of the stereochemical assignments in structurally related systems.<sup>5,6,10,11</sup>

The (-)-base XIIa was then hydrogenolyzed [Pd-C/H<sub>2</sub>, MeOH-AcOH (1 : 1, v/v), 1 atm, 18°C, 3 h] to give the desired (-)-phenolic base I [mp 147°C (sintered at 124°C); [α]<sub>D</sub><sup>12</sup> -55.0° (c 0.50, CHCl<sub>3</sub>)] in 82% yield. A similar debenzoylation of the epimeric base (-)-XIIIa furnished (-)-XIV [mp 178-180°C; [α]<sub>D</sub><sup>12</sup> -94.0° (c 0.36, CHCl<sub>3</sub>)]<sup>12</sup> in 73% yield.

The synthesis of the alternative target structure II was tried next. Alkaline hydrolysis (2N aq. NaOH-EtOH, room temp., 24 h) of the (-)-tricyclic amino ester VIIIb, prepared from (+)-VII according to the recently reported<sup>13</sup> procedure ("cincholoipon-incorporating method"),<sup>3,14-17</sup> gave the (-)-amino acid IXb [98%; [α]<sub>D</sub><sup>18</sup> -56.8° (c 0.50, EtOH)]. Condensation of (-)-IXb with 3-benzyloxy-4-methoxyphenethylamine<sup>18</sup> by the diethyl phosphorocyanidate method<sup>19</sup> [(EtO)<sub>2</sub>POCN, Et<sub>3</sub>N, HCONMe<sub>2</sub>, room temp., 6 h] yielded the (-)-amide Xb [90%; mp 149-151°C; [α]<sub>D</sub><sup>20</sup> -22.2° (c 0.50, EtOH)], which was then cyclized (POCl<sub>3</sub>, boiling toluene, 1.5 h) to furnish (+)-O,O-dibenzyl-10-demethylpsychotrine (XIb) [87%; [α]<sub>D</sub><sup>26</sup> +39.9° (c 0.96, EtOH)]. The subsequent steps to II were essentially the same as described above for the 9-demethyl series, affording first an epimeric pair of (-)-XIIb [48% yield from (+)-XIb; [α]<sub>D</sub><sup>30</sup> -33.2° (c 0.50, EtOH); <sup>13</sup>C nmr (CDCl<sub>3</sub>) δ: 36.7 (C-2), 36.7 (C-1), 51.8 (C-1')] and (-)-XIIIb [29% yield from (+)-XIb; [α]<sub>D</sub><sup>30</sup> -30.9° (c 0.50, EtOH); <sup>13</sup>C nmr (CDCl<sub>3</sub>) δ: 39.0 (C-2), 39.2 (C-1), 55.2 (C-1')], and then (-)-10-demethylcephaeline (II) [73% yield from (-)-XIIb; mp 148°C (sintered at 129-130°C); [α]<sub>D</sub><sup>17</sup> -53.0° (c 0.50, CHCl<sub>3</sub>)]<sup>20</sup> and its 1'-epimer (-)-XV [77% yield from (-)-XIIIb; mp 114-116°C; [α]<sub>D</sub><sup>17</sup> -50.0° (c 0.34, CHCl<sub>3</sub>)]<sup>20</sup>

Now that the two target compounds, (-)-I and (-)-II, became available, it was possible to compare them with natural (-)-demethylcephaeline [lit.<sup>1</sup> mp 147-149°C; [α]<sub>D</sub> -53.5° (CHCl<sub>3</sub>)] by spectroscopic means. The uv (in EtOH or 0.1N ethanolic NaOH), ir (in Nujol), and mass spectra of the three were so closely similar, respectively, that they were impracticable as the means of identification. Although the nmr spectra (in CDCl<sub>3</sub>) of (-)-I and (-)-II were clearly differentiated from one another, that of the natural alkaloid was not available then. Unfortunately, lack of sufficient amount of natural (-)-demethylcephaeline for an nmr spectrum and/or mixture melting point test precluded us from identifying either (-)-I or (-)-II with this alkaloid.

ACKNOWLEDGMENT We are grateful to Dr. S. C. Pakrashi (Calcutta) for a gift of copies of the uv, ir, and mass spectra of natural demethylcephaeline, to Professor S. Yamada (Tokyo) for his financial assistance in the form of a grant from the Foundation for the Promotion of Research on Optically Active Compounds, and to Professor T. Shioiri (Nagoya) for a gift of diethyl phosphorocyanidate.

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Received, 15th February, 1982