

ABSOLUTE STEREOCHEMISTRY OF ALANGICINE: SYNTHETIC
INCORPORATION OF CINCHOLOIPON INTO (+)-ALANGICINE[†]

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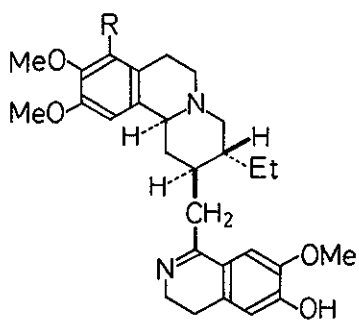
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The chemical correlation of cinchonine (V) with the Alangium alkaloid alangicine, through ethyl cincholoiponate [(+)-VI], lactam acids (-)-IX, (+)-X, tricyclic amino acid (-)-XIV, and amide (-)-XV, unequivocally established the absolute stereochemistry of alangicine as I.

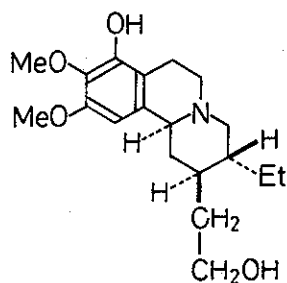
The structure and stereochemistry of alangicine, isolated from Alangium lamackii Thw. (family Alangiaceae),¹ have recently been established by us as I or its mirror image.² We have now observed that the cd spectrum of alangicine [c 5.99×10^{-5} M in EtOH] [θ]²⁶ (nm): 0 (448), +3010 (402), +100 (349), +1500 (315), 0 (285), -2000 (275), -1000 (269), -1670 (265), 0 (255), +1340 (246), 0 (241), -8850 (233), 0 (225)] is very close to that of its 8-desoxy congener psychotrine

[†] Dedicated to Emeritus Professor Dr. Shigehiko Sugawara, University of Tokyo, on the occasion of his eightieth birthday.

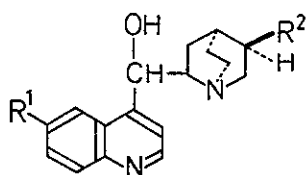


I, R=OH

II, R=H

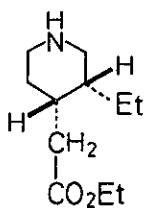


III

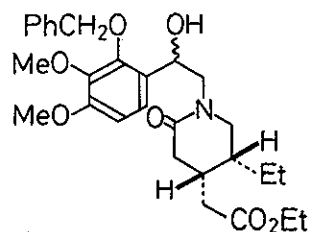


IV, R¹=H or MeO;
R²=vinyl or Et

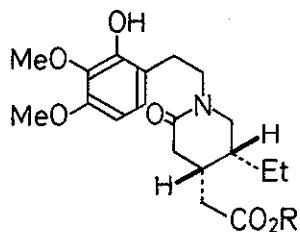
V, R¹=H; R²=vinyl



(+)-VI

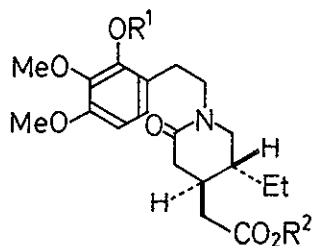


VII



(-)-VIII, R=Et

(-)-IX, R=H



(+)-X, R¹=H; R²=H

(+)-XI, R¹=H; R²=Et

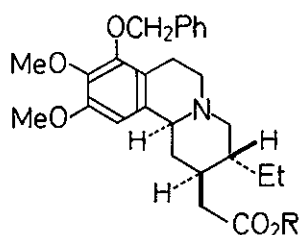
(+)-XII, R¹=PhCH2; R²=Et

(II)³ [ϵ 5.12×10^{-5} M in EtOH] $[\theta]^{26}$ (nm): 0 (460), +3520 (402), +100 (347), +1560 (315), 0 (285), -590 (279), 0 (275), +780 (269), +200 (264), +3320 (244), 0 (239), -11700 (231), 0 (224)]. The absolute stereochemistry of ankorine (III), another Alangium alkaloid,^{4,5} recently determined by some⁶ of us, also corresponds to that of psychotrine.

The target stereoformula I (absolute configuration shown) was, therefore, selected for synthesis in order to establish the absolute stereochemistry of alangicine. In view of our success in the synthetic incorporation of cincholoipon ethyl ester [(+)-VI], derived from the major cinchona alkaloids (IV), into the Ipecac alkaloids⁷ and ankorine,⁶ we decided to extend the method to alangicine also.

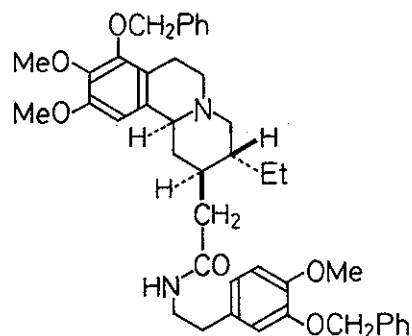
Optically active lactam ester (-)-VIII, the key intermediate, was synthesized from ethyl cincholoiponate [(+)-VI], obtained from cinchonine (V)⁶ by known method,^{8,9} through the lactam alcohol VII in four steps according to previously reported scheme.⁶ Hydrolysis of (-)-VIII with 2 N aq. NaOH-EtOH at room temperature gave the cis acid (-)-IX [97% yield; $[\alpha]_D^{14} - 8.0^\circ$ (ϵ 1.0, EtOH)],¹⁰ which on thermal isomerization^{6,7,11} at 180° for 90 min led to the desired trans acid (+)-X [mp 154-155°; $[\alpha]_D^{15} + 86.5^\circ$ (ϵ 1.0, EtOH)] in 73% yield. Esterification (EtOH-HCl, room temp., 24 hr) of (+)-X produced the lactam ester (+)-XI [99% yield; mp 88-89°; $[\alpha]_D^{21} + 77.9^\circ$ (ϵ 0.8, EtOH)], which was benzylated (PhCH₂Br, K₂CO₃, boiling Me₂CO, 15 hr) to furnish the ether (+)-XII [97% yield; $[\alpha]_D^{16} + 53.3^\circ$ (ϵ 1.0, EtOH); solution ir and nmr spectra identical with those of authentic ($\pm$)-XII¹²] as an oil.

Conversion of (+)-XII into the tricyclic ester (-)-XIII of established⁶ structure and stereochemistry was accomplished in 55% overall yield by Bischler-Napieralsky reaction (POCl₃, toluene, reflux, 2 hr) followed by catalytic reduction (PtO₂/H₂, EtOH, 1 atm, 20°, 20 min). Thus, employment of the cis→trans isomerization at the lactam phenol stage served the purpose of improving the previous-



(-)-XIII, R=Et

(-)-XIV, R=H



(-)-XV

ly reported⁶ low overall yield of (-)-XIII.

The later part of the synthetic route was essentially the same as adopted recently for the racemic series.² Thus, treatment of (-)-XIII with 2 *N* aq. NaOH—EtOH at 25° provided the amino acid (-)-XIV [96% yield; mp 189–192°; $[\alpha]_D^{16}$ -37.2° (*c* 0.6, EtOH)], which was then coupled with 3-benzyloxy-4-methoxyphenethylamine¹³ by the diethyl phosphorocyanidate method¹⁴ (Et₃N, HCONMe₂, 25°, 3 hr) to give the amide (-)-XV [mp 156.5–158°; $[\alpha]_D^{17}$ -9.3° (*c* 0.601, EtOH)] in 88% yield. Dehydrocyclization of the amide (-)-XV (polyphosphate ester,¹⁵ boiling CHCl₃, 3 hr) and debenzoylation of the resulting base (10% aq. HCl—EtOH, reflux, 15 hr) furnished the desired compound (+)-I [mp 145–147° (dec.); $[\alpha]_D^{16}$ +67° ± 2° (*c* 0.113, MeOH)], in 67% overall yield from (-)-XV, identical in all respects [mixed melting point, uv (EtOH or 0.1 *N* NaOH), ir (CHCl₃), nmr (CDCl₃/D₂O), mass spectrum, and tlc] with a sample of natural alangicine¹ [mp 146–148° (dec.); $[\alpha]_D^{16}$ +64.1° (*c* 0.26, MeOH)].

Thus, the stereoformula I is the unique and complete expression for alangicine.

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