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

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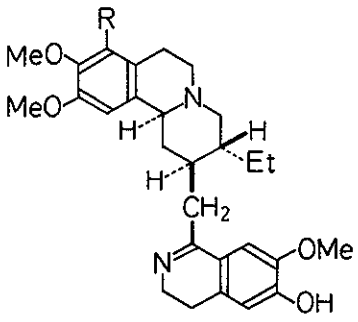
The chemical correlation of cinchonine (V) with the Alangium alkaloid alangicine, through ethyl cincholoiponate [(+)-VI], lactam acids (−)-IX, (+)-X, tricyclic amino acid (−)-XIV, and amide (−)-XV, unequivocally established the absolute stereochemistry of alangicine as I.

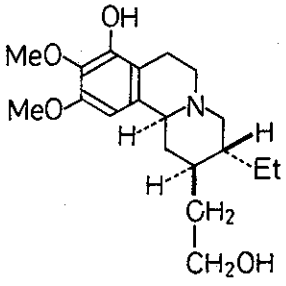
The structure and stereochemistry of alangicine, isolated from Alangium lamarckii Thw. (family Alangiaceae),[1] have recently been established by us as I or its mirror image.[2] We have now observed that the cd spectrum of alangicine [(c 5.99×10^{-5} M in EtOH) $[\theta]^{26}$ (nm): 0 (448), +3010 (402), +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 Sugasawa, University of Tokyo, on the occasion of his eightieth birthday.

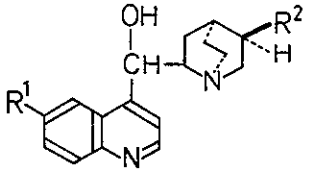


I, R = OH

II, R = H

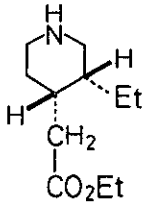


III

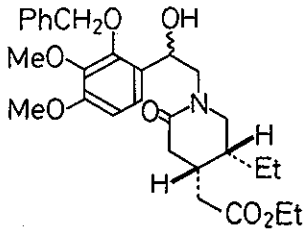


IV, R^1 = H or MeO; R^2 = vinyl or Et

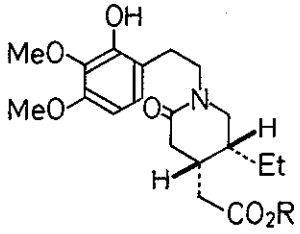
V, R^1 = H; R^2 = vinyl



(+)-VI

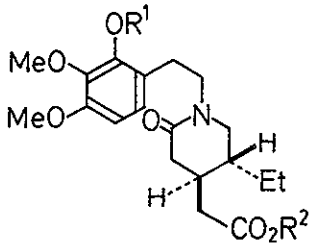


VII



(−)-VIII, R = Et

(−)-IX, R = H



(+)-X, R^1 = H; R^2 = H

(+)-XI, R^1 = H; R^2 = Et

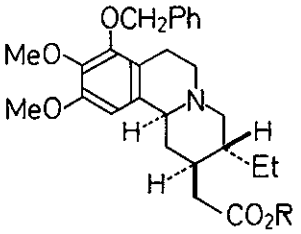
(+)-XII, R^1 = $PhCH_2$; R^2 = Et

(II)[3] [(c 5.12 x 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 some[6] of us, also corresponds to that of psychotrine.

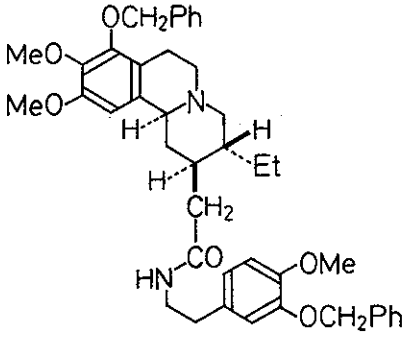
The target stereoformula I (absolute configuration shown) was, therefore, selected for synthesis in order to establish the absolute stereochemistry of alangicine. In view of our success in the synthetic incorporation of cincholoipon ethyl ester [(+)-VI], derived from the major cinchona alkaloids (IV), into the Ipecac alkaloids[7] 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° (c 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° (c 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° (c 0.8, EtOH)], which was benzylated ($PhCH_2Br$, K_2CO_3, boiling Me_2CO, 15 hr) to furnish the ether (+)-XII [97% yield; $[\alpha]_D^{16}$ +53.3° (c 1.0, EtOH); solution ir and nmr spectra identical with those of authentic (±)-XII[12]] as an oil.

Conversion of (+)-XII into the tricyclic ester (−)-XIII of established[6] structure and stereochemistry was accomplished in 55% overall yield by Bischler-Napieralsky reaction ($POCl_3$, toluene, reflux, 2 hr) followed by catalytic reduction (PtO_2/H_2, 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 reported[6] 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-methoxyphenethylamine[13] by the diethyl phosphorocyanidate method[14] (Et_3N, $HCONMe_2$, 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 $CHCl_3$, 3 hr) and debenzylation 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 ($CHCl_3$), nmr ($CDCl_3/D_2O$), mass spectrum, and tlc] with a sample of natural alangicine[1] [mp 146–148° (dec.); $[\alpha]_D$ +64.1° (c 0.26, MeOH)].

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

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