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(−)-ALANGIMARCKINE: SYNTHESIS AND ABSOLUTE CONFIGURATION OF AN ALANGIUM ALKALOID

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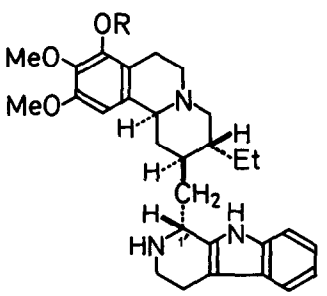
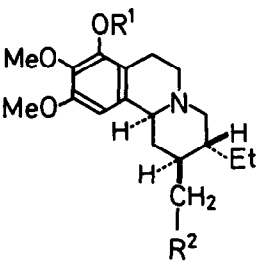
A recent communication[1] from this laboratory has revealed that the structure and stereochemistry of alangimarckine, isolated from Alangium lamarckii Thw. (family Alangiaceae),[2] is expressed in terms of Formula I or its mirror image. Ankorine (III)[2-5] and alangicine (IV)[6-8] are also among the co-occurring alkaloids, and the absolute stereochemistry of the two bases, recently determined[5,8] by us, has been shown to be the same. Assuming that the absolute configuration of all the asymmetric centers in the benzoquinolizidine part of alangimarckine also corresponds to that of ankorine (III) or to that of alangicine (IV), we selected the target stereoformula I (absolute configuration shown) for synthesis with a view to establishing the absolute stereochemistry of alangimarckine. Our previous success in synthetic incorporation of cincholoipon ethyl ester [(+)-VIII] into III,[5] IV,[8] and some of the Ipecac alkaloids[9] would be a valid model for the synthesis of I from the major Cinchona alkaloids (VI). Thus, we tried to extend the scope of this "cincholoipon-incorporating method" to include the target molecule (I).

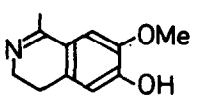


I, R = H
(+)-II, R = CH_2Ph

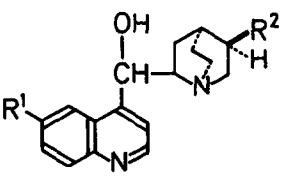


III, R^1 = H; R^2 = CH_2OH

IV, R^1 = H; R^2 =

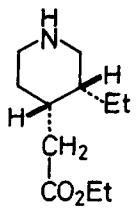


(−)-V, R^1 = CH_2Ph; R^2 = CO_2H

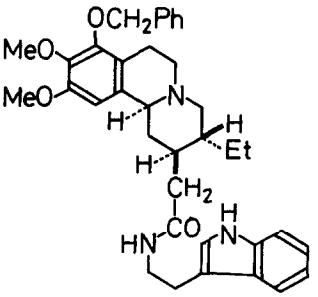


VI, R^1 = H or OMe; R^2 = vinyl or Et
VII, R^1 = H; R^2 = vinyl

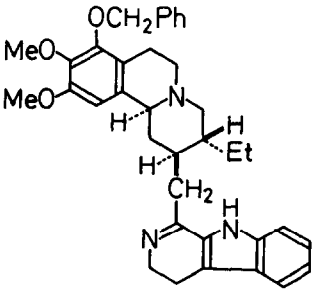
The key intermediate generated on these lines was optically active, tricyclic amino acid (−)-V, and it was prepared as reported previously[8] from cincholoipon ethyl ester [(+)-VIII],[10,11] an easily available degradation product of cinchonine (VII). Condensation of (−)-V with tryptamine by the diethyl phosphorocyanidate method[12] (Et_3N, DMF, 28°, 6 hr) gave the tryptamide (+)-IX [92% yield; mp



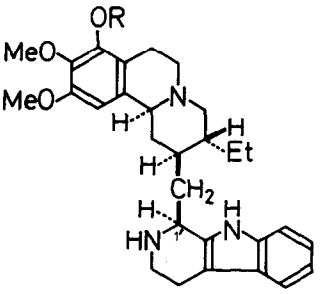
(+)-VIII



(+)-IX

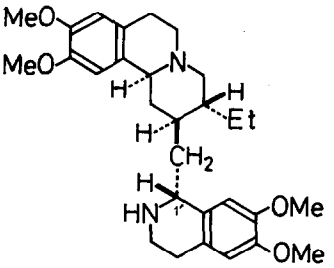


(+)-X

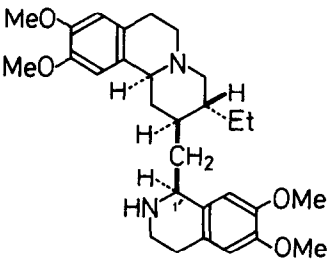


(−)-XI, R = CH_2Ph

(−)-XII, R = H



XIII



XIV

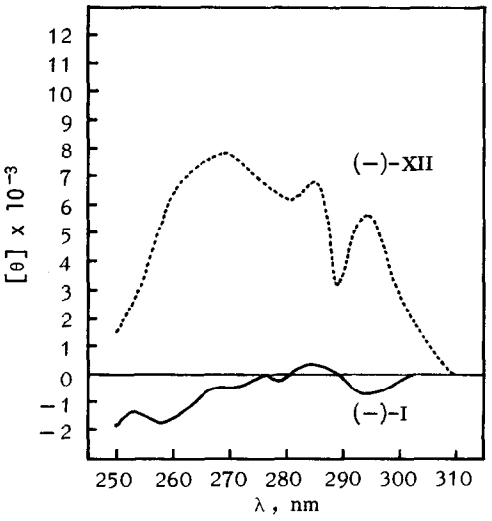


Fig. 1. The CD spectra of (−)-I and (−)-XII in EtOH.

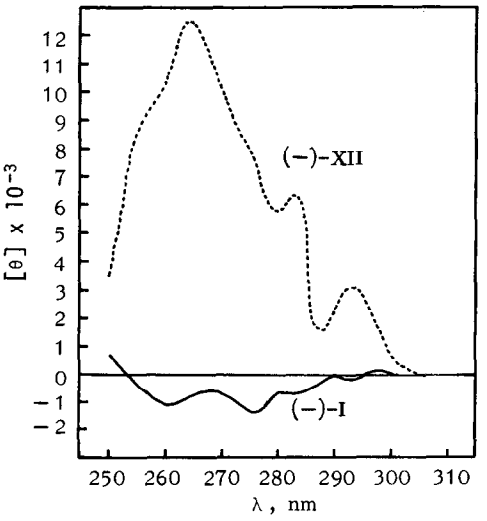


Fig. 2. The CD spectra of (−)-I and (−)-XII in 0.1 N aq. HCl.

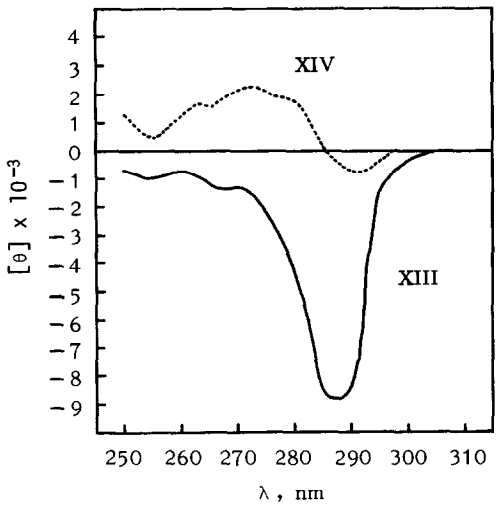


Fig. 3. The CD spectra of emetine (XIII) and isoemetine (XIV) in EtOH.

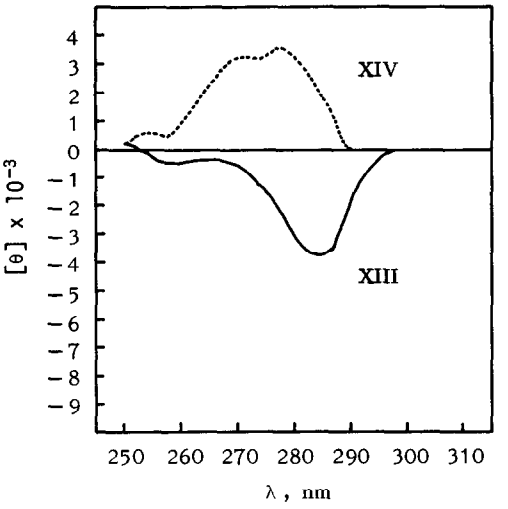


Fig. 4. The CD spectra of emetine (XIII) and isoemetine (XIV) in 0.1 N aq. HCl.

176.5–177.5°; $[\alpha]_D^{28}$ +0.95° (c 2.0, EtOH)],[13] which was then cyclized ($POCl_3$, boiling toluene, 2.5 hr) to (+)-X [82% yield; $[\alpha]_D^{18}$ +9.6° (c 0.5, EtOH)]. Catalytic hydrogenation of (+)-X (Pt/H_2, dioxane, 1 atm, 19°, 40 min) and chromatographic separation (silica gel, $CHCl_3$—EtOH) of the products afforded the base (+)-II [25% yield; $[\alpha]_D^{18}$ +25.2° (c 0.25, EtOH)] and its 1′-epimer [(−)-XI] [48% yield; $[\alpha]_D^{18}$ −31.2° (c 0.5, EtOH)].[13] The base (+)-II was then debenzylated (10% Pd-C/H_2, MeOH—AcOH, 1 atm, 20°, 1.5 hr) to produce the desired phenolic base [(−)-I] (96% yield), which was characterized as a hydrate[14] [mp 185–187° (dec.); $[\alpha]_D^{18}$ −68.5°±0.6° (c 0.34, pyridine)] after recrystallization from AcOEt—isopropyl ether. A similar debenzylation of the epimeric base (−)-XI furnished the corresponding phenolic base [(−)-XII] [mp 130–132° (dec.);[15] $[\alpha]_D^{19}$ −112.0°± 0.5° (c 0.41, pyridine)] in 95% yield.

The absolute configuration at C-1′ of (−)-I and (−)-XII was confirmed by comparison of their IR and NMR spectra and thin-layer-chromatographic mobility with those of the corresponding racemic modifications[1] of established stereochemistry. In addition, we found that (−)-I exhibited a negative CD curve in EtOH or in 0.1 N aq. HCl, whereas (−)-XII, a positive CD curve, as shown in Figs. 1 and 2. Similar chiroptical properties found for the 1′-epimeric pairs of emetine (XIII)—isoemetine (XIV) (see Figs. 3 and 4), ochrolifuanine A—ochrolifuanine B,[16] and certain structural analogs[17] of tubulosine thus afford a further proof of the correctness of the configuration assigned to C-1′ of (−)-I and (−)-XII.

Since the melting point, optical rotation, UV (in 95% aq. EtOH), IR (in $CHCl_3$), PMR (in $CDCl_3$), and mass spectra of the synthetic base [(−)-I] have been found to match those of natural (−)-alangimarckine [lit.[2] mp 184–186°; lit.[2] $[\alpha]_D^{25}$ −67.7° (pyridine)], the results described above prove that the stereoformula I is a complete expression for alangimarckine. It follows that alangimarckine is the 8-hydroxy congener of deoxytubulosine,[16,19] which has also been encountered in Alangium lamarckii.[19]

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kyo) and Y. Ban (Sapporo) for their interest and encouragement. Financial support of this work by a Grant-in-Aid for Scientific Research (B-247119) from the Ministry of Education, Science and Culture, Japan, is also gratefully acknowledged.

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13. The assigned structures of all new compounds were supported by elemental analyses and/or satisfactory spectral data, which matched those of the previously reported[1] racemic modifications.
14. $C_{29}H_{37}N_3O_3 \cdot 1/2\,H_2O$.
15. $C_{29}H_{37}N_3O_3 \cdot 1/3\,H_2O$.
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