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# STRUCTURE AND RELATIVE STEREOCHEMISTRY OF ALANGIMARCKINE: A TOTAL SYNTHESIS OF (±)-ALANGIMARCKINE

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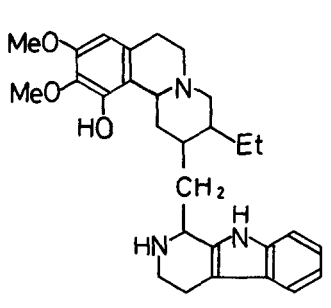
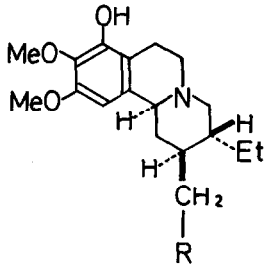
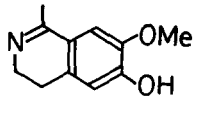
Formula I is the plane structure that has been proposed tentatively by Battersby and co-workers[1] for alangimarckine, an alkaloid isolated from Alangium lamarckii Thw. (family Alangiaceae). The exact placement of the phenolic hydroxyl group and the stereochemistry of this alkaloid remained, however, to be settled. Recently, the structures and absolute configuration of ankorine[1,2] and alangicine,[3] co-occurring bases, have been established by us as II[4,5] and III,[6,7] and we expressed the view that probably alangimarckine possesses the same benzoquinolizidine portion as that of II (or III).[4-6] The present communication describes the results of our further synthetic efforts in this area, which have not only corroborated the above view, but also permitted the assignment of the relative stereoformula IV to alangimarckine.

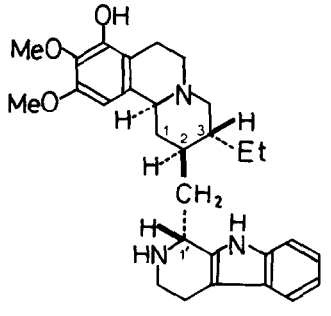


I



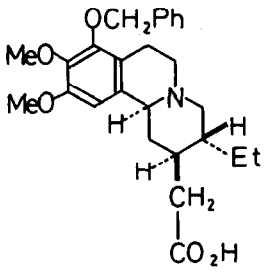
II, R = $CH_2OH$

III, R = 

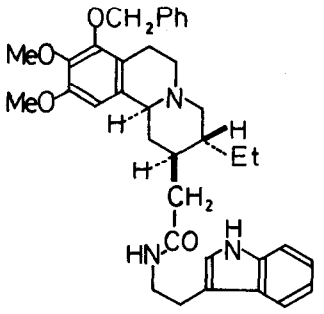


IV

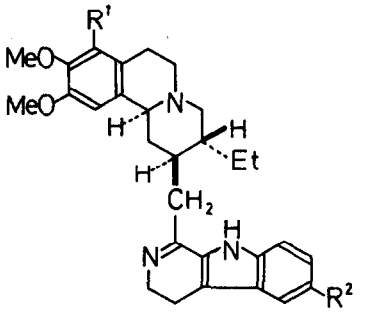
Condensation of the tricyclic amino acid (±)-V, prepared from ethyl trans-5-ethyl-2-oxo-4-piperidineacetate[8] in eight steps according to previously reported scheme,[4,6] with tryptamine by the



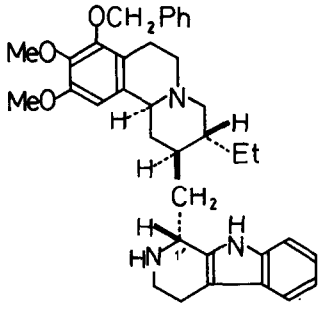
V



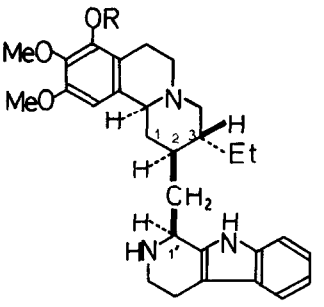
VI



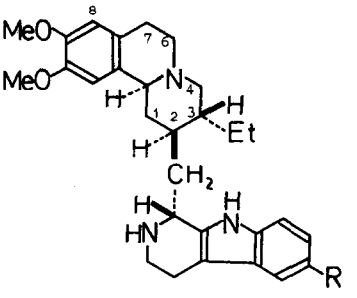
VII, $R^1 = OCH_2Ph$; $R^2 = H$
VIII, $R^1 = H$; $R^2 = OCH_2Ph$



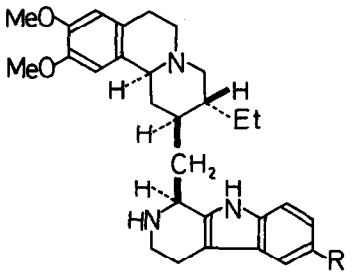
IX



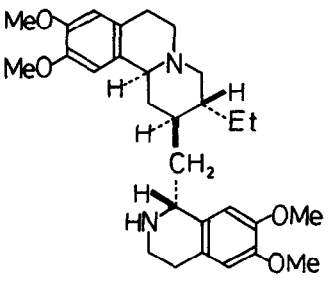
X, R = $PhCH_2$
XI, R = H



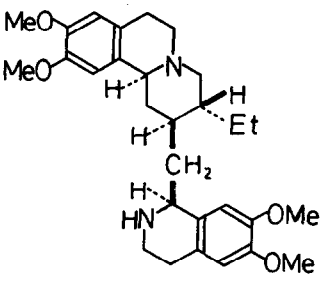
XII, R = $OCH_2Ph$
XIII, R = OH
XIV, R = H



XV, R = $OCH_2Ph$
XVI, R = OH



XVII



XVIII

diethyl phosphorocyanidate method[9] ($Et_3N$, $HCONMe_2$, 30°, 6 hr) produced the tryptamide VI (mp 170–171°)[10] in 93% yield. The amide VI was then treated with $POCl_3$ in boiling toluene for 2.5 hr, and the cyclized product was isolated in the form of the dihydrobromide monohydrate ($VII \cdot 2HBr \cdot H_2O$) [75% yield from VI; mp 201–202° (dec.)]. Reduction of this salt with $NaBH_4$ (MeOH, 25°, 1.5 hr) and column chromatographic separation (silica gel, $CHCl_3$—EtOH) of the products afforded the base IX (as a glassy material) (18% yield) and its 1′-epimer (X) (59% yield; mp 212–213°). Debenzylation of IX [Pd-C/$H_2$, MeOH—AcOH (1 : 1, v/v), 1 atm, 20°, 1.5 hr] gave the phenolic base IV (95% yield), which was characterized as a hydrate[11] [mp 157–159° (dec.); PMR ($Me_2SO$-$d_6$) δ :[12] 3.64 (3H, s, MeO), 3.72 (3H, s, MeO); $^{13}C$ NMR ($CDCl_3$) δ :[12] 36.5 (C-2), 36.8 (C-1), 49.3 (C-1′)] after recrystallization from EtOH. The epimeric base (X) was similarly debenzylated to furnish the corresponding phenolic base (XI) [mp 202–203° (dec.);[13] PMR ($Me_2SO$-$d_6$) δ :[12] 3.48 (3H, s, MeO), 3.64 (3H, s, MeO); $^{13}C$ NMR ($CDCl_3$) δ :[12] 38.0 (C-2), 38.6 (C-1), 52.2 (C-1′)] in 95% yield.

The assignments of the relative configuration at C-1′ of IX, X, IV, and XI were based on the following evidence. The formation of a 1 : 3.3 mixture of IX and X in the $NaBH_4$ reduction of VII corresponds to that[14] of a 1 : 3.5 mixture of O-benzyltubulosine (XII) and O-benzylisotubulosine (XV) in analogous reduction of VIII. On a silica gel TLC plate, IX and IV had higher Rf values than did their 1′-epimers (X and XI), and this behavior corresponds to that observed[15] for a pair of tubulosine (XIII)[14–17] and isotubulosine (XVI).[14,15,17] Emetine (XVII) and isoemetine (XVIII) were also found to behave similarly. In the PMR spectra of IV and XI in $Me_2SO$-$d_6$, the difference in chemical shift between the two methoxyl groups in the same molecule is smaller for IV (0.08 ppm) than for XI (0.16 ppm), and such a relationship has been observed[15] for a pair of tubulosine (XIII) and isotubulosine (XVI). As shown above, each of the C-1, C-2, and C-1′ carbon signals of IV appeared upfield from the corresponding carbon signal of XI by 1.5–2.9 ppm. We have observed that similar relationships hold for the chemical shifts of the corresponding carbons of emetine (XVII)[18] and isoemetine (XVIII). These trends are also similar to those found by Wenkert et al.[18] for ochrolifuanine A and ochrolifuanine B, an epimeric pair of the indoloquinolizidine-type congeners.

An anhydrous sample of (±)-IV was prepared by dissolving the above hydrate in $CHCl_3$ and evaporating the solution to dryness. Its UV (in 95% aq. EtOH), IR (in $CHCl_3$), PMR (in $CDCl_3$), and mass spectra were found to match those of natural (−)-alangimarckine. Thus, the results described above have established the structure and relative stereochemistry of alangimarckine in terms of formula IV. It is of interest to note that, apart from its absolute configuration, alangimarckine (IV) is the 8-hydroxy congener of deoxytubulosine (XIV),[14,19] which also occurs in A. lamarckii.[19]

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10. Complete analytical and/or spectral data were obtained for all new compounds reported.
11. $C_{29}H_{37}N_3O_3 \cdot 3/4\ H_2O$.
12. In ppm downfield from tetramethylsilane.
13. Recrystallized from MeCN. This sample was found to contain 0.5 equivalent mole of MeCN of crystallization.
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