Tetrahedron Letters No. 29, pp 2553 - 2556, 1976. Pergamon Press. Printed in Great Britain.

STRUCTURE AND STEREOCHEMISTRY OF ALANGICINE: SYNTHESIS OF (±)-ALANGICINE

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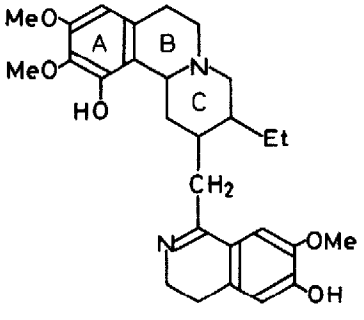
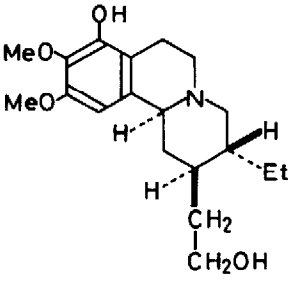
(Received in Japan 15 May 1976; received in UK for publication 10 June 1976)

Alangicine, isolated from Alangium lamarckii Thw. (family Alangiaceae), has been tentatively assigned the gross structure I largely on the basis of mass spectral evidence and biogenetic considerations.[1] The exact location of the phenolic hydroxyl group in ring A and the stereochemistry of the alkaloid remained, however, to be settled. Recently, the structure and absolute stereochemistry of ankorine,[2,3] a co-occurring base, has been established as II by some of us.[4,5] Assuming the structure of the benzoquinolizidine part to be the same in both the alkaloids, the target molecule III was selected for synthesis with a view to establishing the structure of alangicine.



I



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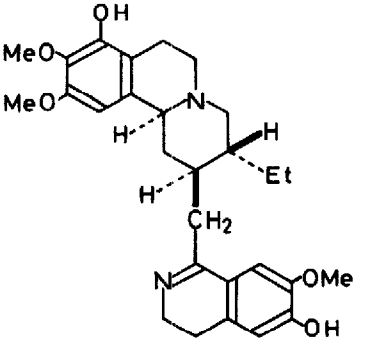
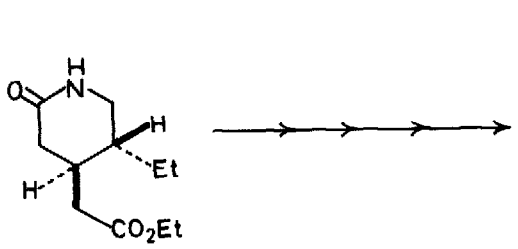
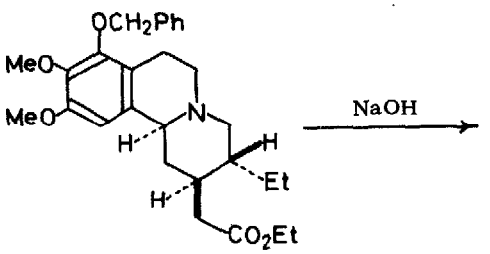


III

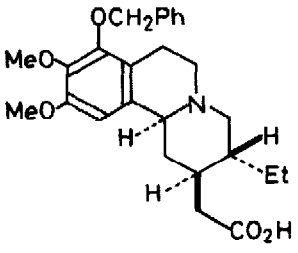
The key intermediate in our synthesis was the racemic tricyclic ester V, prepared in seven synthetic operations from the lactam ester IV[6] as described previously.[4] On alkaline hydrolysis (2 N aq. NaOH—EtOH, 20°, 24 hr), compound V furnished the amino acid VI [mp 168–169°; picrolonate, mp 230–232° (dec.)][7] in 99% yield. Condensation of VI with 3-benzyloxy-4-methoxypheneth-



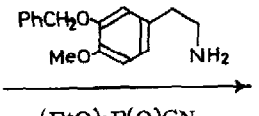
IV

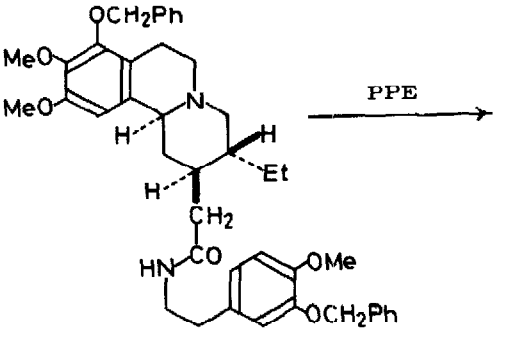


V

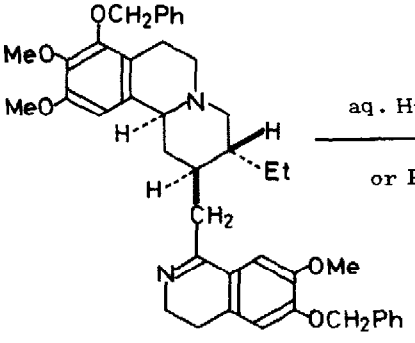


VI

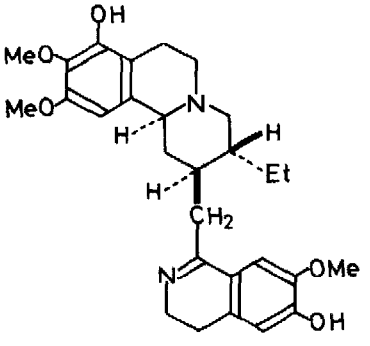




VII



VIII



III

ylamine[8] using the coupling reagent[9] diethyl phosphorocyanidate[10] (Et_3N, $HCONMe_2$, 20°, 4 hr) produced the amide VII (mp 157–159°) in 57% yield.

The amide (VII) was then subjected to dehydrocyclization[11] with polyphosphate ester (PPE)[12] in boiling $CHCl_3$ for 3 hr to give the base VIII (94% yield) as a pale yellow thick oil. Debenzylation of VIII was effected either by refluxing with 10% aq. HCl—EtOH for 15 hr or by hydrogenolysis (10% Pd-C/H_2, EtOH, 19° to 50°, 1 atm) of its hydrochloride (presumably, VIII·2HCl) to obtain the desired product [(±)-III] in 70–74% yield, which was characterized as the triethanolate (mp 145–147°) after recrystallization from EtOH. The UV (in EtOH or 0.1 N aq. NaOH) and mass spectra of the triethanolate matched those of natural alangicine.[1] An ethanol-free sample of (±)-III was prepared by dissolving the triethanolate in $CHCl_3$ and evaporating the solution to dryness. Comparison of the IR (in $CHCl_3$), NMR (in $CDCl_3$, after treatment with D_2O), and mass spectra and thin-layer chromatographic behavior of the solvent-free samples of (±)-III and natural alangicine[13] confirmed their identity.

Thus, the structure and relative stereochemistry of alangicine has been rigorously established to be III except for the absolute stereochemistry. It is, therefore, most likely that yet another phenolic A. lamarckii alkaloid, alangimarckine,[3] also possesses the same benzoquinolizidine moiety as that of III.

Acknowledgment —— One (T. F.) of the authors wishes to thank Emeritus Professor Dr. Shigehiko Sugasawa, University of Tokyo, and Professor Yoshio Ban, Hokkaido University, for their interest and encouragement.

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13. The solvent-free sample was prepared from a sample of alangicine (mp 146–148°), which had been crystallized from acetone—MeOH and was found by NMR spectroscopy to contain ca. one equivalent mole of MeOH of crystallization, by the same method used for the triethanolate of synthetic (±)-III.