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STRUCTURE AND STEREOCHEMISTRY OF ANKORINE: A TOTAL SYNTHESIS OF (±)-ANKORINE

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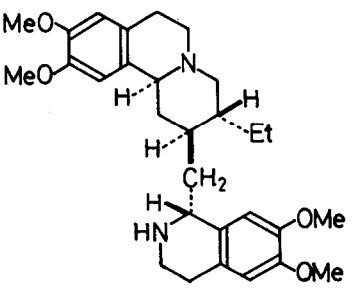
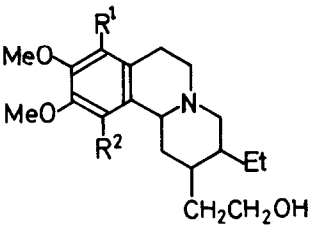
Ankorine is one of the Alangium lamarckii alkaloids[1,2] structurally related to the Ipecac alkaloids, e. g., emetine (I),[3] and has been assigned the plane structure II largely on the basis of physical measurements.[2] However, neither the precise location of the phenolic hydroxyl group nor the stereochemistry of this alkaloid was established at that time. The recent communication by Szántay et al.[4] of the synthesis of four possible racemic stereoisomers of II suggested that the phenol function of ankorine must be placed at an alternative position (structure III). Now we wish to record the results of our own synthetic effort, which have proved that structure IV is a complete expression, apart from its absolute configuration, for ankorine.

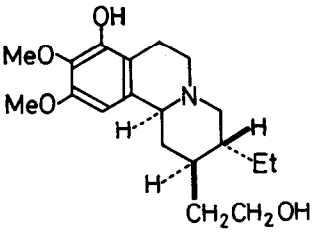


I



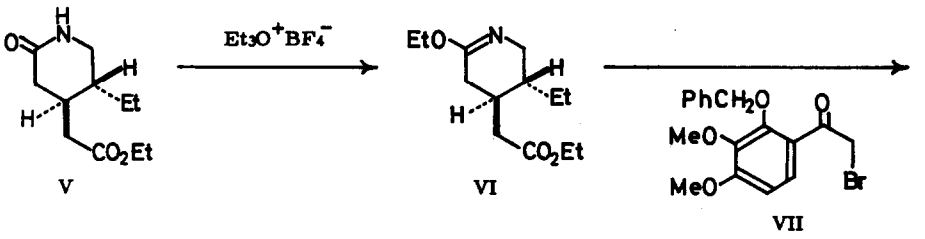
II, R^1=H; R^2=OH

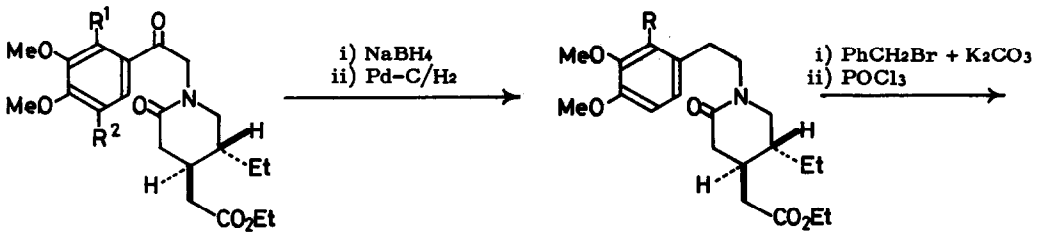
III, R^1=OH; R^2=H



IV

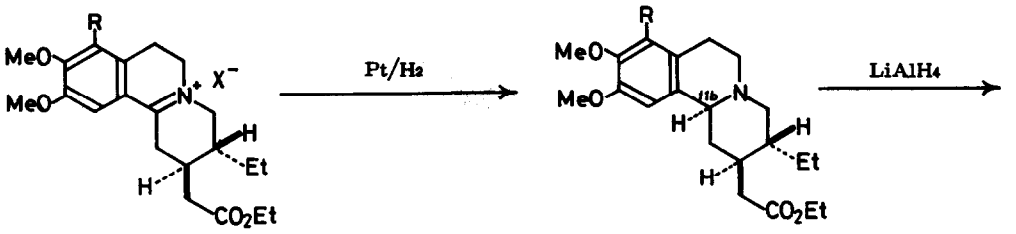
Treatment of lactim ether VI [bp 116–118° (2 mm)], obtained from ethyl trans-5-ethyl-2-oxo-4-piperidineacetate (V, mp 93–94°)[5,6] by a method given in the literature,[7] with 2-benzyloxy-3,4-dimethoxyphenacyl bromide (VII) at 60° for 6 hr produced lactam ketone VIII[8] in 80% yield.[9] The bromide (VII, mp 106–108°) used in this condensation was prepared in 68% yield by the bromination (Br_2, $CHCl_3$ — ether, 0°, 1.5 hr) of 2-benzyloxy-3,4-dimethoxyacetophenone (mp 51–52°), which was derived from 2-hydroxy-3,4-dimethoxyacetophenone[10] in 90% yield by benzylation ($PhCH_2Br$,





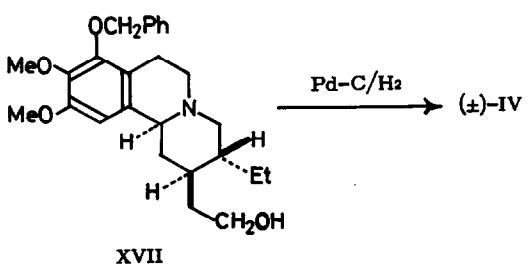
VIII, R^1 = OCH_2Ph; R^2 = H
IX, R^1 = H; R^2 = OMe
X, R^1 = R^2 = H

XI, R = OH
XII, R = H

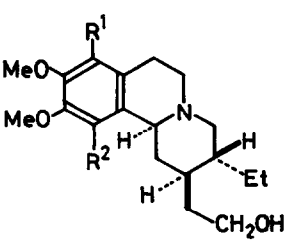


XIII, R = OCH_2Ph
XIV, R = H

XV, R = OCH_2Ph
XVI, R = H



XVII



XVIII, R^1 = OMe; R^2 = H
XIX, R^1 = H; R^2 = OMe

K_2CO_3, acetone, reflux, 12 hr). Reduction of lactam ketone VIII with $NaBH_4$ (EtOH, 0°, 3.5 hr) and hydrogenolysis of the resulting lactam alcohol (Pd-C/H_2, EtOH—70% aq. $HClO_4$, 20°, 4 atm, 3 hr) afforded lactam XI in 86% overall yield. Lactam XI was then benzylated ($PhCH_2Br$, K_2CO_3, refluxing acetone, 8 hr) and the resulting O-benzyl derivative was cyclized ($POCl_3$, toluene, reflux, 1.5 hr) to XIII (X=Cl). On catalytic hydrogenation (PtO_2, EtOH, 20°, 1 atm, 4 hr), XIII (X=Cl) furnished tricycle XV [35% overall yield from XI; ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 2804, 2760 (trans-quinolizidine ring),[11] 1726 (ester CO)].

That all reactions in the above sequence starting with V occurred with retention of trans configuration (in respect of the ethyl and the acetate side chains) and the correctness of the configuration at C-11b in XV were supported by repetition of the reaction sequence with 3,4-dimethoxyphenacyl bromide in place of VII, which led to tricycle XVI (mp 71–72°; perchlorate, mp 149–150°), identical with an authentic sample,[12] through X, XII,[12] and XIV (X=ClO_4,[12] mp 116–117°; X=I,[13] mp 169–170°) but without performance of the benzylation process before cyclization.

Conversion of ester XV into alcohol XVII was effected with $LiAlH_4$ in boiling ether. The final step was the debenzylation of XVII (Pd-C/H_2, EtOH, 20°, 3 hr) and the ultimate compound [(±)-IV] (mp 200–202°) was obtained in 53% overall yield (from XV). The uv (in EtOH or 0.1 N aq. NaOH), ir (in $CHCl_3$), nmr (in $CDCl_3$), and mass spectra and thin-layer chromatographic behavior of this sample were identical with those of the natural sample of ankorine [mp 175–177°; $[\alpha]_D^{16}$ −54° (c=0.18, $CHCl_3$)] that we were provided with through the courtesy of Professor Battersby.[2] The O-methyl derivatives (type XVIII) of both samples, prepared by methylation of the phenols with diazomethane, were also spectroscopically and chromatographically undistinguishable.

A parallel synthetic route starting with lactim ether VI and 3,4,5-trimethoxyphenacyl bromide (mp 68–70°), derived in 50% yield from 3,4,5-trimethoxyacetophenone[14] by bromination (Br_2, $CHCl_3$ and ether, 0°, 1.5 hr), yielded tricycle XIX via lactam ketone IX (75% yield; mp 74–75.5°). The solution ($CHCl_3$) ir and mass spectra and chromatographic behavior of XIX did not match those of O-methylankorine (type XVIII)[2] described above.

The present results have identified the structure and relative stereochemistry of ankorine as IV. Accordingly, it seems most likely that the structure of the benzoquinolizidine moiety of alangicine[15] and alangimarckine[2] is the same as that of IV.

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