Total Synthesis of (±)-Eburnamine, (±)-Homoeburnamenine, and (±)-21-Epihomoeburnamenine

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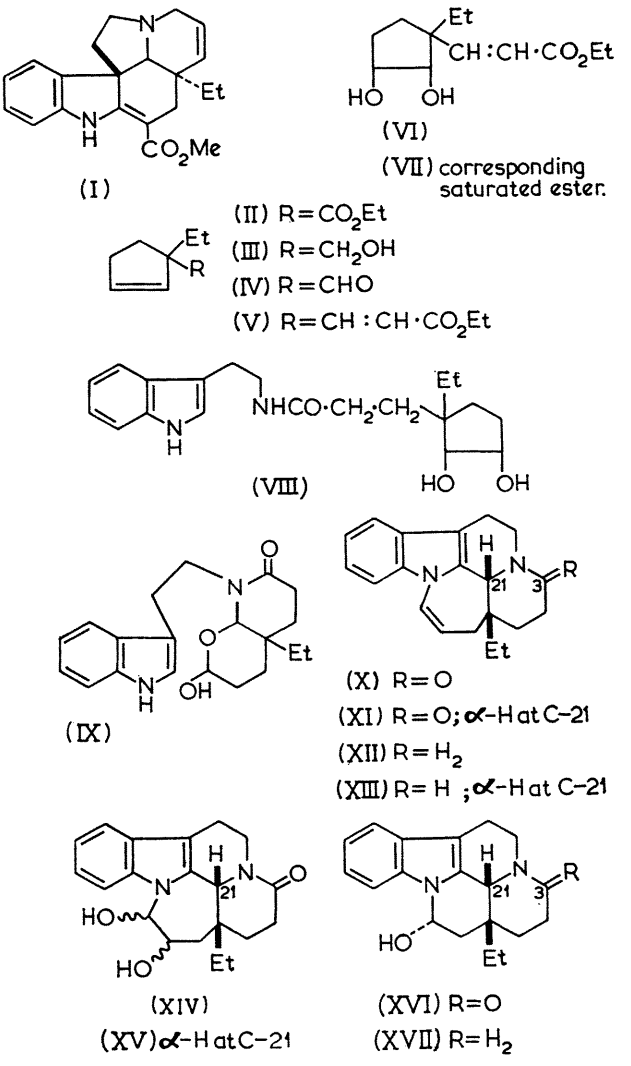
Summary We report a new total synthesis of (±)-eburnamine, together with the first syntheses of (±)-homoeburnamenine and (±)-21-epihomoeburnamenine.

IN the course of our investigations directed primarily towards the synthesis of *Aspidosperma* alkaloids containing substituents in rings D and E, *e.g.* tabersonine (I),[1] we have completed a new total synthesis of (±)-eburnamine (XVII),[2] together with the first syntheses of (±)-homoeburnamenine (XII) and (±)-21-epihomoeburnamenine (XIII). 2-Ethoxycarbonyl-2-ethylcyclopentanone was reduced ($NaBH_4$) to the corresponding hydroxy-ester, which was then dehydrated (P_2O_5 or by xanthate pyrolysis) to the unsaturated ester (II). Reduction ($LiAlH_4$) of (II) to the primary alcohol (III) followed by a modified Oppenauer oxidation [$Al(OBu^t)_3$ and *p*-benzoquinone] afforded the aldehyde (IV), which was converted by Wittig condensation with ethoxycarbonylmethylenetriphenylphosphorane into the unsaturated ester (V). Hydroxylation of (V) by means of osmium tetroxide, or by iodine–silver acetate–aqueous acetic acid followed by acid hydrolysis, gave a mixture of two stereoisomeric *cis*-diols (VI), which was hydrogenated to a mixture of the corresponding saturated esters (VII). Condensation of (VII) with tryptamine afforded the tryptamide (VIII), which on oxidation with sodium metaperiodate gave the carbinolamide-lactol (IX) as two separable isomers, one of which was noncrystalline (M^+, 342·1925), and the chloroform solvate of the other had m.p. 105—112° (M^+, 342·1928). Cyclisation of either isomer of (IX) by glacial acetic acid gave a mixture of (±)-3-oxohomoeburnamenine (X), m.p. 149—151·5°, and (±)-21-epi-3-oxohomoeburnamenine (XI), m.p. 180—183°, which when reduced with lithium aluminium hydride afforded, respectively, (±)-homoeburnamenine (XII), m.p. 86—88°, M^+, 292·1939, and (±)-21-epihomoeburnamenine (XIII), m.p. 94—99·5°, M^+, 292·1939. Hydroxylation (OsO_4) of (X) gave a mixture of the *cis*-diols (XIV), m.p. 215—222°, M^+, 340·1789; the corresponding *trans*-isomer (XI) similarly gave a mixture of *cis*-diols (XV), m.p. 174°, then resolidification, then m.p. 215—216·5°, M^+, 340·1785. Oxidation of (XIV) by lead tetra-acetate in methanol, followed by removal of the *N*-formyl group by potassium carbonate, gave (±)-3-oxoeburnamine (XVI), m.p. 234—240° (lit.[3] m.p. 210—211°, although this was probably not stereochemically homogeneous[4]). Finally reduction of (XVI) by $LiAlH_4$ gave (±)-eburnamine (XVII), m.p. 136—140°, identical in i.r. and mass spectra with authentic (−)-eburnamine, kindly supplied by Dr. M. F. Bartlett (CIBA, Summit, N.J.).

The possibility of transforming the intermediates (VI) and (VIII) and the diols (XIV) and (XV) into products containing the aspidospermine ring system by reported methods [3,5] is at present being investigated.



Satisfactory analytical and spectrographic data have been obtained for all new compounds obtained in this investigation.

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