

SYNTHESES OF PACHYSANDRINES AND EPIPACHYSANDRINE-A FROM ERGOSTEROL

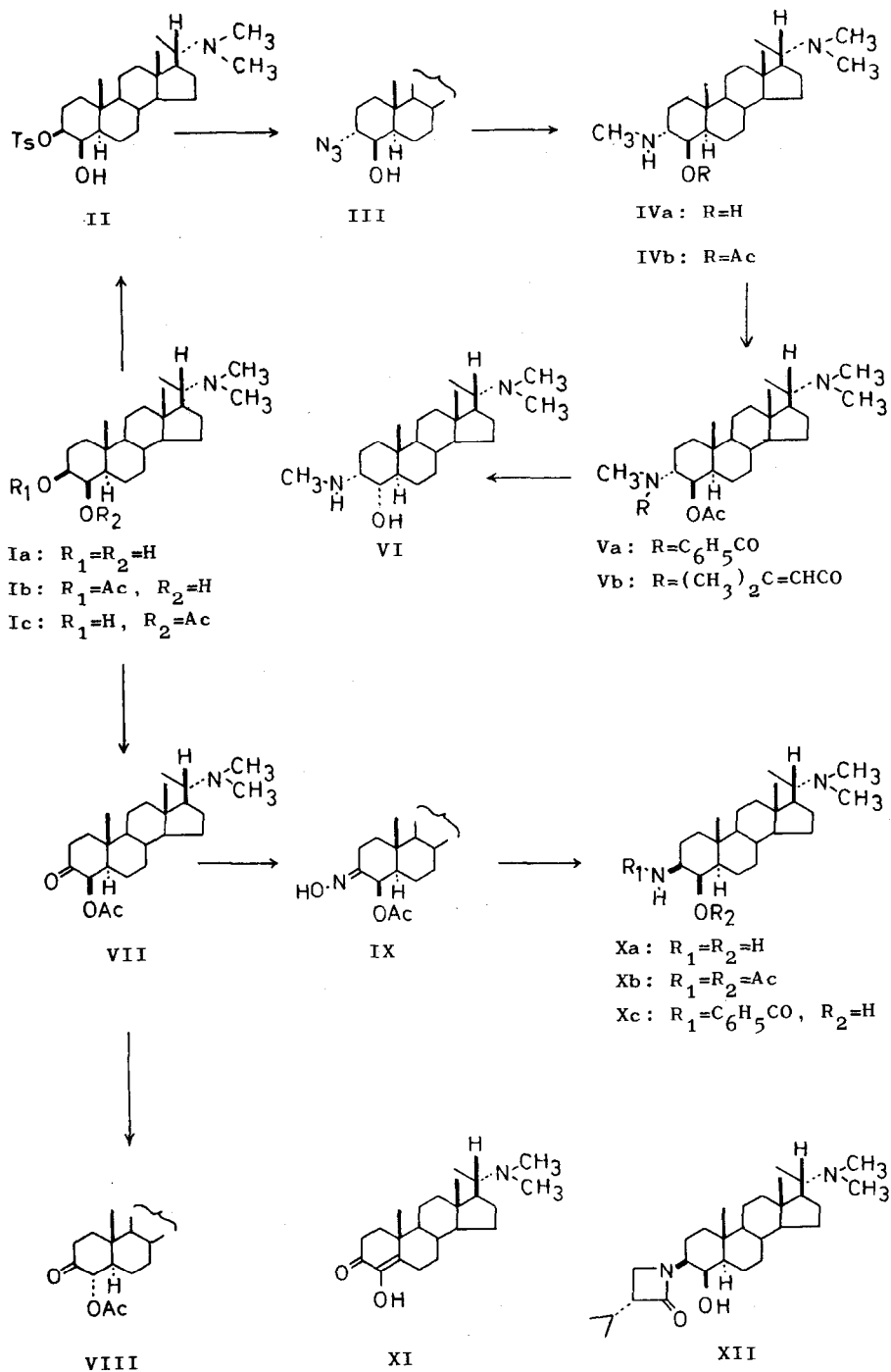
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Pachysandrine-A (Va), B (Vb), C (VI) and epipachysandrine-A (Xc) are 3,20-diamino-pregnane type alkaloids having an oxygen function at 4-position, which were isolated from Pachysandra terminalis SIEB. et ZUCC.^{1,2)} Now we wish to report the syntheses of these alkaloids starting from 3 β ,4 β -dihydroxy-20 α -dimethylamino-5 α -pregnane (Ia)³⁾ which has previously been synthesized from ergosterol and is readily available by a few steps transformation from pachysandrines through a diosphenol (XI)^{3,4)}.

First, the synthesis of pachysandrine-A (Va), one of the major alkaloids of the plant, is described. Reaction of Ia with p-tosyl chloride in pyridine at room temperature gave a mono-tosylate (II) in almost quantitative yield, C₃₀H₄₇O₄NS*, m.p.* 211-213°, [α]_D* -3°, IR* 1170, 1100, 925, 868, 810 cm⁻¹ (tosylate); NMR* 2.22, 2.70 (4H, A₂B₂ q., J=8 c.p.s., aromatic H), 5.58 (1H, m., -CH(OTs)), 6.15 (1H, m., -CH(OH)), 7.56 (3H, s., aryl CH₃), 7.82 (6H, s., N(CH₃)₂), 9.00 (3H, s., 19-CH₃), 9.13 (3H, d., sec. CH₃), 9.38 τ (3H, s., 18-CH₃). On heating with NaN₃ in N-methylpyrrolidone⁵⁾ this tosylate afforded a crude azide (III) (IR 2200 cm⁻¹) which was immediately reduced with LiAlH₄. The total product was then formylated as usual and again subjected to the LiAlH₄ reduction to give a crystalline residue (IVa). Purification of this crude N-methyl compound by alumina chromatography and by recrystallizations of its picrate (m.p. 244-247°, decom.) gave rise to IVa, C₂₄H₄₄ON₂, m.p. 214-215°, [α]_D +28°. This was found to be quite identical with O,N-desacylpachysandrine-A (IVa)¹⁾ by mixed m.p. and IR (KBr), NMR and MS* spectra. We then used the natural IVa in the further synthesis: partial acetylation of IVa using Ac₂O-HOAc-p-TsOH gave an O-acetate (IVb), C₂₆H₄₆O₂N₂, m.p. 182-183°, [α]_D +12°.



IR 1720, 1250 cm^{-1} ; NMR 7.95 τ (OCOCH_3), which on subsequent benzoylation yielded Va, $\text{C}_{33}\text{H}_{50}\text{O}_3\text{N}_2$, m.p. 237-238°, $[\alpha]_D +90^\circ$, identical with natural pachysandrine-A (Va) in every respect. Transformations of pachysandrine-A into pachysandrine-B (Vb) and C (VI) have already been reported¹⁾.

The synthesis of the next alkaloid, epipachysandrine-A (Xc), was initiated by partial acetylation of Ia⁶⁾. Reaction of the diol (Ia) with Ac_2O -pyridine afforded 3-mono-acetate (Ib) in good yield, $\text{C}_{25}\text{H}_{43}\text{O}_3\text{N}$, m.p. 212-213°, $[\alpha]_D +16^\circ$, IR 3550, 1728, 1250 cm^{-1} ; NMR 5.27 (1H, m., $-\text{CH}(\text{OAc})$), 6.17 (1H, m., $-\text{CH}(\text{OH})$), 7.92 τ (3H, s., $-\text{OCOCH}_3$). The facile acyl migration of this acetate was achieved by treating with alumina to give the 4-acetate (Ic), $\text{C}_{25}\text{H}_{43}\text{O}_3\text{N}$, m.p. 206-208°, $[\alpha]_D +18^\circ$, IR 3480, 1725 cm^{-1} ; NMR 4.90 (1H, m., $-\text{CH}(\text{OAc})$), 6.37 τ (1H, m., $-\text{CH}(\text{OH})$), which was subsequently oxidized by CrO_3 -HOAc to a keto acetate (VII), $\text{C}_{25}\text{H}_{41}\text{O}_3\text{N}$, m.p. 185-187°, $[\alpha]_D +89^\circ$, IR 1740, 1725 cm^{-1} ; NMR 5.02 (1H, br. d., $J=3$ c.p.s. $-\text{CH}(\text{OAc})$), 8.87 τ (3H, 19- CH_3). In this oxidation procedure the β -configuration of the 4-acetoxy group was believed to be unchanged, since the acid treatment of VII gave a more stable isomer (VIII), $\text{C}_{25}\text{H}_{41}\text{O}_3\text{N}$, m.p. 185-188°, $[\alpha]_D +5^\circ$, IR 1740, 1725 cm^{-1} ; NMR 4.92 (1H, br. d., $J=11$ c.p.s. $-\text{CH}(\text{OAc})$), 8.87 τ (3H, 19- CH_3) as a sole product.

The above keto acetate (VII) was then converted to an oxime (IX), $\text{C}_{25}\text{H}_{42}\text{O}_3\text{N}_2$, m.p. 205-207°, $[\alpha]_D -7^\circ$, IR 3280, 1734 cm^{-1} ; NMR 4.61 τ (1H, m., $-\text{CH}(\text{OAc})$), and stereospecifically reduced by LiAlH_4 ⁷⁾ to produce a crystalline amino alcohol (Xa) as an essentially single product, which was characterized as a corresponding O,N-diacetate (Xb), m.p. 220-225°, identified with 3β -methyl,acetylamino-20 α -dimethyl-amino-4 β -acetoxy-5 α -pregnane (Xb) derived from pachystermine-B (XII) (mixed m.p., IR in KBr)⁸⁾. Finally the Schotten-Baumann condensation of Xa and benzoyl chloride yielded Xc, $\text{C}_{30}\text{H}_{46}\text{O}_2\text{N}\cdot 1/2\text{H}_2\text{O}$, m.p. 290-293°, $[\alpha]_D +19^\circ$. This compound was shown to be identical with natural epipachysandrine-A (Xc) in all respects.

Thus pachysandrine-A, B, C and epipachysandrine-A were synthesized from ergosterol.

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- * All compounds given by formulas in this communication gave satisfactory elementary analyses. All melting points were determined on a Kofler type microscopic hot stage and are uncorrected. Optical rotation were taken at 20-30 °C in CHCl₃ and NMR spectra in CDCl₃ with SiMe₄ as the internal standard. Mass spectra were taken on a Hitachi Mass Spectrometer Model RMU-6D equipped with a direct inlet system (Model MG-150).
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