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SYNTHESES OF PACHYSANDRINES AND EPIPACHYSANDRINE-A FROM ERGOSTEROL

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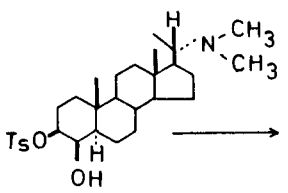
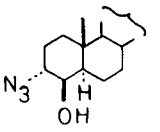
Pachysandrine-A (Va), B (Vb), C (VI) and epipachysandrine-A (Xc) are 3,20-diamino-pregnane type alkaloids having an oxygen function at 4-position, which were isolated from Pachysandra terminalis SIEB. et ZUCC.[1,2] Now we wish to report the syntheses of these alkaloids starting from 3β,4β-dihydroxy-20α-dimethylamino-5α-pregnane (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, $C_{30}H_{47}O_4NS$*, m.p.* 211-213°, $[\alpha]_D$* -3°, IR* 1170, 1100, 925, 868, 810 cm^{-1} (tosylate); NMR* 2.22, 2.70 (4H, A_2B_2 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 CH_3), 7.82 (6H, s., $N(CH_3)_2$), 9.00 (3H, s., 19-CH_3), 9.13 (3H, d., sec. CH_3), 9.38 τ (3H, s., 18-CH_3). On heating with NaN_3 in N-methylpyrrolidone[5] this tosylate afforded a crude azide (III) (IR 2200 cm^{-1}) which was immediately reduced with $LiAlH_4$. The total product was then formylated as usual and again subjected to the $LiAlH_4$ 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, $C_{24}H_{44}ON_2$, m.p. 214-215°, $[\alpha]_D$ +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 Ac_2O-HOAc-p-TsOH gave an O-acetate (IVb), $C_{26}H_{46}O_2N_2$, m.p. 182-183°, $[\alpha]_D$ +12°,



II



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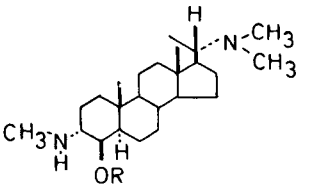
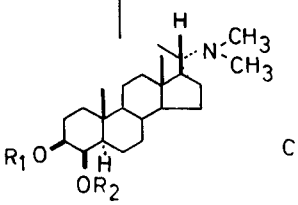


IVa: R=H

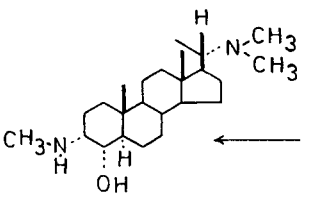
IVb: R=Ac



Ia: R_1=R_2=H

Ib: R_1=Ac, R_2=H

Ic: R_1=H, R_2=Ac



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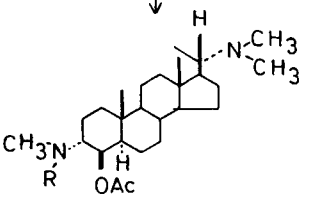
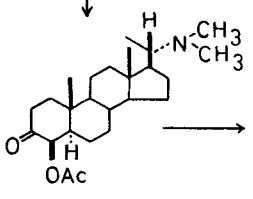
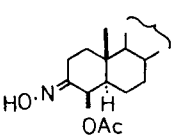


Va: R=C_6H_5CO

Vb: R=$(CH_3)_2C$=CHCO



VII



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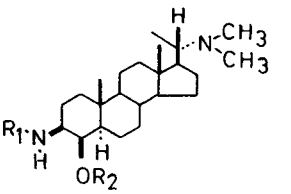
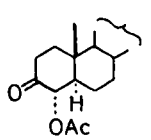


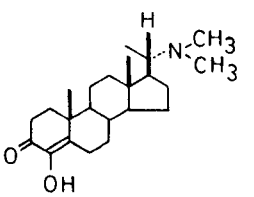
Xa: R_1=R_2=H

Xb: R_1=R_2=Ac

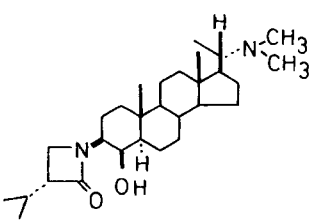
Xc: R_1=C_6H_5CO, R_2=H



VIII



XI



XII

IR 1720, 1250 cm^{-1}; NMR 7.95 τ ($OCOCH_3$), which on subsequent benzoylation yielded Va, $C_{33}H_{50}O_3N_2$, m.p. 237-238°, $[\alpha]_D$ +90°, identical with natural pachysandrine-A (Va) in every respect. Transformations of pachysandrine-A into pachysandrine-B (Vb) and C (VI) have already been reported[1].

The synthesis of the next alkaloid, epipachysandrine-A (Xc), was initiated by partial acetylation of Ia[6]. Reaction of the diol (Ia) with Ac_2O-pyridine afforded 3-mono-acetate (Ib) in good yield, $C_{25}H_{43}O_3N$, m.p. 212-213°, $[\alpha]_D$ +16°, IR 3550, 1728, 1250 cm^{-1}; NMR 5.27 (1H, m., -CH(OAc)), 6.17 (1H, m., -CH(OH)), 7.92 τ (3H, s., $-OCOCH_3$). The facile acyl migration of this acetate was achieved by treating with alumina to give the 4-acetate (Ic), $C_{25}H_{43}O_3N$, m.p. 206-208°, $[\alpha]_D$ +18°, IR 3480, 1725 cm^{-1}; NMR 4.90 (1H, m., -CH(OAc)), 6.37 τ (1H, m., -CH(OH)), which was subsequently oxidized by CrO_3-HOAc to a keto acetate (VII), $C_{25}H_{41}O_3N$, m.p. 185-187°, $[\alpha]_D$ +89°, IR 1740, 1725 cm^{-1}; NMR 5.02 (1H, br. d., J=3 c.p.s. -CH(OAc)), 8.87 τ (3H, 19-CH_3). In this oxidation procedure the β-configuration of the 4-acetoxyl group was believed to be unchanged, since the acid treatment of VII gave a more stable isomer (VIII), $C_{25}H_{41}O_3N$, m.p. 185-188°, $[\alpha]_D$ +5°, IR 1740, 1725 cm^{-1}; NMR 4.92 (1H, br. d., J=11 c.p.s. -CH(OAc)), 8.87 τ (3H, 19-CH_3) as a sole product.

The above keto acetate (VII) was then converted to an oxime (IX), $C_{25}H_{42}O_3N_2$ m.p. 205-207°, $[\alpha]_D$ -7°, IR 3280, 1734 cm^{-1}; NMR 4.61 τ (1H, m., -CH(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-20α-dimethyl amino-4β-acetoxy-5α-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, $C_{30}H_{46}O_2N \cdot 1/2H_2O$, m.p. 290-293°, $[\alpha]_D$ +19°. 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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REFERENCES

* 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 $CHCl_3$ and NMR spectra in $CDCl_3$ with $SiMe_4$ 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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