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A SYNTHETIC APPROACH TOWARDS POLYFUNCTIONAL 5-AZASTEROIDS

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Syntheses of bridgehead azasteroids have been a challenging problem for a long time due to complexity involved with reinsertion of pseudoasymmetric nitrogen in place of an asymmetric carbon atom, this being moreover in immediate vicinity of at least one another asymmetric centre. Since 1962, when the first report on the bridgehead azasteroid synthesis came form this laboratory[1], many papers appeared dealing chiefly with total azasteroid synthesis[2]. A somewhat neglected partial synthetic approach in our hands proved to be a method of choice at least in the synthesis of 5-azasteroids in cholestane and androstane series[3]. The aim of our present work was to find a reliable way to the functionalized 5-azasteroid system, comprising at least two masked β-oriented hydroxylic functions at C-3 and C-17 in the modified steroidal nucleus, conceived as an extension of previously applied routes. We wish to report the synthesis of the key intermediate to 17α-methyl-5-azaandrostanes: 3β,17β-diacetoxy-17α-methyl-5-azaandrosta-4,6-dione (VI), starting from 17α-methyl-B-nortestosterone acetate (I)[4].

Thus I , after reduction by $NaBH_4$ in methanol or $LiAl(t\text{-}BuO)_3H$ in THF afforded allylic alcohol-ester IIa, m.p. 130-132°C, $[\alpha]^{20}_{max}$ -62°; $\nu^{CCl_4}_{max}$ 3628, 3470, 1750, 1719, 1245, 1230 cm^{-1}; p.m.r. (60 MHz, $CDCl_3$, TMS): δ 1.70 (s, 1H, OH), 4.30 (m, 1H, H-3), 5.32 (m, 1H, H-4), 0.88 (s, 3H, H-18), 0.99 (s, 3H, H-19), 1.42 (s, 3H, 17-CH_3), 1.99 (s, 3H, 17-OCOCH_3). Compound IIa, the structure

of which was further confirmed by its oxidation with MnO_2 in benzene at room temperature (r.t.) to give the starting α,β-unsaturated ketone I, appeared to be very labile towards traces of mineral acids. The alcohol-ester IIa gave diacetate (Ac_2O - pyridine, r.t.) IIb, m.p. 179-181.5°C, $[\alpha]_D^{20}$ -102°; ν_{max}: no OH absorption; δ 2.06 (s, 3H, 3-OCOCH$_3$), 5.30 (d, J=4Hz, 1H, H-4), 5.35 (m, 1H, H-3).

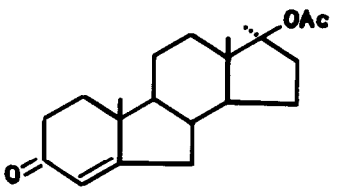
Ozonolysis of IIb and reductive work-up (-60°C, 10% AcOH in CH_2Cl_2 then Zn dust at 0°C) yielded oily ketoaldehyde IIIa; $\nu_{max}^{CCl_4}$ 2881, 2722, 1736, 1729 cm^{-1}, which was subsequently oxidized to ketoacid IIIb with $KMnO_4$ in aq. t-BuOH containing $MgSO_4$. The crude acid was purified as its methyl ester IIIc, m.p. 128.5-130°C, $[\alpha]_D^{20}$ -87°; ν_{max}^{KBr} 1755, 1738, 1722, 1268, 1237, 1212 cm^{-1}; δ 3.78 (s, 3H, 3-OCOCH$_3$), 0.94 (s, 6H, H-18 and H-19).

Hydroxylamine treatment of ketoester IIIb in pyridine (r.t.) afforded, as the major product, an oxime (with expected anti-configuration) IVa, m.p. 138-140.5°C, $[\alpha]_D^{20}$ -43°; $\nu_{max}^{CCl_4}$ 3605, 3310, 1740, 1243, 1208, 922 cm^{-1}; δ 0.88 (s, 3H, H-18), 1.04 (s, 3H, H-19), broad, unresolved multiplet at δ 8.3 (=NO<u>H</u>). There was some evidence for another isomeric oxime presence in a minor quantity in mother liquors from the crystallization of oxime IVa.

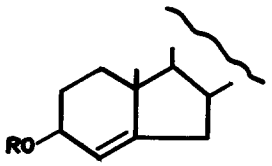
Brief treatment of oxime IVa in ether with $SOCl_2$ (-15°C, 20 min, neutralization with ammonia) furnished the desired lactam-triester Vb as an amorphous solid which melted over a broad range, m.p. 164-186°C. Its spectral properties were those expected for Vb. The <u>NH</u> proton signal appeared as a multiplet centered at δ 7.05 but there were no signals in the δ 3-3.7 region indicative of an isomeric lactam.

In an attempt to hydrolyse methyl ester Vb selectively it was treated with LiI in boiling 2,6-lutidine[5]. Unfortunately - as suggested by ir and p.m.r. data - the complex reaction mixture contained significant quantities of compounds lacking more than one ester group. As other attempts of selective hydrolysis failed, an alternative means of protecting the carboxylic function by the benzhydrylic group was investigated. This group, being readily cleaved under acidic conditions, proved suitable for our purpose.

The ketoacid IIIb, when treated with diphenyldiazomethane in benzene at 30°C, afforded its benzhydrylic ester IIId as a viscous oil; $\nu_{max}^{CCl_4}$ 1746 broad, 1230, 1226, 1236 cm^{-1}; δ 0.82 (s, 3H, H-19), 0.93 (s, 3H, H-18), 2.00 (s, 3H, 17-OCOCH$_3$), 2.13 (s, 3H, 3-OCOCH$_3$); 5.00 (m, 1H, H-3), 6.94 (s, 1H, H-CPh$_2$), 7.36 (m, 10 H-Ph).



I



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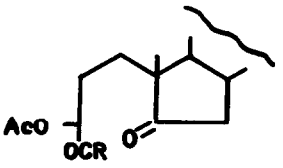
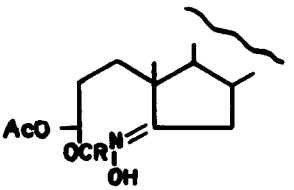
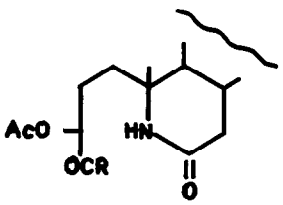
b) R=Ac



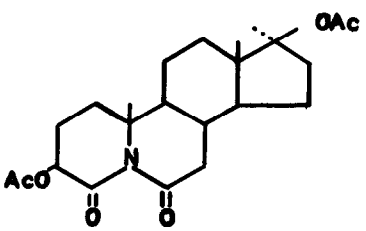
III a) R=H
b) R=OH
c) R=OCH_3
d) R=$OCHPh_2$



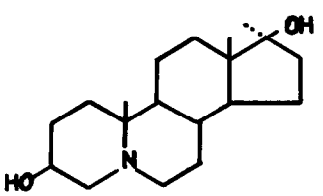
IV a) R=OCH_3
b) R=$OCHPh_2$



V a) R=OH
b) R=OCH_3
c) R=$OCHPh_2$



VI



VII

Hydroxylamine treatment of IIId in boiling methanol afforded after chromatography an amorphous oxime IVb; $\nu_{max}^{CCl_4}$ 3610, 3370-3290, 1750, 1680, 945, 925 cm^{-1}; δ 0.94 (s, 3H, H-19).

Beckmann rearrangement of oxime IVb, carried out in the same way as for IVa yielded crystalline lactam-ester Vc, m.p. 214-216°C, $[\alpha]_D^{20}$ -67°; $\nu_{max}^{CCl_4}$ 3210, 1748, 1672 cm^{-1}; δ 1.03 (s, 3H, H-19), 6.35 (m, 1H, NH), there were no signals within the δ 2.6-4.8 region. As there was no appreciable quantity of acidic products, the benzhydrylic group appeared capable of surviving a short exposure to anhydrous acid conditions. This group could be quickly and completely removed by gaseous HCl in acetic acid or ether. Thus, if a stream of HCl passed through ice-cold ether solution of lactam Vc, the lactam-acid Va deposited in a few minutes as a sparingly soluble oil, crystallizing in prisms, m.p. 237-240°C (acetone), $[\alpha]_D^{20}$ -46°; ν_{max}^{KBr} 3300, 3250 br, 1750, 1663 cm^{-1}, no aromatic bands;

δ 7.95 (m, 2H, COOH and NH).

Intramolecular N-acylation by DCC in CH_2Cl_2 (0°C) led to the desired 5-azasteroid imide VI in moderate yield (45-60%) which was purified by repeated crystallization from acetone and chromatography on Florisil. This compound had m.p. 222-224°C, $[\alpha]_D^{20}$ -75°; ν_{max}^{KBr} 1765-1740 br, 1675, 1270, 1254 cm^{-1}; p.m.r. (100 MHz): δ0.85 (s, 3H, H-18), 1.32 (s, 3H, H-19), 1.95 (s, 3H, 17-$OCOCH_3$), 2.13 (s, 3H, 3-$OCOCH_3$), 5.23 (dd, J=11 and 7.5 Hz); MS (LKB 9000): 419(M^+), 359 (M^+-60), 170, 148. As shown by these data the S-configuration at C-3 was retained in the course of synthesis.

Reduction of the imide VI with large excess of $LiAlH_4$ in boiling 1,2-dimethoxyethane afforded 17α-methyl-5-azaandrosta-3β,17β-diol (VII) as colorless needles, m.p. 234-5°C (from ethyl acetate), m/e 307 (M^+), 292 (M^+-15); methyl iodide m.p. 264°C.

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