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STEROID DERIVATIVES L (1). A SYNTHESIS OF 16-METHYLENE-17α-ACETOXY-19-NOR-PROGESTERONE

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In view of the well recognised enhancement of progestational activity by passing from the regular steroid series to the corresponding 19-nor-analogues (2,3), a synthesis of the title compound offered a logical extension of the broader program on 16-methylene derivatives initiated previously in this laboratory (4a-d, 5a,b).

Since the presence of the 16-methylene group might be expected to interfere with the removal of C-19 angular methyl group by the proposed standard method (6), the synthesis was started with 3β-acetoxy-16β-methyl-16α,17-oxidopregn-5-en-20--one (I) (4a), the oxido group of which might be expected to be satisfactorily void of reactivity in the steps under consideration, but readily convertible to the desired grouping. By addition of hypobromous acid, generated from N-bromoacetamide and perchloric acid in a mixture of aqueous dioxane and acetone,

the starting compound afforded crude 5α-bromo-6β-hydroxy-derivative II, m.p.154-9°, which was in turn treated with lead tetraacetate and iodine in benzene to give rise of 3β--acetoxy-5α-bromo-16β-methyl-6β,19;16α,17-dioxidopregnan-20--one (III), m.p.196-8°, $/\alpha/_D$ + 5°, ν 1728,1703,1253,1035,920 cm^{-1} (7). By reduction with zinc powder in boiling isopropyl-alcohol, the latter compound yielded 3β-acetoxy-19-hydroxy--16β-methyl-16α,17-oxidopregn-5-en-20-one (IVa), m.p.157-9°, $/\alpha/_D$ - 20°, ν 3500,1725,1705,1356,1252,1031 cm^{-1}, and, by the subsequent alkali hydrolysis, the corresponding 3,19-diol IVb, m.p.199-201°, $/\alpha/_D$ -31,6°, ν 3300,1700,1050 cm^{-1}.

At this stage, an unequivocal evidence by independent synthesis seemed to be desirable in support of the structure IV because of an unsufficient conclusiveness of available physico-chemical methods. To this goal, 3β,19-dihydroxyandrost-5--en-17-one (Va) (8,9) was acetylated, and the corresponding diacetate Vb, m.p.108-109,5°, $/\alpha/_D$ -40°(EtOH), ν 1735,1720, 1405,1250,1031 cm^{-1} was converted to 3β,19-diacetoxy-17-cyano--androsta-5,16-diene (VII), m.p.133-4°, $/\alpha/_D$ - 89° (EtOH), λ_{max} 218 nm (log ε 3,88), ν 2215,1723,1590,1250,1031 cm^{-1}, by addition of hydrocyanic acid and the subsequent dehydration of the mixture of epimeric cyano hydrines VI with phosphorus oxychloride in dry pyridine. By Grignard reaction of VII with methyl magnesium bromide in ether or benzene, 3β,19-dihydroxy-pregna-5,16-dien-20-one (VIIIa), m.p.229-233°, $/\alpha/_D$ - 37° (EtOH), λ_{max} 240 nm (log ε 3,82), ν 3400,1650,1582,1040 cm^{-1}, diacetate VIIIb, m.p.157,5-159°, $/\alpha/_D$ - 70°, ν 1725,1655,1600, 1250,1032 cm^{-1} was formed. The diacetate VIIIb was treated

with diazomethane to give rise of the corresponding pyrazoline derivative IX, m.p.162-6°(decomp.), ν 1725,1708,1250,1032 cm^{-1}, which was in turn pyrolysed to 3β,19-diacetoxy-16-methylpregna--5,16-dien-20-one (X), m.p.146-152°, λ_{max} 251 nm (log ε 3,94), ν 1725,1655,1432,1359,1250,1031 cm^{-1}. On treatment with hydrogen peroxide in aqueous methanol in the presence of potassium hydroxide, the latter compound afforded a product,which was identical, in all respects, with the compound IVb obtained <u>via</u> the first route.

This intermediate was oxidised with aluminium isopropoxide and cyclohexanone to the corresponding 3-ketopregn-4-ene derivative XI, m.p.203-4°, $[\alpha]_D$ + 125°, λ_{max} 242 nm (log ε 4,16), ν 3610,3450,1700,1660,1620,1030 cm^{-1}, and further, with Jones reagent (10), to 19-acid XII, m.p.175-7°(decomp.), $[\alpha]_D$ + 171°, λ_{max} 243 nm (log ε 4,02), ν 3200,1705,1695,1665,1620 cm^{-1}. Decarboxylation of the latter in boiling pyridine gave rise to 16β-methyl-16α,17-oxido-19-norpregn-5(10)-ene-3,20-dione (XIII), m.p.125-7°, $[\alpha]_D$ + 180°, ν 1708,1355 cm^{-1}. By treatment with acetic anhydride in boiling toluene in the presence of sulphonylsalicylic acid, 16α,17-oxide ring opening to 17α-acetoxy--16-methylene moiety (4c) was achieved along with a concommitant enol-acetylation and shift of 5(10)-double bond to afford 3,17α-diacetoxy-16-methylene-19-norpregna-3,5-dien-20-one (XIV), m.p.186-9°, λ_{max} 235 nm (log ε 4,21).On mild hydrolysis with methanolic potassium hydroxide in ethyl acetate, the 3-acetate group of XIV was removed selectively, and there was obtained the desired 16-methylene-17α-acetoxy-19-norpregn-4-ene-3,20-dione XV, m.p.174-5°, $[\alpha]_D$ -92°, λ_{max} 240 nm (log ε 4,21),

ν 1725,1708,1660,1618,1356,1260,892 cm^{-1}.

All these physico-chemical properties are in full agreement with the proposed structure. Data on biological activity of the title compound and several intermediates will be published separately elsewhere.

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