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STEROIDS.II[1] SYNTHESIS OF 19-NORPROGESTERONE via 19-NORDIOSGENIN AND SYNTHESIS OF A-AROMATIC DIOSGENIN

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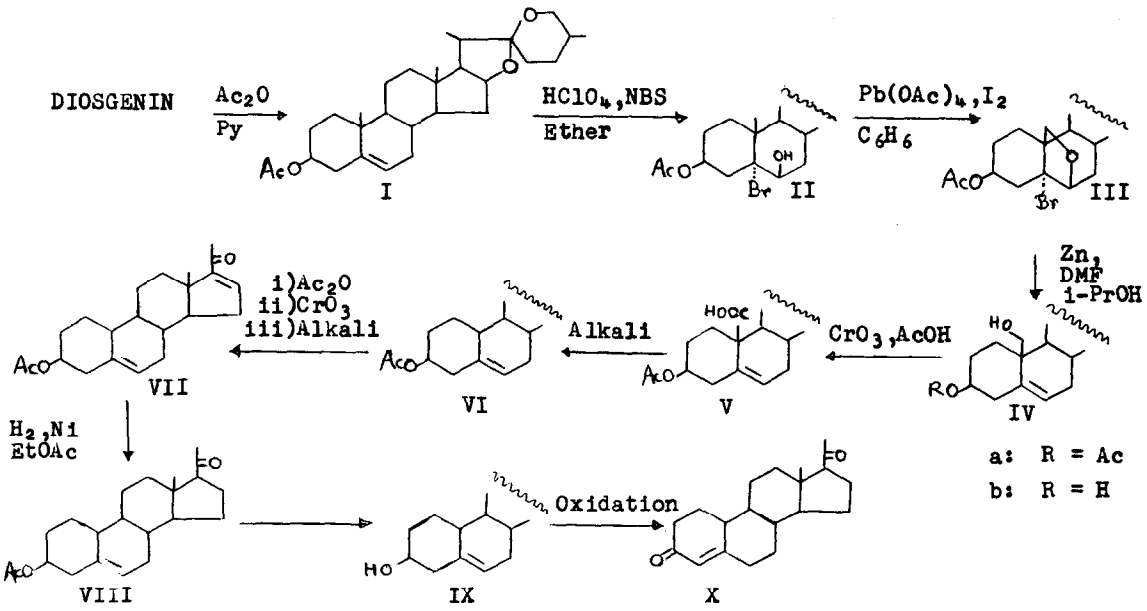
19-Norprogesterone and 19-nortestosterone are normally prepared from the corresponding pregnane and androstane derivatives involving functionalisation and subsequent degradation of the 19-methyl group. In connection with our studies in the preparation of 19-norsteroids, it was of interest to investigate whether a change in the sequel introduced by carrying out the sensitive reactions with less expensive primary intermediate - diosgenin, at an earlier stage, would result into higher yields. This approach also has an additional interest, in that the 19-hydroxydiosgenin-3-acetate (IVa) would conveniently be converted into A-aromatic diosgenin(XIII), which forms a key intermediate in the synthesis of estrone[2]. Expectedly in both the cases the yields, as obtained in the initial experiments without any attempts

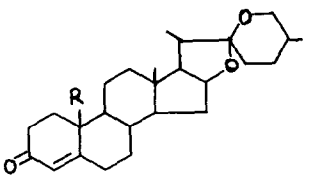


to optimize the yields, were much higher. The over-all yields of 19-norprogesterone from diosgenin were about 30% as against 21% by the conventional procedure; and that of A-aromatic diosgenin were about 25% as against 3.5% by the process reported in the literature.

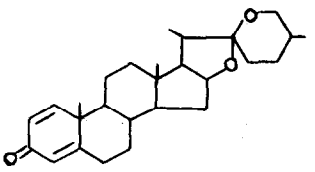
Diosgenin was acetylated with acetic anhydride and pyridine to diosgenin acetate(I), m.p.198°. This on treatment with N-bromosuccinimide and dilute perchloric acid in ether gave 5α-bromo-6β-hydroxytigogenin-3-acetate(II), m.p.[3] 220°-221°,(acetone), in 98% yield. The bromohydrin (II) on treatment with lead tetraacetate in the presence of iodine and $CaCO_3$ in refluxing benzene[4] gave 5α-bromo-6β,19-oxidotigogenin-3-acetate(III) in 80% yield m.p.215°, (MeOH), ν_{max}^{nujol} 1750, 1235 cm^{-1}; NMR in $CDCl_3$ showed absence of 19-CH_3 peak at δ1.03 and also the absence of C-6 vinyl proton at δ5.34. The solution of (III) in the mixture of dimethyl formamide and isopropyl alcohol (1:1) was reduced with activated zinc to yield 19-hydroxy-diosgenin-3-acetate (IVa) in 90% yield; m.p.242°, (EtOH-CH_2Cl_2), ν_{max}^{nujol} 3500,1740,1247 cm^{-1}; NMR in $CDCl_3$ showed the absence of 19-CH_3 peak at δ1.03 and the presence of C-6 vinyl proton at δ5.34. The 19-hydroxy compound (IVa) on oxidation with chromium trioxide in acetic acid at ambient temperature gave 19-carboxylic acid(V). The 19-carboxylic acid (V) when dissolved in methylene chloride and stirred with 5% potassium hydroxide solution gave 19-nor-Δ^5-diosgenin-3-acetate (VI) in 78% yield; m.p.204°, (MeOH-CH_2Cl_2), ν_{max}^{nujol} 1722, 1235 cm^{-1}. This structure was assigned from the NMR spectrum which showed a triplet at δ5.35 which is possible only for $\Delta^{5(6)}$-structure. Although both on mechanistic and thermodynamic grounds the decarboxylation of (V) was expected to give $\Delta^{5(10)}$ compound and in fact this has been reported in other cases[4], in our case the decarboxylated compound was 19-nor-Δ^5-diosgenin-3-acetate. The reason for this anomalous result is under investigation. The 19-nor compound (VI) on acetolysis, oxidation and treatment with alkali[5] gave 19-nor-$\Delta^{5,16}$ – pregnadiene-3-acetate (VII) in 65% yield , m.p.176°, (MeOH), ν_{max}^{nujol} 1730,1710,1240 cm^{-1}. The catalytic hydrogenation of (VII) using Raney Nickel in ethyl acetate afforded 19-nor-Δ^5 -pregnene-3-acetate(VIII) in quantitative yield; m.p.144°, (MeOH-THF), ν_{max}^{nujol} 1725, 1710,1250 cm^{-1}. The compound (VIII) was hydrolysed in alcohol containing 3% concentrated sulphuric acid to 19-nor-Δ^5 -pregnene-3β-ol (IX); m.p.174°, (EtOH). The 3-hydroxy compound (IX) when subjected to the Oppenauer

oxidation gave 19-norprogesterone (X) in 80% yield; m.p.142°(lit.m.p.142-144°)[6], (MeOH), ν_{max}^{nujol} 1706, 1674 cm^{-1} .

The 19-hydroxydiosgenin-3-acetate(IVa) was hydrolysed in alcohol containing 3% conc. sulphuric acid to give corresponding diol (IVb), m.p.186°, (MeOH-CH_2Cl_2), ν_{max}^{nujol} 3400, 3350 cm^{-1}. The diol (IVb), when subjected to Oppenauer oxidation gave 19-hydroxy-Δ^4-tigogenin-3-one (XIa), m.p.194°, (MeOH), ν_{max}^{nujol} 3500, 1650 cm^{-1}.



XI



XII

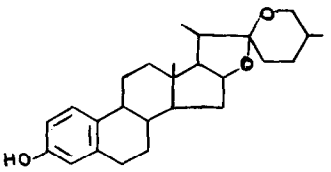
a: R = CH_2OH

b: R = COOH

c: R = H

d: R = OAc

e: R = CH_3



XIII

The oxidation of (XIa) by Jone's Reagent in acetone gave 19-carboxy-Δ^4-tigogenin-3-one (XIb), which on treatment with 5% aqueous potassium hydroxide solution was subsequently converted to 19-nor-Δ^4-tigogenin-3-one (XIc); m.p. 194°, (MeOH), ν_{max}^{nujol} 1650 cm^{-1}. On refluxing (XIa), in benzene with lead tetra-acetate[7,8], 10-acetoxy-Δ^4-tigogenin-3-one (XId), was obtained in 78% yield; m.p. 176°, (EtOH), λ_{max}^{EtOH} at 242 mμ (ϵ=15,000). This on treatment with p-toluenesulphonic acid in benzene gave the required 19-nor-$\Delta^{1,3,5(10)}$-tigogenin-3-ol(XIII)in 50% yield; m.p. 245°, (ether), (lit. m.p.245°)[8], λ_{max}^{EtOH} at 280 mμ (ϵ=2512).

Alternatively, (XIII) was synthesised as follows; Δ^4-tigogenin-3-one (XIe) was converted into $\Delta^{1,4}$-tigogenin-3-one (XII); m.p.194°,[10] (acetone). The dienone on treatment with biphenyl lithium in tetrahydrofuran[11] gave the required (XIII) in 30% yield m.p.245°, (ether), which was identical with the previously obtained product. Since this compound has already been converted into estrone by degradation of spiroketal rings[2,9], this process constitutes an alternative method for the synthesis of estrone.

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