Tetrahedron Letters No.50, pp. 4603-4607, 1965. Pergamon Press Ltd.
Printed in Great Britain.

STEROIDS XXV*

DISPROPORTIONATION OF 19-NOR-ANDROSTANE-DERIVATIVES

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(Received 25 October 1965)

The formylation of estra-4-ene-17β-ol-3-one(I)(1) in benzene with three equivalents of sodium methoxide as the condensing agent resulted in the formation of 2-hydroxymethylene-estra-4-ene-17β-ol-3-one(II), which was isolated as a pure crystalline product(2) in 50% yield, m.p. 178-180°, $[\alpha]_D = -43°$ ($CHCl_3$), λ_{max} 248,303 mμ (lg ε =4,06; 3,72).

This product, by reaction with hydroxylamine hydrochloride(3), gave a crystalline [2,3-d]-isoxazole-estra-4-ene-17β-ol(IIIa), m.p. 184-185°, $[\alpha]_D = -22°$ ($CHCl_3$), λ_{max} 285 mμ (lg ε =4,01)** from which, by acetylation, its 17-acetate(IIIb), m.p. 140-141°, $[\alpha]_D = -33°$ ($CHCl_3$), λ_{max} 285 mμ (lg ε = 4,00) was obtained.

The [2,3-d]-isoxazole (IIIa) in dioxane solution at 20°C was treated for five minutes with a methanol solution of sodium methoxide; the precipitated sodium salt of the cyano-ketone was filtered, dissolved in water and the resulting clear solution was acidified to produce the pure

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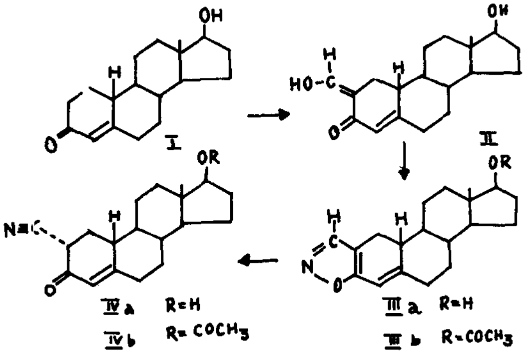
* For Steroidi XXIV, see Gazzetta Chimica Italiana, in press.

** U.V. spectra were determined in ethanolic solutions.

2α-cyano-estra-4-ene-17β-ol-3-one(IVa), m.p. 163-165°, $[\alpha]_D$= +104° ($CHCl_3$), λ_{max} 241 mμ (lg ε =4,20).



The above structures were all confirmed by N.M.R.spectra(*).

In addition to this normal reaction sequence, our aim was to investigate the mother liquors, derived from the preparation of the hydroxymethylene(II) and for this purpose we treated them with hydroxylamine hydrochloride. The crude product obtained was then reacted in dioxane with a solution of sodium methoxide and the precipitated sodium salt, treated as shown in the preparation of IVa, afforded an oily residue, which, after chromatography on acid alumina, allowed to isolate, besides IVa (m.p. 160-162°), three other cyano derivatives:

a) 2α-cyano-5α-estrane-17β-ol-3-one(V)(4), m.p. 238-240°, further characterized through its acetylation product: 2-cyano-5α-estra-2-ene-3,17β-diol-3,17-diacetate, m.p. 181-182° (VIII)(5);

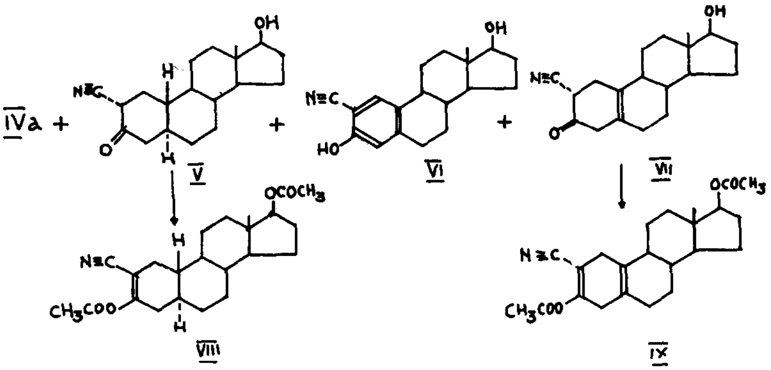
b) 2-cyano-estra-1,3,5(10)-triene-3,17β-diol (VI), m.p.336-338°, $[\alpha]_D$= +41° (pyridine), λ_{max} 236;305 mμ (lg ε =4,04; 3,57);

(*) - A more detailed report on N.M.R. spectra will be soon published elsewhere.

c) 2α-cyano-estra-5(10)-ene-17β-ol-3-one(VII), m.p. 253-255°, $[\alpha]_D$= +99° (pyridine),λ_{max}240 mμ (lg ε = 3,77).

Starting from VII, its diacetate (IX) was prepared, showing m.p. 177-179°, $[\alpha]_D$= +72° ($CHCl_3$).

The three cyano-derivatives were also found in small amounts during the purification of IVa, which had been obtained from the pure IIIa.



VII was also obtained, in good yield, by two other independent routes:

a) by the alkaline cleavage of an ethanolic solution of the pure crystalline IIIa with sodium ethoxide, under reflux;

b) by rearrangement during the saponification of 2α-cyano-estra-4-ene-17β-ol-3-one-17-acetate (IVb)(5) with a boiling solution of potassium hydroxide in methanol-water.

The structures of V, VI,VII were all confirmed by N.M.R. spectra.

The formation of VII from IIIa and IVb is to be closely connected with the formation, widely demonstrated by Wiedhaup et al.(6) of 2-hydroxymethylene-decal-9(10)-ene-2-one through formylation of decal(10)-ene-2-one, in toluene in the presence of sodium methoxide.

The formation of V and VI, starting from a certainly Δ^4-3-keto compound (N.M.R. spectra) can only be rationalized through the following disproportionation:

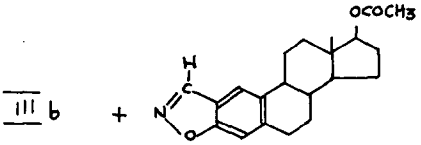
$$2\ \Delta^{4}\text{-3-keto} \longrightarrow 5\alpha\text{-3-keto} + \Delta^{1,3,5(10)}\text{-triene-3-ol}$$

which explains the results described in the mentioned paper (6).

Finally, the uncrystallizable mother liquors of IIIa (18%), after acetylation with acetic anhydride-pyridine at room temperature, gave an oily residue, which was chromatographed on acid alumina and the first hexane elution allowed to isolate an apparently pure product, m.p. 138-140°, depressing into mixture with IIIb.

This product could not correspond, anyway, to [2,3-d]-isoxazole-5α-estrane-17β-ol-17-acetate, m.p. 174-176°, $[\alpha]_D = +92°$ ($CHCl_3$), λ_{max} 224 mμ (lg ε =3,70), prepared by acetylation of the 17β-hydroxy-derivative formerly synthesized by us(4); after N.M.R. investigations, this product showed to be constituted by about 35% of IIIb and by 65% of [2,3-d]-isoxazole-estra-1,3,5(10)-triene-17β-ol-17-acetate (X), m.p. 145-147°, prepared by us (*) also separately.

(*) - The preparation of X will be the subject of a future communication.



Also this aromatization to a benzoisoxazole might be related to a case of disproportionation.

Acknowledgments - We are deeply grateful to Drs.G.G.Gallo and A.Vigevani of Lepetit S.p.A. - Milano, for the execution of N.M.R. spectra and for their discussing the experimental data.

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