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AROMATIZATION REACTIONS OF SOME 19-NOR-ANDROSTANE DERIVATIVES

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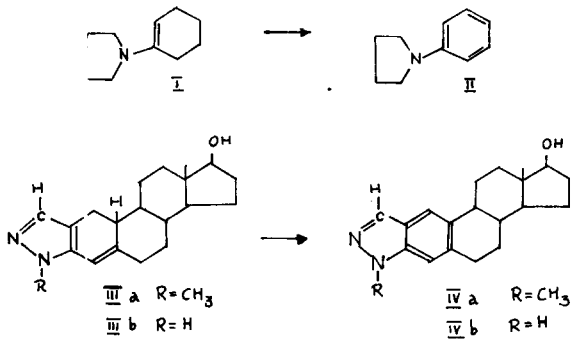
Recently, G.Bianchetti(2), refluxing cyclohexanone enamines in dioxane, noted the disproportionation of the same to N-cycloalkyl-anilines and N-cycloalkyl-cyclohexylamines. In addition, when the reaction was conducted in the presence of Pd/C and hydrogen acceptors (such as ethyl cinammate or stilbene) he obtained quantitative aromatization of cyclohexanone enamines (I for instance) and in the meantime quantitative formation of ethyl phenylpropionate or 1,2-diphenyl-ethane.

Some [2,3-d]-pyrazoles of Δ^4-19-nor-androstene being synthesized by us, we considered the heterocyclic nitrogen in position 3, structurally similar to the enaminic nitrogen of Bianchetti's pirrolydyl-cyclohexanone(I)(2) and thus we assumed that the above mentioned compound might undergo aromatization of the steroidal A-ring to estratriene through a similar mechanism.



Accordingly, we allowed to react [2,3-d]-1'-methyl-pyrazole-estra-4-ene-17β-ol (IIIa)*, m.p. 209-211°, $[\alpha]_D$= +12°($CHCl_3$), λ_{max}276 mμ ** (lg ε= 4.00) under reflux in dioxane with two moles of ethyl maleate and 10% Pd/C as hydrogen transfer. After 24 hours we isolated from the reaction mixture the [2,3-d]-1'-methyl-pyrazole-estra-1,3,5(10)-triene-17β-ol(IVa), m.p. 191-193°, $[\alpha]_D$= +8°($CHCl_3$); λ_{max}257, 263, 272, 293, 299, 304, 312 mμ (lg ε = 3.81; 3.85; 3.81; 3.73; 4.74; 3.72; 3.64); I.R. 1639 1504 and 883 cm^{-1} (aromatic absorption).

Similarly, starting from IIIb, m.p. 242-245°, $[\alpha]_D$= +27° (pyridine); λ_{max}260 mμ (lg ε = 3.95) we obtained IVb, m.p. 170-173°, λ_{max}260, 266, 289, 305 mμ (lg ε = 3.98; 3.96; 3.86; 3.69); I.R. 1639, 1504 and 883 cm^{-1} (aromatic absorption). The U.V. spectra of the aromatization products IVa,b are in good agreement with those of the simpler benzopyrazoles (4).

The reaction, which was expected to be only limited to enamines, proved much more employable and not closely connected with the presence of an enaminic or enaminic-like structure.

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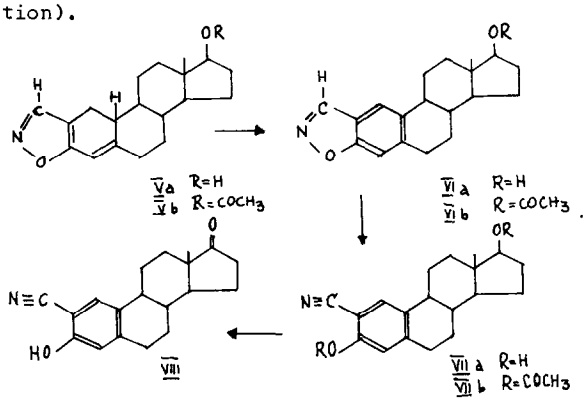
* - III and IIIb were prepared according to the usual procedure (3), starting from 2-hydroxymethylene-estra-4-ene-17β-ol-3-one (1).

**- All I.R. spectra were executed in nujol suspension, while the U.V. spectra were determined in ethanolic solution.

Under similar experimental conditions (ethyl maleate,10% Pd/C in dioxane under reflux), but starting from [2,3-d]-isoxazole (Va)(1), through the probable intermediate benzoisoxazole (VIa) we obtained 2-cyano-estra-1,3,5(10)-triene-3,17β-diol (VIIa)(1), m.p. 336-338°, $[\alpha]_D$= +41° (pyridine), λ_{max}236,305 mμ (lg ε =4.04; 3.57); $\lambda_{max}^{EtOH-NaOH}$ 223, 246, 337 mμ (lg ε = 4.39; 4.00; 3.59); I.R. 3425, 3125 cm^{-1} (-OH); 2227 cm^{-1} (-C≡N); 1616, 1506, 894, 873 cm^{-1} (aromàtic absorption), which was acetylated to give VIIb, m.p. 149-150°, $[\alpha]_D$= +45° (CHCl); λ_{max}236, 278, 288 mμ (lg ε = 4.05; 3.27; 3.25). I.R. 2230 cm^{-1}(-C≡N); 1783 cm^{-1}(C-3 acetate); 1739 cm^{-1}(C-17 acetate); 1610, 1575, 1500, 897 cm^{-1}(aromatic absorption).



Oxidation of VIIa, conducted with Jones' reagent(5) afforded 2-cyano-estra-1,3,5(10)-triene-3-ol-17-one (VIII), m.p. 264-266°, λ_{max}236,304 mμ (lg ε = 4.04; 3.60); I.R. 3322 cm^{-1}(OH-phenolic); 2232 cm^{-1} (-C≡N); 1730 cm^{-1} (17-ketone); 1616, 1592, 1511, 883 cm^{-1} (aromatic absorption).

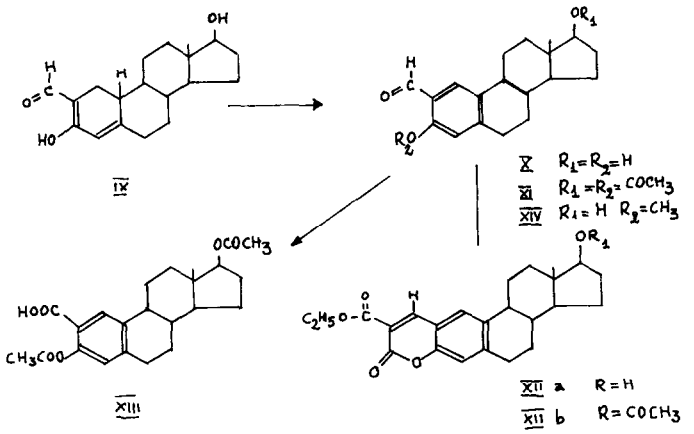
The facility with which these aromatization reactions occurred, prompted us to verify the behaviour of some Δ^4-estrene derivatives in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, which is widely employed in steroid chemistry for dehydrogenation.

Working in dioxane under conditions similar to those employed by J.A.Edwards et al.(6) for the preparation of 2-formyl-3-keto-steroids, or in benzene under reflux starting from 2-hydroxymethylene-estra-4-ene-17β-ol-3-one (IX)(4) we obtained in quantitative yields 2-formyl-estra-1,3,5(10)-triene-3,17β-diol(X), m.p. 232-234°, $[\alpha]_D$= +88° (dioxane); λ_{max} 226.5, 267.5, 337.5 mμ (lg ε = 4.19; 4.16; 3.54); $\lambda^{EtOH-NaOH}_{max}$ 239, 275, 289 mμ (lg ε =4.25; 4.02; 3.77); I.R. 3390, 3125 cm^{-1} (-OH); 1664 cm^{-1}, 1618 cm^{-1} (formyl chelated form); 877 cm^{-1} (aromatic absorption).

Its diacetate (XI) shows m.p. 151-152°, $[\alpha]_D$= +53°($CHCl_3$), λ_{max} 261 and 295.5 mμ (lg ε = 4.05; 3.36); I.R. no OH; 1783 cm^{-1} (C-3 acetate); 1745 cm^{-1} (C-17 acetate); 1692 cm^{-1} (C-2 formyl), 1610, 1575, 1563, 1550, 892 cm^{-1}(aromatic absorption).

The 2-formylestradiol provides the typical reactions of aromatic o-hydroxy-aldehydes: yellow colour, when treated with alkaline hydroxide and violet colour, when reacted with $FeCl_3$. In the presence of piperidine X reacts with ethyl malonate to give estra-1,3,5(10)-triene-17β-ol-[2,3-d]-2'-carboethoxy-2',3'-dihydropyrane-2'-one (XIIa), m.p. 188-190°; $[\alpha]_D$= +83° ($CHCl_3$), λ_{max} 307,344 mμ (lg ε = 4.16; 3.95), which was acetylated to give XIIb, m.p.204.5-206°; $[\alpha]_D$= +27° ($CHCl_3$); λ_{max} 306,345 mμ (lg ε = 4.21;4.02).

Upon oxidation of XI with Jones reagent we obtained estra-1,3,5(10)-triene-3,17β-diol-3,17-diacetate-2-carboxilic acid (XIII), m.p. 183-185°; $[\alpha]_D$= +54°; λ_{max} 237 mμ (lg ε = 3.88).



By reaction of X with dimethyl sulfate we obtained 2-formyl-estra-1,3,5(10)-triene-3-methoxy-17β-ol (XIV), m.p. 190-192°, $[\alpha]_D$= +105° ($CHCl_3$).

By reaction of Va or Vb with DDQ in dioxane solution at room temperature or in benzene solution under reflux, we obtained [2,3-d]-isoxazole-estra-1,3,5(10)-triene-17β-ol (VIa), m.p. 178-180°, λ_{max} 246,288 mμ (lg ε = 3.72; 3.85) and/or its acetate (VIb), m.p. 145-147°; λ_{max} 246, 253, 288 mμ (lg ε = 3.74; 3.72; 4.00).

Successively, heating VIa and VIb under reflux with a 1% solution of potassium hydroxide in methanol-water, we obtained VIIa (1).

The benzoisoxazole VIa, obtained as above described, was heated under reflux for 48 hours in dioxane solution and it appeared evident, that, under such conditions, the cleavage of the heterocyclic ring occurred, to give 2-cyano-estradiol (VIIa); this behaviour rationalizes our inability to isolate VIa in the course of the aromatization of Va with ethyl maleate in the presence of Pd/C, working in boiling dioxane.

Further aromatization experiments of 19-nor-steroids with DDQ and interpretation of the reaction mechanism will be soon reported elsewhere.

REFERENCES

1. P. de Ruggieri, C.Gandolfi and U.Guzzi, Steroids XXV, Tetrahedron Letters, in press.

2. G.Bianchetti, D.Pocar and A.Marchesini, Rend.Ist.Lomb. Sci.Lett., Milano, A 99, 223(1965).

3. R.O.Clinton, A.J.Manson, F.W.Stonner, H.C.Neumann, R.G.Christiansen, R.L.Clarke, J.H.Acherman, D.F.Page, J.W.Dean, W.B.Dickinson and C.Carabateas, J.Amer.Chem. Soc., 83, 1478(1961).

4. A.Bellotti and G.Pappalardo, Boll.Sci.fac.Chim.Ind. (Bologna), 16, 29(1958).

5. J.K.Bowden, I.M.Heilbron, E.R.H.Jones and B.C.L.Weedon, J.Chem.Soc., 39(1946).

6. J.A.Edwards, M.C.Calzada, L.C.Ibanez, M.E.Cabezas Rivera, R.Marquiza, L.Cardona, J.C.Orr and A.Bowers, J.Org. Chem., 29, 3481 (1965).