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ON THE ACTION OF THE VILSMEIER-HAACK REAGENT ON STEROIDAL KETONES AND DERIVATIVES

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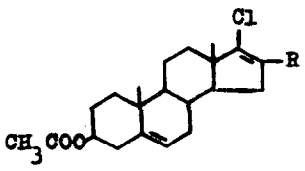
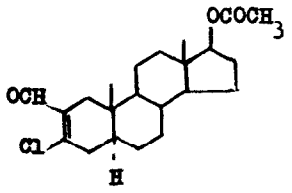
Although the action of the Vilsmeier-Haack reagent on aromatic (1) and aliphatic (2) compounds has been extensively studied, only a few applications of this reagent in the steroid field have been published (3,4,5). We report now some transformations performed by this reagent on steroid derivatives such as ketones, ketals and enamines.

Treatment of dehydroisoandrosterone acetate in trichloroethylene with the dimethylformamide-phosphorus oxychloride (DMF - $POCl_3$) reagent at 70° for three hours followed by decomposition of the resulting complex with aqueous CH_3COONa, extraction and chromatographic purification, gave 17-chloro-$\Delta^{5,16}$-androstadien-3β-ol-acetate (I)(+) (m.p. 174-5°, [α] -52°) and 16-formyl-17-chloro-$\Delta^{5,16}$-androstadien-3β-ol-acetate (II) (m.p. 178-9°, [α] -113°, λ_{max} 261 mμ, ε 12,100); this compound was converted by refluxing with C_2H_5ONa in anhydrous ethanol into the known (6) 16-hydroxymethylen-dehydroisoandrosterone.

(+) Correct analytical values have been obtained for all the compounds described; rotations have been determined in $CHCl_3$ at 20-22° at the sodium D line; U.V. spectra have been recorded in 95% ethanol. Melting points are taken on a Fisher-Johns block and are uncorrected.

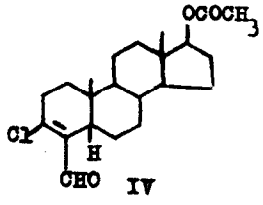


I; R=H
II; R=CHO

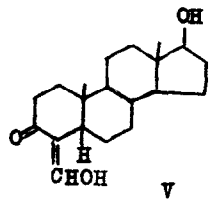


III

When treated in the same conditions, 5α-androstan-17β-ol-3-one-acetate was transformed into 2-formyl-3-chloro-Δ^2-5α-androsten-17β-ol-acetate (III) (m.p. 215-7°, [α] +103°, λ_{max} 260 mμ, ε 10,400) which by the action of C_2H_5ONa in anhydrous ethanol gave the known (7) 2-hydroxymethylen-5α-androstan-17β-ol-3-one. In the same manner 5β-androstan-17β-ol-3-one acetate furnished 3-chloro-4-formyl-Δ^3-5β-androsten-17β-ol-acetate (IV) (m.p. 146-8°, [α] +107°, λ_{max} 255 mμ, ε 6,500 which by alkaline hydrolysis was transformed into the unknown 4-hydroxymethylen-5β-androstan-17β-ol-3-one (V) (m.p. 176-80°, [α] +105°, λ_{max} 280 mμ, ε 11,600). When subjected to the action of the DMF-$POCl_3$ reagent, testosterone propionate gave 3-chloro-$\Delta^{3,5}$-androstadien-17β-ol-propionate (m.p. 169-71°, [α] -157°, λ_{max} 240 mμ (sh), ε 18,700, 244 mμ, ε 23,000 and 252 mμ (sh), ε 16,700)

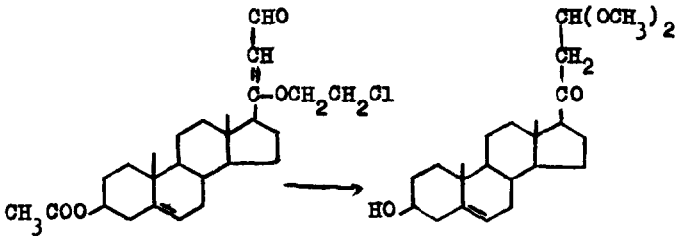


IV



V

20-(2'-Chloroethoxy)-21-formyl-$\Delta^{5,20}$-pregnadien-3β-ol-acetate (VI) (m.p. 145-8°, λ_{max} 265 mμ, ε 20,000) was prepared from pregnenolone acetate-ethyleneketal by reaction with DMF-$POCl_3$ reagent in trichloroethylene at 60° for 3 hours. By hydrolysis with methanolic hydrochloric acid VI furnished 21-formyl-pregnenolone-dimethylacetal (VII) (m.p. 121-2°). In

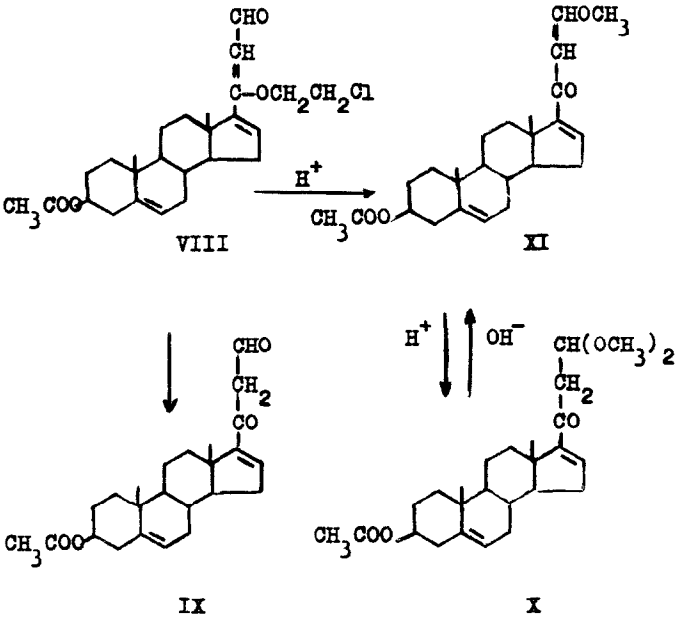


VI VII

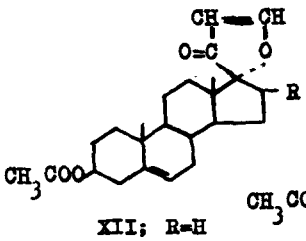
the same manner 16-dehydropregnenolone-acetate-ethyleneketal gave 20-(2'-chloroethoxy)-21-formyl-$\Delta^{5,16,20}$-pregnatrien-3β-ol-acetate (VIII) (m.p. 129-35°, λ_{max} 270 mμ, ε 14,100). This compound when treated with H_2SO_4 in dioxane at 50° for one hour gave the 21-formyl derivative IX (m.p. 228-31°, λ_{max} 271 mμ, ε 10,200, λ_{max}^{KOH} 298 mμ, λ_{max}^{KBr} 2700-2300, 1730, 1640, 1597, 1240 cm^{-1}) and with H_2SO_4 in CH_3OH at 50° for 20' the corresponding dimethylacetal X (m.p. 88-96°, λ_{max} 243 mμ, ε 8,900). When this hydrolysis was interrupted after five minutes we obtained 21-methoxymethylen-$\Delta^{5,16,21}$-pregnatrien-3β-ol-20-one-acetate (XI) (+) (m.p. 208-10°, λ_{max} 279 mμ, ε 14,100) which was transformed into the dimethylacetal X when subjected again to the acid treatment. The compound XI could also be obtained

(+) The alternative structure 20-methoxy-21-formyl-$\Delta^{5,16,20}$-pregnatrien-3β-ol-acetate was ruled out by the absence in the N.M.R. spectrum of an aldehydic proton.

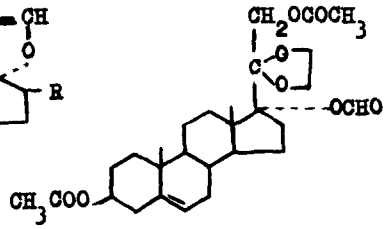
by alkali - catalyzed elimination of CH_3OH from the dimethyl-acetal X.



We have then examined the transformations of 17α -substituted-20 ketals when subjected to the Vilsmeier-Haack reagent. 17α -Hydroxy-pregnenolone-20-ethyleneketal-3-acetate gave the dihydrospirofuranone XII (m.p. 228–30°, λ_{max} 262 mμ , ε 10,300, λ^{KBr}_{max} 3160, 3080, 1730, 1685, 1566, 1240, 1180 cm^{-1}); this compound was converted into 17α -hydroxy-pregnenolone by refluxing with $Ba(OH)_2$ in aqueous ethanol thus demonstrating its structure. In the same manner 16 α ,17 α -epoxy-pregnenolone-ethylene-ketal-3-acetate gave the 16 β -chloro-dihydrospirofuranone XIII (m.p. 274–7°, λ_{max} 262 mμ , ε 8,100, λ^{KBr}_{max} 3150, 3070, 1730, 1690, 1570,1240,1180 cm -1). However 17α -hydroxy-20-ketals substituted by an acetoxy group at C 21 are only esterified in position



XII; R=H
XIII; R=Cl



XIV

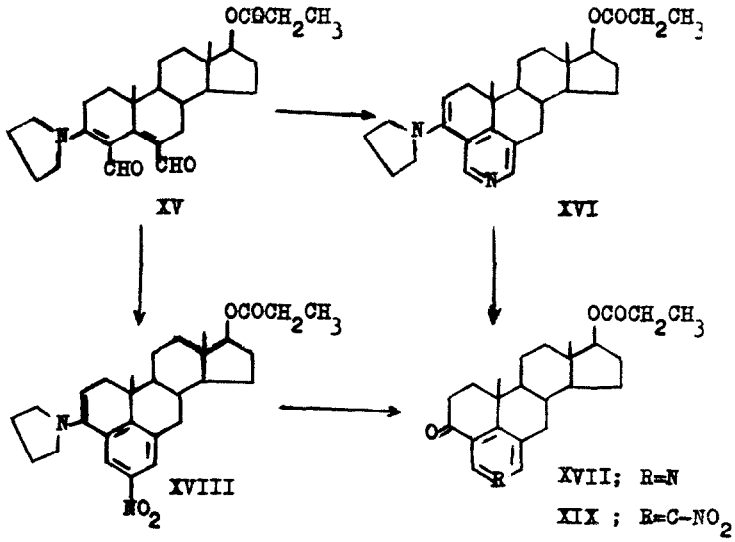
17. Δ^5-pregnen-3β ,17α ,21-triol-20-one-ethyleneketal-3,21-diacetate furnished although in low yield the corresponding 17-formate XIV (m.p. 182-5°) hydrolyzed by alkali to the known (8) Δ^5-pregnen-3 β ,17 α ,21-triol-20-one-ethyleneketal.

Two products were obtained when dehydroisoandrosterone acetate-ethyleneketal was treated with the DMF-$POCl_3$ reagent in trichloroethylene at 60° for three hours: 16-formyl-17-(2'-chloroethoxy)- $\Delta^{5,16}$-androstadien-3 β -ol-acetate (m.p. 138-43°, [α] -79°, λ_{max} 273 mμ , ε 15,200) transformed by alkaline hydrolysis into the known (6) 16-hydroxymethylen-dehydroisoandrosterone and a compound $C_{24}H_{33}ClO_5$ (found C 65,74, H 7,55, m.p. 104-5°,[α] -63°, no U.V. absorption, no reaction with $FeCl_3$, N.M.R. 0,47(1H), two triplets centered at 5,71 and 6,34(4H), J=6 c.p.s., λ^{KBr}_{max} 1745 (broad), 1245, 1110 cm^{-1}) whose structure will be reported at a later date.

3-Pyrrolydil- $\Delta^{3,5}$-androstadien-17β -ol-propionate was formylated by DMF-$POCl_3$ reagent both at C_4 and C_6 giving 3-pyrrolydil-4,6-diformyl- $\Delta^{3,5}$-androstadien-17β -ol-propionate (XV) (m.p. 157-8° and 202-5°,[α] -9°, λ_{max} 230 mμ , ε 16,500, 315 mμ (sh), 343 mμ, ε 10,100, 392 mμ , ε 12,000) which by the action of gaseous NH_3 in CH_3OH at room temperature gave the pyridine derivative XVI (m.p. 192-4°, λ_{max} 250 mμ , ε 8,400 and 295 mμ , ε 3,000). Acetic acid-sodium acetate hydrolysis of XVI in a-

queous acetone gave the corresponding 3-keto derivative XVII (m.p. 163-5°, $[\alpha]$ -7°, λ_{max} 218 mμ, ε 14,000, 249 mμ, ε 7,200, 285 mμ, ε 2,800).

When XV was cyclized with CH_3NO_2 in anhydrous ethanol at room temperature in the presence of C_2H_5ONa, the nitrobenzene derivative XVIII (m.p. 208-12°, λ_{max} 283 mμ, ε 30,500) was obtained, which could be hydrolyzed with aqueous hydrochloric acid to the corresponding 3-keto compound XIX (m.p. 156-61°, $[\alpha]$ +14°, λ_{max} 249 mμ, ε 22,200).



The same sequence of reactions has been carried out starting from 3-pyrrolydil- $\Delta^{3,5}$-pregnadien-17α-ol-20-one-acetate.

Experimental details as well as other transformations on the products described and on other functional groups will be reported in the full papers which will be published in the Gazzetta Chimica Italiana.

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