The Reaction of 3-Oxo-Δ^4-steroids with Isocyanuric Chloride

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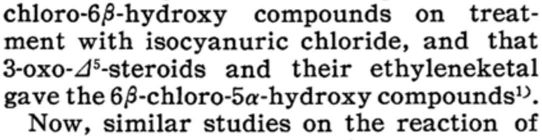
It has been reported that 3β-substituted-Δ^5-steroids gave the corresponding 5α-chloro-6β-hydroxy compounds on treatment with isocyanuric chloride, and that 3-oxo-Δ^5-steroids and their ethyleneketal gave the 6β-chloro-5α-hydroxy compounds[1].

Now, similar studies on the reaction of 3-oxo-Δ^4-steroids (I) with isocyanuric chloride are reported herewith.

Treating the model compound progesterone with isocyanuric chloride in acetone-acetic acid (or perchloric acid) yielded a chloro compound, having an ultraviolet absorption typical for the 4-substituent-4-en-3-one system ($\lambda_{\max}^{\mathrm{EtOH}}$ 256 mμ, log ε 4.12)[2-4]. The identity of the product with 4-chloroprogesterone was established by its melting point and the infrared spectrum. Therefore, it appears that 4-chloroprogesterone (Ic) is formed through an intermediate 4ξ-chloro-5ξ-hydroxy compound (II):



(a) $R_1=OAc$, $R_2=H$, $R_3=CH_3$, $R_4=H_2$
(b) $R_1=OCOC_2H_5$, $R_2=H$, $R_3=CH_3$, $R_4=H_2$
(c) $R_1=COCH_3$, $R_2=H$, $R_3=CH_3$, $R_4=H_2$
(d) $R_1=COCH_3$, $R_2=OH$, $R_3=CH_3$, $R_4=H_2$
(e) $R_1=COCH_3$, $R_2=OAc$, $R_3=CH_3$, $R_4=H_2$
(f) $R_1=OH$, $R_2=CH_3$, $R_3=H$, $R_4=H_2$
(g) $R_1=COCH_2OAc$, $R_2=OH$, $R_3=CH_3$, $R_4=O$

Extension of this chlorination method to 3-oxo-Δ^4-steroid hormones, led to 4-chloro-derivatives, several of which were characterized by their absorption maximum.

Since this work was completed, Oliveto et al. reported[5] the preparation of 4-chlorocortisone acetate by *N*-chlorosuccinimide and perchloric acid.

4-Chlorotestosterone acetate (IIIa) and 4-chlorotestosterone propionate (IIIb) exhibited greater anabolic and smaller androgenic effect in comparison to administeral testosterone propionate, and showed no inhibitory effects on the gonadotropic secretion upon intraspleenic ovarian transplantation[6].

4-Chloroprogesterone (IIIc) and 4-chloro-17α-acetoxyprogesterone (IIIe) showed no progestational activity.

Experimental*

5α-Chloro-3β-acetoxy-pregnan-6β-ol. — To a mixture consisting of 1.0 g. of pregnenolone acetate, 0.5 g. of isocyanuric chloride and 30 ml. of acetone were added ten drops of 30% acetic acid. The whole was refluxed for 5 min. After cooling to room temperature, the mixture was poured with stirring into 10% aqueous sodium carbonate, and then extracted with ether. The extract was washed with water and dried over magnesium sulfate, after removal of the solvent, the residue was recrystallized from acetone-water to yield 0.6 g. of needles, m. p. 195°C (decomp.), $[\alpha]_D^{17}$ +36 (c. 1.2).

Anal. Found: C, 67.26; H, 8.65; Cl, 8.42. Calcd. for $C_{23}H_{35}O_4Cl$: C, 67.37; H, 8.60; Cl, 8.65%.

Preparation of 4-Chloro-3-oxo-Δ^4-steroids. — A solution of 0.5 g. of 3-oxo-Δ^4-steroid and 0.3 g. of isocyanuric chloride in 30 ml. of acetone was refluxed for 1 hr. with 3 ml. of acetic acid or 10% perchloric acid. The reaction mixture was then poured into 10% sodium carbonate solution and extracted with ether. Washing of the extract with water, drying over magnesium sulfate, and evaporation of the solvent led to a residue which was purified by recrystallization or chromatography on florisil.

The following 4-chloro-3-oxo-Δ^4-steroids were prepared by this method:

4-Chlorotestosterone acetate (IIIa), needles, m. p. 228°C (from acetone), $\lambda_{\max}^{\mathrm{EtOH}}$ 255 mμ (log ε 4.12);

4-Chlorotestosterone propionate (IIIb), needles, m. p. 164°C (from methanol), $\lambda_{\max}^{\mathrm{EtOH}}$ 256 mμ (log ε 4.12);

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[1] F. Mukawa, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*) **78**, 452 (1957).

[2] B. Camerino, B. Patelli and A. Vercellone, *J. Am. Chem. Soc.*, **78**, 3540 (1956).

[3] D. N. Kirk, D. K. Patel and V. Petrow, *J. Chem. Soc.*, **1956**, 1184.

[4] J. Ringold, B. Batres, O. Mancera and G. Rosenkranz, *J. Org. Chem.*, **21**, 1432 (1956).

[5] E. P. Oliveto, C. Gerold and E. B. Hershberg, *J. Am. Chem. Soc.*, **79**, 3596 (1957).

[6] The parabiotic rat technique was reported: V. Clini, G. Baldratti and G. Sala, *Experientia*, **14**, 94 (1958).

* All melting points are uncorrected. Optical rotation was measured in chloroform solution.

4-Chloroprogesterone (IIIc), needles, m. p. 220°C (from acetone), $\lambda_{\max}^{\mathrm{EtOH}}$ 256 mμ (log ε 4.20);

4-Chloro-17α-hydroxy-progesterone (IIId), needles, m. p. 218°C (from methylene chloride-methanol), $\lambda_{\max}^{\mathrm{EtOH}}$ 256 mμ (log ε 4.11);

Anal. Found: C, 68.90; H, 8.10. Calcd. for $C_{21}H_{29}O_3Cl$: C, 69.29; H, 8.03%.

4-Chloro-17α-acetoxyprogesterone (IIIe), needles, m. p. 194°C (from acetone after being separated by chromatography from benzene on florisil), $\lambda_{\max}^{\mathrm{EtOH}}$ 256 mμ (log ε 4.20);

Anal. Found: C, 67.85; H, 7.53. Calcd. for $C_{23}H_{31}O_4Cl$: C, 68.04; H, 7.70%.

4-Chloro-17α-methyl-19-nortestosterone (IIIf), needles, m. p. 148°C (from ether-hexane after being separated by chromatography from benzene on florisil), $\lambda_{\max}^{\mathrm{EtOH}}$ 256 mμ (log ε 4.20);

Anal. Found: C, 70.93; H, 8.90. Calcd. for $C_{19}H_{27}O_2Cl$: C, 70.87; H, 8.45%.

4-Chlorocortisone acetate (IIIg), needles, m. p. 234°C (from acetone-*n*-hexane), $\lambda_{\max}^{\mathrm{EtOH}}$ 254 mμ (log ε 4.11).

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