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The Hemiacetal of Chloral with Testosterone and Derivatives thereof

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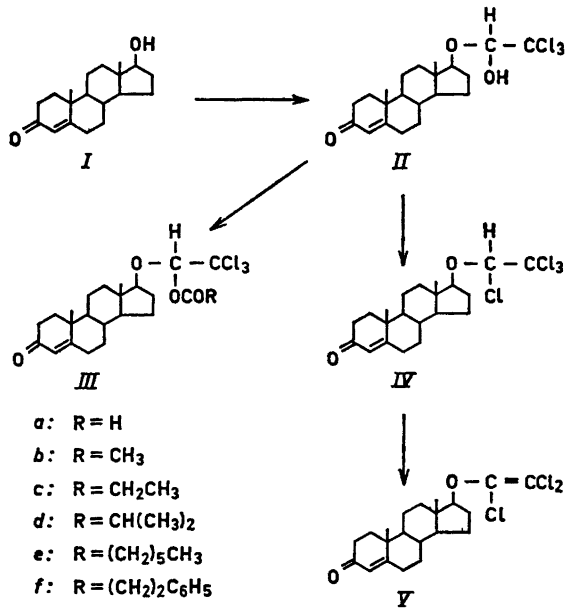
Treatment of testosterone with chloral yields the 1-hydroxy-2,2,2-trichloroethyl ether of testosterone. With acid anhydrides or acyl chlorides the corresponding esters are obtained. The hydroxyether reacts with PCl_5 to the 1,2,2,2-tetrachloroethyl ether, which together with KOH in ethanol leads to the 1,2,2-trichlorovinyl ether.

For the purpose of preparing 6-derivatives of testosterone (I) experiments were made with the 3-ethylene ketal of testosterone and chloral in the presence of peroxides to obtain a free-radical reaction. It was possible to isolate a substance of the desired composition $C_{23}H_{33}Cl_3O_4$. The ultraviolet spectrum showed no maxima, but hydrolysis in aqueous acetone with sulphuric acid transformed the substance into testosterone.

The formation of testosterone by hydrolysis indicated that no reaction between the Δ^5-double bond and chloral had taken place. According to the analysis it seemed possible that the free OH-group in the 17-position had reacted with chloral and yielded a hemiacetal. Therefore testosterone was treated with chloral at room temperature without catalysts. This yielded a compound with an elementary analysis in agreement with the hemiacetal of chloral with testosterone (II). This substance, 17-(1-hydroxy-2,2,2-trichloroethoxy)-androst-4-ene-3-one, showed in the infrared spectrum (in KBr) the normal bands for a Δ^4-3-keto group, a band for a hydroxyl-group, and a very strong band at 1 117 cm^{-1}, which indicated an ether-group. Compared to the infrared spectrum of testosterone the new strong bands at 797 and 832 cm^{-1} must be due to the CCl_3-group.

By reaction of II with acetic anhydride in pyridine the corresponding acetate (IIIb) was formed. In the infrared spectrum of testosterone acetate the ester-carbonyl group shows a band at 1 735 cm^{-1}, in the acetate of the hemiacetal of chloral with testosterone this band was shifted to 1 765 cm^{-1}. The ether band, from the hemiacetal, was shifted to 1 142 cm^{-1}, but the bands for the CCl_3-group were identical. A number of esters are listed in Table 1.



Treatment of II with PCl_5 in chloroform yielded 17-(1,2,2,2-tetrachloroethoxy)-androst-4-ene-3-one (IV) and reflux of IV with KOH in aqueous ethanol yielded 17-(1,2,2-trichloroethenoxy)-androst-4-ene-3-one (V). The two compounds (IV and V) showed in the infrared spectrum normal bands for a Δ^4-3-keto group, and no absorption for a OH-group. The ether band was shifted to 1 150 cm^{-1} for the tetrachloro ether and to 1 165 cm^{-1} for the trichlorovinyl ether. The above-mentioned bands for the CCl_3-group were weak in the tetrachloro ether, but the spectrum showed a new strong band for a C—Cl-group at 700 cm^{-1} whereas in the trichlorovinyl ether the C—Cl frequency is as high as 805 cm^{-1} with a very strong absorption.

Biological properties. Gaunt *et al.*[1] have established that the androgenic activity is greatly reduced by transforming the 17—OH group in testosterone to a methoxy group. The activity of the new ether (II) is in the rat test three to four times that of testosterone propionate whereas the activity of the acetate (IIIb) is only half of that of testosterone propionate, but the acetate shows a markedly protracted action. In aqueous suspension its activity as regards intensity and duration is higher than that of testosterone isobutyrate *. The compounds IV and V showed no androgenic activity.

EXPERIMENTAL

All melting points are uncorrected.

17-(1-Hydroxy-2,2,2-trichloroethoxy)-androst-4-ene-3-one (II). Testosterone (2.9 g) was added to a solution of chloral (1.7 g) in anhydrous benzene (10 ml). By shaking the

* These experiments were carried out in the biological department of Leo Pharmaceutical Products.

Table 1.

Compound	R	Preparation	Recrystallized from	Yield %	M.p. °C	U.V. (ethanol) λ_{max} mμ	U.V. (ethanol) ε	Formula	C % Calc.	C % Found	H % Calc.	H % Found	Cl % Calc.	Cl % Found
The formate IIIa	H		acetone	84	239–41°	241	16 800	$C_{22}H_{29}Cl_3O_4$	56.97	56.98	6.30	6.31	22.93	22.92
The acetate IIIb	CH_3	1	ethyl acetate	88	192–93°	241	16 400	$C_{23}H_{31}Cl_3O_4$	57.81	57.69	6.54	6.61	22.26	22.46
The propionate IIIc	CH_2CH_3	1	methanol	58	151–52°	240	16 800	$C_{24}H_{33}Cl_3O_4$	58.60	58.55	6.76	6.74	21.63	21.59
The isobutyrate IIId	$CH(CH_3)_2$	1	methanol	52	127–28°	242	17 100	$C_{25}H_{35}Cl_3O_4$	59.35	59.41	6.97	7.21	21.03	21.03
The enanthate IIIe	$(CH_2)_5CH_3$	2	96 % ethanol	61	82–83°	241	17 000	$C_{28}H_{41}Cl_3O_4$	61.37	61.21	7.54	7.56	19.41	19.42
The β-phenylpropionate IIIf	$(CH_2)_2C_6H_5$	2	96 % ethanol	72	99–100°	240	16 600	$C_{30}H_{37}Cl_3O_4$	63.44	63.56	6.57	6.62	18.73	18.67

mixture for a few minutes a clear solution was obtained, and after a few more minutes of shaking a solid precipitate was formed. The precipitate was collected on a filter, washed with benzene, and dried at room temp. in order to obtain the hemiacetal (2.5 g), m.p. 194–196°C, raised by crystallization from ethyl acetate to 200–201°C. U.V. λ_{max} 241 mμ in ethanol (ε 16 300). (Found: C 57.62; H 6.70; Cl 24.61. Calc. for $C_{21}H_{29}Cl_3O_3$: C 57.87; H 6.71; Cl 24.41).

The same properties are present if acetic acid is used as solvent. It is also possible to form II with chloral hydrate in chloroform in the presence of benzoyl peroxide.

Esters of the hemiacetal (IIIa, b, c, d, e, and f).

1. *With anhydride.* II (3.0 g) was dissolved in a mixture of the anhydride (10 ml) and pyridine (10 ml). The solution was allowed to stand at room temp. for about 16 h and evaporated *in vacuo*. The residue was crystallized from ethyl acetate, acetone, or methanol to yield the ester.

2. *With acyl chloride.* To a chilled solution of II (2.2 g) in a mixture of dry benzene (10 ml) and pyridine (6 ml), a solution of the acyl chloride (1.3 g) in dry benzene (5 ml) was slowly added while stirred. After standing for about 16 h at + 2°C ether (150 ml) and ethyl acetate (25 ml) were added, and the mixture was washed with 0.5 N H_2SO_4, 0.5 N NaOH and water. The solution was dried with sodium sulphate after which the solvent was removed *in vacuo* and the residue was crystallized from 96 % ethanol in order to yield the ester.

The formate. Formic acid (2.8 ml) was mixed with acetic anhydride (7.5 ml), and the mixture was allowed to stand at room temp. for about 16 h. This solution was added to a solution of II (3.0 g) in pyridine (15 ml), and after standing for 5 h at room temp. the mixture was evaporated to dryness *in vacuo*. The solid residue was triturated with ether, filtered off and dried in order to yield the formate.

17-(1,2,2,2-Tetrachloroethoxy)-androst-4-ene-3-one (IV). To a chilled solution of II (2.0 g) in dry chloroform (50 ml) PCl_5 (1.0 g) was added in small portions under continuous stirring. Having been stirred for about 1 h at + 2°C and for 1 h at room temp. the mixture was poured into a cold NaOH-solution. The chloroform phase was separated from the aqueous phase, washed three times with water, and dried. The solvent was removed *in vacuo*, and the residue was crystallized from methanol to give the tetrachloro ether (1.5 g), m.p. 151–155°C, raised by recrystallization to 156–158°C. U.V. λ_{max} 240 mμ in ethanol (ε = 16 800). (Found: 55.68; H 6.27; Cl 31.00. Calc. for $C_{21}H_{28}Cl_4O_2$: C 55.52; H 6.21; Cl 31.22).

17-(1,2,2-Trichloroethenoxy)-androst-4-ene-3-one (V). IV (2.3 g) in 15 ml of a 5 % solution of KOH in ethanol was refluxed for 20 min. The mixture was then poured into water and the product was extracted with ether (2 × 100 ml). When the extract had been dried the ether was removed *in vacuo* and the residue was crystallized from methanol in order to yield the trichlorovinyl ether (1.6 g), m.p. 120–122°C, raised by recrystallization to 128–130°C. U.V. λ_{max} 240 mμ in ethanol (ε = 19 000). (Found: C 60.48; H 6.56; Cl 25.38. Calc. for $C_{21}H_{27}Cl_3O_2$: C 60.37; H 6.51; Cl 25.46).

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REFERENCE

1. Gaunt, R., Tuthill, C.H., Antonchak, N. and Leathem, J.H. *Endocrinology* **52** (1953) 420.

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