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Preparation and Configuration of 17-Chloro-5α-androstan-3β-ols and Related Compounds

Westphal1) prepared in 1939 17-chloro steroids by the reaction of 17β-hydroxy steroids with phosphorus pentachloride in chloroform, but the configuration of the chlorine atom at C-17 in these compounds has not been determined. The present communication describes a synthesis of two isomeric 17-chloro-5α-androstan-3β-ols and related compounds.

The preceding paper2) it was described that the reaction of 3-oxo-4-en steroids with sulfuryl chloride in pyridine gave 3-oxo-4-chloro-4-en steroids in good yields. 5α-Androstan-3β,17β-diol acetate, when treated with sulfuryl chloride in pyridine in the same manner, gave a 17-chloro-5α-androstan-3β-ol acetate (I), 102~104°, $[\alpha]^{20}_{D}$ +27° (*Anal.* Calcd. for $C_{21}H_{33}O_2Cl$: C, 71.46; H, 9.43. Found : C, 71.43; H, 9.62).

A similar displacement of 17β-hydroxy-5α-androstan-3-one gave the corresponding 17-chloro-5α-androstan-3-one (II), m.p. 180~183°, $[\alpha]^{20}_{D}$ -23° (*Anal.* Calcd. for $C_{19}H_{29}OCl$: C, 73.88; H, 9.46. Found : C, 73.72; H, 9.44), which was also obtained from I by two steps, hydrolysis of I to 17-chloro-5α-androstan-3β-ol (III), m.p. 186~188°, $[\alpha]^{20}_{D}$ −37° and oxidation of III with chromium trioxide.

Testosterone was also converted into the corresponding 17-chloroandrost-4-en-3-one (IV), m.p. 150~153°, $[\alpha]^{20}_{D}$ +32°, UV : λ^{EtOH}_{max} 241 mμ (*Anal.* Calcd. for $C_{19}H_{27}OCl$: C, 74.36; H, 8.87. Found : C, 74.23; H, 8.90.), which seems to be identical with the 17-chloroandrost-4-en-3-one, m.p. 148°, reported by Westphal.1)

In order to examine the nature of the displacement of the hydroxyl group by chlorine with sulfuryl chloride in pyridine, the reactions of androsterone and of isoandrosterone were carried out. When treated with this reagent, androsterone gave 3β-chloro-5α-androstan-17-one while isoandrosterone afforded 3α-chloro-5α-androstan-17-one. It is well known that the 3-hydroxyl group in saturated 5α-steroid is replaced by chlorine with inversion of configuration by phosphorus pentachloride, but with retention by thionyl chloride.3) Thus the displacement of the hydroxyl group by chlorine with sulfuryl chloride-pyridine is similar to that with phosphorus pentachloride rather than with thionyl chloride, as far as inversion and retention of configuration is concerned. It is of interest to note that sulfuryl chloride-pyridine can be used as a general reagent for the displacement of the hydroxyl group by chlorine.

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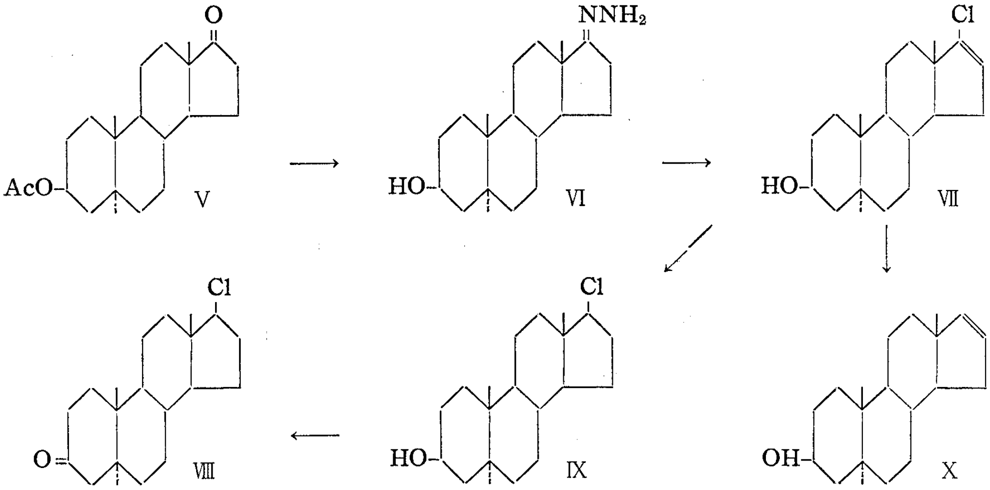
1) U. Westphal : Ber., **72**, 1233 (1939).
2) H. Mori : This Bulletin, **10**, 429 (1962).
3) R.E. Marker : J. Am. Chem. Soc., **57**, 1755 (1935). R.E. Marker, F.C. Whitmore, O. Kamm: *Ibid.*, **57**, 2358 (1935).

Recently Barton, *et al.*[4] reported a new elegant reaction of aldehyde and ketone hydrazones with iodine in the presence of triethylamine to give vinyl iodides. The present authors expected possibility of a similar reaction of hydrazones with N-chlorosuccinimide to give vinyl chloride. In fact, the hydrazone (VI) prepared from 3β-acetoxy-5α-androstan-17-one (V) easily reacted with N-chlorosuccinimide at room temperature in pyridine to give 17-chloro-5α-androst-16-en-3β-ol (VII), m.p. 127~129°, $[\alpha]_D^{20}$ +13° (*Anal.* Calcd. for $C_{19}H_{29}OCl$: C, 73.88; H, 9.46. Found : C, 73.70; H, 9.61.), which was transformed into 5α-androst-16-en-3β-ol (X) on reduction with sodium and ethanol, and was hydrogenated on 5% palladium charcoal to 17β-chloro-5α-androstan-3β-ol (IX), m.p. 123~125°, $[\alpha]_D^{20}$ +5° (*Anal.* Calcd. for $C_{19}H_{31}OCl \cdot \frac{1}{4}H_2O$: C, 72.34; H, 10.06. Found : C, 72.22; H, 10.38.), the configuration of which is considered to be 17β-chloro, because it is generally accepted that the Δ^{16}-double bond is attacked from the back side.[5] When oxidized with chromium trioxide in acetic acid, compound IX gave 17β-chloro-5α-androstan-3-one (VIII), m.p. 120~121°, $[\alpha]_D^{20}$ +38° (*Anal.* Calcd. for $C_{19}H_{29}OCl$: C, 73.88; H, 9.46. Found: C, 73.68; H, 9.62.).



Compound IX is not identical with 17-chloro-5α-androstan-3β-ol (III) and compound VIII is not identical with 17-chloro-5α-androstan-3-one (II). Thus it has been established that compound III is 17α-chloro-5α-androstan-3β-ol, the acetate (I) is 17α-chloro-5α-androstan-3β-ol acetate, and the 17-chloro-3-one (II) is 17α-chloro-5α-androstan-3-one. Molecular rotations of the two isomeric 17-chloro-5α-androstan-3β-ols and the two corresponding 3-ones support this conclusions.

If a similar inversion of the configuration occurred in the displacement reaction of testosterone with sulfuryl chloride in pyridine, the product IV must be 17α-chloroandrost-4-en-3-one, and it is probable that the 17-chloro steroids obtained by Westphal were also 17α-chloro compounds.

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[4] D. H. R. Barton, R. E. Obrien, S. Sternhell : J. Chem. Soc., **1962**, 470.

[5] R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith, C. H. Ruof : J. Am. Chem. Soc., **69**, 2167 (1947). D. K. Fukushima, T. F. Gallagher : *Ibid.*, **73**, 196 (1951).