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STEROIDS. LXV.[1] A SYNTHESIS OF ANDROSTERONE

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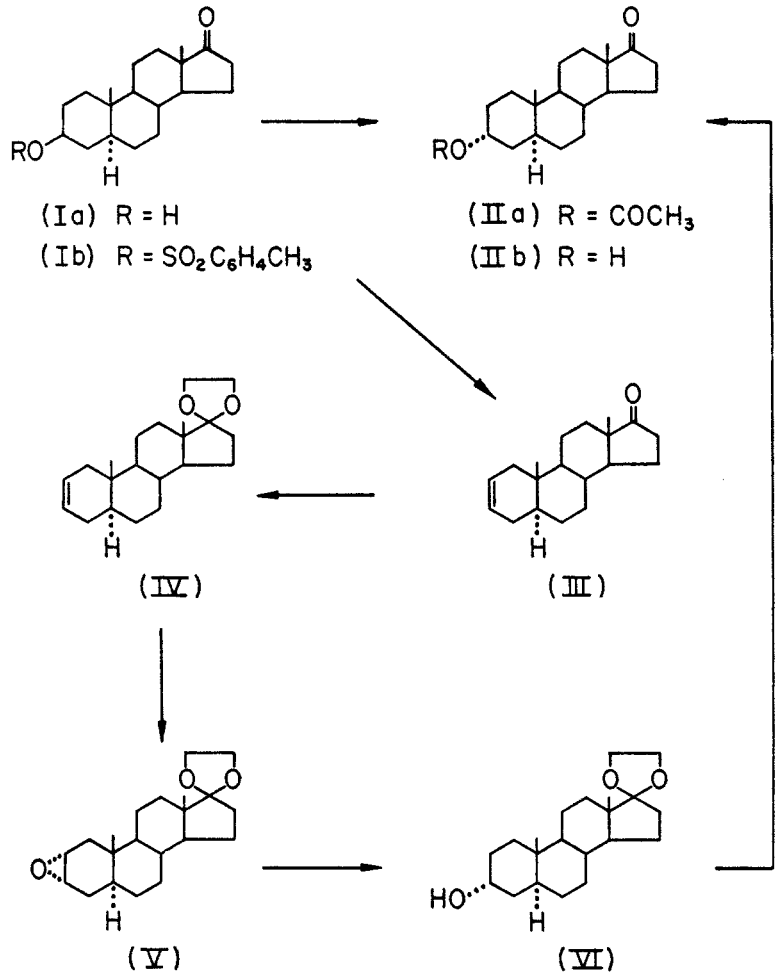
Comparatively large quantities of androsterone (IIb) were required in these Laboratories for biological studies, and for this reason we became interested in developing a more efficient synthesis of IIb than those hitherto reported (1). In the present paper we describe such a synthesis, which employs epiandrosterone (androstan-3β-ol-17-one) (Ia) [easily obtained by catalytic hydrogenation (2) of



the available Δ^5-androsten-3β-ol-17-one acetate] as starting material and proceeds in *ca.* 60% over-all yield.

[1] For Paper LXIV see Sondheimer, Velasco, Batres, and Rosenkranz, *Chemistry & Industry*, 1482 (1954).

Epimerization at C-3 through acetolysis of a 3β-chloro compound, a reaction used previously (3) to prepare androsterone, is known to be unsatisfactory since elimination takes place predominantly (4). Instead we chose to investigate the acetolysis of a 3β-*p*-toluenesulfonate (5, 6), especially since Plattner and Fürst (6) had reported that this reaction in the methyl 5α-etianate series yields the 3α-acetoxy compound in over 50% yield. However, when epiandrosterone *p*-toluenesulfonate (Ib) [prepared (5) from isoandrosterone (Ia) in over 90% yield] was treated with sodium acetate in boiling acetic acid and acetic anhydride, it was converted to a mixture which was resolved readily by silica chromatography into Δ^2-androsten-17-one (III) as major component (54%)[2] and androsterone acetate (IIa) as minor component (39%).[3] The latter could be saponified quantitatively to androsterone (IIb). The structures assigned to these substances follow from the elementary analyses, infrared spectra and the similarity of physical properties to those of the known compounds (1, 7, 9).

Since Δ^2-androsten-17-one (III) was the major product formed in the acetolysis step and changing the reaction conditions did not appreciably alter the ratio of III to IIa, it was highly desirable to effect the conversion of this Δ^2-compound to androsterone. The analogous transformation of Δ^2-cholestene to cholestan-3α-ol had previously been performed, through successive treatments with perbenzoic acid and lithium aluminum hydride (8). In the present case it was necessary to protect the 17-keto grouping of III against attack by the metal hydride and this was accomplished by conversion to the 17-cycloethylene ketal IV with ethylene glycol and *p*-toluenesulfonic acid in boiling benzene. The Δ^2-double bond of IV then was oxidized with perbenzoic acid and the resulting 2α,3α-oxide V was reduced with lithium aluminum hydride. The androsterone cycloethylene ketal (VI) thus produced on hydrolysis at C-17 with aqueous acetic acid furnished androsterone (IIb), identical with that obtained above. The over-all yield from Δ^2-androsten-17-one (III) was 55%, bringing the total yield of androsterone from isoandrosterone to 61%.

EXPERIMENTAL[4]

Epiandrosterone p-toluenesulfonate (Ib). A mixture containing 100 g. of epiandrosterone (Ia), 100 g. of *p*-toluenesulfonyl chloride (freshly recrystallized from ether), and 250 cc. of dry pyridine was allowed to stand at room temperature for 20 hours. Chloroform and dilute hydrochloric acid then were added, and the chloroform extract was washed successively with dilute hydrochloric acid, sodium bicarbonate solution, and water. Drying, evaporation, and crystallization of the residue from ether furnished 136.1 g. of the *p*-toluenesulfonate Ib with m.p. 160–161° (dec.). Chromatography of the mother liquors on neutral alumina furnished another 2.6 g. of the same purity (total yield, 91%). The analytical sam-

[2] This formulation is more likely than the alternative Δ^3-structure, although the latter cannot definitely be excluded.

[3] The acetolysis of epiandrosterone *p*-toluenesulfonate has been described briefly in the patent literature (5); androsterone acetate was the only product isolated, in unspecified yield.

[4] Melting points are uncorrected. We are indebted to Mrs. P. Lopez and staff for the infrared spectra (determined in chloroform solution on a Perkin-Elmer model 12 C single beam spectrophotometer) and to Mrs. A. Gonzalez for the microanalyses.

ple showed m.p. 163–164° (dec.), $[\alpha]_D^{20}$ +46° (chloroform), $\nu_{max.}$ 1736 cm.$^{-1}$ and no free hydroxyl band; reported (5): m.p. 164–166°.

Anal. Calc'd for $C_{26}H_{36}O_4S$: C, 70.39; H, 8.12.

Found: C, 70.55; H, 8.30.

Androsterone acetate (IIa) *and* Δ^2*-androsten-17-one* (III) *from Ib.* A solution containing 112.5 g. of Ib and 112.5 g. of anhydrous sodium acetate in 1 l. of glacial acetic acid and 100 cc. of acetic anhydride was boiled under reflux for 5 hours. Chloroform and water were added, the aqueous layer was reextracted with chloroform, and the combined organic layers were washed with sodium carbonate solution and water, dried, and evaporated. The residue was chromatographed on 1.3 kg. of silica gel. The fractions eluted with benzene furnished 37.5 g. (54%) of Δ^2-androsten-17-one with m.p. 99–103°, which after crystallization from ether showed m.p. 105–106°, $[\alpha]_D^{20}$ +146° (ethanol), $\nu_{max.}$ 1736 cm.$^{-1}$; reported (7): m.p. 104.5–105.5°, $[\alpha]_D^{17}$ +146° (ethanol).

Anal. Calc'd for $C_{19}H_{28}O$: C, 83.77; H, 10.36.

Found: C, 83.78; H, 10.44.

The fractions eluted with benzene-ether (2:1) on crystallization from acetone-ether produced 32.8 g. (39%) of androsterone acetate with m.p. 164–165°, $[\alpha]_D^{20}$ +87° (ethanol), $\nu_{max.}$ 1736 cm.$^{-1}$; reported (9): m.p. 164.5–165.5°.

Anal. Calc'd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70.

Found: C, 75.44; H, 9.72.

Androsterone (IIb). A solution of 34.1 g. of androsterone acetate and 40 g. of potassium carbonate in 2 l. of methanol and 400 cc. of water was refluxed for 3 hours. The solution after concentration to about half its volume was diluted with water and the product was extracted with chloroform in the usual way. Crystallization from acetone-ether produced 28.9 g. (97%; 34% over-all from isoandrosterone) of androsterone with m.p. 180–183°. The analytical sample showed m.p. 184–185°, $[\alpha]_D^{20}$ +95° (ethanol), $\nu_{max.}$ 1736 cm.$^{-1}$ and free hydroxyl band; reported (9): m.p. 182–183°, $[\alpha]_D$ +94.6° (ethanol).

Anal. Calc'd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41.

Found: C, 78.92; H, 10.30.

17-Ethylenedioxy-Δ^2*-androstene* (IV). A mixture of 30 g. of Δ^2-androsten-17-one, 0.25 g. of *p*-toluenesulfonic acid and 25 cc. of freshly distilled ethylene glycol was refluxed in 200 cc. of anhydrous benzene for 15 hours, a water-separator being employed. The mixture then was poured into sodium carbonate solution, and the organic layer was washed with water, dried, and evaporated. Crystallization from methanol furnished 25.2 g. (72%) of the ketal IV with m.p. 112–113°, $[\alpha]_D^{20}$ +25° (chloroform containing 1 drop of pyridine), no infrared absorption in the carbonyl region.

Anal. Calc'd for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19.

Found: C, 79.25; H, 10.00.

The mother liquors were heated with 100 cc. of acetic acid and 25 cc. of water for 1 hour on the steam-bath. Neutralization with sodium bicarbonate followed by extraction with chloroform furnished 7.4 g. of recovered Δ^2-androsten-17-one with m.p. 97–100°; the yield of ketal was thereby increased to 96%.

2α*,3*α*-Oxido-17-ethylenedioxyandrostane* (V). 17-Ethylenedioxy-Δ^2-androstene (25.2 g.) in 100 cc. of benzene was treated with 0.09 mole (10% excess) of a solution of perbenzoic acid in benzene. After being allowed to stand overnight at room temperature, the solution was washed with sodium carbonate solution and water, dried, and evaporated. Crystallization of the residue from methanol produced 22.7 g. (86%) of the oxide V with m.p. 145–147°, which on further crystallization showed m.p. 151–152°, $[\alpha]_D^{20}$ −6° (chloroform containing 1 drop of pyridine), no infrared absorption in the carbonyl region.

Anal. Calc'd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70.

Found: C, 76.08; H, 9.60.

Androsterone (IIb) *from* V. A solution of 22.7 g. of the oxide V in 300 cc. of dry ether was added gradually to 6 g. of lithium aluminum hydride in 300 cc. of ether. The mixture was stirred for 1 hour and then was allowed to stand overnight at room temperature. The

excess reagent was destroyed by carefully adding ethyl acetate, and the product was isolated by the sodium sulfate procedure, as described previously (10). The total residue, consisting of crude androsterone 17-cycloethylene ketal (VI) weighed 22.4 g. and showed m.p. 134–136°. A small sample was crystallized from acetone-pentane and then had m.p. 140–141°, $[\alpha]_D^{20}$ −16° (chloroform containing 1 drop of pyridine), $\nu_{max.}$ free hydroxyl band only.

Anal. Calc'd for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25.

Found: C, 75.58; H, 10.36.

The total crude ketal VI (22.4 g.) was heated with 200 cc. of glacial acetic acid and 200 cc. of water for 1 hour on the steam-bath. Careful addition of excess sodium bicarbonate solution followed by extraction with chloroform yielded a solid which was crystallized from acetone-ether, and the mother liquors were chromatographed on silica. In this way a total of 13.1 g. (66% from V; 55% over-all from III) of androsterone with m.p. 183–184° was obtained, which proved to be identical (mixture m.p., infrared comparison) with that obtained above.

SUMMARY

Isoandrosterone *p*-toluenesulfonate (Ib) on acetolysis is shown to yield 54% of Δ^2-androsten-17-one (III) and only 39% of the desired androsterone acetate (IIa). A method is described for the conversion of the Δ^2-compound III to androsterone (IIb), which may thereby be obtained from isoandrosterone in over 60% total yield.

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