An Improved Synthesis for 2β-Hydroxytestosterone

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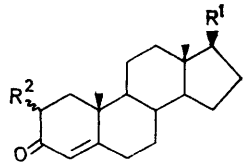
2β-Hydroxytestosterone has been obtained in 21% overall yield from testosterone, together with a similar quantity of the 2α-isomer.

THE biologically important 2β-hydroxytestosterone [1] has been synthesised in low yield by several workers [2-5] since 1960. The present synthesis is a modification of Osawa's method,[5] and gives an improved yield by eliminating one step.

Acetoxylation of testosterone 17-chloroacetate (I) [6] with an excess of lead tetra-acetate under mild conditions [7] gave a mixture of the 2α- and 2β-acetoxy-



	R^1	R^2
(I)	$O_2C{\cdot}CH_2Cl$	H
(II) a;	$O_2C{\cdot}CH_2Cl$	α-OAc
b;	$O_2C{\cdot}CH_2Cl$	β-OAc
(III) a;	OH	α-OH
b;	OH	β-OH

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derivatives (IIa and b) in approximately equal proportions. The 2-acetate 17-chloroacetate was readily hydrolysed to give 2β-hydroxytestosterone (IIIb), which was sufficiently pure for direct crystallisation, without the preparative t.l.c. which had been required previously.[5]

EXPERIMENTAL

I.r. spectra were determined for KBr discs, u.v. spectra for solutions in ethanol, n.m.r. spectra at 100 MHz for solutions in $CDCl_3$, and c.d. spectra for solutions in ethanol; m.p.s were determined on a Kofler hot-stage apparatus. Analytical g.l.c. was carried out at 250 °C on a 7 ft column of 3% QF1 on Anakrom ABS (80—100 mesh). Alumina for column chromatography was Spence grade H, deactivated with 10% of aqueous 10% acetic acid.

2α- *and* 2β-*Acetoxy*-17β-*chloroacetoxyandrost*-4-*en*-3-*ones* (IIa and b).—Testosterone 17β-chloroacetate (I) (4·76 g) was heated under reflux, with stirring, in anhydrous benzene (200 ml) containing lead tetra-acetate (20 g). After 49 h, when reaction was at least 90% complete (g.l.c.), the excess of lead tetra-acetate was destroyed by addition of potassium carbonate. Extraction with ether gave oily crystals (5·3 g), and successive crystallisations from methanol and ethyl acetate (twice) produced the 2β-isomer (IIb) (1·07 g), m.p. 198—200° (lit.,[5] 190—191°). The ethyl acetate mother liquors, rich in the 2β-isomer, were evaporated and the residue (1·6 g) was subjected to column chromatography on alumina (400 g), with toluene–light petroleum mixtures of increasing polarity as eluants. The first fractions [toluene–light petroleum (3 : 2)] gave pure 2α-*acetoxy*-17β-*chloroacetoxyandrost*-4-*en*-3-*one* (IIa) (130 mg), needles from methanol, m.p. 189—192°, $\lambda_{max.}$ 240 nm (ε 15,600); $\nu_{max.}$ 1758, 1747, 1683, and 1617 cm^{-1}; δ 0·85 (s, 18-H_3), 1·33 (s, 19-H_3), 2·14 (s, OAc), 4·03 (s, O·CO·CH_2Cl), 4·71 (t, 17α-H, $W_{\frac{1}{2}}$ 16 Hz), 5·45 (q, 2β-H, $J_{2\beta,1\alpha}$ 13·6, $J_{2\beta,1\beta}$ 5·6 Hz), and 5·74 (s, 4-H); c.d. (*c* 0·10) $\Delta\varepsilon_{322}$ −2·5, $\Delta\varepsilon_{240}$ +9·8, $\Delta\varepsilon_{217}$ +7·7 (Found: C, 65·1; H, 7·3; Cl, 8·7. $C_{23}H_{31}ClO_5$ requires C, 65·3; H, 7·4; Cl, 8·4%).

Succeeding fractions contained steadily increasing proportions of 2β-isomer (g.l.c.). All fractions of >70% 2β-isomer (relative to 2α-isomer) were combined, yielding a further 0·67 g of pure 2β-isomer, after crystallisation from ethyl acetate.

The methanolic mother liquors from the original crystallisation were rich in the 2α-isomer, and gave the 2α-isomer (0·98 g; pure by g.l.c.) after seeding with the pure material; m.p. 180—190°.

Total yields: 2β 1·74 g, 32%; 2α 1·11 g, 20%.

2β-*Hydroxytestosterone* (IIIb).—To a suspension of the 2-acetate 17-chloroacetate (IIb) (1·06 g) in anhydrous methanol (70 ml), under nitrogen, was added 1·03N-potassium hydroxide in methanol (2·6 ml) and the mixture was stirred at 27 °C, becoming homogeneous after 50 min. Water (0·2 ml) and N-acetic acid (4 ml) were then added. The solution was concentrated under reduced pressure, and the product was extracted with ether and crystallised from light petroleum (b.p. 60—80°)–acetone (1 : 1) at 0° to give pure 2β-hydroxytestosterone (IIIb), needles (266 mg, 35%), m.p. 163—165° (lit.,[2] 163—164°; lit.,[5] 157—159°); c.d. (*c* 0·05) $\Delta\varepsilon_{318}$ +1·4, $\Delta\varepsilon_{244}$ −22·6, $\Delta\varepsilon_{210}$ +16·4. The mother liquors gave a second crop of crystals (241 mg, 31%), m.p. 160—162°.

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