5α-Androst-6-ene Derivatives as Intermediates for Labelling with Isotopic Hydrogen

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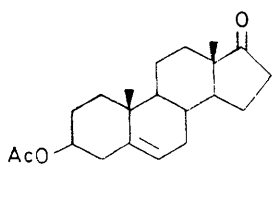
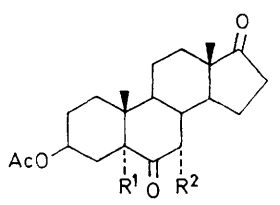
5α-Androst-6-ene-3β,17β-diol, 17β-hydroxy-5α-androst-6-en-3-one, and 3α-hydroxy-5α-androst-6-en-17-one have been prepared, and have been reduced with deuterium to give [6,7-$^2H_2$]-5α-androstane derivatives.

THE preparation of some Δ^6-5β-steroids was reported recently.[1] We have now extended this work to 5α-androst-6-ene derivatives, which are convenient precursors for [6,7-$^3H_2$]-5α-androstanes. The required compounds were the Δ^6-analogues of 3α-hydroxy-5α-androstan-17-one (androsterone), 17β-hydroxy-5α-androstan-3-one (dihydrotestosterone), and 5α-androstane-3β,17β-diol. Δ^6-5α-Steroids have been obtained previously in a number of ways,[2-4] but only one route seemed to offer the prospect of a high yield of a suitable common intermediate, namely the preparation and reduction of a 7α-bromo-5α-androstan-6β-ol derivative.[3]

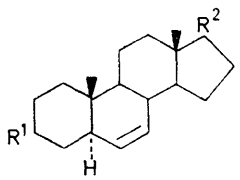
Treatment of 17-oxoandrost-5-en-3β-yl acetate (1) with hypobromous acid (*N*-bromoacetamide–perchloric acid), followed by oxidation of the resulting 5,6-bromohydrin, gave the 3β-acetoxy-5α-bromo-6,17-diketone (2). On treatment with hydrogen bromide–acetic acid at 50° the bromo-substituent migrated to the 7α-position (3), as was evident from the change in optical rotation of the solution, and the inversion of the c.d curve of the product, as compared with that of the 5α-bromo-diketone. A similar bromo-ketone rearrangement has long been known in the cholestane series.[5] Reduction of the 7α-bromo-diketone (3) with sodium borohydride, and subsequent reduction of the 7α-bromo-6-alcohols with zinc dust in ethanol, gave the key intermediate, 17β-hydroxy-5α-androst-6-en-3β-yl acetate (4), from which the required diol (5) was obtained after hydrolysis.



(1)



(2) R^1 = Br, R^2 = H
(3) R^1 = H, R^2 = Br



(4) R^1 = β-AcO, R^2 = β-OH
(5) R^1 = R^2 = β-OH
(6) R^1 = β-AcO, R^2 = :O
(7) R^1 = β-HO, R^2 = :O
(8) R^1 = β-TsO, R^2 = :O
(9) R^1 = α-AcO, R^2 = :O
(10) R^1 = α-HO, R^2 = :O
(11) R^1 = O:, R^2 = β-OH

Oxidation of the 17β-hydroxy-3β-acetate (4) with Jones reagent gave the acetate (6) of 3β-hydroxy-5α-androst-6-en-17-one (7). The derived 3β-tosylate (8) reacted with tetra-n-butylammonium acetate in butan-2-one (*cf.* Baker *et al.*[6]) to give the corresponding 3α-acetoxy-compound (9), which afforded 3α-hydroxy-5α-androst-6-en-17-one (10) on hydrolysis.

17β-Hydroxy-5α-androst-6-en-3-one (11) was prepared from the 3β-acetate (4) by benzoylation at C-17, selective hydrolysis of the acetate group, oxidation at C-3, and hydrolysis of the benzoate group.

Catalytic reduction of each of the unsaturated compounds (5), (10), and (11) with deuterium gave their 6,7-saturated analogues, each containing essentially two atoms of deuterium. Palladium–calcium carbonate was the most satisfactory catalyst for general use: palladium–charcoal caused over-reduction affecting the 3-oxo-group of compound (11), although the products were not fully characterised. Reduction of the 6,7-double bond is presumed to occur mainly from the α-face since this is the more exposed, in contrast to our findings in the 5β-series where both the α- and β-faces of the 6,7-double bond are subject to steric hindrance, and reduction is not stereoselective.[1]

Tritiation of the Δ^6-compounds is being carried out by Professor A. E. Kellie and his colleagues, at The Middlesex Hospital Medical School, London.

EXPERIMENTAL

I.r. spectra were measured for KBr discs unless otherwise indicated. N.m.r. spectra were obtained for solutions in $CDCl_3$ at 100 MHz. T.l.c. was carried out on Keiselgel PF (Merck).

5-Bromo-6,17-dioxo-5α-androstan-3β-yl Acetate (2).—17-Oxoandrost-5-en-3β-yl acetate (1) (5 g) in dioxan (80 ml) and water (15 ml) was treated with freshly prepared *N*-bromoacetamide (2 g) in water (5 ml), followed by perchloric acid (72%; 1 ml), and the mixture was stirred at room temperature for 1 h; the reaction was then complete (t.l.c.). Water was added to precipitate the product, which was collected

[1] D. N. Kirk and D. R. A. Leonard, *J.C.S. Perkin I*, 1973, 1836.

[2] D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 1949, 2459; O. Wintersteiner and M. Moore, *J. Amer. Chem. Soc.*, 1950, **72**, 1923; Y. Mazur, M. Nussim, and F. Sondheimer, *Proc. Chem. Soc.*, 1959, 314; L. Cagliotti, G. Cainelli, and G. Maina, *Tetrahedron*, 1963, **19**, 1057; R. Ledger, A. J. Smith, and J. McKenna, *Tetrahedron*, 1964, **20**, 2413; D. R. James, R. W. Rees, and C. W. Shoppee, *J. Chem. Soc.*, 1955, 1370; H. B. Kagan and J. Jacques, *Bull. Soc. chim. France*, 1960, 871.

[3] D. L. Garmaise and C. W. Shoppee, *J. Chem. Soc.*, 1953, 245.

[4] T. Komeno, S. Hayashi, and K. Sadao, *Shionogi Kenkyusho Nempo*, 1969, **19**, 3 (*Chem. Abs.*, 1970, **72**, 12,955q).

[5] I. M. Heilbron, E. R. H. Jones, and F. S. Spring, *J. Chem. Soc.*, 1937, 801; C. W. Shoppee, R. H. Jenkins, and G. H. R. Summers, *ibid.*, 1958, 1657; E. J. Corey, *J. Amer. Chem. Soc.*, 1954, **76**, 175.

[6] R. Baker, J. Hudec, and K. L. Rabone, *J. Chem. Soc. C*), 1969, 1605.

and dissolved in chloroform. The solution was washed with aqueous sodium iodide and then with aqueous sodium thiosulphate and water, dried (Na_2SO_4), and evaporated under reduced pressure below 40°. The residue crystallised from acetone to give 5-bromo-6β-hydroxy-17-oxo-5α-androstan-3β-yl acetate (3·2 g), m.p. 173—175° (lit.,[7] 173—175°), $\nu_{max.}$ 3350 (OH), 1735 (AcO), and 1720 cm^{-1} (CO).

This product (3·2 g) in acetone was oxidised with 8N-chromic acid (Jones reagent). Water was added to precipitate the steroid, which was collected and crystallised from acetone–hexane to give the acetoxy-diketone (2) (3·1 g), m.p. 180° (decomp.) (lit.,[7] 178—180°), $\nu_{max.}$ 1742 [C(17)O], 1735 (AcO), and 1710 cm^{-1} [C(6)O]; $\Delta\varepsilon$ −6·23 (315 nm) (in MeOH) (Found: C, 59·2; H, 6·9; Br, 18·6. Calc. for $C_{21}H_{29}BrO_4$: C, 59·3; H, 6·9; Br, 18·8%).

7α-Bromo-6,17-dioxo-5α-androstan-3β-yl Acetate (3).—The 5-Bromo-acetoxy-diketone (2) (3 g) was dissolved in acetic acid (80 ml) containing 45% hydrogen bromide–acetic acid (12 ml). A portion (1 ml) of the mixture in a polarimeter cell was maintained at 50° while the remainder was kept in a thermostat at 50°. After 4·5 h the optical rotation, initially $[\alpha]_D$ −111°, became constant at +133°, indicating that the reaction was complete. The mixture was then poured into ice-cold water, and the precipitate was collected after 3 h. Crystallisation from acetone–hexane gave the *7α-bromo-diketone* (1·7 g), m.p. 180°; $\Delta\varepsilon$ +6·85 (303 nm) (in MeOH) (Found: C, 59·2; H, 6·8; Br, 18·5. $C_{21}H_{29}BrO_4$ requires C, 59·3; H, 6·9; Br, 18·8%).

17β-Hydroxy-5α-androst-6-en-3β-yl Acetate (4).—The 7α-bromo-diketone (3) (1·6 g) in propan-2-ol containing sodium borohydride (0·5 g) was stirred at room temperature; the reaction was followed by t.l.c., and was complete in 1 h. Most of the solvent was then evaporated off under reduced pressure below 40°. Water was added to the residue and the mixture was cooled at 0° for 1 h. The precipitated bromohydrin was filtered off and dried *in vacuo* at 25° [$\nu_{max.}$ 3400 (OH) and 1735 (OAc) cm^{-1}; no absorption at 1742 or 1705 cm^{-1}]. The crude bromohydrin (1·5 g) in ethanol (100 ml) containing acetic acid (5 ml) was stirred under reflux with zinc dust (1·5 g). The reduction was complete after 2 h (t.l.c.). After filtration, the solution was reduced to about one third of its volume, then water was added to precipitate the product. Crystallisation from ethanol gave the *17β-hydroxy-6-ene 3β-acetate* (1 g), m.p. 135—138°, $\nu_{max.}$ (CS_2) 3600 (OH) and 1738 cm^{-1} (AcO), τ 9·22 (calc.[8] 9·217) (s, 13β-Me), 9·18 (calc.[8] 9·183) (s, 10β-Me), 7·97 (s, AcO), 6·32 (t, 17α-H), 5·25 (septet, 3α-H), and 4·55 and 4·74 (d, d, *J* 10·5 Hz, HC=CH) (Found: C, 76·1; H, 9·8. $C_{21}H_{32}O_3$ requires C, 75·9; H, 9·7%).

5α-Androst-6-ene-3β,17β-diol (5).—The 3-acetate (4) (0·1 g) was heated under reflux with 1% potassium carbonate in 95% ethanol (20 ml) for 1 h to give 5α-androst-6-ene-3β,17β-diol (80 mg), m.p. 180—182° (from acetone) (lit.,[3] 181—182°), τ 9·22 (s) and 9·20 (s) (10β- and 13β-Me), 6·31 (m, 3α- and 17α-H), and 4·55 and 4·74 (d, d, *J* 10 Hz, HC=CH) (Found: C, 78·5; H, 10·4. Calc. for $C_{19}H_{30}O_2$: C, 78·6; H, 10·4%).

17-Oxo-5α-androst-6-en-3β-yl Acetate (6).—The hydroxy-acetate (4) (0·3 g) was oxidised in acetone (25 ml) with Jones reagent to give the acetoxy-ketone (6) (0·29 g), m.p. 143—146° (from aqueous acetone) (lit.,[4] 143—145°), $\nu_{max.}$ 1742 and 1738 cm^{-1} (Found: C, 76·0; H, 9·1. Calc. for $C_{21}H_{30}O_3$: C, 76·3; H, 9·2%).

[7] V. Grenville, D. K. Patel, V. Petrow, I. A. Stuart-Webb, and D. M. Williamson, *J. Chem. Soc.*, 1957, 4105.

3β-Hydroxy-5α-androst-6-en-17-one (7).—Hydrolysis of the 3-acetate (6) (0·29 g) as for (5) gave the *3β-hydroxy-17-ketone* (7) (0·25 g), m.p. 173—174° (from acetone), $\nu_{max.}$ 3300 (OH) and 1740 cm^{-1} (CO) (Found: C, 79·0; H, 9·7. $C_{19}H_{28}O_2$ requires C, 79·1; H, 9·8%).

17-Oxo-5α-androst-6-en-3β-yl Toluene-p-sulphonate (8).—The hydroxy-ketone (7) (0·2 g) in pyridine (10 ml) was treated with toluene-*p*-sulphonyl chloride (0·5 g) overnight. Water (5 ml) was added to hydrolyse the excess of acid chloride, and after 30 min the mixture was extracted with ether. Removal of the solvent under reduced pressure gave the crude *3-tosylate* (0·2 g), $\nu_{max.}$ 1600 and 1180 cm^{-1}.

17-Oxo-5α-androst-6-en-3α-yl Acetate (9).—The crude tosylate (8) (0·2 g) in dry butan-2-one (50 ml) containing tetra-n-butylammonium acetate (2 g) was heated under reflux in nitrogen for 72 h; reaction was then complete (t.l.c.). The t.l.c. plates revealed the presence of a non-polar product (probably the 2,6-diene) (15—20%), as well as the required 3α-acetate.

Crystallisation of the crude product first from acetone and then from hexane at 0° gave the *3α-acetate* (0·08 g), m.p. 184—185° (the olefinic by-product remained in the mother liquors), $\nu_{max.}$ 1742 (CO), 1735 (AcO), and 1645 cm^{-1} (C=C), τ 9·22 (s, 13β-Me), 9·12 (s, 10β-Me), 8·00 (s, AcO), 4·93, (m, $W_{\frac{1}{2}}$ 8 Hz, 3-H), and 4·45 and 4·69 (d, d, *J* 10 Hz, HC=CH) (Found: C, 76·1; H, 9·02. $C_{21}H_{30}O_3$ requires C, 76·3; H, 9·1%).

A fraction of this product was hydrogenated in ethanol over palladium–charcoal to give 17-oxo-5α-androstan-3α-yl acetate, identical (i.r., g.l.c., m.p.) with an authentic sample.

3α-Hydroxy-5α-androst-6-en-17-one (10).—The 3-acetate (9) (60 mg) was hydrolysed as above to give *3α-hydroxy-ketone* (48 mg), m.p. 174—178° (from acetone), τ 9·21 (s, 10β-Me), 9·09 (s, 13β-Me), 5·93 (m, $W_{\frac{1}{2}}$ 8 Hz, 3β-H), and 4·50 and 4·71 (d, d, *J* 10 Hz, HC=CH) (Found: C, 78·9; H, 9·7. $C_{19}H_{28}O_2$ requires C, 79·1; H, 9·8%).

A fraction was hydrogenated over palladium–charcoal to give 3α-hydroxy-5α-androstan-17-one, identical (i.r., g.l.c., m.p.) with an authentic sample.

5α-Androst-6-ene-3β,17β-diyl 3-Acetate 17-Benzoate.—The 3-acetate (4) (0·2 g) in pyridine (10 ml) was treated with benzoyl chloride (5 ml) at room temperature for 2 h to give the 3-acetate 17-benzoate as leaflets (from methanol), m.p. 135—140°, $\nu_{max.}$ 3450 (OH), 1735 (AcO), and 1710 and 1600 cm^{-1} (BzO); τ 9·18 (s, 10β-Me), 9·02 (s, 13β-Me), 7·97 (s, AcO), 5·25 (m, 3α-H), 5·10 (t, 17α-H), 4·51 and 4·67 (d, d, *J* 10 Hz, HC=CH), and 2·6—1·9 (aromatic) (Found: C, 76·8; H, 8·2. $C_{28}H_{36}O_4$ requires C, 77·0; H, 8·3%).

3β-Hydroxy-5α-androst-6-en-17β-yl Benzoate.—The 3-acetate 17-benzoate (0·12 g) in methanol (15 ml) containing 1·2 mol. equiv. (18 mg) of potassium hydroxide was heated under reflux for 1 h; the reaction was then complete (t.l.c.). Work-up in the usual way gave the *hydroxy-benzoate* (85 mg), m.p. 225°, τ 9·18 (s, 10β-Me), 9·02 (s, 13β-Me), 6·35 (m, 3α-H), 5·10 (s, 17-H), 4·52 and 4·68 (d, d, *J* 10 Hz, HC=CH), and 2·6—1·7 (aromatic) (Found: C, 78·8; H, 8·7; $C_{26}H_{34}O_3$ requires C, 79·1; H, 8·7%).

3-Oxo-5α-androst-6-en-17β-yl Benzoate.—The 3β-hydroxy-17β-benzoate (60 mg) was oxidised in acetone with Jones reagent to give the *3-ketone* (50 mg), m.p. 200—201° (from methanol; τ 9·18 (s, 10β-Me), 9·02 (s, 13β-Me), 5·15 (m, 17α-H), 4·51 and 4·67 (d, d, *J* 10 Hz, HC=CH), and 2·6—1·7

[8] N. S. Bhacca and D. H. Williams, 'Applications of N.M.R. Spectroscopy in Organic Chemistry,' Holden-Day, San Francisco, 1964, pp. 19—24.

(aromatic) (Found: C, 79·3; H, 8·2. $C_{26}H_{32}O_3$ requires C, 79·55; H, 8·2%).

17β-*Hydroxy*-5α-*androst*-6-*en*-3-*one* (11).—The 17-benzoate (60 mg) was hydrolysed with ethanolic 0·1N-potassium hydroxide (25 ml) under reflux for 5 h, giving the 17β-*hydroxy-ketone* (11) (35 mg), m.p. 182—184° (from acetone), $\nu_{max.}$ (CS_2) 3600 (OH) and 1710 cm^{-1} (CO), τ 9·22 (s, 13β-Me), 9·06 (s, 10β-Me), 4·48 and 4·77 (d, d, *J* 10 Hz, HC=CH), and 6·34 (t, 17α-H) (Found: C, 79·0; H, 9·7. $C_{19}H_{28}O_2$ requires C, 79·1; H, 9·8%).

[6α,7α-$^2H_2$]-5α-*Androstane*-3β,17β-*diol*.— 5α-Androst-6-ene-3β,17β-diol (10 mg) in 95% ethanol was shaken with deuterium over 2% palladium–calcium carbonate (2 mg) at room temperature to give the saturated diol (7 mg), M^+ 294 (unlabelled species, M^+ 292). Analysis of mass spectral peak intensities indicated 83% of the [$^2H_2$]-species.

[6α,7α-$^2H_2$]-3α-*Hydroxy*-5α-*androstan*-17-*one*.— 3α-Hydroxy-5α-androst-6-en-17-one (10 mg) treated as above gave the saturated compound (8 mg), M^+ 292, containing 93% of the [$^2H_2$]-species.

[6α,7α-$^2H_2$]-17β-*Hydroxy*-5α-*androstan*-3-*one*.— 17β-Hydroxy-5α-androst-6-en-3-one (10 mg) treated as above gave the saturated compound, M^+ 292, containing 86% of the [$^2H_2$]-species.

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