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SYNTHESIS OF 1-α-HYDROXYTESTOSTERONE

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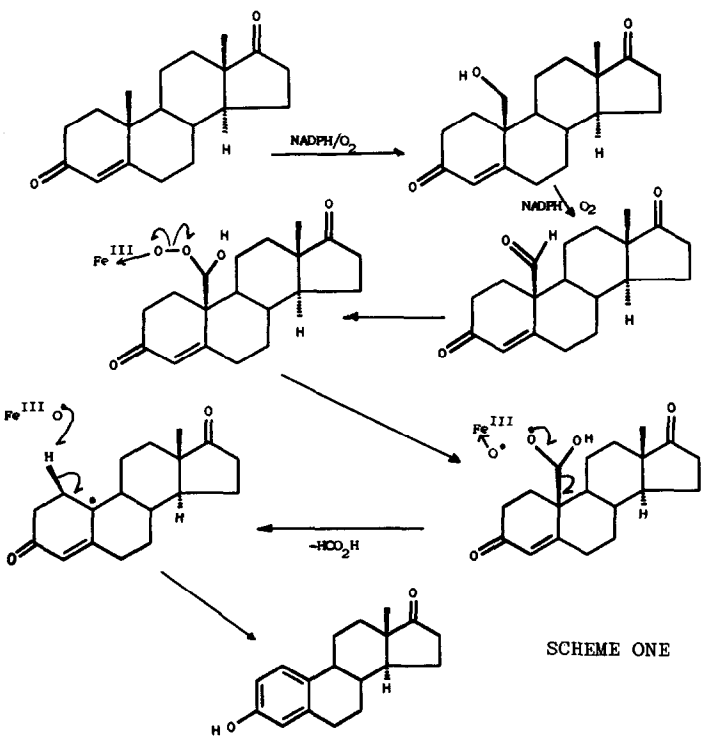
Abstract - A nine-stage synthesis of androst-4-ene-1α,17β-diol-3-one (1-α-testosterone) from 5α-androstan-17β-ol-3-one-17-benzoate (dihydrotestosterone benzoate) has been accomplished. This is the first synthesis of this compound other than via microbiological methods.

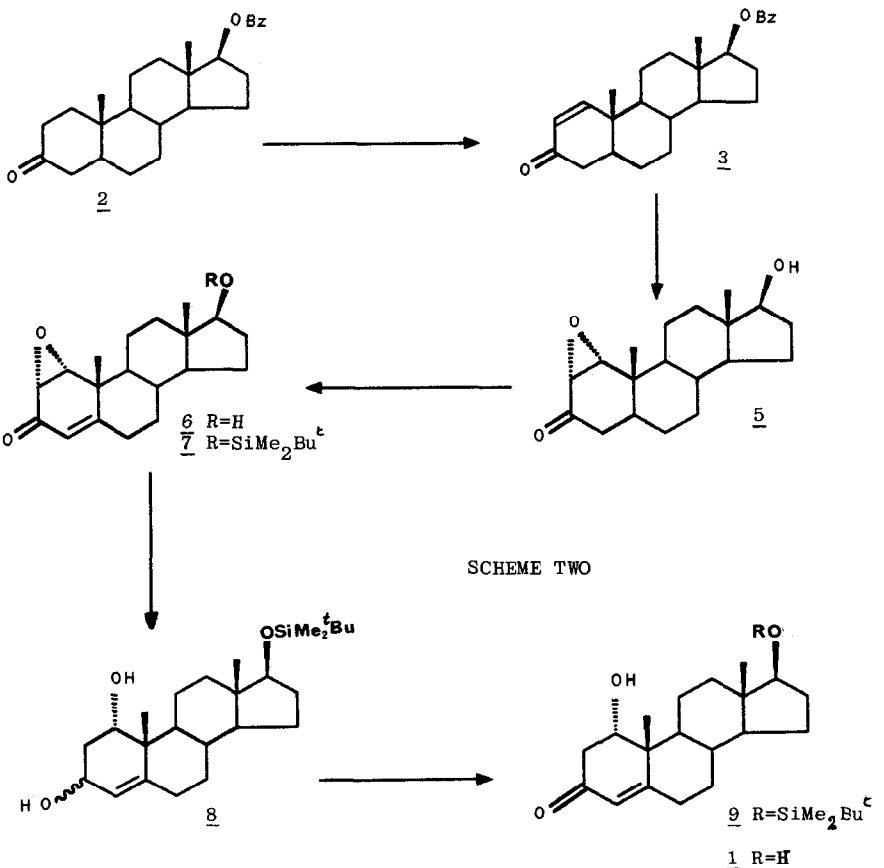
The enzyme aromatase mediates the conversion of androst-4-ene-3,17-dione into estrone, and the evidence presently available is most consistent with the mechanism shown in SCHEME ONE.[1]



SCHEME ONE

Clearly androstendiones with functionality at C-1 that would interact with the proposed free radical intermediates, are of great interest. To this end we have devised a route to 1α-hydroxytestosterone 1. Somewhat surprisingly this steroid had not been synthesised previously, but had been isolated as a product of microbiological conversion.[2]

The synthesis, shown in SCHEME TWO, proceeds from 5α-androstan-17β-ol-3-one-17-benzoate 2 (dihydrotestosterone benzoate), with initial introduction of a double bond between C-1 and C-2 (bromination and dehydrobromination) forming 5α-androstan-1-ene-17β-ol-17-benzoate 3. Subsequent ester hydrolysis provides the corresponding alcohol 4, and thence the α-epoxide 5 (alkaline H_2O_2) in an overall yield of ca. 35% for the four steps. Introduction of the double bond between C-4 and C-5 was expected to be troublesome, but in the event, use of SeO_2 allows obtention of the alkene 6 in up to 70% yield. Protection of the 17β-hydroxyl as its silyl ether 7 then allows completion of the synthesis via reduction to the diol mixture 8, and selective oxidation (with MnO_2) to yield the silyl ether of 1-α-hydroxy-testosterone 9 in an overall yield (for the three steps) of around 70%. This compound has potential as a key intermediate for the synthesis of other 1-substituted steroids, and can also be converted into androst-4-ene-1α,17β-diol (1-α-hydroxytestosterone) 1 through cleavage of the silyl ether.



SCHEME TWO

EXPERIMENTAL

I.r. spectra were recorded with a Perkin-Elmer 157 double-beam grating spectrophotometer (liquid films for oils and Nujol mulls for solids); ^{1}H n.m.r. spectra were recorded with a Varian T-60 (60 MHz), Perkin-Elmer R34 (220 MHz), or (at Warwick) on a Bruker WH 400 (400 MHz) instruments (tetramethylsilane as internal standard); and mass spectra were recorded on an A.E.I. MS12 spectrometer. Kieselgel GF_{254} Merck) was used for analytical t.l.c., and flash chromatography was performed with Merck silica gel (230-400 mesh). Organic solvents were distilled from calcium hydride when required anhydrous, and petrol is pet. ether (40-60).

5α-Androst-1-en-17β-ol-3-one-17-benzoate, 3.

Bromine (7.6 ml of a 1M solution in acetic acid) was added over a period of 5 minutes to a solution of 5α-androstan-17β-ol-3-one-17-benzoate, 2 (3g, 7.6mM) in glacial acetic acid (100 ml). After 3 hours, the reaction mixture was concentrated in vacuo, and rapidly chromatographed eluting with CCl_4:ether (4:1) to yield the crude 2α-bromo-product (4.8g). This was added in small portions to a mixture of $CaCO_3$ (4g) in refluzing dimethylacetamide (50 ml). After 15 minutes refluxing, the solution was cooled and concentrated in vacuo. The residue was extracted with dichloromethane (20 ml), and the organic extract washed successively with water then brine. Chromatography eluting with CCl_4:ether (3:2) yielded 2.2g of 3 (73% from 2) as colourless crystals.
M.pt. 182-4° (from CH_2Cl_2/ether);
δ($COCl_3$,60MHz) 0.95(s,18Me), 1.10(s,19-Me), 4.83(br.t.,17-H), 5.82(d,J 10Hz, 2-H), 7.04(d,J 10Hz,1-H); found C 79.05%, H 8.10%, calculated for $C_{26}H_{32}O_3$ C 79.55%, H 8.21%.

1α,2α-Epoxyandrostan-3-one-17β-ol, 7

The benzoate 3 (4.0g, 10mM) was hydrolysed by treatment with 5% methanolic NaOH solution (200 ml), and after neutralisation with glacial acetic acid, the solution was concentrated in vacuo, and the residue extracted with dichloromethane. The organic extract was washed successively with aqueous $NaHCO_3$, water, and brine, to yield after concentration 2.3g of the alcohol 4 (80%). [δ($CDCl_3$,60MHz) 0.85(s,18-Me), 1.05(s,19-Me), 3.60(br,t,17-H), 5.78(d,J 10Hz, 2-H), 7.08(d,J 10Hz,1-H)].

This was dissolved in methanol (40 ml) and treated with 4N NaOH solution (2 ml) and 30% H_2O_2 (12 ml) at 0°. The reaction mixture was kept overnight at 4°, then poured onto ice, and the precipitated product was collected and dried in vacuo to produce 1.62g (67%) of the epoxide 5. [δ($CDCl_3$,60MHz) 0.85(s,18-Me), 1.05(s,19-Me), 3.10(d,J 4Hz,1-H), 3.35(d,J 4Hz , 2-H), 3.64(br t,17-H)].

A solution of this epoxide in tert-butanol (40 ml) containing glacial acetic acid (4.5 ml) was treated with SeO_2 (1.5g), and the solution refluxed for 20 hours. The solvent was removed in vacuo, and the residue extracted with dichloromethane (50ml). After washing with dilute aqueous $NaHCO_3$ solution, then water, the organic extract was chromatographed (CCl_4:ether, 3:2) to yield epoxy alkene 6 (1.05g, 68%). [δ($CDCl_3$, 60MHz) 0.98 (s,18-H), 1.18(s,19-H), 3.38-3.46(m,1-H and 2-H), 3.64(br.t,17-H), 5.62(m,4-H)].

This alcohol was protected using tert-butyl, dimethyl silyl chloride (0.94g, 6.2mM), and imidazole (0.85g, 12.4mM) in DMF (25 ml). After 20 hours

at RT, the solution was treated with water and extracted with dichloromethane. Chromatography of the organic extract (CCl_4:ether 2:1) yielded 0.99g (64%) of 7. M.pt. 173-6°;
δ($CDCl_3$, 60MHz) 0.78(s,18-H), 0.84(s,^{t}Bu), 1.22(s,19-H), 3.35-3.70(m,1-H,2-H, 17-H), 5.68(m, 4-H).

17-tert-Butyldimethylsiloxy-androst-4-ene-1α,17β-diol-3-one, 9

A solution of the epoxide 7 (2.31g, 5.5mM) in dry THF (25 ml) was treated with $LiAlH_4$ (16 ml of a 1M solution in THF), and the solution stirred at RT for 2.5 hours. After quenching with ethyl acetate, the organic phase was washed with saturated aqueous Na_2SO_4 solution, dried and concentrated to produce 1.77g (76%) of diols 8. This mixture was treated with active MnO_2 (12g) in chloroform (100 ml). After 20 hours, the reaction mixture was filtered and after removal of solvent, the colourless crystalline product 9 was obtained (1.7g, 97%). An analytical sample was obtained after two recrystallisations from CH_2Cl_2/petrol.

M.pt. 182-5°C;
δ($CDCl_3$,220MHz) 0.75(s,18-H), 0.86(s,t-Bu), 1.18(s,19-H), 2.50-2.62(m,J_{gem}6.8Hz, 2β-H), 2.70-2.80(m,J_{gem} 6.8,$J_{2\alpha,1}$1.2Hz, 2α-H), 3.58(t,J 4Hz,17-H), 4.08(m,1-H), 5.77(s,4-H); found C 71.74%, H 9.86%, calculated for $C_{25}H_{42}O_3Si$: C 71.71%, H 10.11%½

Androst-4-ene-1α,17β-diol-3-one, 1.

The silyl ether 9 (0.35g, 0.73mM) was treated at 0° with 40% aqueous HF solution (5 ml) in acetonitrile (100 ml), and deprotection was complete after 1 hour. The reaction mixture was poured onto crushed ice, and extracted with dichloromethane (5x15 ml). After concentration, the crude diol was washed with petrol, and recrystallised from acetone/hexane to yield 1-α-hydroxy-testosterone (0.065g, 30%).
M.pt. 170-172°C;
δ($CDCl_3$,400MHz) 0.77(s,18-Me), 1.18(s,19-Me), 2.52-2.57(ddd,J_{gem} 6.9, $J_{2\beta,4}$ 1.1Hz,2β-H), 2.71-2.76(dd,J_{gem}6.9,$J_{2\alpha,1}$ 2.8Hz,2α-H), 3.71(br.t,17-H), 4.07-4.10(m,1-H), 5.77(m,$J_{2\beta,4}$ 1.1Hz,4-H); found C 75.00%, H 9.22%, calculated for $C_{19}H_{28}O_3$ C 74.96%, H 9.27%.

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2. W.C.Schwarzel, W.G.Kruggel, and H.J.Brodie. Endocrinology, 1973, 92, 866.

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