The Synthesis of 4-Hydroxyandrost-4-ene-3,17-dione and other Potential Aromatase Inhibitors

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We describe novel syntheses of 4-hydroxyandrost-4-ene-3,17-dione (Ia) and related compounds, some containing fluorine. In addition we provide further evidence of the general tendency of 2- and 6-substituted androst-4-ene-3,17-diones to undergo rearrangement reactions, and thus provide new routes to 6-fluoro- and 2,6-difluoro-derivatives. Several of these compounds are potent aromatase inhibitors.

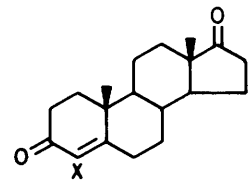
In the Western World breast cancer is the most common malignancy in women. About one third of the tumours require a source of estrogen for growth, and current chemotherapy relies heavily upon the use of antiestrogens which block the uptake of estrogens by the tumour cells.[1] An alternative strategy would involve the use of inhibitors of the biosynthesis of estrogens, and this is the approach that we have taken. The enzyme aromatase catalyses the final stages of estrogen biosynthesis,[2] and it has been known for some time that 4-hydroxyandrost-4-ene-3,17-dione (Ia) can inhibit this enzyme.[3] Previous syntheses of (Ia) [4] appear to be complicated or are low-yielding, and we sought to devise new routes to (Ia) and certain related compounds. In particular, fluoro-analogues are attractive since fluorine has a known propensity to modify the biological activity of drugs without drastically altering their three-dimensional shapes.

Our synthesis of (Ia) proceeds *via* the 4,5-epoxides (II; β : α ratio *ca.* 4 : 1), formed from androst-4-ene-3,17-dione using alkaline hydrogen peroxide, and reaction of these with methanolic sodium hydroxide solution to produce 4-methoxyandrost-4-ene-3,17-dione (Ib) in an overall yield of *ca.* 50%. Treatment of this with acid (12M-HCl in dioxane) gave (Ia) in fair yield (50%). These two compounds, and the corresponding acetate (Ic), were evaluated and shown to have excellent inhibitory activity against aromatase from rat placental tissue.

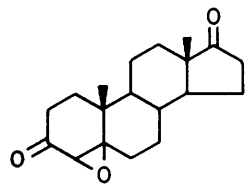
This encouraged us to prepare the related compounds (IIIa—c). Compound (Ib) was converted into the unstable 6β-bromo-derivative [*N*-bromosuccinimide (NBS) in CCl_4], which lost HBr during flash chromatography on silica to yield 4-hydroxyandrosta-4,6-diene-3,17-dione (IIIa). Alternatively slow loss of HBr without concomitant ether cleavage occurred during storage in dichloromethane at room temperature over a period of 48 h, with obtention of 4-methoxyandrosta-4,6-diene-3,17-dione (IIIb).

When the epoxide mixture was treated with Olah's reagent [$(HF)_x$·pyridine] [5] in dichloromethane at 0 °C, 5α-fluoro-4α-hydroxyandrostane-3,17-dione (IV) was the major isolated product, while treatment of the epoxide mixture (II) with tetrabutylammonium fluoride in tetrahydrofuran (THF) gave exclusive formation of the alternative fluorohydrins 4α- and 4β-fluoro-5α-hydroxyandrostane-3,17-dione (V); we are investigating the scope of this reaction with non-steroidal substrates, and for a synthesis of (Id).

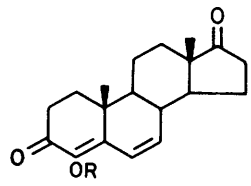
We then focussed our attention upon the synthesis of 6-fluoro-analogues of (Ia), and thus far our efforts have been frustrated owing to the propensity of 6β-bromoandrost-4-ene-3,17-dione (VI) to rearrange. The 'molecular acrobatics' displayed by this compound are not without precedent,[6] but the synthetic utility of some of these transformations is worth noting. Thus, treatment of (VI) with Olah's reagent in admixture with mercury(II) oxide [5] (room temperature, 3 h) provided 6β-fluoroandrost-4-ene-3,17-dione (VIIa) in an isolated yield of 50%.



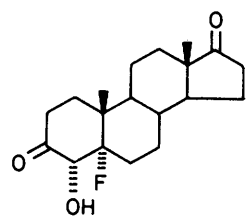
(I) a : X = OH
b : X = OMe
c : X = OAc
d : X = F



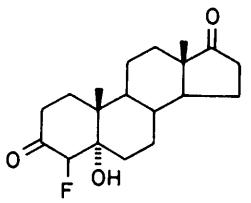
(II)



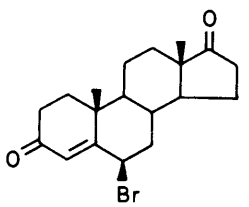
(III) a : R = H
b : R = Me
c : R = Ac



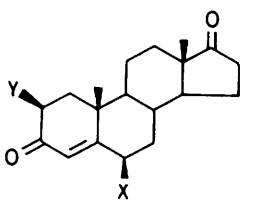
(IV)



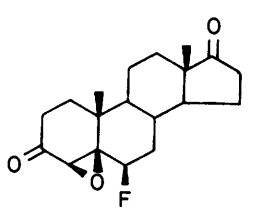
(V)



(VI)



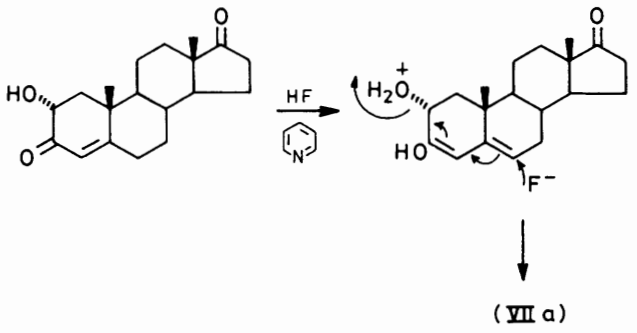
(VII) a : X = F, Y = H
b : X = Y = F



(VIII)

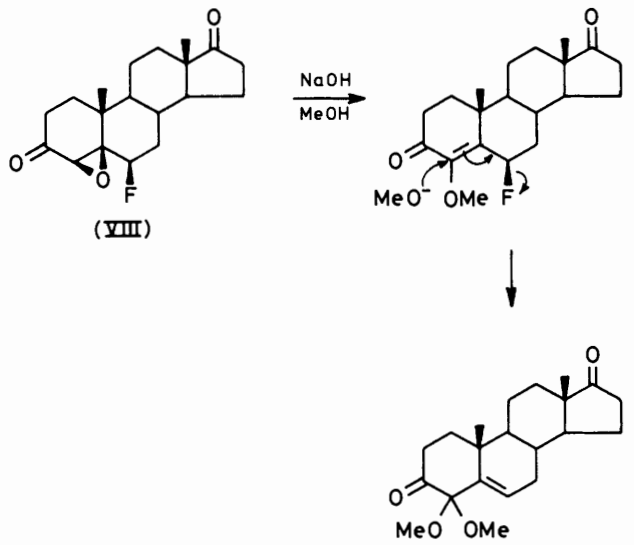
Androsta-4,6-diene-3,17-dione could be obtained as the

major product (57%) if tetrabutylammonium fluoride was utilised (room temperature, THF, 1 h), while exposure of (VI) to refluxing methanol (as previously reported)[7] allowed obtention of androstane-3,6,17-trione as the main product (55%). These are all preparatively useful reactions, especially since the bromide (VI) is so easily accessible from androst-4-ene-3,17-dione (NBS in CCl_4). It might also be noted that the alternative route to (VIIa), introduced by Ringold,[8] involves five steps.



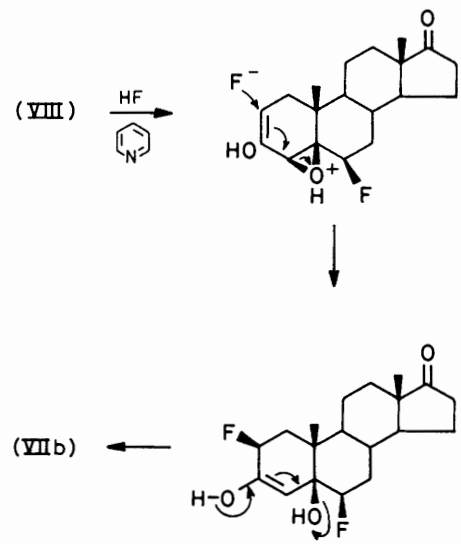
Scheme 1.

We have also obtained (VIIa) in serendipitous fashion from 2α-hydroxyandrost-4-ene-3,17-dione[4] and Olah's reagent in CH_2Cl_2 (50% isolated yield), and a possible mechanism is shown in Scheme 1. This is now our method of choice for preparing (VIIa).



Scheme 2.

Having obtained quantities of (VIIa) we attempted to convert it into the corresponding 4-hydroxy-compound. The 4β,5β-epoxide (VIII) was obtained in fair yield (alkaline H_2O_2), but upon treatment with methanolic sodium hydroxide solution rearrangement occurred to yield 4,4-dimethoxy-androst-5-ene-3,17-dione, and a possible mechanism is shown in Scheme 2. In a further attempt, the epoxide (VIII) was refluxed with 98% formic acid [a method which we and others[4] have used to prepare (Ia) from (II)] with obtention of 2α-hydroxy-6β-fluoroandrost-4-ene-3,17-dione (50% isolated yield). This experiment demonstrates the reversibility of part of the process shown in Scheme 1. Finally, treatment of (VIII) with Olah's reagent yielded 2β,6β-difluoroandrost-4-ene-3,17-dione (VIIb) in excellent yield (73%) (Scheme 3).



Scheme 3.

The process involved here is formally an S_N2' reaction and the stereochemistry at C-2 is not unexpected. That both fluorines in (VIIb) were axial was evident from the fluorine coupling between both atoms and the C-19 methyl. It is of interest to note that reaction of 4β,5β-epoxy-17-hydroxy-androstan-3-one wtih anhydrous HF in an ethanol–chloroform mixture provided 2α-fluorotestosterone exclusively,[6] and that such changes of stereochemical outcome are a common feature of this kind of reaction.

The 6β-fluoro-compound (VIIIa) had excellent activity as an aromatase inhibitor, but the 2,6-difluoro-compound (VIIb) only possessed weak activity.

Experimental

I.r. spectra were recorded with a Perkin-Elmer 157 double-beam grating spectrophotometer (solution spectra using chloroform as solvent); ^1H n.m.r. spectra were recorded with a Varian T-60 (60 MHz) or a Varian HA 100 (100 MHz) instruments (tetramethylsilane as internal standard); ^{13}C n.m.r. spectra were recorded by Dr. Brian Wood at the City of London Polytechnic on a Jeol FX90Q (90 MHz) instrument; and mass spectra were recorded on an A.E.I. MS12 spectrometer. Kieselgel $GF_{254+366}$ (Merck) was used for analytical t.l.c., and flash chromatography[9] was performed with Merck silica gel (230—400 mesh). Organic solvents were distilled from calcium hydride when required anhydrous. Light petroleum refers to that fraction boiling in the range 40—60 °C.

4β,5β-*Epoxyandrostane*-3,17-*dione* 4β,5β-(II).—Aqueous sodium hydroxide (4M; 25 ml) and hydrogen peroxide (30%; 40 ml) were added dropwise to a stirred ice-cold solution of androst-4-ene-3,17-dione (I; X = H) (10 g, 0.035 mol) in AnalaR methanol (300 ml). The reaction mixture was stored at 4 °C overnight and was then poured onto crushed ice (500 g). Filtration afforded a *ca.* 4 : 1 mixture of 4β,5β- and 4α,5α-epoxides in variable yields of 33—90%, or an average of 68%

over thirteen recorded runs. Recrystallisation of the epimeric mixture from benzene afforded the pure 4β,5β-epoxide as prisms, m.p. 201—203 °C (lit.,[4] 202—203 °C); $\nu_{max.}$ (Nujol) 1 735 (C-17 ketone), 1 707 (C-3 ketone), 1 450, 1 400, 1 355, and 1 240 cm^{-1}; δ ($CDCl_3$) 0.9 (3 H, s, 18-H_3), 1.2 (3 H, s, 19-H_3), and 3.0 (1 H, s, epoxide H).

4-*Methoxyandrost*-4-*ene*-3,17-*dione* (Ib).—Aqueous sodium hydroxide (4M; 30 ml) was added to a solution of 4,5-epoxyandrostane-3,17-dione (II) (a mixture of epimers; 3 g, 0.01 mol) in AnalaR methanol (375 ml), and the reaction mixture was then refluxed for 3 h. The bulk of the solvent was removed under reduced pressure, the residue was treated with water (100 ml), and the product was extracted into dichloromethane (4 × 50 ml). The combined organic extracts were washed in turn with water (2 × 50 ml) and brine (50 ml), and were then dried over sodium sulphate and purified by flash chromatography with diethyl ether–tetrachloromethane (2 : 1) as eluant to yield pale yellow needles of the *vinyl ether* (Ib) (1.94 g, 62%). Recrystallisation from diethyl ether provided an analytical sample, m.p. 136—138 °C; $[\alpha]_D^{20}$ +177° (*c* 7.6, $CHCl_3$); $\nu_{max.}$ (CCl_4) 2 945, 2 890, 2 860, 2 830, 1 745 (C-17 ketone), 1 685 (C-3 ketone), 1 610, 1 453, 1 375, 1 360, 1 313, 1 240, 1 210, 1 150, 1 100, and 1 090 cm^{-1}; δ ($CDCl_3$) 0.9 (3 H, s, 18-H_3), 1.25 (3 H, s, 19-H_3), and 3.6 (3 H, s, OMe); *m/z* 316 (88%), (M^+), 273 (100), 154 (44), 152 (43), 125 (47), 124 (48), 91 (44), and 79 (48) (Found: C, 75.8; H, 9.1. $C_{20}H_{28}O_3$ requires C, 75.91; H, 8.92%).

4-*Hydroxyandrost*-4-*ene*-3,17-*dione* (Ia).—*Method* (*a*). Hydrochloric acid (12M; 3.5 ml) was added to a solution of 4-methoxyandrost-4-ene-3,17-dione (Ib) (0.33 g, 1 mmol) in dioxane (42 ml) and the mixture was refluxed for 24 h. After being cooled the solution was poured into water (200 ml) and extracted with dichloromethane (4 × 50 ml). The combined organic extracts were washed in turn with water (2 × 50 ml), aqueous sodium hydrogen carbonate (5%; 2 × 50 ml), and then water (4 × 50 ml), and purified by flash chromatography using ethyl acetate–light petroleum (9 : 11) as eluant. The pure product (Ia) was obtained as needles (0.17 g, 53%), m.p. 201—203 °C (lit.,[4] 202—203 °C); $[\alpha]_D^{20}$ +181° (*c* 7.7, $CHCl_3$); $\nu_{max.}$ (Nujol) 3 420 and 3 395 (OH), 1 740 (C-17 ketone), 1 665 (C-3 ketone), 1 633, 1 460, 1 385, and 1 163 cm^{-1}; δ_H ($CDCl_3$) 0.9 (3 H, s, 18-H_3), 1.2 (3 H, s, 19-H_3), and 6.1 (1 H, br s, OH); δ_C ($CDCl_3$) 138.921 (C-5), 141.150 (C-4), 193.220 (C-3), and 220.252 p.p.m. (C-17) (Found: C, 75.55; H, 8.6. Calc. for $C_{19}H_{26}O_3$: C, 75.50; H, 8.61%).

Method (*b*). A solution of compound (II) (3 g, 0.01 mol) in AnalaR formic acid (45 ml) was refluxed for 45 min and was then poured into hot water (150 ml; 60 °C). The mixture was allowed to cool and was kept at room temperature overnight, and the brown, waxy residue was purified by flash chromatography with diethyl ether–CCl_4 (1 : 1) as eluant. The product (Ia) was obtained as almost colourless needles (1.35 g, 45%), m.p. 199—202 °C, and spectroscopic data identical with those reported above.

4-*Acetoxyandrost*-4-*ene*-3,17-*dione* (Ic).—A solution of the epimeric epoxides (II) (5 g, 0.017 mol) in dry THF (80 ml) was added to stirred pyridinium poly(hydrogen fluoride) (50 ml) at 0 °C. The reaction mixture was stirred vigorously at 0 °C for 2.5 h, then was poured onto ice–water and the products were extracted into dichloromethane (5 × 50 ml). The combined organic extracts were washed in turn with water (3 × 50 ml) and brine (50 ml), and dried over sodium sulphate. The solvent was then removed and the residual oil was dissolved in anhydrous pyridine (60 ml). Acetic anhydride (35 ml, *ca.* 0.37 mol) was added and the mixture was stirred at room temperature for 3 h and was then poured onto ice (500 g). The product was extracted with dichloromethane (6 × 50 ml), and the extract was washed in turn with HCl (2M; 2 × 50 ml), aqueous sodium hydrogen carbonate (5%; 2 × 50 ml), and brine (50 ml), and was then dried. Concentration yielded a yellowish waxy solid which was triturated with a mixture of ethyl acetate and light petroleum (1 : 1; *ca.* 60 ml). Unchanged epoxides (2.31 g) could then be filtered off, and flash chromatography of the filtrate residuum using ethyl acetate–light petroleum (1 : 1) as eluant afforded the crystalline product (Ic) (0.5 g, 15%), m.p. 183—184 °C (lit.,[3] 184—184.5 °C); $\nu_{max.}$ (CCl_4) 2 950, 2 890, 2 865, 1 740 (ester and C-17 ketone), 1 700 (C-3 ketone), 1 550, 1 373, 1 250, 1 213, 1 197, 1 147, 1 005, 980, and 910 cm^{-1}; δ ($CDCl_3$) 0.9 (3 H, s, 18-H_3), 1.25 (3 H, s, 19-H_3), and 2.25 (3 H, s, acetate methyl).

4-*Hydroxyandrosta*-4,6-*diene*-3,17-*dione* (IIIa).—A mixture of NBS (2.23 g, 13 mmol), 4-methoxyandrost-4-ene-3,17-dione (Ib) (2.05 g, 8 mmol), and dibenzoyl peroxide (0.09 g) dissolved in AnalaR tetrachloromethane (325 ml) was heated under reflux for 20 min. After being cooled to room temperature, the mixture was filtered and the filtrate was washed in turn with water (2 × 50 ml), aqueous sodium hydrogen carbonate (5%; 50 ml), water (50 ml), and brine (50 ml). The organic extract was dried then concentrated to *ca.* 20 ml and adsorbed onto silica gel (*ca.* 20 g). The latter was then applied to a column of silica for flash chromatography and elution with diethyl ether–tetrachloromethane (3 : 1) afforded the *dienol* (IIIa) as the sole elution product (1.09 g, 46%) in the form of needles, m.p. 189—191 °C; $[\alpha]_D^{20}$ +137° (*c* 1.4, $CHCl_3$); $\nu_{max.}$ 3 450br (OH), 3 030 and 3 010 (olefin), 2 970, 2 950, 2 920, 2 870, 1 740 (C-17 ketone), 1 663 (C-3 ketone), 1 620, 1 385, and 1 103 cm^{-1}; δ_H ($CDCl_3$) 0.95 (3 H, s, 18-H_3), 1.1 (3 H, s, 19-H_3), 6.15 (1 H, dd, $J_{6,7}$ 10 and $J_{6,8}$ 2 Hz, 6-H), 6.3 (1 H, br s, OH), and 6.65 (1 H, dd, $J_{6,7}$ 10 and $J_{7,8}$ 3 Hz, 7-H); δ_C ($CDCl_3$) 122.217 (C-6), 134.027 (C-5), 135.057 (C-7), 140.528 (C-4), 193.728 (C-3), and 219.948 p.p.m. (C-17) (Found: C, 75.9; H, 8.25. $C_{19}H_{24}O_3$ requires C, 75.97; H, 8.05%).

4-*Methoxyandrosta*-4,6-*diene*-3,17-*dione* (IIIb).—A mixture of NBS (0.91 g, 5 mmol), 4-methoxyandrost-4-ene-3,17-dione (Ib) (1 g, 3.2 mmol), and dibenzoyl peroxide (0.04 g) dissolved in AnalaR CCl_4 was heated at reflux for 20 min, precisely as described above. After an identical work-up, the oily product was dissolved in dichloromethane (100 ml), and the solution was kept at room temperature, in an open flask, for 48 h. The solution was then washed in turn with aqueous sodium hydrogencarbonate (5%; 25 ml), water (25 ml), and brine (25 ml), and was then dried and concentrated. Purification by flash chromatography with diethyl ether–tetrachloromethane (3 : 1) as eluant provided the *dienyl ether* (IIIb) (0.33 g, 33%) as pale yellow needles. An analytical sample was produced upon recrystallisation from diethyl ether, m.p. 162—163 °C; $\nu_{max.}$ 3 030 and 3 003 (olefin), 2 965, 2 945, 2 865, 1 737 (C-17 ketone), 1 665 (C-3 ketone), 1 615, 1 320, and 1 100 cm^{-1}; δ ($CDCl_3$) 0.95 (3 H, s, 18-H_3), 1.15 (3 H, s, 19-H_3), 3.7 (3 H, s, OMe), 6.15 (1 H, dd, $J_{6,7}$ 9 and $J_{6,8}$ 2 Hz, 6-H), and 6.7 (1 H, dd, $J_{6,7}$ 9 and $J_{7,8}$ 2 Hz, 7-H) [Found: M^+, 314.1877 (100%). $C_{20}H_{26}O_3$ requires *M*, 314.1882].

4-*Acetoxyandrosta*-4,6-*diene*-3,17-*dione* (IIIc).—Acetic anhydride (1.75 ml, *ca.* 18.5 mmol) was added to a stirred solution of compound (IIIa) (1.09 g, 3.6 mmol) in anhydrous pyridine (10 ml). The solution was stirred at room temperature for 1.5 h, then was poured into ice–water (150 ml) and extracted with dichloromethane (4 × 50 ml). The combined organic extracts were washed in turn with hydro-

chloric acid (2M; 40 ml) and brine (40 ml), and were then purified by flash chromatography using diethyl ether–tetrachloromethane (4 : 1) as eluant. This afforded the *dienyl acetate* (IIIc) (1.05 g, 84%) as pale yellow needles, and an analytical sample was obtained by recrystallisation from diethyl ether–CH_2Cl_2, m.p. 165—167 °C; $\nu_{max.}$ 3 030 and 3 010 (olefin), 2 950, 2 870, 1 763 (ester), 1 740 (C-17 ketone), 1 680 (C-3 ketone), 1 625, 1 597, 1 200, and 1 093 cm^{-1}; δ ($CDCl_3$) 0.95 (3 H, s, 18-H_3), 1.2 (3 H, s, 19-H_3), 2.25 (3 H, s, acetate methyl), and 6.2—6.6 (2 H, m, 6- and 7-H) [Found: M^+, 342.1820 (100%). $C_{21}H_{26}O_4$ requires M, 342.1831].

5α-*Fluoro*-4α-*hydroxyandrostane*-3,17-*dione* (IV).—Pyridinium poly(hydrogen fluoride) (65 ml) was added to a mixture of the epimeric epoxides (II) (4 g, 0.013 mol), and the resultant red solution was immediately immersed in a bath at −78 °C. The reaction mixture was maintained at this temperature for 1.5 h and was then poured onto crushed ice (*ca.* 400 g) and extracted with dichloromethane (5 × 50 ml). The combined extracts were washed in turn with water (3 × 50 ml) and brine (50 ml), and were dried before concentration. Trituration with CCl_4 (*ca.* 10 ml) gave the product (IV) (1.16 g, 27%) as a microcrystalline solid, m.p. 205—206 °C (lit.,[10] 207—208 °C); $\nu_{max.}$ (Nujol) 3 485 (OH), 1 735 (C-17 ketone), 1 720 (C-3 ketone), 1 457, and 1 377 cm^{-1}; δ ($CDCl_3$) 0.9 (3 H, s, 18-H_3), 1.1 (3 H, d, J 1 Hz, 19-H_3), 3.4 (1 H, br m, OH), and 4.55 (1 H, dm, J 32 Hz, 4-H).

6β-*Fluoroandrost*-4-*ene*-3,17-*dione* (VIIa) *Method* (*a*).—A solution of 2α-hydroxyandrost-4-ene-3,17-dione (prepared by Kirk's method [4]) (6.5 g, 21.5 mmol) in dichloromethane (100 ml) was added to a vigorously stirred solution of $(HF)_x$·pyridine (80 ml) in dichloromethane (100 ml) at 0 °C. The reaction mixture was stirred at 0 °C for one hour, then allowed to warm to room temperature, and then stirred at this temperature overnight. The mixture was poured onto crushed ice (*ca.* 500 g) and the organic layer was collected. The aqueous layer was extracted with dichloromethane (5 × 50 ml), and the combined organic phases were washed successively with water (3 × 50 ml), aqueous sodium hydrogen carbonate (5%; 50 ml), water (50 ml), and brine (50 ml). After the solution had been dried, and the solvent removed, the residue was purified by flash chromatography with diethyl ether–CH_2Cl_2 (3 : 2) as eluant to produce the allylic fluoride (VIIa) (2.06 g, 54% based upon the amount of starting steroid consumed), and also unchanged starting steroid (2.73 g). Compound (VIIa) was isolated as needles, m.p. 134—136 °C (lit.,[8] 136—138 °C); $[\alpha]_D^{20}$ +78° (*c* 8.9, $CHCl_3$) (lit.,[8] +82°); $\nu_{max.}$ 3 037 and 3 010 (olefin), 2 955, 2 925, 2 870, 2 850, 1 740 (C-17 ketone), 1 685 (C-3 ketone), 1 623, and 1 015 cm^{-1}; δ_H ($CDCl_3$) 0.95 (3 H, s, 18-H_3), 1.35 (3 H, d, $J_{H,F}$ 3 Hz, 19-H_3), 5.05 (1 H, dt, $J_{H,F}$ 49 and 2.5 Hz, 6-H), and 5.9 (1 H, d, $J_{H,F}$ 5 Hz, 4-H); δ_C ($CDCl_3$) 219.598 (C-17), 199.309 (C-3), 161.018 (d, J 13.3 Hz, C-5), 128.621 (d, J 9.3 Hz, C-4), 92.999 (d, J 167.2 Hz, C-6) (*cf.* lit. spectrum [11]) (Found: C, 75.0; H, 8.5; F, 5.8. Calc. for $C_{19}H_{25}FO_2$: C, 74.97; H, 8.28; F, 6.24%).

Androsta-4,6-*diene*-3,17-*dione*.—A solution of tetrabutylammonium fluoride in THF (4.1 ml; 4.1 mmol) was added to a solution of 6β-bromoandrost-4-ene-3,17-dione (VI) (0.5 g, 1.4 mmol) in dry THF (25 ml). After 1 h at room temperature the solvent was removed under reduced pressure and the residual brown oil was redissolved in dichloromethane (50 ml). The solution was washed in turn with water (5 × 10 ml) and brine (10 ml), and subjected to flash chromatography using diethyl ether–CCl_4 (2 : 1) as eluant. This afforded androsta-4,6-diene-3,17-dione (0.22 g, 58%) as crystals, m.p. 168—169 °C (lit.,[12] 169—170 °C); $\nu_{max.}$ 3 030 and 3 005 (olefin), 2 970, 2 950, 2 865, 1 737 (C-17 ketone), 1 660 (C-3 ketone), 1 620, and 1 585 cm^{-1}; δ ($CDCl_3$) 1.0 (3 H, s, 18-H_3), 1.15 (3 H, s, 19-H_3), 5.65 (1 H, s, 4-H), and 6.15 (2 H, s, 6- and 7-H).

4-*Fluoro*-5α-*hydroxyandrostane*-3,17-*diones* (V).—A solution of tetrabutylammonium fluoride in THF (10 ml, 10 mmol) was added to a solution of the epoxides (II) (1 g, 3.3 mmol) in dry THF (34 ml). The reaction mixture was refluxed for 20 min, the solvent was removed under reduced pressure, and the residual orange oil was then redissolved in dichloromethane (35 ml) and the solution was washed successively with water (5 × 20 ml) and brine (20 ml). Flash chromatography using ethyl acetate–light petroleum (9 : 1) as eluant provided an inseparable mixture of the epimeric fluorohydrins (V) (0.64 g, 60%); $\nu_{max.}$ 3 450br (OH), 1 740 (C-3 and C-17 ketones), 1 465, 1 453, and 1 375 cm^{-1}; δ ($CDCl_3$) 3.6 (1 H, dm, J 56 Hz, 4-H).

6β-*Fluoroandrost*-4-*ene*-3,17-*dione* (VIIa) *Method* (*b*).— 6β-Bromoandrost-4-ene-3,17-dione (VI) (0.7 g, 1.9 mmol) (prepared from androst-4-ene-3,17-dione by the method of Numazawa and Osawa [7]) was added to a vigorously stirred suspension of yellow mercury(II) oxide (0.83 g, 3.8 mmol) in pyridinium poly(hydrogen fluoride) (7 ml) at room temperature.[5] After 3 h the mixture was poured onto crushed ice (30 g) and extracted with dichloromethane (4 × 20 ml). The combined extracts were washed successively with water (2 × 20 ml) and brine (20 ml) and were then dried and concentrated before purification by flash chromatography with diethyl ether–CCl_4 (4 : 1). Further chromatography and several recrystallisations were necessary in order to free the product of small amounts of a mercury-containing impurity whose structure is as yet unknown. The yield was then 0.29 g (50%), and spectral and chromatographic characteristics were identical with those observed with the product obtained using method (a) above.

4β,5β-*Epoxy*-6β-*fluoroandrostane*-3,17-*dione* (VIII).—Aqueous sodium hydroxide (4M; 10 ml) and hydrogen peroxide (30%; 17 ml) were added dropwise to a stirred ice-cold solution of 6β-fluoroandrost-4-ene-3,17-dione (VIIa) (4.59 g, 15 mmol) in AnalaR methanol (150 ml). The reaction mixture was stored at 4 °C overnight and was then poured onto crushed ice (250 g). Filtration afforded a crude product which was then dried *in vacuo* and recrystallised from dichloromethane–diethyl ether to yield crystals of *compound* (VIII) (2.83 g, 58%), m.p. 215—217 °C; $[\alpha]_D^{20}$ −19° (*c* 10, $CHCl_3$); $\nu_{max.}$ 3 035 and 3 015, 2 955, 2 925, 2 900, 2 870, 2 850, 1 735 (C-17 ketone), 1 725 (C-3 ketone), 1 263, 1 233, and 1 210 cm^{-1}; δ ($CDCl_3$) 0.95 (3 H, s, 18-H_3), 1.2 (3 H, d, J 3.5 Hz, 19-H_3), 3.3 (1 H, s, 4-H), and 4.05 (1 H, dt, $J_{H,F}$ 48 and 2 Hz, 6-H) (Found: C, 71.3; H, 7.9; F, 5.6. $C_{19}H_{25}FO_3$ requires C, 71.22; H, 7.87; F, 5.93%).

4,4-*Dimethoxyandrost*-5-*ene*-3,17-*dione*.—Aqueous sodium hydroxide (4M; 6.5 ml) was added to a solution of compound (VIII) (0.66 g, 2.1 mmol) in AnalaR methanol (70 ml) and the reaction mixture was refluxed for 3 h. The bulk of the solvent was removed under reduced pressure and the residue was diluted with water (20 ml) and then extracted with dichloromethane (4 × 10 ml). The combined organic extracts were washed in turn with water (2 × 7 ml) and brine (7 ml), and were then dried and concentrated. Flash chromatography using diethyl ether–CCl_4 (2 : 1) as eluant afforded 4,4-*dimethoxyandrost*-5-*ene*-3,17-*dione* (0.31 g, 44%) as crystals, m.p. 148—149 °C; $[\alpha]_D^{20}$ +6.5° (*c* 7.8, $CHCl_3$); $\nu_{max.}$ 3 030 and

3 010 (olefin), 2 955, 2 925, 2 865, 2 850, 1 737 (C-3 and C-17 ketones), 1 377, 1 155, 1 140, 1 087, 1 070, 1 050, and 1 020 cm^{-1}; δ_H ($CDCl_3$) 0.9 (3 H, s, 18-H_3), 1.3 (3 H, s, 19-H_3), 3.15 (3 H, s, OMe), 3.4 (3 H, s, OMe), and 6.2 (1 H, m, 6-H); δ_C ($CDCl_3$) 220.544 (C-17), 206.838 (C-3), 139.011 (C-5), 128.664 (C-6), and 100.331 p.p.m. (C-4) [Found: M^+, 346.2146 (100%). $C_{21}H_{30}O_4$ requires M, 346.2144].

2α-*Hydroxy*-6β-*fluoroandrost*-4-*ene*-3,17-*dione*.—Formic acid (5.5 ml, 146 mmol) was added to compound (VIII) (0.35 g, 1.09 mmol) and the resulting solution was refluxed for 45 min, then poured into hot water (100 ml), and the mixture was allowed to cool to room temperature. The mixture was extracted with dichloromethane (5 × 20 ml) and the combined organic extracts were then washed with brine (20 ml), dried, and concentrated. The residue was purified by flash chromatography with ethyl acetate–light petroleum (3 : 1) as eluant. Recrystallisation of the product provided crystals of 2α-*hydroxy*-6β-*fluoroandrost*-4-*ene*-3,17-*dione* (0.18 g, 51%), m.p. 148—150 °C; $\nu_{max.}$ 3 030 and 3 010 (olefin), 2 970, 2 950, 2 925, 2 865, 1 740 (C-17 ketone), 1 697 (C-3 ketone), 1 120, 1 087, and 1 020 cm^{-1}; δ ($CDCl_3$) 1.0 (3 H, s, 18-H_3), 1.35 (3 H, d, $J_{H,F}$ 4 Hz, 19-H_3), 3.6 (1 H, br m, OH), 4.2 (1 H, dd, J 5.5 and 13.5 Hz, 2-H), 5.15 (1 H, dt, J 3, $J_{H,F}$ 50 Hz, 6-H), and 5.95 (1 H, d, J 3.5 Hz, 4-H) [Found: M^+, 320.1787 (100%). $C_{19}H_{25}FO_3$ requires M, 320.1788].

2β,6β-*Difluoroandrost*-4-*ene*-3,17-*dione* (VIIb).—Pyridinium poly(hydrogen fluoride) (25 ml) was added to compound (VIII) (1.40 g, 4.38 mmol) at 0—4 °C, and the mixture was held at this temperature for 24 h. It was then poured onto ice (*ca.* 200 g) and extracted with dichloromethane (5 × 30 ml). The combined organic extracts were washed successively with water (30 ml), aqueous sodium hydrogencarbonate (5%; 30 ml), water (2 × 30 ml), and finally brine (30 ml). After flash chromatography using diethyl ether–CCl_4 (3 : 1) as eluant, the *title compound* was isolated as crystals (1.0 g, 72%), m.p. 185 °C (decomp.); $[\alpha]_D^{20}$ −14.5° (*c* 7.2, $CHCl_3$); $\nu_{max.}$ 3 010 (olefin), 2 950, 2 925, 2 890, 1 737 (C-17 ketone), 1 705 (C-3 ketone), 1 017, and 863 cm^{-1}; δ_H ($CDCl_3$) 0.95 (3 H, s, 18-H_3), 1.45 (3 H, q, $J_{H,F}$ 3.5 and 2 Hz 19-H_3), 2.7 (1 H, d of dd, J 2 and 7, $J_{H,F}$ 40 Hz, 2-H), 5.1 (1 H, dd, J 2.5, $J_{H,F}$ 50 Hz, 6-H), and 6.05 (1 H, m, 4-H); δ_C ($CDCl_3$) 219.491 (C-17), 192.939 (d, J 16.2 Hz, C-3), 163.560 (d, J 13.7 Hz, C-5), 124.595 (d, J 8.1 Hz, C-4), 92.865 (d, J 172.4 Hz, C-6), and 87.492 p.p.m. (d, J 180.2 Hz, C-2); δ_F ($CDCl_3$; relative to $CFCl_3$) −168.6 (d, $J_{F,C}$ 172.4 Hz, 6-F) and −187.7 (d, $J_{F,C}$ 180.2 Hz, 2-F) [Found: C, 70.55; H, 7.5; F, 10.8 (and 10.7 and 10.8; three determinations). $C_{19}H_{24}F_2O_2$ requires C, 70.81; H, 7.45; F, 11.80%].

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