Regiospecific Syntheses of Modified Steroid Hormones. Part V.[1] 6β-Fluoro-7α-hydroxy-17β-oestradiol, 7α-Fluoro-6α-hydroxy-17β-oestradiol, and 7α-Fluoro-17β-oestradiol

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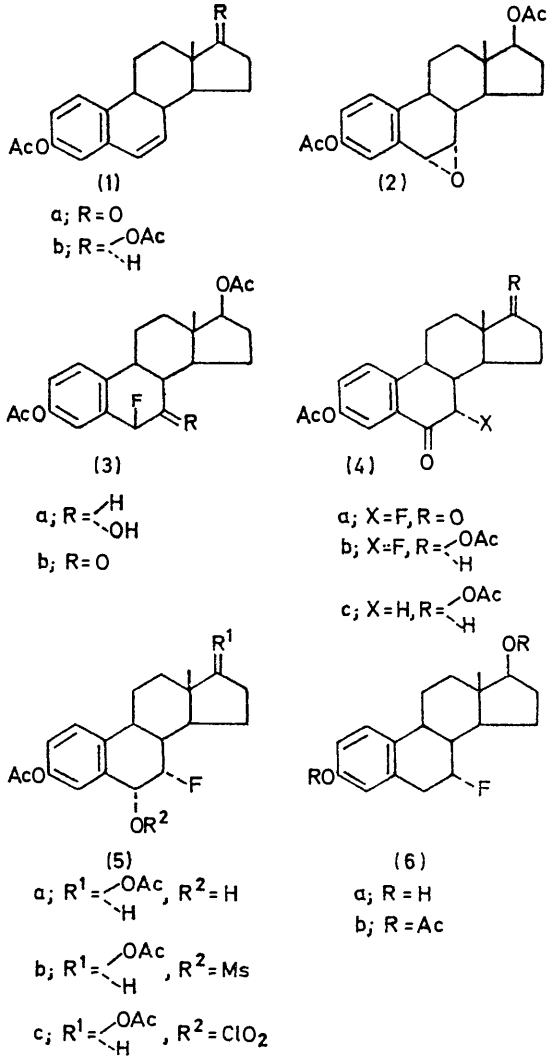
6β-Fluoro-7α-hydroxy-17β-oestradiol 3,17-diacetate (3a) was obtained by reaction of hydrogen fluoride with 6α,7α-epoxy-17β-oestradiol diacetate (2). Oxofluorination of oestra-1,3,5(10),6-tetraene-3,17β-diol diacetate (1b) gave 7α-fluoro-6-oxo-17β-oestradiol diacetate (4b), which was reduced stereoselectively to 7α-fluoro-6α-hydroxy-17β-oestradiol 3,17-diacetate (5a). Conversion of the 6α-ol (5a) into the 6-methanesulphonate (5b), followed by reaction with lithium aluminium hydride, gave 7α-fluoro-17β-oestradiol (6a).

REGIOSPECIFIC syntheses of ring-A-monohalogeno ring-A-aromatic steroids are described in the preceding papers.[1b-d] A preliminary communication [1a] outlined the synthesis of the ring-B-monohalogeno ring-A-aromatic steroid, 7α-fluoro-17β-oestradiol (6a), *via* 7α-fluoro-6-oxo-17β-oestradiol diacetate (4b), 7α-fluoro-6α-hydroxy-17β-oestradiol 3,17-diacetate (5a), and 7α-fluoro-6α-mesyloxy-17β-oestradiol diacetate (5b). We now give details of this synthesis, together with that of the fluorohydrin isomeric with (5a), 6β-fluoro-7α-hydroxy-17β-oestradiol 3,17-diacetate (3a), and the fluoro-ketone isomeric with (4b), 6β-fluoro-7-oxo-17β-oestradiol diacetate (3b).

The common starting material was oestra-1,3,5(10),6-tetraene-3,17β-diol diacetate (1b).[2] Epoxidation of (1b) with *m*-chloroperbenzoic acid in methylene chloride gave the 6α,7α-epoxide (2).[3] The best conditions for the regio-specific oxiran ring opening by hydrogen fluoride to give the *trans*-fluorohydrin (3a) involved addition of hydrogen fluoride in tetrahydrofuran (molar ratio 1 : 1·7) at −65° in 470-fold excess to the epoxide (2) in methylene chloride, and work-up after 64 h at 0°. The assignment of the stereochemistry of the *trans*-fluorohydrin (3a) was supported by its n.m.r. spectrum, and by its i.r. spectrum, which exhibited bands at 3622 and 3590 cm^{-1}, the relative intensity of which was dependent on concentration in the range 0·005—0·015M in carbon tetrachloride solution. Chromic acid oxidation of the *trans*-fluorohydrin (3a) gave 6β-fluoro-7-oxo-17β-oestradiol diacetate (3b). This compound showed an enhanced Cotton effect (*a* 416), suggesting chiral orbital overlap in the homobenzylic ketone system.

The synthesis of 7α-fluoro-17β-oestradiol (6a) required the design of a new reaction for regiospecific and stereoselective fluorination at C-7α; no such procedure was known.[4] The oxofluorination reaction [5] was developed with indene as a model compound for ring-A-aromatic Δ^6-steroids, *e.g.* (1a and b). The major product of oxofluorination of indene was 2-fluoroindanone,[5] corresponding to 3-acetoxy-7α-fluoro-oestra-1,3,5(10)-triene-6,17-dione (4a),[5b] obtained by oxofluorination of 3-acetoxy-oestra-1,3,5(10),6-tetraen-17-one (1a). The oxofluorination of oestra-1,3,5(10),6-tetraene-3,17β-diol diacetate (1b), used in the synthesis of 7α-fluoro-17β-oestradiol (6a),[1a] was envisaged as regiospecific fluorination at C-7,



concomitant with *cis*-chloryloxylation at C-6, by stereoselective α-side approach of perchloryl fluoride to the

[1] (*a*) Part I, M. Neeman and Y. Osawa, *Tetrahedron Letters*, 1963, 1987; (*b*) Part II, M. Neeman, Y. Osawa, and T. Mukai, *J.C.S. Perkin I*, 1972, 2297; (*c*) Part III, M. Neeman, T. Mukai, J. S. O'Grodnick, and A. L. Rendall, *ibid.*, p. 2300; (*d*) Part IV, M. Neeman, J. S. O'Grodnick, and K. Morgan, *ibid.*, p. 2302.

[2] C. Djerassi, G. Rosenkranz, J. Romo, S. Kaufmann, and J. Pataki, *J. Amer. Chem. Soc.*, 1950, **72**, 4534.

[3] J. Iriarte, H. J. Ringold, and C. Djerassi, *J. Amer. Chem. Soc.*, 1958, **80**, 6105.

[4] A. A. Akhrem, I. G. Reshetova, and Y. A. Titov, *Uspekhi Khim.*, 1965, **34**, 2171 (*Russ. Chem. Rev.*, 1965, 926).

[5] (*a*) M. Neeman and Y. Osawa, Abstracts of the 2nd International Symposium of Fluorine Chemistry, Estes Park, Colorado, July 1962, p. 44; (*b*) M. Neeman and Y. Osawa, *J. Amer. Chem. Soc.*, 1963, **85**, 232.

styrene bond of (1b); the postulated intermediate 6α-chloryloxy-7α-fluoro-17β-oestradiol diacetate (5c) was expected to undergo ready elimination of chlorous acid to give 7α-fluoro-6-oxo-17β-oestradiol diacetate (4b), which was the major isolable product. The 7α-fluoro-6-ketone (4b) showed a 16 nm bathochromic shift on its o.r.d. maximum relative to 6-oxo-oestradiol diacetate (4c).[6]

Reduction of the fluoro-ketone (4b) with sodium borohydride afforded stereoselectively the *cis*-fluorohydrin (5a), which was converted into its 6-mesylate (5b). The assigned stereochemistry of the 7α,6α-fluorohydrin (5a) was supported by its i.r. spectrum, which showed a band at 3590 cm^{-1} (CCl_4) independent of concentration (5—15mM). The 6-mesylate (5b) gave 7α-fluoro-17β-oestradiol (6a) on reductive removal of the mesyloxy-group with lithium aluminium hydride.

EXPERIMENTAL

For general directions see Part II.[1b]

7α-Fluoro-6-oxo-17β-oestradiol Diacetate (4b).—A slow stream of perchloryl fluoride was passed through a solution of oestra-1,3,5(10),6-tetraene-3,17β-diol diacetate (1b)[2] (8·96 g) in dioxan–water (99 : 1; 70 ml) at 23° for 70 h. Nitrogen was bubbled through the mixture for 5 min, most of the solvent was evaporated off at 0—10° under reduced pressure,* and the residue was taken up in benzene–diethyl ether (5 : 2; 700 ml). The solution was washed with water, dried (Na_2SO_4), and evaporated to dryness. The product was chromatographed on Fluorisil (100 g), first with benzene (1 l) as eluant, and then with a gradient of benzene (2 l) changing to acetone–benzene (1 : 4) (200 ml). Eluate (1500 ml) from the gradient elution gave crystalline material (2·127 g), which afforded *7α-fluoro-6-oxo-17β-oestradiol diacetate* (4b) (1·267 g, 13%), m.p. 174—175° (from ethanol); $\lambda_{max.}$ (EtOH) 211 (ε 20,000), 255 (10,500), and 305 nm (2200); $\nu_{max.}$ (CH_2Cl_2) 1764, 1727, and 1695 cm^{-1}; δ($CDCl_3$) 4·81 (1H, m, *J* 50 Hz, 7β-H), 2·32 (3H, s, 3-OAc), and 2·07 (3H, s, 17-OAc); o.r.d. (*c* 0·10 in dioxan) $[\Phi]_{700}$ −175°, $[\Phi]_{589}$ −315°, $[\Phi]_{420}$ −773°, $[\Phi]_{391}$ −155°, $[\Phi]_{382}$ −1348°, $[\Phi]_{374}$ −935°, $[\Phi]_{363}$ −2900°, $[\Phi]_{358}$ −2630°, and $[\Phi]_{348}$ −4290° (Found: C, 67·95; H, 6·25; F, 5·1. $C_{22}H_{25}FO_5$ requires C, 68·0; H, 6·5; F, 4·9%). Rechromatography and recrystallization of combined materials from the initial benzene eluate (1 l) and the mother liquor of the first recrystallization of (4b) gave an additional 1·155 g (12%) of fluoro-ketone (4b).

7α-Fluoro-6α-hydroxy-17β-oestradiol 3,17-Diacetate (5a).—To a stirred suspension of 7α-fluoro-6-oxo-17β-oestradiol diacetate (4b) (0·191 g) in methanol (10 ml) at −5° was added a solution of sodium borohydride (0·054 g) in methanol (3 ml) during 10 min; after 30 min at −5° the mixture was acidified with aqueous acetic acid (10%; 1·5 ml). The solvent was removed at 0° under reduced pressure and the residue was washed with water and dried to give a solid product (0·186 g), which was chromatographed on Merck acid-washed alumina (18 g), first with benzene (50 ml) as eluant, and then with a gradient of benzene (500 ml) changing to ethanol–benzene (1 : 4) (100 ml). Eluate (121—180 ml) from the gradient elution afforded crystals (0·158 g), which gave *7α-fluoro-6α-hydroxy-17β-oestradiol 3,17-diacetate* (5a) (0·148 g, 77%), m.p. 192—198° [from benzene–hexane (1 : 1)]; $\lambda_{max.}$ (EtOH) 267 (ε 540) and 274 nm (510); $\nu_{max.}$ (CH_2Cl_2) 3610, 1754, and 1727 cm^{-1} (Found: C, 68·35; H, 6·9; F, 4·9. $C_{22}H_{27}FO_5$ requires C, 67·65; H, 6·95; F, 4·85%).

7α-Fluoro-6α-mesyloxy-17β-oestradiol 3,17-Diacetate (5b).—To a solution of 7α-fluoro-6α-hydroxy-17β-oestradiol 3,17-diacetate (5a) (0·094 g) in pyridine (1·5 ml) at 0° was added methanesulphonyl chloride (0·4 ml). After 1 h at 23° the mixture was poured into ice–water. The white precipitate was washed with water, dried, and chromatographed on Fluorisil (5 g) with a gradient of benzene (500 ml) changing to acetone–benzene (1 : 1) (100 ml). The eluate (91—240 ml) afforded *7α-fluoro-6α-mesyloxy-17β-oestradiol 3,17-diacetate* (5b) (0·094 g, 83%), m.p. 206—208°; $\lambda_{max.}$ ($CHCl_3$) 269 (ε 710) and 276 nm (700); $\nu_{max.}$ (CH_2Cl_2) 1757 and 1727 cm^{-1}; δ($CDCl_3$) 3·22 (3H, s, 6-OMs), 2·30 (3H, s, 3-OAc), and 2·07 (3H, s, 17-OAc) (Found: C, 58·45; H, 6·05; S, 6·8. $C_{23}H_{29}FO_7S$ requires C, 58·95; H, 6·25; S, 6·85%).

7α-Fluoro-17β-oestradiol (6a).—To a stirred suspension of lithium aluminium hydride (0·600 g) in ether (200 ml) at 0° was added a suspension of 7α-fluoro-6α-mesyloxy-17β-oestradiol 3,17-diacetate (5b) (0·430 g) in ether (700 ml) during 2 h. More lithium aluminium hydride (0·400 g) was then added, and the mixture was stirred for 7 h at 0°. The excess of reagent was decomposed with wet ether (100 ml) and the mixture was shaken with aqueous sulphuric acid (10%; 50 ml). The aqueous layer was separated and extracted with ethyl acetate. The extract was combined with the ethereal solution, washed with water, aqueous sodium hydrogen carbonate (5%), and water, dried (Na_2SO_4), and evaporated. The combined product from three runs (0·949 g) was chromatographed on a column of Woelm anionotropic alumina containing 8% water (100 g), first with methylene chloride (500 ml) as eluant, and then with a gradient of methylene chloride (1500 ml) changing to ethanol–methylene chloride (2 : 3) (220 ml). Eluate (361—780 ml) from the gradient elution gave crystalline material (0·507 g), which afforded *7α-fluoro-17β-oestradiol* (6a) (0·393 g, 49%), m.p. 167° (decomp.) (from benzene); $\lambda_{max.}$ (EtOH) 280 (ε 2000) and 287 nm (1800); $\lambda_{max.}$ (EtOH–KOH) 300 nm (ε 2700); $\nu_{max.}$ (KBr) 3378 and 3125 cm^{-1} (Found: C, 76·6; H, 7·75; F, 5·1. $C_{18}H_{23}FO_2,0{\cdot}5C_6H_6$ requires C, 76·5; H, 7·95; F, 5·75%). Acetylation (acetic anhydride–pyridine) gave *7α-fluoro-17β-oestradiol diacetate* (6b), m.p. 115—116°, $\lambda_{max.}$ (EtOH) 267 (ε 960) and 274 nm (900); $\nu_{max.}$ (CH_2Cl_2) 1754 and 1727 cm^{-1}; δ($CDCl_3$) 5·00 (1H, m, J_{HF} 50 Hz, 7β-H), 2·28 (3H, s, 3-OAc), and 2·06 (3H, s, 17-OAc) (Found: C, 70·25; H, 7·05; F, 5·1. $C_{22}H_{27}FO_4$ requires C, 70·55; H, 7·25; F, 5·05%).

6α,7α-Epoxy-17β-oestradiol Diacetate (2).—To a stirred solution of oestra-1,3,5(10),6-tetraene-3,17β-diol diacetate (1b)[2] (3·480 g) in methylene chloride (100 ml) at 23° was added, during 10 min, *m*-chloroperbenzoic acid (85%; 2·264 g) in methylene chloride (60 ml). After being stirred at 28° for 1·5 h, the mixture was washed with aqueous sodium sulphite (10%), sodium hydrogen carbonate (10%), and saturated sodium chloride solution, dried (Na_2SO_4), and evaporated, leaving a white solid (3·641 g), which gave 6α,7α-epoxy-17β-oestradiol diacetate (2)[3] (1·924 g, 53%), m.p. 167—169° (from propan-2-ol).

* A product of unknown structure, obtained by reaction of perchloryl fluoride with a steroidal enamine, was reported to have detonated when the solvent was removed, after chromatography.[7]

[6] O. Wintersteiner, M. Moore, and A. I. Cohen, *J. Org. Chem.*, 1964, **29**, 1325.

[7] A. H. Goldkamp, *J. Medicin. Pharm. Chem.*, 1962, **5**, 1176.

6β-*Fluoro*-7α-*hydroxy*-17β-*oestradiol* 3,17-*Diacetate* (3a).—A solution of hydrogen fluoride (6·85 g) in tetrahydrofuran (42·54 g) was added to a solution of 6α,7α-epoxy-17β-oestradiol diacetate (2) (0·264 g) in methylene chloride (30 ml) at −65°. The mixture was kept at 0° for 64 h, then poured into aqueous sodium hydrogen carbonate (0°). The aqueous layer was extracted with methylene chloride and ether. The combined organic layers were washed with saturated sodium chloride, dried (Na_2SO_4), and evaporated. The residue was chromatographed on a column of Fluorisil (25 g), first with benzene (180 ml) as eluant, then with a gradient of benzene (1320 ml) changing to benzene–ethyl acetate (1 : 1) (500 ml). The eluate (720—1090 ml) yielded a residue (0·166 g). A sample (0·118 g) crystallized from benzene gave 6β-*fluoro*-7α-*hydroxy*-17β-*oestradiol* 3,17-*diacetate* (3a) (0·095 g, 57%), m.p. 141—144°; $\lambda_{max.}$ (EtOH) 270 (ε 745) and 277 nm (702); δ($CDCl_3$) 5·25 (1H, q, $J_{HF\text{-}gem}$ 49 $J_{HH\text{-}ee}$ 2·5 Hz, 6α-H), 4·13br (1H, m, $J_{HF\text{-}ae}$ 11, $J_{HH\text{-}ee}$ *ca.* 2·5 Hz, 7β-H), 2·28 (3H, s, 3-OAc), and 2·05 (3H, s, 17-OAc) (Found: C, 68·25; H, 7·1; F, 5·05. $C_{22}H_{27}FO_5$ requires C, 67·65; H, 6·95; F, 4·85%). Chromic acid oxidation [8] of the 6β,7α-fluorohydrin (3a) gave 6β-*fluoro*-7-*oxo*-17β-*oestradiol diacetate* (3b), m.p. 138—143°, $\lambda_{max.}$ (EtOH) 267 (ε 753) and 272 nm (773); o.r.d. (*c* 0·270 in dioxan) $[\Phi]_{700}$ 260°, $[\Phi]_{589}$ 390°, $[\Phi]_{327}$ 21,500°, $[\Phi]_{317}$ 17,700°, and $[\Phi]_{298}$ 0°, $[\Phi]_{277}$ −20,100° (Found: C, 67·45; H, 6·5; F, 4·35. $C_{22}H_{25}FO_5$ requires C, 68·0; H, 6·5; F, 4·9%).

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[8] C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, 1956, **21**, 1547.