Regiospecific Syntheses of Modified Steroid Hormones. Part III.[1b] 2-Fluoro-oestrone and -17β-oestradiol

By **M. Neeman,* T. Mukai, J. S. O'Grodnick,** and **A. L. Rendall,** Roswell Park Memorial Institute, New York State Department of Health, and the Chemistry Program, Roswell Park Division of the State University of New York at Buffalo, Buffalo, New York 14203, U.S.A.

In a regiospecific synthesis of 2-fluoro-oestrone (5), 2α-fluoro-10β-hydroxyoestr-4-ene-3,17-dione (4), obtained by *cine*-fluorination of 4β,5β-epoxy-10β-hydroxyoestr-4-ene-3,17-dione (3) was dehydrated with thionyl chloride in collidine. The product (5) was identical with material independently synthesized by the Schiemann–Balz reaction.

REGIOSPECIFIC routes to monohalogeno-ring-A aromatic steroids, *via* 19-norsteroid intermediates have been outlined.[1] The regiospecific synthesis of 4-fluoro-17β-oestradiol [1] exploited, in the key step, the reaction of the enamine of 19-nortestosterone with perchloryl fluoride, which was proved to involve exclusive axial electrophilic attack at C-4 to yield 4β-fluoro-17β-hydroxyoestr-5-en-3-one.[1] In principle, 'electrophilic fluorine' reagents [2] could be exploited to introduce a fluorine substituent at C-2 of a suitable 19-norsteroid intermediate.† A novel approach to the regiospecific syntheses of 2-fluoro-oestrone (5) and -17β-oestradiol (8), exploits a reaction [3] which involves regiospecific *cine*-fluorination of αβ-epoxy-ketones at the α′-carbon atom by F^- (or its equivalent, HF_2^-). This α′-mode nucleophilic fluorination then gives access to a 19-norsteroid route to the title compounds, the key intermediate in this synthesis being 2α-fluoro-10β-hydroxyoestr-4-ene-3,17-dione (4).

The αβ-epoxy-ketone precursor (3) for the synthesis of the α′-fluoro-αβ-enone intermediate (4) was prepared by epoxidation with alkaline hydrogen peroxide of 10β-hydroxyoestr-4-ene-3,17-dione (1),[4] which afforded a single isolable product, 4β,5β-epoxy-10β-hydroxyoestrane-3,17-dione (3). This was identified by its n.m.r. spectrum, which showed one singlet, at δ 3·16, assigned to H-4, and by its c.d. curve ($\Delta\varepsilon_{304}$ +6·68).[5] The high stereoselectivity ‡ of the epoxidation may be attributed to hydrogen bonding between the 10β-hydroxy-group and the OH leaving group of the 5β-hydroperoxide system, in the postulated hydroperoxy-enolate intermediate,[6a] oriented favourably for rear-side attack by the enolate anion [(A) or (B); see Figure]. The conversion of the epoxy-ketone precursor (3) into the key intermediate, 2α-fluoro-10β-hydroxyoestr-4-ene-3,17-dione (4) was accomplished by α′-mode oxiran opening with hydrogen fluoride in chloroform–ethanol.[3] The structure and stereochemistry of the intermediate (4) were supported by the n.m.r. spectrum (see Experimental section). The u.v. spectrum [$\lambda_{max.}$ 233 nm

† Ethoxalylation of 10β,17β-dihydroxyoestr-4-en-3-one (2) followed by *C*-fluorination at C-2 with perchloryl fluoride, was attempted, but abandoned after preliminary experiments had yielded largely fluorine-free products, presumably owing to aromatization.

‡ Most reported cases of epoxidation of steroidal conjugated ketones by alkaline hydrogen peroxide are not highly stereoselective.[6] In some early work in which single products were obtained after isolation and purification, stereospecificity is not proved.[7] Recently the n.m.r. signal of the epoxide proton has been used as a criterion of epoxide stereochemistry.[8] In the present study, the high stereoselectivity of the epoxidation of the 10β-hydroxy-4-en-3-one (1) was established by comparing the n.m.r. signal of the C-4 proton of the epoxidation product prior to purification with the signals from the corresponding mixture of epoxides obtained from testosterone: the former was a single singlet whereas the latter consisted of two singlets at δ 3·05 and 3·00 p.p.m., in a 1 : 2 ratio, indicating partial β-stereoselectivity. The high stereoselectivity in the case of the 10β-hydroxy-4-en-3-one (1) has a counterpart in the case of 3β-acetoxycholest-4-en-6-one, which gave the 3β-acetoxy-4β,5β-epoxycholestan-6-one with 96% stereoselectivity.[9]

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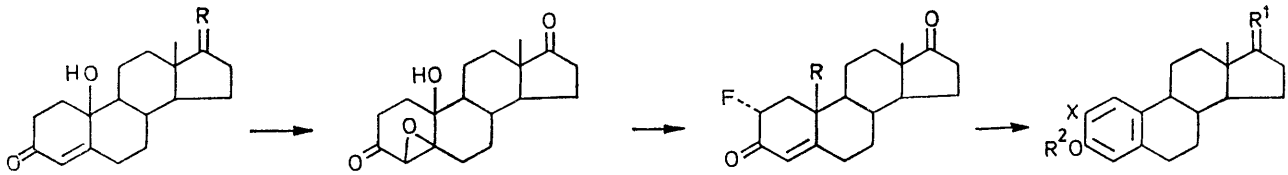
(ε 15,500)] was consistent with the α′-fluoro-γ-hydroxy-αβ-en-one structure (4).

The intermediate (4) was aromatized by dehydration with thionyl chloride–collidine to yield 2-fluoro-oestrone (5) (see Experimental section for spectral data), identical with an authentic sample prepared as follows. The Schiemann–Balz reaction [10] of 2-amino-3-*O*-methyloestrone (6) [11] gave 2-fluoro-3-*O*-methyloestrone (7), which was demethylated by pyridine hydrochloride.

Reduction of 2-fluoro-oestrone (5) with sodium borohydride gave 2-fluoro-17β-oestradiol (8) showing



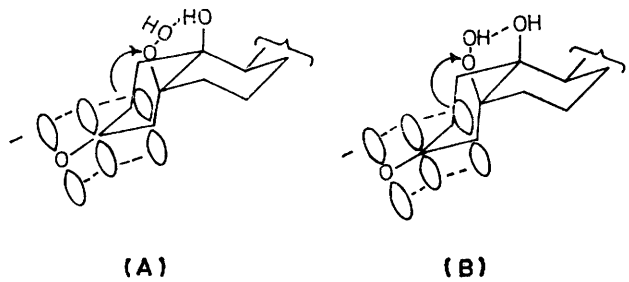
(1) R = O
(2) R = α-H, β-OH

(3)

(4) R = OH

(5) X = F, R^1 = O, R^2 = H
(6) X = NH_2, R^1 = O, R^2 = Me
(7) X = F, R^1 = O, R^2 = Me
(8) X = F, R^1 = α-H, β-OH, R^2 = H
(9) X = $N_2^+BF_4^-$, R^1 = O, R^2 = Me

characteristics (m.p., u.v., and i.r. data) in agreement with those reported [12] for a specimen prepared by a



(A) (B)

FIGURE

non-regiospecific synthesis *via* ring-A aromatic intermediates.

EXPERIMENTAL

For general directions see Part II.[1b] Mass spectral analyses were performed by Morgan Schaffer Corporation, Montreal, Canada. Nylon tubing used for dry columns was obtained from Walter Coles and Co., 47/49 Tanner Street, London, England. Dry column adsorbent was Woelm silica gel, obtained from Waters Associates, Framingham, Massachusetts, and was pre-equilibrated with 10% by weight of benzene–ethyl acetate–ethanol (80 : 20 : 1).

4β,5β-*Epoxy*-10β-*hydroxyoestrane*-3,17-*dione* (3).—To a stirred solution of 10β-hydroxyoestr-4-ene-3,17-dione (1) [4] (1·206 g) in anhydrous methanol (68 ml) at 0°, aqueous hydrogen peroxide (30%; 8·1 ml) and aqueous sodium hydroxide (10%; 2·9 ml), both at 0°, were slowly added. The solution was kept at 0° for 7 h, poured into water, and extracted with ethyl acetate. The combined extracts were washed with water, dried (Na_2SO_4), filtered, and evaporated to dryness to yield the *epoxide* (3) (1·268 g, 99%), δ ($CDCl_3$) 3·16 p.p.m. (1H, s, 4-H). This material was used directly for the preparation of the intermediate (4). A sample twice recrystallized from ethyl acetate–light petroleum had m.p. 199—200°, $\nu_{max.}$ ($CHCl_3$) 1730 [C(17)=O] and 1712 [shoulder, C(3)=O] cm^{-1}, δ ($CDCl_3$) 3·16 p.p.m. (1H, s, 4-H), c.d. (0·00163M in dioxan) $\Delta\varepsilon_{304}$ +6·68 (shoulder at 334 nm), o.r.d. (*c* 0·05 in dioxan) $[\Phi]_{700}$ +180°, $[\Phi]_{589}$ +534°, $[\Phi]_{335}$ +10,400° (shoulder), $[\Phi]_{321}$ +12,900°, $[\Phi]_{277}$ −12,680° (Found: C, 70·75; H, 8·0. $C_{18}H_{24}O_4$ requires C, 71·05; H, 7·95%).

2α-*Fluoro*-10β-*hydroxyoestr*-4-*ene*-3,17-*dione* (4).—Hydrogen fluoride was bubbled into chloroform–ethanol (10 : 1; 58 ml) for 20 min at 0°, and the epoxide (3) (2·088 g) in chloroform–ethanol (10 : 1; 38 ml) was added at 0°. After 3 min the mixture was poured into 2N-sodium hydroxide containing ice, the chloroform layer was separated, and the aqueous phase was extracted with chloroform. The combined extracts were washed with water, dried (Na_2SO_4), and evaporated to yield a solid (1·183 g), $\lambda_{max.}$ (EtOH) 228 nm (ε 16,200). This material was placed on a column (2 × 65 in) of dry column adsorbent (860 g).[13] The column was developed with benzene–ethyl acetate–ethanol (80 : 20 : 1) and cut into fractions,* and the steroid was removed from the silica gel with ethyl acetate. The fraction R_F 0·06—0·28 yielded 2α-*fluoro*-10β-*hydroxyoestr*-4-*ene*-3,17-*dione* (4) (0·885 g, 30% by u.v.), $\lambda_{max.}$ (EtOH) 233 nm (ε 10,700). Recrystallization from ethyl acetate yielded material (4) of m.p. 235—238°, $\lambda_{max.}$ (EtOH) 233 nm (ε 15,500), $\nu_{max.}$ (KBr) 3600 and 3460 (OH), 1739 [C(17)=O], 1704 [C(3)=O], and 1628 (C=C) cm^{-1}, δ ($CDCl_3$) 5·84br (1H, d, $^4J_{HF}$ 5 Hz, 4-H), and 5·33 p.p.m. (1H, octet, $J_{HF\text{-}gem}$ 49, $J_{Hax,Hax}$ 14, $J_{Hax,Heq}$ 7 Hz, 2β-H), c.d. (0·00209M in dioxan) $\Delta\varepsilon_{344}$ −1·21, $\Delta\varepsilon_{334}$ −1·32, $\Delta\varepsilon_{316}$ 0, $\Delta\varepsilon_{296}$ +1·69 (Found: M^+, 306. $C_{18}H_{23}FO_3$ requires 306).

2-*Fluoro-oestrone* (5) *by the* 19-*Norsteroid Route*.—To a solution of 2α-fluoro-10β-hydroxyoestr-4-ene-3,17-dione (4) (0·366 g) in chloroform (20 ml; ethanol-free) at 0° were added thionyl chloride (0·08 ml) and collidine (0·18 ml). The mixture was stirred at 23° for 20 h, washed with hydrochloric acid (10%) and water, dried (Na_2SO_4), and evaporated. The residue (0·277 g) was placed on a nylon column (2 × 44 in) of dry column adsorbent (540 g). The column was developed with benzene–ethyl acetate–ethanol (80 : 20 : 1) and cut into fractions,* and the steroid was removed from the adsorbent with ethyl acetate. The fraction R_F 0·50—0·59 yielded 2-*fluoro-oestrone* (5) (0·057 g,

* Products were located by illumination with u.v. light.

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15%), $\lambda_{max.}$ (EtOH) 280 (ε 2540) and 287sh nm, $\lambda_{max.}$ (EtOH–NaOH) 296 nm (ε 4050), $\nu_{max.}$ (KBr) 1725 [C(17)=O], 1621 and 1600 (C=C) cm^{-1}, δ (Me_2CO) 7·08 (1H, d, J_{HF} 13 Hz, 1-H) and 6·77 p.p.m. (1H, d, $^4J_{HF}$ 9 Hz, 4-H). Recrystallization from acetone–water yielded crystals of m.p. 219—223° (Found: C, 75·0; H, 7·3; F, 6·35. $C_{18}H_{21}FO_2$ requires C, 74·95; H, 7·35; F, 6·6%).

2-*Fluoro*-3-O-*methyloestrone* (7).—To a suspension of 2-amino-3-*O*-methyloestrone (6) [11] (0·652 g, 2·18 mmol) in aqueous hydrochloric acid (18%; 2 ml) at −10° was added sodium nitrite (0·157 g, 2·28 mmol) in water (0·6 ml). Aqueous tetrafluoroboric acid (48%; 0·27 ml) was added, followed by water (0·5 ml), and the suspension was stirred for 2 h at 0°. The precipitate was filtered off, washed with aqueous fluoroboric acid (6%), followed by fluoroboric acid (1·5%) in aqueous methanol (25%), methanol, and diethyl ether, and dried at 0·05 mmHg and 21° for 16 h to yield the 2-diazonium tetrafluoroborate (9) of 3-*O*-methyloestrone [first crop 0·556 g, decomp. 160°; second crop 0·186 g, decomp. 155—159° (total 85%)]. The diazonium salt (9) (0·654 g) was suspended in dry xylene (20 ml) and heated under reflux for 1 h. The precipitate was filtered off and washed with dichloromethane. The washings and xylene filtrate were combined, washed with aqueous sodium hydrogen carbonate (10%) and water, and dried (Na_2SO_4). Removal of the solvents yielded a brown oil (0·454 g), which was chromatographed on alumina to yield 2-fluoro-3-*O*-methyloestrone (7) (0·151 g, 26%), m.p. 133—138°, with sintering at 129° (lit.,[12] 125—128°), $\lambda_{max.}$ (EtOH) 277 nm (ε 2680) [lit.,[12] $\lambda_{max.}$ 277 nm (ε 2470)].

2-*Fluoro-oestrone* (5) *by the Ring-A Aromatic Route.*—Demethylation of 2-fluoro-3-*O*-methyloestrone (7) (0·240 g, 0·793 mmol) with pyridine hydrochloride at 190° for 2 h gave 2-fluoro-oestrone (5) (0·208 g, 91%), identical (mixed m.p., i.r., u.v., and n.m.r. spectra, t.l.c.) with a specimen prepared by thionyl chloride dehydration of 2α-fluoro-10β-hydroxyoestr-4-ene-3,17-dione (4).

2-*Fluoro*-17β-*oestradiol* (8).—Reduction of 2-fluoro-oestrone (5) with sodium borohydride yielded 2-fluoro-17β-oestradiol (8), m.p. 173—175°, with a phase transition at 138—142° (lit.,[12] 173—175°), $\lambda_{max.}$ (EtOH) 280 (ε 2750) and 286sh nm [lit.,[12] $\lambda_{max.}$ 280 nm (ε 2810)].

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