Tetrahedron Vol. 46, No. 6, pp. 2059-2068, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

EFFICIENT REGIOSELECTIVE A-RING FUNCTIONALIZATION OF OESTROGENS

Philip C. Bulman Page*, Fazal Hussain, James L. Maggs†, Paul Morgan, and B. Kevin Park†*

Robert Robinson Laboratories, Department of Chemistry and
†Department of Pharmacology and Therapeutics,
University of Liverpool, P.O. Box 147, Liverpool L69 3BX, U.K.

(*Received in UK* 1 *November* 1989)

Complete series of 2-halo- and 2-cyano-oestrogens have been prepared in good to high yields: 2-chloro, 2-bromo, 2-iodo, and 2-cyano derivatives *via* oestrogen-thallium (III) bis(trifluoroacetate) intermediates, and 2- and 4-fluorooestrogens by direct functionalization using *N*-fluoropyridinium triflate.

Introduction

Mild and selective halogenation of medicinal and related organic compounds has received considerable attention because of the effects of halogen substituents on the physical properties, metabolic fates, and biological actions of such compounds.[1]

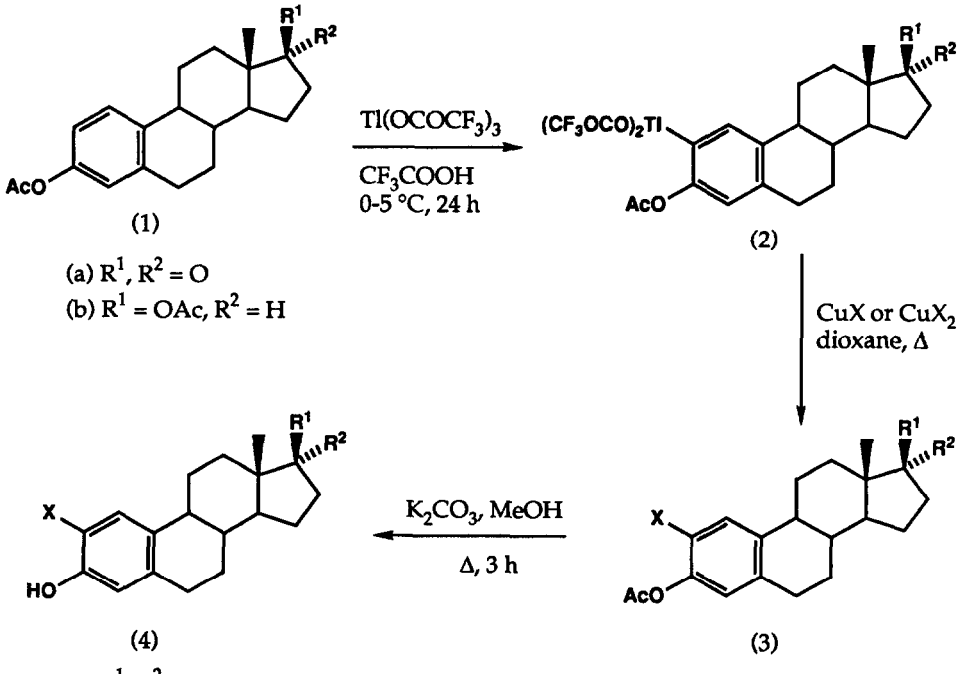
The present work arose from the observation that substitution of fluorine into the C2 position of 17β-oestradiol reduces the carcinogenicity of the oestrogen while not affecting its hormonal activity.[2] It was presumed that the C2-F bond is resistant to metabolic cleavage, and this effect was therefore interpreted as evidence for the involvement of the normal C2-hydroxylated (catechol) metabolites in the carcinogenic action of steroidal oestrogens. However, later studies using non-radiolabelled derivatives showed appreciable oxidative dehalogenation of 2-fluoro-17β-oestradiol and some other halooestrogens to catechols *in vitro*, and hence brought into question the usefulness of halooestrogens as metabolic probes of the mechanisms of oestrogen carcinogenesis.[3] Nevertheless, because a complete assessment of the influence of A-ring substituents on oestrogen metabolism necessitates the employment of radiolabelled derivatives,[4] we sought preparative routes applicable to radiochemical syntheses.

Several procedures for chlorination,[5,6] bromination,[5-8,41-44] and iodination[6,9-11] of oestrogens are available but there is still a need for practical and general methods for regiospecific A-ring functionalization. Direct arene thalliation with thallic trifluoroacetate in trifluoroacetic acid and subsequent displacement of the thallium moiety with nucleophiles enables convenient and regiospecific preparation of a number of simple derivatives,[12-15] including halides[16-19] and nitriles.[13] The efficient iododethalliation of oestrogen thallium (III) bis(trifluoroacetate) by aqueous potassium iodide has been reported[9]. However, although this method gave excellent yields of 2-iodooestrogens, all attempts to utilise it in the preparation of other halogenated and 2-cyanooestrogens—using

potassium halide (F, Cl, Br) and cyanide ions—were unsuccessful in our hands. Copper (I) and (II) halides and copper (I) cyanide also dethalliate simple aromatics[12,17,18], and from these reactions we have developed a convenient, general, and regiospecific procedure for the synthesis of C2-substituted oestrogens. We have also developed a method for the preparation of 2- and 4-fluorooestrogens in high overall yields from oestrone using an electrophilic source of fluorine; other reported syntheses of fluorooestrogens involve less efficient and less regioselective procedures.[2]

Results and discussion

A typical procedure involved the conversion of an oestrogen acetate[20] (1) into the corresponding oestrogen thallium (III) bis(trifluoroacetate) (2) and treatment of the complex in dioxane or pyridine solution with a copper salt to afford 2-substituted oestrogen acetate (3), which upon deacetylation gave 2-substituted oestrogen (4) in excellent yield (Scheme 1). Copper (II) salts gave better yields than copper (I) in halogenation reactions; for example copper (I) bromide gave a 57% overall yield of 2-bromooestradiol from oestradiol diacetate compared with 84% using copper (II) bromide.[17]



(1)

(a) R^1, R^2 = O
(b) R^1 = OAc, R^2 = H

(2)

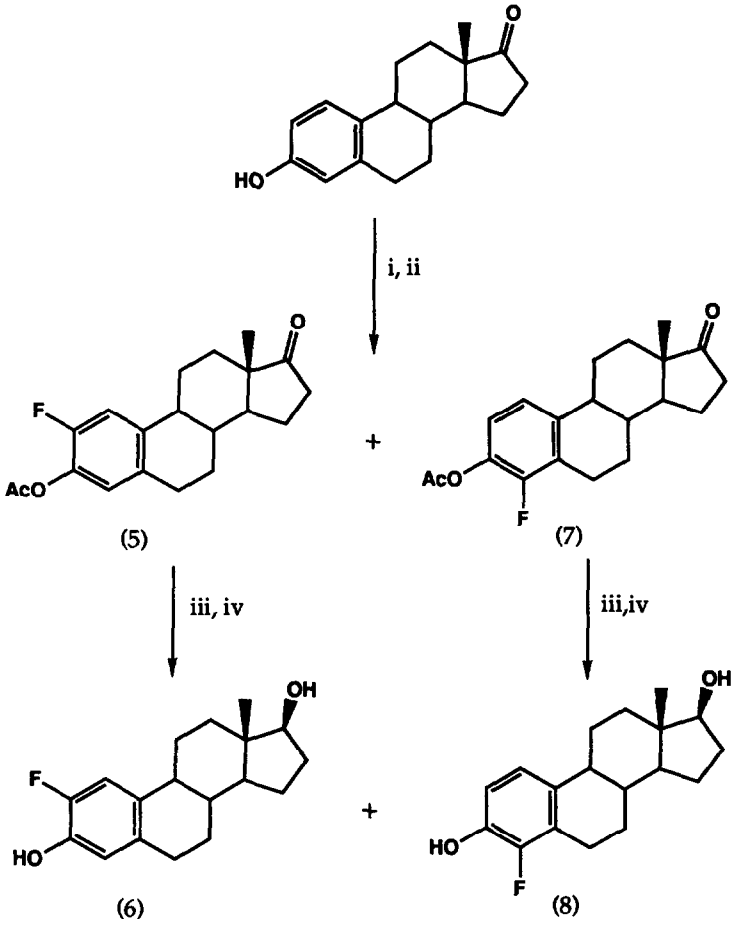
(3)

(4)

(a) R^1, R^2 = O
(b) R^1 = OH, R^2 = H

Scheme 1

We extensively attempted similar fluorodethalliation of the thallium (III) complexes with copper (II) fluoride, tetrabutyl ammonium fluoride, copper (II) fluoride-boron trifluoride, and tris(dimethylamino) sulphur(trimethylsilyl)difluoride (TASF) in dioxane under reflux. No fluorooestrogens were formed; instead, starting material together with a small amount of 2-hydroxyoestrogen were commonly obtained,[21] showing that hydroxylation as well as protonation had occurred at the thalliation position. In our hands the classic Balz-Schiemann sequence[22] gave an unacceptably low overall yield (6%) of 2-fluorooestrogen.



Reagents: (i)*N*-fluoropyridinium triflate, 1,1,2-trichloroethane, 118 °C, 24 hours
(ii) Ac_2O, pyridine, Δ, 1 hour
(iii) K_2CO_3, MeOH, Δ, 3 hours
(iv) $NaBH_4$, THF, 50 °C, 1 hour

Scheme 2

Aromatic fluorides—including fluorooestrogens[23-25]—have been prepared with several established

electrophilic fluorinating reagents, *viz.* caesium fluoroxysulphate,[23,26,27] perchloryl fluoride,[24] perfluoromethanol,[25,33] xenon difluoride,[28] and acetyl hypofluorite,[29-32] but these reagents are commonly toxic and unstable, and have all given poor yields of 2- and 4-fluoroestrogens (5-25% overall). In contrast, the newer electrophilic fluorinating reagents such as *N*-fluoroiminium salts[34-37] are effective under conventional mild conditions. However, in our hands *N*-fluoroquinuclidinium triflate[35] gave no more than 20% conversion of β-oestradiol to monofluorinated products, and also yielded tetraene[38] and pentaene side products, although the starting oestrogen was largely recovered unchanged. We were therefore pleased to find that *N*-fluoropyridinium triflate[36,37]—which fluorinates phenol with an overall conversion of 75% to give 2-fluorophenol, 4-fluorophenol and 2,4-difluorophenol—efficiently converted oestrone into 2- and 4-fluorooestrone (Scheme 2) together with several uncharacterized or only partially characterized products;[39] completion of the reaction was established by TLC, HPLC and mass spectrometry. 17β-Oestradiol gave 2- and 4-fluorinated derivatives under the same conditions but oestriol underwent extensive dehydration to oestrone[40]. Neither oestrone acetate nor 17β-oestradiol dimethyl ether yielded monofluorinated products. Separation of 2- and 4-fluorooestrone by fractional recrystallization, or by thin-layer or flash-column chromatography, could be achieved only after acetylation. Subsequent recrystallization yielded the 2- and 4-isomers in the ratio 2.6:1. However, the most persistent impurity[39] (R_t on HPLC column, 29 min; R_t for fluorooestrones, 26 min) could only be removed by successive recrystallizations. Mass spectral and chromatographic analyses[39] suggested that this material was a mixture of 2- and 4-chlorooestrone.

Experimental section

General experimental details

Melting points (uncorrected) were measured with a Kofler block apparatus. IR spectra were obtained on a Perkin Elmer 298 spectrophotometer. ^{1}H NMR spectra were recorded in $(CD_3)_2CO$ or $CDCl_3$ with reference to internal $(CH_3)_4Si$ using Bruker AC200 (200 M Hz) or WM250 (250 M Hz), or Perkin Elmer R34 (220 M Hz) spectrometers. All mass spectra were low-resolution (800) EI (70eV), and were acquired on VG Tritech TS-250 or VG Micromass 7070E instruments. Elemental analyses were performed by the Microanalysis Laboratory of the Department of Chemistry. High performance liquid chromatography columns were packed with 10 μm ODS (μ-Bondapak) and were eluted using a linear gradient of acetonitrile (20% to 75% over 40 min) in 43 mM $NH_4H_2PO_4$ (p H 3.0) at a flow rate of 1.5 ml/min; the eluate was monitored at 280 nm.

Oestrone acetate (1a)[20]

Oestrone (10 g, 37.0 mmol) was dissolved in pyridine (70 ml) and treated with acetic anhydride (17.5 ml) under reflux for two hours. The solvent was evaporated and the residue poured into ice-water.

The precipitate was filtered, dried, and recrystallized from ethanol-water to give colourless plates (11.14 g, 96%), mp 116-118 °C, (Found: C, 76.79; H, 7.73. $C_{20}H_{24}O_3$ requires C, 76.89; H, 7.74%); $\nu_{max.}$ 1775 and 1740 cm^{-1}; δ 0.90 (3 H, s) 1.25-2.21 (11 H, m), 2.30 (3 H, s), 2.35-2.60 (2 H, m), 2.83-3.00 (2 H, m), 6.75-6.90 (2 H, m), and 7.30 (1 H, d, J 8.3 Hz); m/z (EI) 312 (M^+), 270, 242, 226, 213, 185, and 172.

17β-Oestradiol diacetate (1b)[20]

17β-Oestradiol (10g, 36.8 mmol) was dissolved in pyridine (140 ml) and treated with acetic anhydride (35 ml) as described above for (1a). After work-up the product was recrystallized from ethanol-water to give colourless plates (12.80 g, 98%), mp 124-126 °C, (Found: C, 74.35; H, 8.17. $C_{22}H_{28}O_4$ requires C, 74.13; H, 7.92%); $\nu_{max.}$ 1755 and 1735 cm^{-1}; δ 0.85 (3 H, s) 1.30-2.00 (11 H, m), 2.10 (3 H, s), 2.30 (3 H, s), 2.20-2.40 (2 H, m), 2.85-2.95 (2 H, m), 4.68-4.80 (1 H, m), 6.82-6.91 (2 H, m), and 7.32 (1 H, d, J 8.3 Hz); m/z (EI) 356 (M^+), 314, 254, 225, 213, and 172.

General method for preparation of 2-substituted oestrogens (4a), (4b); Scheme 1

Oestrone acetate or 17β-oestradiol diacetate (1 mmol) and thallic trifluoroacetate (2 mmol) were dissolved in trifluoroacetic acid (10 ml) and stirred at 0-5 °C for 24 hours. The acid was evaporated under reduced pressure at <50 °C. The complex was washed twice with 1,2-dichloroethane. 1,4-Dioxane or pyridine (25 ml) and either copper (I) or (II) chloride, bromide, iodide, or cyanide were added to the oestrogen-thallium (III) complex, and the resulting mixture was heated under reflux for 1-5 hours. Product formation was monitored by TLC and mass spectrometry. After evaporation of the solvent, water (50 ml) was added and the product extracted with dichloromethane. The extract was dried over magnesium sulphate, evaporated under reduced pressure, and purified by flash-column chromatography on silica gel (Merck 9385). Elution with petroleum ether (bp 60-80 °C)-ethyl acetate (4 : 1, v/v) gave the 2-substituted oestrogen acetate. Deacetylation was performed by heating a methanol solution of the acetate (25 ml) with potassium carbonate (5 equiv.) under reflux for 3 hours. The methanol was evaporated, water (50 ml) added to the residue, and the product extracted with dichloromethane. Evaporation of solvent from the dried ($MgSO_4$) extract gave a solid which was recrystallized from petroleum ether (bp 60-80 °C)-ethyl acetate (2:3, v/v).

For 2-chlorooestrone

Oestrone acetate (312 mg, 1.0 mmol) was treated as described above; the reaction with copper (II) chloride required heating for five hours under reflux in dioxane. After work-up the product was recrystallized to give colourless plates (253 mg, 83%), mp 223-225 °C, (Found: C, 70.72; H, 7.09. $C_{18}H_{21}ClO_2$ requires C, 70.81; H, 7.10%); $\nu_{max.}$ 3350, 1730, 1390, and 882 cm^{-1}; δ 0.96 (3 H, s) 1.40-2.99 (15 H, m), 6.88 (1 H, s), 7.22 (1 H, s), and 8.50 (1 H, br s); m/z (EI) 304 (M^+), 260, 247, 233, 194, and 180.

For 2-bromooestrone

Oestrone acetate (312 mg, 1.0 mmol) was treated as described above; the reaction with copper (II) bromide required heating for three hours under reflux in dioxane. After work-up the product was recrystallized to give colourless plates (295 mg, 85%), mp 194-195 °C, (Found: C, 61.78; H, 6.28. $C_{18}H_{21}BrO_2$ requires C, 61.81; H, 6.19%); $\nu_{max.}$ 3380, 1720, 1380, and 884 cm^{-1}; δ 0.98 (3 H, s) 1.46-3.00 (15 H, m), 6.78 (1 H, s), 7.30 (1 H, s), and 8.50 (1 H, br s); m/z (EI) 350 (M^+), 348, 291, 270, and 238.

For 2-iodooestrone

Oestrone acetate (312 mg, 1.0 mmol) was treated as described above; the reaction with copper (II) iodide required heating for one hour under reflux in dioxane. After work-up the product was recrystallized to give colourless plates (350 mg, 88%), mp 167-168 °C, (Found: C, 54.56; H, 5.40. $C_{18}H_{21}IO_2$ requires C, 54.48; H, 5.46%); $\nu_{max.}$ 3369, 1738, 1496, and 885 cm^{-1}; δ 0.85 (3 H, s) 1.40-2.98 (15 H, m), 6.74 (1 H, s), 7.55 (1 H, s), and 8.52 (1 H, br s); m/z (EI) 396 (M^+), 339, 286, 270, and 252.

For 2-cyanooestrone

Oestrone acetate (312 mg, 1.0 mmol) was treated as described above; the reaction with copper (I) cyanide required heating for five hours under reflux in pyridine. After work-up the product was recrystallized to give colourless plates (215 mg, 73%), mp 265-266 °C, (Found: C, 77.08; H, 7.42; N, 4.61. $C_{19}H_{21}NO_2$ requires C, 77.13; H, 7.32; N, 4.73%); $\nu_{max.}$ 3310, 2270, 1750, and 1250 cm^{-1}; δ 0.86 (3 H, s) 1.48-2.98 (15 H, m), 6.72 (1 H, s), 7.46 (1 H, s), and 8.52 (1 H, br s); m/z (EI) 295 (M^+), 251, 238, 224, 197, and 185.

For 2-chloro-17β-oestradiol

17β-Oestradiol diacetate (356g, 1.0 mmol) was treated as described above; the reaction with copper (II) chloride required heating for five hours under reflux in dioxane. After work-up the product was recrystallized to give colourless plates (255 mg, 83%), mp 187-189 °C, (Found: C, 70.61; H, 7.59. $C_{18}H_{23}ClO_2$ requires C, 70.46; H, 7.55%); $\nu_{max.}$ 3400, 1590, 1270, and 883 cm^{-1}; δ 0.82 (3 H, s) 1.60-2.30 (13 H, m), 2.74-2.86 (2 H, m), 3.54-3.86 (2 H, m), 6.60 (1 H, s), 7.20 (1 H, s), and 8.50 (1 H, br s); m/z (EI) 306 (M^+), 247, 194, and 180.

For 2-bromo-17β-oestradiol

17β-Oestradiol diacetate (356 mg, 1.0 mmol) was treated as described above; the reaction with copper (II) bromide required heating for three hours under reflux in dioxane. After work-up the product was recrystallized to give colourless plates (294 mg, 84%), mp 155-156 °C, (Found: C, 61.38; H, 6.60. $C_{18}H_{23}BrO_2$ requires C, 61.54; H, 6.60%); $\nu_{max.}$ 3420, 1595, 1382, and 880 cm^{-1}; δ 0.84 (3 H, s) 1.50-2.19 (13 H, m), 2.75-2.88 (2 H, m), 3.58-3.88 (2 H, m), 6.70 (1 H, s), 7.40 (1 H, s), and 8.52 (1 H, br s); m/z (EI) 352 (M^+), 350, 293, 240, and 226.

For 2-iodo-17β-oestradiol

17β-Oestradiol diacetate (356 mg, 1.0 mmol) was treated as described above; the reaction with copper (II) iodide required heating for one hour under reflux in dioxane. After work-up the product was recrystallized to give colourless plates (355 mg, 89%), mp 177-178 °C, (Found: C, 53.99; H, 5.59. $C_{18}H_{23}IO_2$ requires C, 54.06; H, 5.73%); $\nu_{max.}$ 3420, 1585, 1268, and 886 cm^{-1}; δ 0.84 (3 H, s) 1.40-2.40 (13 H, m), 2.70-2.98 (2 H, m), 3.60-3.90 (2 H, m), 6.72 (1 H, s), 7.52 (1 H, s), and 8.52 (1 H, br s); m/z (EI) 398 (M^+), 339, 286, 272, and 259.

For 2-cyano-17β-oestradiol:

17β-Oestradiol diacetate (356 mg, 1.0 mmol) was treated as described above; the reaction with copper (I) cyanide required heating for five hours under reflux in pyridine. After work-up the product was recrystallized to give colourless plates (224 mg, 75%), mp 237-238 °C, (Found: C, 76.75; H, 7.83; N, 4.68. $C_{19}H_{23}NO_2$ requires C, 76.73; H, 7.79; N, 4.71%); $\nu_{max.}$ 3330, 2295, 1580, and 1250 cm^{-1}; δ 0.84 (3 H, s) 1.50-2.30 (13 H, m), 2.76-2.90 (2 H, m), 3.60-3.90 (2 H, m), 6.88 (1 H, s), 7.40 (1 H, s), and 8.50 (1 H, br s); m/z (EI) 297 (M^+), 238, 224, and 171.

2- and 4-fluorooestrone acetates (5), (7); Scheme 2

Oestrone (500 mg; 1.85 mmol) and *N*-fluoropyridinium triflate (915 mg, 3.70 mmol, 2 equiv.) in 1,1,2-trichloroethane (8 ml) were refluxed under nitrogen for 24 hours. Solvent was removed under reduced pressure, and the residue poured into water and extracted with dichloromethane. Evaporation of the dried ($MgSO_4$) extract yielded a brown oil which was acetylated as described above for oestrone. The crude mixture of 2- and 4-fluorooestrone acetate was partially purified by flash-column chromatography using petroleum ether (b.p. 60-80 °C)-ethyl acetate (9:1 to 7:3) as eluent. The co-eluted isomers were separated by fractional recrystallization from petroleum ether (b.p. 60-80 °C)-absolute ethanol (2:8), the 2-isomer being obtained as first crop, to yield 2-fluoro- (325 mg, 53%) and 4-fluoro- (123 mg, 20%) oestrone acetates as colourless crystals.

For 2-fluorooestrone acetate: mp 88-90 °C; $\nu_{max.}$ 1770 and 1758 cm^{-1}; δ 0.93 (3 H, s) 1.40-2.21 (11 H, m), 2.30 (3 H, s), 2.35-2.40 (2 H, m), 2.80-2.90 (2 H, m), 6.90 (1 H, d, J 8.3 Hz), and 7.20 (1 H, d, J 13.2 Hz); m/z (EI) 330 (M^+), 288, 260, 244, 231, 217, 203, and 190.

For 4-fluorooestrone acetate: mp 97-99 °C; $\nu_{max.}$ 1765 and 1750 cm^{-1}; δ 0.90 (3 H, s) 1.30-2.22 (11 H, m), 2.30 (3 H, s), 2.40-2.50 (2 H, m), 2.70-2.93 (2 H, m), 6.95-7.10 (1 H, m), and 7.19 (1 H, d, J 9.2 Hz); **m/z** m/z (EI) 330 (M^+), 288, 260, 244, 231, 217, 203, and 190.

2-Fluorooestrone

2-Fluorooestrone acetate (320 mg, 0.97 mmol) was dissolved in methanol (10 ml), and deacetylated by heating with potassium carbonate (670 mg, 5 equiv.) under reflux for 3 hours. The crude product was worked up with addition of water (20 ml) as described above for (4a) and (4b) and was

recrystallized from petroleum ether (b.p. 60-80 °C)-absolutue ethanol (2:8) to give 2-fluorooestrone as colourless crystals (265 mg, 95%), mp 220-222 °C; $\nu_{max.}$ 3370, 1720, 1580, and 1385 cm^{-1}; δ 0.95 (3 H, s), 1.35-3.00 (15 H, m), 6.74 (1 H, d, J 9 Hz), 7.02 (1 H, d, J 13 Hz), and 8.32 (1 H, br s); m/z (EI) 288 (M^+), 260, 244, 231, 217, 203, and 190.

4-Fluorooestrone

4-Fluorooestrone acetate (120 mg, 0.36 mmol) was dissolved in methanol (10 ml), and deacetylated by heating with potassium carbonate (251 mg, 5 equiv.) under reflux for 3 hours. The crude product was worked up with addition of water (20 ml) as described above for (4a) and (4b) and was recrystallized from petroleum ether (b.p. 60-80 °C)-ethyl acetate (1:1) to give 4-fluorooestrone as colourless crystals (100 mg, 95%), mp 222-224 °C; $\nu_{max.}$ 3368, 1725, 1580, and 1450 cm^{-1}; δ 0.90 (3 H, s), 1.33-3.02 (15 H, m), 6.93-7.02 (1 H, m), 7.14 (1 H, d, J 9 Hz), and 8.33 (1 H, br s); m/z (EI) 288 (M^+), 260, 244, 231, 217, 203, and 190.

2-Fluoro-17β-oestradiol (6); Scheme 2

A solution of 2-fluorooestrone (260 mg, 0.90 mmol) in tetrahydrofuran (10 ml) was treated with sodium borohydride (172 mg, 5 equiv.) at 50°C over 2 hours. The reaction mixture was worked up with addition of water (10 ml) as described above for (4a) and (4b). Recrystallization from absolute ethanol gave 2-fluoro-17β-oestradiol (240 mg, 45% from oestrone), mp 172-174 °C. (Found: C, 74.34; H, 8.25. C_{18} $H_{23}FO_2$ requires C, 74.45; H, 7.98); $\nu_{max.}$ 3370, 3550, 1610, 1580, and 1505 cm^{-1}; δ 0.82 (3 H, s), 1.20-2.30 (13 H, m), 2.70-2.84 (2 H, m), 3.61-3.92 (2 H, m), 6.72 (1 H, d, J 9 Hz), 7.01 (1 H, d, J 13 Hz), and 8.30 (1 H, br s); m/z (EI) 290 (M^+), 272, 246, 231, 217, 204, 190 and 178.

4-Fluoro-17β-oestradiol (8); Scheme 2

A solution of 4-fluorooestrone (95 mg, 0.33 mmol) in tetrahydrofuran (10 ml) was treated with sodium borohydride (63 mg, 5 equiv.) at 50°C over 2 hours. The reaction mixture was worked up with addition of water (10 ml) as described above for (4a) and (4b). Recrystallization from petroleum ether (b.p. 60-80 °C)-ethyl acetate (3:2) gave 4-fluoro-17β-oestradiol (90 mg, 17% from oestrone), mp 189-190 °C. (Found: C, 73.97; H, 8.02. C_{18} $H_{23}FO_2$ requires C, 74.45; H, 7.98); $\nu_{max.}$ 3375, 3555, 1605, 1580, and 1500 cm^{-1}; δ 0.83 (3 H, s), 1.20-2.30 (13 H, m), 2.70-2.85 (2 H, m), 3.62-3.91 (2 H, m), 6.95-7.05 (1 H, m), 7.15 (1 H, d, J 9 Hz), and 8.35 (1 H, br s); m/z (EI) 290 (M^+), 272, 246, 231, 217, 204, 190 and 178.

Acknowledgements

PCBP is currently a Nuffield Foundation Science Research Fellow. BKP is a Wellcome Trust Reader. Financial support was provided by the North West Cancer Research Fund (F H) and the Department of Education, Northern Ireland (PM). The TS-250 mass spectrometer in the Department of

Pharmacology and Therapeutics was purchased with generous grants from the Wellcome Trust and the University of Liverpool.

References and notes

1. R. Filler and Y. Kobayashi, in "Biomedical Aspects of Fluorine Chemistry", Elsevier Biomedical Press, New York, 1982.
2. J.G. Liehr, *Mol. Pharmacol.*, 1983, **23**, 278.
3. J.J. Li, R. H. Purdy, E. H. Appleman, J.K. Klicka, and S.A. Li, *Mol. Pharmacol.*, 1985, **27**, 559.
4. J.L. Maggs, P. Morgan, F. Hussain, P.C.B. Page, and B.K. Park, *Xenobiotica*, in press.
5. E. Schwenk, C.G. Castle, and E. Joachim, *J. Org. Chem.*, 1963, **28**, 136.
6. E. Santaniello and P. Ferraboschi, *J. Steroid Biochem.*, 1983, **19**, 767.
7. V.N. Zontova, V.M. Rzheznikov, and K.E. Pivnitsky, *Steroids*, 1975, **25**, 827.
8. W.R. Slaunwhite and L. Neely, *J. Org. Chem.*, 1962, **27**, 1749.
9. H. Ali, M.A. Ghaffari, and J.E. Van Lier, *J. Steroid Biochem.*, 1987, **28**, 21.
10. F. Sweet, T.B. Patrick, and J.M. Mudd, *J. Org. Chem.*, 1979, **44**, 2296.
11. C.A. Horiuchi, A. Haga, and J.Y. Satoh, *Bull. Chem. Soc. Japan*, 1986, **59**, 2459.
12. A. McKillop and E.C. Taylor, in"Advances in Organometallic Chemistry", eds. F.G.A. Stone and R. West, Academic Press, New York, 1973, Vol. 11, pp. 147-206.
13. S. Uemura, Y. Ikeda, and K. Ichikawa, *Tetrahedron*, 1972, **28**, 3025.
14. E.C. Taylor, R. H. Danforth, and A. McKillop, *J. Org. Chem.*, 1973, **38**, 2088.
15. E.C. Taylor, H.W. Altland, and A. McKillop, *J. Org. Chem.*, 1975, **40**, 3441.
16. E.C. Taylor, E.C. Bigham, and D.K. Johnson, *J. Org. Chem.*, 1977, **42**, 362.
17. S. Uemura, Y. Ikeda, and K. Ichikawa, *Tetrahedron*, 1972, **29**, 5499.
18. S. Uemura, K. Sohma, M. Okano, and K. Ichikawa, *Bull. Chem. Soc. Japan*, 1971, **44**, 2490.
19. A. McKillop, J.D. Hunt, M.J. Zelesko, J.S. Fowler, E.C. Taylor, G. McGillivray, and F. Kienzle, *J. Am. Chem. Soc.*, 1971, **93**, 4841.
20. P.D.G. Dean, D. Exley, and M.W. Johnson, *Steroids*, 1971, **18**, 593.
21. 2- Hydroxyoestrogen was characterised as 2-hydroxyoestrone-2,3-diacetate by ^{1}H nmr and mass spectrometry.
22. T. Utne, R.B. Jobson, and R.D. Babson, *J. Org. Chem.*, 1968, **33**, 2469.
23. E. H. Appleman, L.J. Basile, and R. Hayatsu, *Tetrahedron*, 1984, **40**, 189.

24. M. Neeman, Y. Osawa, and T. Mukai, *J. Chem. Soc., Perkin Trans. 1*, 1972, 2297.

25. P.W. le Quesne, K. Allam, S. Abdel-Baky, K.D. Onan, and R. H. Purdy, *Steroids*, 1989, **53**, 649.

26. T.B. Patrick and D.L. Darling, *J. Org. Chem.*, 1986, **51**, 3242.

27. S. Stauber and M. Zupan, *J. Chem. Soc., Chem. Commun.*, 1981, 148.

28. S.P. Anand, L.A. Quarterman, H. H. Hyman, K.G. Migliorese, and R. Filler, *J. Org. Chem.*, 1975, **40**, 807.

29. C.M. Sharts and W.A. Sheppard, *Organic Reactions*, 1974, **21**, 125.

30. T.B. Patrick, G.L. Cantrell, and C.-Y. Chang, *J. Am. Chem. Soc.*, 1979, **101**, 7434.

31. R. H. Hesse, *Isr. J. Chem.*, 1978, **17**, 60.

32. O. Lerman, Y. Tor, D. Hebel, and S. Rozen, *J. Org. Chem.*, 1984, **49**, 806.

33. M. Hudlicky, in "Chemistry of Organic Fluorine Compounds", Ellis Horwood, Chichester, 1976, 2nd. edn.

34. S. Singh, D.D. des Marteau, S.S. Zuberi, M. Witz, and H.N. Hwang, *J. Am. Chem. Soc.*, 1987, **109**, 7194.

35. R.E. Banks, R.A. du Boisson, W.D. Morton, and E. Tsiliopoulos, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2805.

36. T. Umemoto, K. Kawada, and K. Tomita, *Tetrahedron Lett.*, 1986, **27**, 3271.

37. T. Umemoto, K. Kawada, and K. Tomita, *Tetrahedron Lett.*, 1986, **27**, 4465.

38. Material isolated by reversed-phase HPLC gave a mass spectrum which matched library spectrum of oestra-1,3,5(10),9(11)-tetraene-3,17β-diol.

39. The major side product was partially resolved into two components by HPLC, and following its isolation by HPLC it gave m/z 306 (36%); other peaks >5% were seen at m/z 304 (100%), 288, 260, 247, 233, 219, 206, 194, 180, and 167. This spectrum matched that of 2-Cl-oestrone, and the minor of the two components co-eluted with 2-Cl-oestrone.

40. G.F. Marrian and G.A.D. Haslewood, *Biochem. J.*, 1932, **26**, 25. Oestrone identified by matching acquired with library spectrum and by co-chromatography on HPLC column.

41. T.Utne, R.B.Jobson, and F.W.Landgraf, *J. Org. Chem.*, 1968, **33**, 1654.

42. M.Neeman, J.S.O'Grodnick, and K.Morgan, *J. Chem. Soc., Perkin Trans. 1*, 1972, 2302.

43. D.S.Wilbur and H.A.O'Brien, *J. Org. Chem.*, 1982, **47**, 359.

44. M.Numazawa, K.Kimura, M.Ogata, and M.Nagaoka, *J. Org. Chem.*, 1985, **50**, 5421.