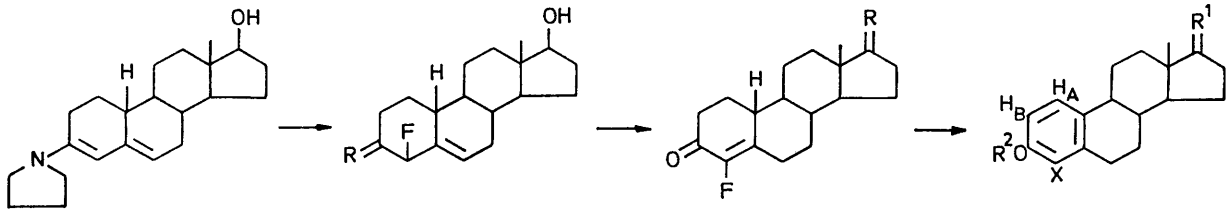
Regiospecific Syntheses of Modified Steroid Hormones. Part II.[1a] 4-Fluoro-17β-oestradiol and -oestrone †

By M. Neeman,* Y. Osawa, and T. Mukai, Roswell Park Memorial Institute, Buffalo, New York 14203, U.S.A.

Dehydrogenation of 17β-hydroxy- (4) and 17β-acetoxy-4-fluoro-oestr-4-en-3-one (5) with selenium dioxide gives 4-fluoro-17β-oestradiol (7) and its 17-acetate (8), respectively. The 19-norsteroid intermediates (2) and (3) were obtained by regiospecific 4β-axial electrophilic fluorination of the pyrrolidine enamine of 19-nortestosterone (1) by perchloryl fluoride.

SYNTHESES of steroidal oestrogens modified in ring A, as well as their crystal structures [1h,i] and electron densities [1j] have been the subjects of earlier studies.[1] In a preliminary communication [1a] we have described syntheses of 4-fluoro-17β-oestradiol (7) and its 17-acetate (8), by a route *via* 19-norsteroid intermediates. We now give details of this synthesis; the following papers [2] report new syntheses of 2-fluoro-oestrone, 4-bromo-oestrone, and 4-bromo-17β-oestradiol *via* 19-norsteroid approaches.



(1)

(2) R = α-OMe, β-OH
(3) R = O

(4) R = α-H, β-OH
(5) R = α-H, β-OAc

(6) X = F, R^1 = O, R^2 = H
(7) X = F, R^1 = α-H, β-OH R^2 = H
(8) X = F, R^1 = α-H, β-OAc R^2 = H
(9) X = F, R^1 = α-H, β-OAc R^2 = Ac
(10) X = F, R^1 = O, R^2 = Me
(11) X = NH_2, R^1 = O, R^2 = Me
(12) X = $N_2^+BF_4^-$, R^1 = O, R^2 = Me
(13) X = $N_2^+PF_6^-$, R^1 = O, R^2 = Me

The merit of the 19-norsteroid routes to ring-A monohalogeno-oestrogens is the regiospecificity achieved in the halogenation reactions leading to the key 19-norsteroid intermediate [the 4-fluoro-19-nortestosterone intermediates (4) and (5) in the present synthesis leading to 4-fluoro-oestradiol (7), the 2α-fluoro-19-nortestosterone intermediate [3a] leading to 2-fluoro-oestrone,[2a] and the 4-bromo-19-nortestosterone intermediates leading to 4-bromo-oestrone and -oestradiol [2b]]. Novel regiospecific reactions, leading to ring-A monohalogeno-oestr-4-en-3-ones, which were exploited in designing syntheses of these key intermediates, suitably substituted for aromatization to monohalogeno-ring-A aromatic steroids,[2] are the recently reported α′-mode *cine*-fluorination of αβ-epoxy-ketones [3a] and α-mode bromination of αβ-epoxy-ketones [3b] to 4-bromo-4-en-3-ones *via* the αβ-bromohydrin intermediate, as well as the regio- and stereo-specific 4β-fluorination of 19-nortestosterone enamine (1) by perchloryl fluoride reported earlier.[1a,4] In contrast, electrophilic substitution reactions [1d-g] on the aromatic A ring of oestrogens, although reported [1e,f] to have shown regioselectivity in some brominations, cannot be considered reliably regiospecific on the basis of a recent reinvestigation [1g] of earlier procedures.[1e,f]

The synthesis of 4-fluoro-17β-oestradiol (7) by a 19-norsteroid route [1a] started from the readily available pyrrolidine enamine of 19-nortestosterone (1),[4] which afforded, on treatment with perchloryl fluoride in aqueous methanol, the hemiacetal (2) of 4β-fluoro-17β-hydroxyoestr-5-en-3-one (3), which showed only end absorption in the u.v., and no C=O band in the i.r. spectrum; this hemiacetal (2) and the corresponding ketone (3) were readily interconvertible.‡ The stereochemistry assigned to the 4-fluoro-5-en-3-one (3) was supported by the n.m.r. signal of H-6, an unresolved

† Presented in part at the XIXth International Congress of Pure and Applied Chemistry, London, July 1963.

‡ The hemiacetal (2) decomposed at 158°, as did the ketone (3), after first losing methanol; in contrast, Joly and Warnant [4] report isolation of a product of m.p. 171° from fluorination of 19-nortestosterone enamine, which they formulated as 4ξ-fluoro-17β-hydroxyoestr-5-en-3-one containing 0·75 mol. equiv. of methanol.

[1] (*a*) Part I, M. Neeman and Y. Osawa, *Tetrahedron Letters*, 1963, 1987; (*b*) T. Utne, R. B. Jobson, and F. W. Landgraf, *J. Org. Chem.*, 1968, **33**, 1654; (*c*) R. B. Woodward, *J. Amer. Chem. Soc.*, 1940, **62**, 1625; (*d*) A. J. Tomson and J. P. Horwitz, *J. Org. Chem.*, 1959, **24**, 2056; (*e*) W. R. Slaunwhite and L. Neely, *ibid.*, 1962, **27**, 1749; (*f*) E. Schwenk, C. G. Castle, and E. Joachim, *ibid.*, 1963, **28**, 136; (*g*) T. Utne, R. B. Jobson, and R. D. Babson, *ibid.*, 1968, **33**, 2469; (*h*) D. A. Norton, G. N. Kartha, and C. T. Lu, *Acta Cryst.*, 1963, **16**, 89; (*i*) D. A. Norton, G. N. Kartha, and C. T. Lu, *ibid.*, 1964, **17**, 77; (*j*) K. Saudaram and R. K. Mishra, *Biochim. Biophys. Acta*, 1965, **94**, 601; (*k*) A. J. Birch, J. M. H. Graves, and J. B. Siddall, *J. Chem. Soc.*, 1963, 4234; (*l*) A. J. Birch, J. M. H. Graves, and G. S. R. Subba Rao, *ibid.*, 1965, 5137.

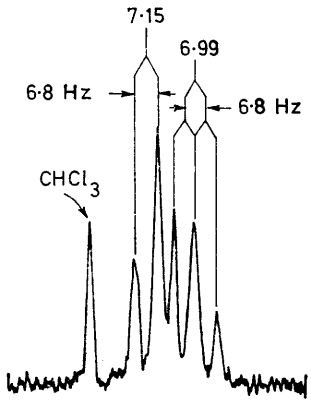
[2] (*a*) Part III, M. Neeman, T. Mukai, J. S. O'Grodnick, and A. L. Rendall, following paper; (*b*) Part IV, M. Neeman, J. S. O'Grodnick, and K. Morgan, *J.C.S. Perkin I*, 1972, 2302.

[3] (*a*) M. Neeman and J. S. O'Grodnick, *Tetrahedron Letters*, 1971, 4847; (*b*) M. Neeman and J. S. O'Grodnick, *ibid.*, 1972, 783.

[4] R. Joly and J. Warnant, *Bull. Soc. chim. France*, 1961, 569.

multiplet centred at δ 3·96 p.p.m., $W_{\frac{1}{2}}$ 17 Hz, indicative of $^4J_{HF}$ 5 Hz, as expected for an olefinic proton coupled to an axial allylic fluorine atom.[5] This axial conformation of the 4-fluoro-substituent was further supported by an 18 cm^{-1} hypsochromic shift of the carbonyl i.r. band [6] of compound (3), as well as a 16 nm bathochromic shift [7] of the first extremum in the o.r.d. of compound (3) relative to cholest-5-en-3-one.

The 4β-fluoro-5-en-3-one (3) was isomerized by acid to 4-fluoro-17β-hydroxyoestr-4-en-3-one (4),[4] $\lambda_{max.}$ 248 nm (ε 15,900).* This key intermediate (4), as well as its 17-acetate (5), were aromatized by selenium dioxide, affording respectively 4-fluoro-17β-oestradiol (7), $\lambda_{max.}$ 274 nm (ε 1210), and its 17-acetate (8). The 100 MHz n.m.r. spectrum (Figure) of the diacetate (9) of 4-fluoro-17β-oestradiol (7) exhibited signals for two aromatic protons, forming an ABX pattern in which both the AB



and the BX splittings were 6·8 Hz and no AX splitting was observed; thus the H_A signal, centred at δ 7·15 p.p.m., is assigned to H-1, and that of H_B, centred at δ 6·99, is assigned to H-2, in confirmation of the structure (9).

Oxidation of 4-fluoro-oestradiol (7), synthesized by the 19-norsteroid route, by Jones reagent,[9] gave 4-fluoro-oestrone (6), which on methylation was converted into the 3-methyl ether (10). The product was identical with material prepared independently *via* the Schiemann–Balz reaction, from 4-amino-oestrone methyl ether (11),[10] which was converted into 4-fluoro-oestrone methyl ether (10), *via* either the tetrafluoroborate [11] or the hexafluorophosphate [12] procedure.

* At the time when the 19-norsteroid approach to 4-fluoro-oestradiol was planned, two conflicting '4-fluorotestosterone' characterizations had been reported: the material of Camerino and his co-workers,[8] showing $\lambda_{max.}$ 241 nm, apparently to be derived from 4β,5β-epoxy-17β-hydroxyandrostan-3-one by reaction with hydrogen fluoride; and that of Nakanishi and his co-workers,[8c] and of Joly and Warnant,[4] showing $\lambda_{max.}$ 248 nm. The latter $\lambda_{max.}$ value appeared to be more likely for the 4-fluoro-4-en-3-one than the former, but definitive proof of this was desirable. The structures of the other series of compounds having $\lambda_{max.}$ *ca.* 240 nm, which Camerino and his co-workers had claimed to be 4-fluoro-4-en-3-ones, were recently revised [3a] to to 2α-fluoro-4-en-3-ones, and the reaction leading to them, erroneously considered by Camerino and his co-workers to be α-mode oxiran opening, was recognized as a regiospecific α′-mode *cine*-fluorination.[3a]

EXPERIMENTAL

M.p.s were determined with a Thomas microstage and are corrected. The u.v. spectra were recorded with a Cary 14 spectrophotometer, and the i.r. spectra with a Beckmann IR-9 spectrophotometer. N.m.r. spectra were determined at 60 MHz with a Varian A60A spectrometer, and at 100 MHz with a Varian HA100 spectrometer, with tetramethylsilane as internal standard. O.r.d. and c.d. measurements were made with a Jasco ORD/UV 5 spectropolarimeter with c.d. attachment. Microanalyses were performed by Huffman Laboratories, Wheatridge, Colorado.

3-Pyrrolidin-1-yloestra-3,5-dien-17β-ol (1).—To a solution of 19-nortestosterone (5·747 g) in methanol (46 ml), refluxed under nitrogen, was added freshly distilled pyrrolidine (6 ml) in methanol (6 ml) during 2 min. The mixture was refluxed for 4 min. The product, deposited as needles, was filtered off, washed with methanol, and dried under reduced pressure to give the enamine (1) [4] (6·750 g, 98%), m.p. 132—137° (decomp.), $\lambda_{max.}$ (Et_2O) 280 nm (ε 23,500), $\nu_{max.}$ (CH_2Cl_2) 3636 (OH), 1631, and 1603 (C=C) cm^{-1}, which was fluorinated without further purification.

4β-Fluoro-3α-methoxyoestr-5-en-3β,17β-diol (2).—Perchloryl fluoride (Pennsalt Corporation, Philadelphia) was passed through a suspension of the pyrrolidine enamine (1) (6·730 g) in 90% methanol (70 ml) at −25 to −30° for 10 min. Suspended crystals disappeared during the first 5 min. Nitrogen was bubbled through the mixture for 5 min, and aqueous sodium hydrogen carbonate solution (5%; 10 ml) was added. Slow addition of water (110 ml) gave a precipitate which was filtered off, triturated with 50% aqueous methanol (15 ml), and dried to give prisms of the *hemiacetal* (2) (3·686 g, 55%), of sufficient purity for the next step. A sample crystallized from methanol as prisms [which were transformed at 120—125° into the 5-en-3-one (3), m.p. 157—158° (decomp.) (see later)], which showed no appreciable u.v. absorption above 220 nm, $\nu_{max.}$ (KBr) 3356 (OH) cm^{-1} (Found: C, 70·2; H, 8·95; F, 5·6; CH_3O, 9·75. $C_{19}H_{29}FO_3$ requires C, 70·35; H, 9·0; F, 5·85; CH_3O, 9·6%).

4β-Fluoro-17β-hydroxyoestr-5-en-3-one (3).—(*a*) A suspension of the hemiacetal (2) (0·458 g) in dioxan (5 ml) was refluxed for 15 min. The solvent was evaporated off and the residue was recrystallized from n-hexane–benzene (1 : 1) to give the *ketone* (3) as needles, m.p. (decomp.) 159° [from n-hexane–benzene (1 : 2)], $\lambda_{max.}$ (Et_2O) 307 nm (ε 240), $\nu_{max.}$ (CH_2Cl_2) 3623 (OH) and 1730 (C=O) cm^{-1}, o.r.d. (*c* 0·10 in dioxan) $[\Phi]_{700}$ +240°, $[\Phi]_{589}$ +340°, $[\Phi]_{334}$ +11,500°, $[\Phi]_{330}$ +8870°, δ ($CDCl_3$) 3·96 (1H, m, $W_{\frac{1}{2}}$ 17 Hz, H-6) (Found: C, 73·95; H, 8·4; F, 6·3. $C_{18}H_{25}FO_2$ requires C, 73·75; H, 8·6; F, 6·5%).

(*b*) The hemiacetal (2) (2 mg), heated at 130° for 2 min on

[5] T. A. Wittstruck, S. K. Malhotra, H. J. Ringold, and A. D. Cross, *J. Amer. Chem. Soc.*, 1963, **85**, 3038.
[6] N. L. Allinger and H. M. Blatter, *J. Org. Chem.*, 1962, **27**, 1523.
[7] C. Djerassi, J. Osiecki, R. Riniker, and B. Riniker, *J. Amer. Chem. Soc.*, 1958, **80**, 1216.
[8] (*a*) B. Camerino, B. Patelli, and A. Vercellone, *J. Amer. Chem. Soc.*, 1956, **78**, 3540; (*b*) B. Camerino, R. Modelli, and B. Patelli, *Il Farmaco Ed. Sci.*, 1958, **13**, 52; (*c*) S. Nakanishi, R. L. Morgan, and E. V. Jensen, *Chem. and Ind.*, 1960, 528.
[9] K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 1946, 39.
[10] S. Kraychy, *J. Amer. Chem. Soc.*, 1959, **81**, 1702.
[11] (*a*) G. Balz and G. Schiemann, *Ber.*, 1929, **60***B*, 1186; (*b*) A. Roe, *Org. Reactions*, 1949, **5**, 193.
[12] (*a*) K. G. Rutherford, W. Redmond, and J. Rigamonti, *J. Org. Chem.*, 1961, **26**, 5149; (*b*) K. G. Rutherford and W. Redmond, *Org. Synth.*, 1963, **43**, 12.

a hot plate, was converted into needles, m.p. 157—158° (decomp.), identical (i.r. spectrum) with the fluoro-ketone (3) prepared by procedure (*a*).

Conversion of 4β-*Fluoro*-17β-*hydroxyoestr*-5-*en*-3-*one* (3) *into its Hemiacetal* (2).—The fluoro-ketone (3) (0·078 g) was dissolved in methanol (2 ml), and the solution was concentrated (to 1 ml) to give prisms of the hemiacetal (2) (0·045 g), identical (i.r. spectrum) with that from fluorination of the enamine (1) [transformed into the 5-en-3-one (3) at 120—125° (see before)].

4-*Fluoro*-17β-*hydroxyoestr*-4-*en*-3-*one* (4).—To a solution of the hemiacetal (2) in dimethylformamide (10 ml) was added concentrated hydrochloric acid (1·0 ml), and the mixture was kept at 23° for 20 min. The solution was diluted with water (15 ml) and cooled to afford needles of the ketone (4) [4] (0·772 g, 86%), m.p. 149—150° [from n-hexane–benzene (1 : 1)], $\lambda_{max.}$ (EtOH) 248 nm (ε 15,900), $\nu_{max.}$ (CH_2Cl_2) 3636 (OH), 1692 (C=O), and 1642 (C=C) cm^{-1}. 17β-*Acetoxy*-4-*fluoro*-*oestr*-4-*en*-3-*one* (5) formed leaflets (from n-hexane), m.p. 135—136°, $\lambda_{max.}$ (EtOH) 247 nm (ε 16,300), $\nu_{max.}$ (CH_2Cl_2) 1727 (ester C=O), 1690 (ketone C=O), and 1639 (C=C) cm^{-1} (Found: C, 71·95; H, 8·1; F, 5·5. $C_{20}H_{27}FO_3$ requires C, 71·85; H, 8·15; F, 5·7%).

4-*Fluoro*-17β-*oestradiol* 17-*Acetate* (8).—To a solution of 17β-acetoxy-4-fluoro-oestr-4-en-3-one (5) (4·925 g) in t-butyl alcohol (400 ml) and glacial acetic acid (15 ml) was added sublimed selenium dioxide (2·50 g) and powdered glass (0·30 g), and the mixture was refluxed with stirring under nitrogen for 29 h.[13] Additional selenium dioxide (2·50 g) and powdered glass (0·030 g) were added, and the mixture was refluxed for another 21 h and cooled to room temperature. The precipitate was filtered off and washed with t-butyl alcohol and ethyl acetate; solvents were removed from the combined filtrate and washings. A solution of the residue in ethyl acetate (600 ml) was washed with water, aqueous sodium hydrogen carbonate (5%), and water, dried (Na_2SO_4), and evaporated. The residue (5·083 g) was chromatographed on a column of Woelm anionotropic alumina (200 g; containing 8% of water). Elution with benzene (fractions from 421 to 1800 ml) gave material (3·366 g) which (from benzene) afforded 4-*fluoro*-17β-*oestradiol* 17-*acetate* (8) (2·453 g, 50%), as needles, m.p. 238—240° [from n-hexane–benzene (1 : 1)], $\lambda_{max.}$ (EtOH) 273 nm (ε 1310), $\lambda_{max.}$ (EtOH–KOH) 291 nm (ε 2460), $\nu_{max.}$ (KBr) 3378, 1692, 1634, 1587, 1502, and 1449 cm^{-1} (Found: C, 72·65; H, 7·6; F, 5·4. $C_{20}H_{25}FO_3$ requires C, 72·25; H, 7·6; F, 5·7%). 4-*Fluoro*-17β-*oestradiol diacetate* (9) had m.p. 133·5—134·5°, $\lambda_{max.}$ (EtOH) 263 (ε 520), and 271 nm (440), $\nu_{max.}$ (CS_2) 1779 (3-ester C=O) and 1737 (17-ester C=O) cm^{-1} (Found: C, 70·25; H, 7·05; F, 5·9. $C_{22}H_{27}FO_4$ requires C, 70·55; H, 7·25; F, 5·05%).

4-*Fluoro*-17β-*oestradiol* (7).—To a solution of 4-fluoro-17β-hydroxyoestr-4-en-3-one (4) (0·396 g) in t-butyl alcohol (30 ml) and glacial acetic acid (1·0 ml) was added sublimed selenium dioxide (0·165 g),[13] and the mixture was heated under nitrogen to 75° with stirring for 10 h, and then refluxed for 2 h. Additional selenium dioxide (0·154 g) was added; the mixture was refluxed for 12 h and worked up as described for compound (8). The solid product (0·430 g) was chromatographed on a column of Woelm anionotropic alumina (40 g; containing 8% water), by the gradient elution method [benzene (700 ml) as recipient and ethanol–benzene (1 : 1; 100 ml) as donor solvent]. Fractions from 220 to 260 ml gave 4-fluoro-17β-oestradiol (7) (0·101 g, 26%), as needles, m.p. 190—190·5° (from benzene) (lit.,[1g] 189—191°), $\lambda_{max.}$ (EtOH) 274 nm (ε 1290), $\lambda_{max.}$ (EtOH–KOH) 291 nm (ε 2530) [lit.,[1g] $\lambda_{max.}$ (MeOH) 277 nm (ε 1280), $\lambda_{max.}$ (MeOH–OH^-) 290 (ε 2300) and 238 nm (9700)], $\nu_{max.}$ (KBr) 3460, 3135, 1617, 1587, 1497, and 1449 cm^{-1} [lit.,[1g] $\nu_{max.}$ (Nujol) 1610, 1580, and 1490 cm^{-1}] (Found: C, 72·25; H, 8·0; F, 6·3%. Calc. for $C_{18}H_{23}O_2F,0{\cdot}5H_2O$: C, 72·21; H, 8·08; F, 6·35%), identical with material (7) obtained by saponification of 4-fluoro-17β-oestradiol 17-acetate (8) with ethanolic 4N-potassium hydroxide. Fractions from 170 to 210 ml gave unchanged starting material (0·151 g, 38%).

4-*Fluoro*-*oestrone* (6).—Oxidation of 4-fluoro-17β-oestradiol (7) with Jones reagent [9] gave 4-fluoro-oestrone (6), m.p. 222—225° (lit.,[1g] 223—225°), $\lambda_{max.}$ (EtOH) 273·5 (ε 1340) and 278 nm (1340) [lit.,[1g] 277·5 nm (ε 1420)], $\lambda_{max.}$ (EtOH–KOH) 291 nm (ε 2540).

4-*Fluoro*-3-O-*methyloestrone* (10).—(*a*) To a solution of 4-fluoro-oestrone (6) (0·038 g, 0·131 mmol) in aqueous sodium hydroxide (0·625%; 8·0 ml), dimethyl sulphate (1·5 ml) and aqueous sodium hydroxide (10%; 5 ml) were added with stirring at 22—27° during 2 h under nitrogen. The mixture was warmed to 50° for 30 min and cooled; the product was filtered off, washed with aqueous sodium hydroxide (10%) and water, and dried under reduced pressure to yield plates (0·036 g, 90%). Chromatography on alumina (Merck, acid-washed) gave plates of the methyl ether (10), m.p. 176—177° (lit.,[1g] 160—163°), identical (mixed m.p., i.r., u.v., and n.m.r. spectra, t.l.c.) with specimens prepared by procedures (*b*) and (*c*).

(*b*) *Tetrafluoroborate procedure.* Diazotization [19] of 4-amino-3-*O*-methyloestrone (11) [1d,10] (0·152 g, 0·51 mmol) in aqueous tetrafluoroboric acid (24%; 0·30 ml) gave the 4-diazonium tetrafluoroborate of 3-*O*-methyloestrone (12) (0·184 g, 91%), decomp. 168—170° [lit.,[1g] 160—165° (decomp.)]. The fluoroborate was suspended in dry xylene (5·0 ml) and heated under reflux for 2 h. The precipitate was filtered off and washed with dichloromethane. The washings and the filtrate were combined, washed with aqueous sodium hydrogen carbonate (10%) and water, dried (Na_2SO_4), and evaporated. The product crystallized in needles (0·129 g), $\lambda_{max.}$ (EtOH) 276 nm. Chromatography on alumina (13 g, Merck, acid-washed) afforded (on elution with benzene) 4-fluoro-3-*O*-methyloestrone (10) (0·049 g, 31%) as needles, $\lambda_{max.}$ (EtOH) 273—276 nm (ε 1310) [lit.,[1g] 274 nm (1410)], m.p. 171—176° (from acetone), with a phase transition at 167° (lit.,[1g] m.p. 160—163°).

(*c*) *Hexafluorophosphate procedure.* To 4-amino-3-*O*-methyloestrone (11) [1d,10] (0·157 g, 0·525 mmol) were added aqueous hydrochloric acid (12N; 0·13 ml) and water (1·0 ml). To the suspension of the white hydrochloride was added aqueous sodium nitrite (0·042 g, 0·61 mmol) in water (0·2 ml) at −5°. To the resulting orange gel, aqueous hexafluorophosphoric acid (65%; *d* 1·81; 0·1 ml, 0·86 mmol) was added in one portion with stirring, to give a yellow paste. After 30 min at −5°, the precipitate was filtered off, washed with water (6 × 3 ml), benzene (4 × 2·8 ml), and diethyl ether (4 × 2·8 ml), and dried at 27° and 0·1 mmHg for 22 h. The 4-diazonium hexafluorophosphate of 3-*O*-methyloestrone (13) (0·227 g, 95%), decomp. 154°, was suspended in dry xylene (5·0 ml), and heated under reflux for 1 h. The mixture was worked up as in procedure (*b*) to yield brown crystals (0·152 g). Chromatography as

[13] (*a*) C. Meystre, H. Frey, W. Voser, and A. Wettstein, *Helv. Chim. Acta*, 1956, **39**, 734; (*b*) S. A. Szpilfogel, T. A. P. Posthumus, M. S. de Winter, and D. A. van Dorp, *Rec. Trav. chim.*, 1956, **75**, 475.

in procedure (*b*) was repeated twice to yield 4-fluoro-3-*O*-methyloestrone (10) (0·069 g, 43%) as plates, m.p. 166—171° [from acetone–pentane (1 : 1)] after sintering at 161°, identical (i.r., u.v., and n.m.r. spectra, t.l.c.) with specimens prepared by procedures (*a*) and (*b*).

We thank the American Cancer Society for a grant (to M. N.) and the National Science Foundation for a grant for the purchase of the A60A n.m.r. spectrometer.

[2/712 *Received*, 27*th March*, 1972]