33.35 (t), 28.79 (d), 26.50 (d), 26.33 (t), 24.98 (t), 23.75 (t), 18.63 (t). Anal. Calcd for $C_{11}H_{19}NO$: C, 72.87; H, 10.57; N, 7.73. Found: C, 73.00; H, 10.73; N, 7.68.

1,4,4a,5,6,7,8,8a-Octahydro-9-methylnaphthalen-1,6-imine (1). Procedure A. A mixture of **21** (0.020 g, 0.11 mmol) and 85% phosphoric acid (0.4 mL) was heated at 195 °C for 2 h. The mixture was cooled, made basic with a 50% aqueous solution of potassium hydroxide, and extracted with ether (4×). The organics were combined, washed with brine, and dried over $MgSO_4$. The crude product was chromatographed on basic alumina (Merck, type T), with a mixture of chloroform, cyclohexane, and diethylamine (1:1:0.03) as eluent to give 4.0 mg (22%) of **1** as a pale yellow oil: IR (neat) 3050, 1650, 1455, 1360, 1240, 1165, 1150, 1015 cm^{-1}; ^1H NMR (100 MHz) δ 6.1–5.85 (m, 1 H), 5.75–5.50 (m, 1 H), 2.80 (m, 1 H), 2.58 (m, 1 H), 2.46 (s, 3 H), 2.40–1.10 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 130.86, 126.05, 56.53, 46.64, 41.71, 33.92, 29.89, 26.64, 23.78, 19.62; MS (15 eV), *m/e* 163 (M^+, base), 148, 134, 129, 122, 94. Exact mass calcd for $C_{11}H_{17}N$ 163.136, found 163.136.

Procedure B. To an ice-cooled solution of **21** (0.30 g, 1.66 mmol) in 16 mL of acetone was added Jones reagent until an orange color persisted. The resulting mixture was stirred at room temperature for 1 h, excess Jones reagent destroyed by addition of isopropanol, and the green mixture made basic with a 5% aqueous solution of sodium hydroxide. The solution was decanted and concentrated and the residue extracted with a mixture of ether and methylene chloride (4×). The organic layers were combined, washed once with brine, and dried over $MgSO_4$. The azaundecanone **27** was obtained as a pale yellow oil and was used without further purification; IR (neat) 1710 cm^{-1}; ^1H NMR (100 MHz) δ 3.26 (m, 1 H), 2.62 (br s, 2 H), 2.33 (s, 3 H), 2.20–1.10 (br m, 11 H).

A solution of **27** (0.265 g, 1.48 mmol) and *p*-toluenesulfonohydrazide (0.28 g, 1.50 mmol) in 4 mL of methanol was stirred at room temperature for 36 h. The mixture was concentrated, and the resulting solid residue was chromatographed on silica gel with a mixture of chloroform and methanol (10:1) as eluent to give 0.50 g of **28** as an amorphous white solid: IR ($CHCl_3$) 3320, 1680, 1610, 1455, 1385, 1340, 1160, 1085, 1010, 900 cm^{-1}; ^1H NMR (100 MHz) δ 7.80 (d, 2 H), 7.25 (d, 2 H), 2.72 (m, 1 H), 2.48 (m, 1 H), 2.37 (s, 3 H), 2.07 (s, 3 H), 2.3–1.0 (m, 12 H); MS (15 eV), *m/e* 348, 347 (M^+), 278, 226, 192, 177 (base), 91.

To a stirred solution of the hydrazone **28** in 75 mL of tetrahydrofuran at −78 °C was added 3.8 mL (4 equiv) of a 1.6 M hexane solution of *n*-butyllithium over a 3-min period. The resulting orange solution was allowed to gradually reach room temperature and then stirred for 1.5 h. The mixture was quenched with methanol and concentrated, the residue diluted with water, and the aqueous solution extracted with a mixture of ether and methylene chloride (4×). The extracts were combined, washed once with brine and dried over $MgSO_4$. The brown oil obtained on rotary evaporation was subjected to preparative TLC (aluminum oxide, F-254, Merck type T), employing a mixture of chloroform, cyclohexane, and diethylamine (1:1:0.03) as the developing solvent to give 0.045 g (17% overall from **21**) of **1** as a pale yellow oil: ^1H NMR (250 MHz) δ 5.96 (m, 1 H), 5.69 (m, 1 H), 2.89 (m, 1 H), 2.62 (m, 1 H), 2.47 (s, 3 H), 2.40–1.20 (m, 10 H). The 100-MHz ^1H NMR, ^{13}C NMR, IR, MS, and TLC R_f of this material were found to be identical with those obtained for the sample prepared by procedure A.

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Registry No. **1**, 84694-66-6; **9**, 84694-63-3; **10**, 936-37-8; **10** *N*-methylimine, 84694-69-9; **11** (isomer 1), 768-77-4; **11** (isomer 2), 768-78-5; **12**, 2220-40-8; **16**, 84694-64-4; **17**, 84694-65-5; **19**, 84773-35-3; **20**, 84773-37-5; **21**, 84773-36-4; **27**, 84694-68-8; **28**, 84694-67-7; 5-cyanobicyclo[2.2.2]oct-2-ene, 38258-93-4; 5-chloro-5-cyanobicylo[2.2.2]oct-2-ene, 6962-73-8; acrylonitrile, 107-13-1; 1,3-cyclohexadiene, 592-57-4; vinyl bromide, 593-60-2; *p*-tolylsulfonylhydrazine, 1576-35-8.

Synthesis of 4-Fluoroestradiol Analogues

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The synthesis of several 4-fluoro analogues of estradiol is described.

For ongoing studies of the noninvasive differentiation of hormone-dependent from hormone-independent mammary tumors[1-5] we have prepared several 4-fluorinated analogues of estradiol, the syntheses of which are the subject of this paper. Results of the biological studies will be published elsewhere.

The required 4-fluoroestradiol (**4**, Chart I) was prepared from 19-nortestosterone (**1**) via enamine **2** and 4-fluoro-19-nortestosterone (**3**), as described by Joly and Warnant.[6] Jones' oxidation of **4** gave 4-fluoroestrone (**5a**), which on treatment with isopropenyl acetate in the presence of catalytic amounts of H_2SO_4, gave the expected 4-fluoroestrone enol diacetate (**6b**). Bromine was allowed to react with **6b** in the presence of potassium carbonate to yield 4-fluoro-16α-bromoestrone acetate (**7**) in excellent yield. Reduction of 4-fluoro-16α-bromoestrone acetate (**7**) with sodium borohydride in ethanol at 4 °C gave 4-fluoroestradiol (**4**, 15%) and the isomeric bromo alcohols 4-fluoro-16α-bromo-3,17β-diol **8a** (51%) and 4-fluoro-16a-bromo-3,17α-diol **8b** (30%). We have previously reported similar results for the reduction of 16-bromoestrone-3-acetate.[3]

Equilibration of 4-fluoro-16α-bromoestra-1,3,5(10)-triene-3,17β-diol (**8a**) with sodium iodide in ethyl methyl ketone under reflux for 24 h gave the 4-fluoro-16α-iodoestra-3,17β-diol (**9**, δ 0.75 (18-H)). The retention of configuration at C-16 is presumably the result of the neighboring group participation.[2,3]

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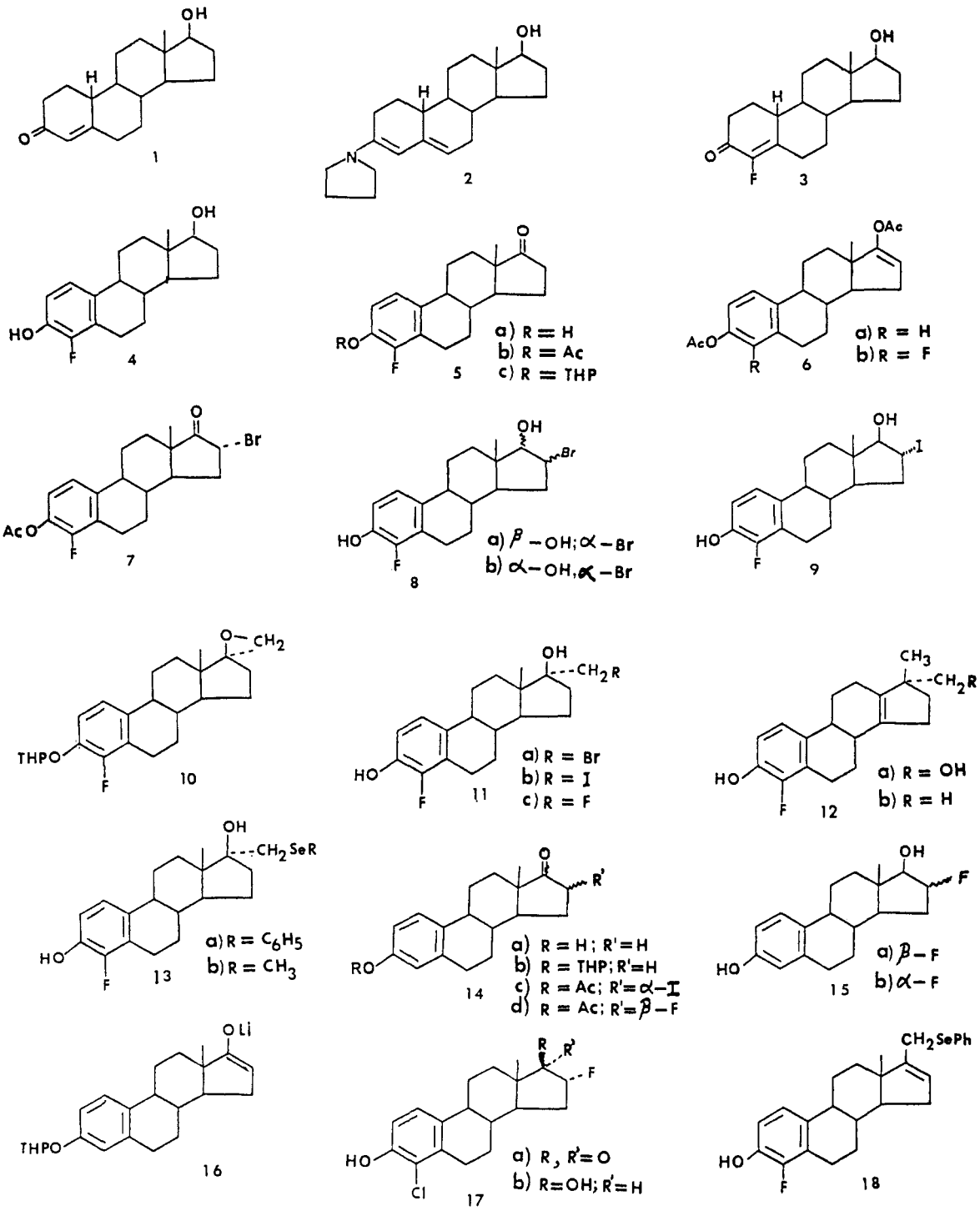
Chart I



4-Fluoro-17α-(bromomethyl)estradiol (**11a**) and 4-fluoro-17α-(iodomethyl)estradiol (**11b**) were synthesized by the hydrolytic cleavage of the 17β-oxirane-3-THP ether **10** with hydrobromic and hydroiodic acids, respectively. The attempts to prepare 4-fluoro-17α-(fluoromethyl)estradiol (**11c**) by treatment of **10** with 47% aqueous hydrofluoric acid at both ambient temperature and at −30 °C failed, but 4-fluoro-17α-(hydroxymethyl)-18-nor-17β-methylestra-1,3,5(10),13-tetraen-3-ol (**12a**, 30%) was obtained instead. The NMR spectrum of **12a** showed signals at δ 1.0 (3 H, s, 17β-CH_3), 3.37 (2 H, AB quartet, δ_{AB} = 8 Hz, J_{AB} = 8 Hz) and a multiplet centered at δ 6.85 (2 H, 1- and 2-H). The mass spectrum showed fragments at *m/e* 302 (M^+) and 271 ($M^+ - 31$). These results indicate that hydrofluoric acid, unlike hydrobromic and hydroiodic acids, opened the oxirane ring (**10**) between C-17 and the oxygen atom with consequent migration of the 13β-methyl group as shown in (Figure 1, **10** → A → **12a**).

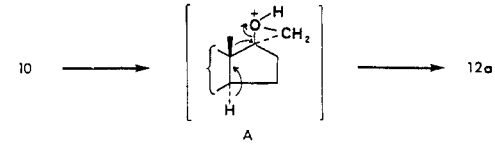


Figure 1.

Treatment of the 17β-oxirane-3-THP ether **10** with sodium benzeneselenoate[3] and cleavage of the THP ether gave 4-fluoro-17α-[(phenylseleno)methyl]estra-3,17β-diol (**13a**) in excellent yield.

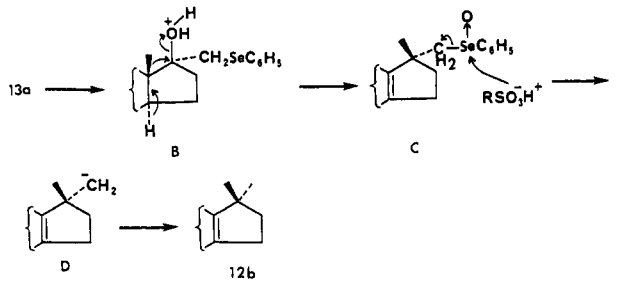


Figure 2.

Refluxing of an ethanolic solution of the 3-THP ether analogue of **13a** and *p*-toluenesulfonic acid monohydrate gave two products. The expected removal of the THP moiety was accompanied by elimination of the 17β-hydroxyl group to give 4-fluoro-17-[(phenylseleno)-methyl]estra-1,3,5(10),16-tetraen-3-ol (**18**). The second product was identified as 4-fluoro-17,17-dimethyl-18-norestra-1,3,5(10),13-tetraen-3-ol (**12b**) on the basis of its mass spectrum, which showed fragments at *m/e* 286 (M^+) and 271 ($M^+ - 15$), and NMR δ 1.0 (6 H, s, 17-$(CH_3)_2$) and δ 6.9 (2 H, m, C-1- and C-2-H). The product very likely is the result of the acid-catalyzed elimination of the 17β-hydroxy group and concomitant migration of the 13β-methyl group to the 17-position to give C (Figure 2). In addition, it is also likely that the phenylseleno moiety underwent oxidative cleavage to yield D, which was protonated by a hydrogen from the medium (Figure 2, **13a** → C → D → **12b**).

Treatment of the oxirane **10** with methylselenoate and removal of the THP moiety gave 4-fluoro-17α-[(methylseleno)methyl]estra-1,3,5(10)-triene-3,17β-diol (**13b**).

Equilibration of 3-acetoxy-16α-iodide **14c** with silver fluoride[7] gave the corresponding 16β-fluoride **14d**, which was reduced ($NaBH_4$ in ethanol at 4 °C) to give 16β-fluoroestradiol (**15a**). The NMR spectrum of **15a** showed signals at δ 0.85 (s, 3 H, C-18H), 3.43 (1 H, dd, J_1 = 21 Hz, J_2 = 6 Hz, C-17α-H), 4.97 (1 H, m, *J* = 57 Hz, C-16α-H). On the basis of inspection of models and consideration of possible coupling constants, the doublet of doublets at δ 3.43 was attributed to the 17α-H, which is coupled to 16α-H and 16β-F. The estimated coupling constants for the 17α-H with 16β-F and 16α-H are ca. 25 and 5 Hz, respectively,[8] and are in agreement with the observed values 21 and 6 Hz. The multiplet of multiplets centered at δ 4.97 was attributed to the 16α-H. The estimated coupling constant for the 16α-H and 16β-F atoms of approximately 55 Hz[8] is in accord with the observed value 57 Hz. The downfield shift of C-18 protons, usually influenced by 16β polar substituent,[3] is in agreement with the 16β orientation of the fluorine. On this basis the structure **15a** was assigned to the product.

Treatment of lithium enolate[9] **16** with perchloryl fluoride unexpectedly gave 4-chloro-16α-fluoro-17-one **17a**, which was reduced ($NaBH_4$) to 4-chloro-16α-fluoroestradiol (**17b**). The mass spectrum of **17b** showed a pair of molecular ions at *m/e* 324 and 326 (~3:1 ratio) for a molecular composition $C_{18}H_{22}O_2FCl$. The NMR of **17b** had two doublets at 6.85 (1 H) and 7.16 (1 H) each with a *J* = 9 Hz for the hydrogen atoms at C-1 and C-2. The multiplet at δ 4.97 (1 H) is assigned to the 16β-hydrogen atom. The lack of downfield displacement of 13β-methyl protons (δ 0.81) is consistent with the presence of a 16β-hydrogen. In the absence of additional splitting of the doublet for the C-2-hydrogen atom, the chlorine atom must be located at C-4, and therefore, the fluorine atom has the 16α-configuration. The introduction of chlorine at the C-4-position of the aromatic ring is probably due to the presence of some free chlorine in the perchloryl fluoride used.

Experimental Section

General Procedures. Melting points were taken on a Kofler hot-stage apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer 237 spectrophotometer as 5% solutions in $CHCl_3$. NMR spectra were recorded on a Varian EM 360 or EM 390 spectrometer using tetramethylsilane as internal reference. The spectra were recorded in $CDCl_3$ or $CDCl_3$ + Me_2SO-d_6. Mass spectra were determined on a Finnigan 1015D instrument updated to Model 3200. The Merck A. G. silica gel 60 (2.06–0.2 nm) was used for column chromatography. Analytical and preparative TLC was carried out, using plates coated with Merck A. G. silica gel 60 (HF 254 + 366).

19-Nortestosterone Enamine 2. The compound was prepared as described by Joly and Warnant[6] and showed the following: mp 134–135 °C (lit. mp 133–135 °C); ^1H NMR δ 0.8 (3 H, s, 18-H), 3.17 (4 H, t, N-CH_2CH_2), 3.68 (1 H, t, *J* = 7 Hz, 17α-H), 4.9 (1 H, s, 4-H), 5.17 (1 H, m, 6-H).

4-Fluoro-19-nortestosterone (3). Perchloryl fluoride was bubbled slowly through a suspension of the enamine **2** (5 g) in 94% aqueous methanol (133 mL) maintained at −20 °C for about 2.5 h. The resulting clear solution was then poured into ice-cold water (1.4 L) and the product extracted with ethyl acetate. The organic extract was washed with water and dried (Na_2SO_4) and the solvent removed under reduced pressure. The resulting gummy residue (4.2 g) was dissolved in dimethylformamide (50 mL), concentrated HCl (5 mL) was added, and the mixture was stirred for 24 h at room temperature. The reaction mixture was poured into cold water (1.4 L) and extracted with ether. The ether extract was washed with water, dried, and evaporated to give a fluffy solid (3.4 g). TLC [silica gel, hexane–ethyl acetate (1:1)] revealed this product to be homogeneous; mp 136–138 °C; ^1H NMR δ 0.83 (3 H, s, 18-H), 3.67 (1 H, t, *J* = 8 Hz, 17α-H); the absence of a signal for the C-4 hydrogen is in accordance with the expected spectrum for 4-fluoro-19-nortestosterone.

4-Fluoroestradiol (4). A mixture of 4-fluoro-19-nortestosterone (3.2 g, 0.011 m) and selenium dioxide (4.6 g, 0.04 m) in *tert*-butyl alcohol (320 mL) was refluxed under argon atmosphere for 24 h. The cooled mixture was filtered and evaporated to give a crude product, which was purified by column chromatography [silica gel, hexane–ethyl acetate (2:1)]. Recrystallization from 80% aqueous ethanol gave 2.56 g of 4-fluoroestradiol (4): mp 174–176 °C; ^1H NMR δ 0.77 (3 H, s, 18-H), 3.68 (1 H, t, *J* = 8 Hz, 17α-H), 6.67–6.97 (2 H, m, C-1, C-2-H) (identical with that of an authentic sample);[10] mass spectrum, *m/e* 290 (M^+).

4-Fluoroestrone (5a). Jones' reagent (ca. 2 mL) was added dropwise to a stirring solution of 4-fluoroestradiol (2 g, 6.8 mmol) in acetone (10 mL) at 0 °C. The reaction was then maintained at room temperature for about 20 min and the excess reagent destroyed by addition of methanol (5 mL). The solution was concentrated to half of its original volume and then diluted with water. The crude product was filtered, washed with cold water, dried, and recrystallized from methanol to give 4-fluoroestrone (**5a**, 1.6 g): mp 197–200 °C; ^1H NMR δ 0.92 (3 H, s, 18-H), 6.67–6.97 (2 H, m, 1- and 2-H); mass spectrum, *m/e* 288 (M^+).

3,17-Diacetoxy-4-fluoroestra-1,3,5(10),16-tetraene (6b). A mixture of 4-fluoroestrone (1 g, 3.4 mmol), freshly distilled isopropenyl acetate (10 mL), and a stock solution of sulfuric acid (0.3 mL) [isopropenyl acetate (5 mL) and concentrated H_2SO_4 (0.1 mL)] was first refluxed for 2 h, and then about 5 mL of solvent was slowly distilled over a period of 1 h. More isopropenyl acetate (10 mL) and stock solution of sulfuric acid (0.3 mL) was added and the reaction mixture concentrated to half its original volume over 1 h. The reaction mixture was chilled, diluted with ether, washed successively with ice-cold aqueous sodium bicarbonate

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and then water, dried, and evaporated. The crude enol acetate was dissolved in hot hexane and filtered quickly through a short (ca. 5 cm) column of neutral alumina. The column was washed with hexane (500 mL) and the combined filtrate concentrated and dried to yield the enol acetate (70%): mp 97–100 °C; ^{1}H NMR δ 0.92 (3 H, s, 18-H), 2.08 (3 H, s, 17-OAc), 2.33 (3 H, s, 3-OAc), 5.5 (1 H, s, 16-H), 6.67–6.97 (2 H, m, 1- and 2-H).

3-Acetoxy-4-fluoro-16α-bromoestra-1,3,5(10)-trien-17-one (7). To a stirring mixture of the enol acetate **6b** (450 mg, 1.2 mmol) and potassium carbonate (310 mg) in carbon tetrachloride (10 mL) at 0 °C was added a solution of bromine (224 mg, 1.4 mmol) in CCl_4 (15 mL) over 30 min. The mixture was poured into water (100 mL) containing sodium bisulfate (100 mg), and the aqueous layer was extracted with chloroform. The combined extract was washed with water, dried, and evaporated to dryness. The crude product was recrystallized to give the bromo ketone **7** (70%): mp 166–168 °C; ^{1}H NMR, δ 0.95 (3 H, s, 18-H), 2.33 (3 H, s, 3-OAc), 4.55 (1 H, t, J = 6 Hz, 16β-H); mass spectrum, m/e 408, 410 (M^+ ions), 366, 368 ($M^+ - CH_2CO$).

4-Fluoro-16α-bromoestra-1,3,5(10)-triene-3,17β-diol (8a) and -3,17α-diol (8b). A solution of 4-fluoro-16α-bromoestrone acetate (**7**) (100 mg) in absolute ethanol (5 mL) was treated with $NaBH_4$ (50 mg) at 4 °C for 24 h. The mixture was diluted with water, neutralized with 1% aqueous H_2SO_4, and then extracted with ethyl acetate. The extract was washed, dried, and concentrated. The residue was fractionated by preparative TLC [hexane–ethylacetate (4:1)] to give 4-fluoro-16α-bromoestra-1,3,5-(10)-teiene-3,17α-diol (**8b**), 4-fluoro-16α-bromo-17β-ol **8a**, and 4-fluoroestradiol. The 16α-bromo-17α-ol **8b** (20 mg) showed the following: mp 242–244 °C; ^{1}H NMR δ 0.79 (3 H, s, 18-H), 3.64 (1 H, d, J = 3 Hz, 17β-H), 4.71 (1 H, m, 16β-H). The 16α-bromo-17β-ol **8a** (32 mg) showed the following: mp 214–216 °C; ^{1}H NMR δ 0.78 (3 H, s, 18-H), 3.73–4.3 (2 H, m, 16β-H and 17α-H); mass spectrum, m/e 368, 370 (M^+ ions), 288 ($M^+ - HBr$).

4-Fluoro-16α-iodoestra-1,3,5(10)-triene-3,17β-diol (9). A mixture of 4-fluoro-16α-bromoestra-3,17β-diol (**8a**) (20 mg) and dry NaI (100 mg) in freshly distilled ethylmethyl ketone (5 mL) was refluxed for 24 h. The solvent was evaporated, water (10 mL) was added, and the product was extracted with ethyl acetate. The extract was washed with 5% sodium thiosulfate and then water, dried (Na_2SO_4), and concentrated. The resulting semisolid (ca. 22 mg) was fractionated by preparative TLC [silica gel, hexane–ethyl acetate (2:1)], to yield crystalline 4-fluoro-16α-iodoestradiol (**9**, 18 mg). An aliquot (10 mg of **10**) was further purified by HPLC (Alltech silica, 10/25; 5% ethanol in isooctane; flow rate 1.5 mL/min; UV detector); mp 195–197 °C dec; ^{1}H NMR δ 0.75 (3 H, s, 18-H), multiplet centered at 4.12 (2 H, 16β-H and 17α-H); mass spectrum, m/e 416 (M^+), 288 ($M^+ - HI$).

Spiro-3-(tetrahydropyran-2′-yloxy)-4-fluoroestra-1,3,5-(10)-triene-17β,2″-oxirane (10). A mixture of dry dimethyl sulfoxide (25 mL) and sodium hydride (2.21 g, 46 mmol, 50% dispersion in oil, washed with dry THF) was stirred (under argon) for 1 h at 70–75 °C. Dry THF (30 mL) was added, and the mixture was cooled to −5 °C. A solution of trimethylsulfonium iodide (8.44 g, 41.3 mole) in Me_2SO (50 mL) was added rapidly. After 5 min a solution of 3-THP-4-fluoroestrone **5c** (2.3 g, 6.18 mmol) in THF (80 mL) was added and the stirring continued for 2 h at −5 °C. The mixture was then allowed to warm up to room temperature, diluted with water (1 L), and extracted with ether. The extract was washed with water, dried, and evaporated to given spiro-3-(tetrahydropyran-2-yloxy)-4-fluoroestra-1,3,5(10)-triene-17β,2′-oxirane (**10**, 2.01 g) as a semisolid. Analytical TLC [hexane–ethyl acetate (2:1)] showed the compound to be homogeneous; ^{1}H NMR δ 0.93 (3 H, s, 18-H), 2.79 (2 H, AB q δ_{AB} = 20 Hz, J_{AB} = 5.5 Hz, $\overline{COCH_2}$), 3.66 (8 H, m, 2′-, 5′-H), 5.37 (1 H, m, 1′-H), 6.9 (2 H, m, 1- and 2-H); mass spectrum, m/e 386 (M^+), 301 ($M^+ - 85$).

4-Fluoro-17α-(bromomethyl)estra-1,3,5(10)-triene-3,17β-diol (11a). A 47% solution of hydrobromic acid (0.5 mL) was added dropwise to a stirred solution of 17β-oxirane **10** (50 mg) in dioxane (0.5 mL), and the stirring was continued for 3 h at room temperature. The reaction was terminated by addition of cold water (40 mL), and the product was recovered with ethyl acetate. The extract was washed with a 2% solution of sodium bicarbonate and then water and dried (Na_2SO_4). Removal of the solvent gave a gummy residue, which was fractionated by preparative TLC [silica gel, hexane–ethyl acetate (2:1)] to give crystalline 4-fluoro-17α-(bromomethyl)estradiol **11a** (40 mg). A sample purified by HPLC (same conditions as for **9**) showed the following: mp 149–150 °C; ^{1}H NMR δ 1.03 (3 H, s, 18-H), 3.7 (2 H, AB q, δ_{AB} = 14 Hz, J_{AB} = 10 Hz, CH_2Br); mass spectrum, m/e 384 ($M^+(^{80}Br)$), 382 ($M^+(^{78}Br)$), 304 ($M^+ - Br$).

4-Fluoro-17α-(iodomethyl)estra-1,3,5(10)-triene-3,17β-diol (11b). Treatment of the 17β-oxirane **10** (50 mg) with a 47% aqueous solution of hydroiodic acid as described above for the bromide **11a** gave 4-fluoro-17α-(iodomethyl)estradiol **11b** (70% yield): mp 90–92 °C dec.; ^{1}H NMR δ 1.03 (3 H, s, 18-H), 3.57 (2 H, AB quartet, δ_{AB} = 14 Hz, J_{AB} = 10 Hz, CH_2I); mass spectrum, m/e 430 (M^+), 303 ($M^+ - I$).

4-Fluoro-17α-(hydroxymethyl)-17β-methyl-18-norestra-1,3,5(10),13-tetraen-3-ol (12a). Treatment of the 17β-oxirane **10** with 48% aqueous hydrofluoric acid, as described above, gave **12a** (30%); mp 188–190 °C; ^{1}H NMR δ 1.0 (3 H, s, 17β-CH_3), 3.37 (2 H, AB q, δ_{AB} = 8 Hz, J_{AB} = 8 Hz); mass spectrum, m/e 302 (M^+), 271 $M^+ - CH_2{=}^+OH$).

4-Fluoro-17α-[(phenylseleno)methyl]estra-1,3,5(10)-triene-3,17β-diol (13a). To a stirred solution of diphenyl diselenide (24 mg, 0.075 mmol) in absolute ethanol (3 mL), $NaBH_4$ (6 mg, 0.15 mmol) was added in portions until the bright-yellow solution became colorless.[3] The 17-oxirane **10** (50 mg, 0.13 mmol) was added to the stirring solution. After 3 h, cold water (50 mL) was added, and the product was extracted with ether and processed in the conventional manner to give a white solid (71 mg). Analytical TLC [silica gel, hexane–ethyl acetate (2:1)] indicated the presence of one major product, identified as 3-(tetrahydropyran-2′-yloxy)-4-fluoro-17α-[(phenylseleno)methyl]estra-1,3,5-(10)-triene-17β-ol: ^{1}H NMR δ 0.97 (3 H, s, 18-H), 3.3 (2 H, AB q, δ_{AB} = 18 Hz, J_{AB} = 12 Hz, CH_2SePh), 3.66 (8 H, m, 2′-, 5′-H), 5.37 (1 H, m, 1′-H), 6.9 (2 H, m, 1-, 2-H), and two sets of multiplets centered at 7.22 and 7.52 (SeC_6H_5).

A mixture of the above product (71 mg, 3 mL) and 0.4 M HCl (1 mL) was heated at 70 °C for 20 min. Water was then added, and the product was recovered with ether. The extract was processed in the conventional manner to give a white solid, which was purified by preparative TLC [silica gel, hexane–ethyl acetate (2:1)] to give 4-fluoro-17α-[(phenylseleno)methyl]estradiol **13a** as white crystals (50 mg): mp 72–74 °C; ^{1}H NMR δ 0.97 (3 H, s, 18-H), 3.3 (2 H, AB quartet, δ_{AB} = 18 Hz, J_{AB} = 12 Hz, CH_2SePh), 6.6–7.0 (2 H, m, C-1, C-2H), and two sets of multiplets centered at 7.22 and 7.52 (SeC_6H_5); mass spectrum, m/e 460 ($M^+(^{80}Se)$), 458 ($M^+(^{78}Se)$).

4-Fluoro-17-[(phenylseleno)methyl]estra-1,3,5(10),16-tetraen-3-ol (18) and 4-Fluoro-17,17-dimethyl-18-norestra-1,3,5(10),13-tetraen-3-ol (12b). A solution of the 3-THP ether of **13a** (65 mg) in 3 mL of 95% ethanol containing *p*-toluenesulfonic acid monohydrate (50 mg) was refluxed for 12 h. After dilution with water and processing in the conventional manner, 40 mg of crude material was obtained. This material was fractionated by preparative TLC [hexane–ethyl acetate (2:1)] to yield 4-fluoro-17-[(phenylseleno)methyl]estra-1,3,5(10),16-tetraen-3-ol (**18**, 11 mg) and 4-fluoro-17,17-dimethyl-18-norestra-1,3,5-(10),13-tetraen-3-ol (**12b**, 16 mg). **18**, a semisolid, showed the following: ^{1}H NMR δ 1.18 (3 H, s, 18-H), 3.07 (2 H, AB q, J_{AB} = 3 Hz, CH_2Se), 5.53 (1 H, m, 16-H), 6.9 (2 H, m, 1-, and 2-H), and two multiplets at 7.25 and 7.53 (5 H, SeC_6H_5); mass spectrum, m/e 442 ($M^+(^{80}Se)$), 440 ($M^+(^{78}Se)$). **12b** showed the following: mp 112–114 °C; ^{1}H NMR δ 1.0 (6 H, s, 17-$(CH_3)_2$), 6.9 (2 H, m, 1-, 2-H); mass spectrum, m/e 286 (M^+), 271 ($M^+ - 15$).

4-Fluoro-17α-[(methylseleno)methyl]estra-1,3,5(10)-triene-3,17β-diol (13b). To a stirred solution of dimethyl diselenide (14.4 mg, 0.075 mmol) in absolute ethanol (3 mL), sodium borohydride (6 mg, 0.15 mmol) was added in small portions.[3] When the solution became colorless, 17-oxirane **10** (50 mg, 0.13 mmol) was added, and the mixture was stirred for 3 h. The reaction was terminated with cold water (50 mL), extracted with ether, and processed in the usual manner to yield a solid (60 mg). Analytical TLC of the product showed one major spot, and NMR showed this to be the desired product. The THP ether group was cleaved as described earlier to give 4-fluoro-17α[(methylseleno)-methyl]estradiol **13b** (45 mg). Crystallization from absolute methanol gave **13b**: mp 110–112 °C; ^{1}H NMR δ 0.97 (3 H, s, 18-H),

2.08 (3 H, s, $SeCH_3$), 2.93 (2 H, AB q, δ_{AB} = 22.5 Hz, J_{AB} = 12 Hz, CH_2SeCH_3), 6.6–7.0 (2 H, m, C-1, C-2H); mass spectrum, *m/e* 398 ($M^+(^{80}Se)$), 396 ($M^+(^{78}Se)$).

3-Acetoxy-16α-iodoestra-1,3,5(10)-trien-17-one (14c). This compound was prepared as described by Mueller and Johns[7] and showed the following: mp 143–144 °C (lit.[7] mp 142–143.6 °C); ^1H NMR δ 1.03 (3 H, s, 18-H), 2.3 (3 H, s, 3-OAc), 4.92 (1 H, m, 16β-H), 6.86 (s, C-4H), 6.94 (d, *J* = 2 Hz, C-2H), 7.3 (d, *J* = 9 Hz, C-1H).

3-Acetoxy-16β-fluoroestra-1,3,5(10)-trien-17-one (14d). A mixture of 3-acetoxy-16α-iodoestrone **14c** (1 g, 2.37 mmol, 40 mL) and anhydrous silver fluoride (2.8 g, 22 mmol) in dry acetonitrile was refluxed for 3 h and allowed to stand at room temperature for 3 days. The mixture was heated to boiling and filtered. The cooled filtrate was diluted with ether, washed, dried, and evaporated. The resulting brown gum (0.76 g) was dissolved in acetic anhydride (10 mL), refluxed (30 min), and then concentrated in vacuo. The residue was resolved by preparative TLC (same system as above) to give **14c** and 3-acetoxy-16β-fluoroestra-1,3,5(10)-trien-17-one (**14d**, 10%): mp 181–183 °C (182–184 °C); ^1H NMR δ 1.03 (3 H, s, 18-H), 2.27 (3 H, s, 3-OAc), 4.7 (1 H, tt, J_1 = 50 Hz, J_2 = 8 Hz, 16α-H), 6.86 (s, C-4H), 6.94 (d, *J* = 3 Hz, C-2-H), 7.3 (d, *J* = 9 Hz, C-1H); mass spectrum, *m/e* 330 (M^+), 287 ($M^+ - CH_3COOH$).

16β-Fluoroestra-1,3,5(10)-triene-3,17β-diol (15a). A solution of 3-acetoxy-16β-fluoroestrone **14d** (50 mg) in absolute ethanol (25 mL) was treated with sodium borohydride (25 mg) at 4 °C for 24 h. The mixture was diluted with water, neutralized with 1% H_2SO_4, extracted with ethyl acetate, and processed in the conventional manner to give a greyish solid. This was fractionated by TLC (hexane–ethyl acetate (2:1)] to yield 16β-fluoroestradiol **15a** (80%): mp 220–223 °C (from methanol); ^1H NMR δ 0.85 (s, 3 H, 18-H), 3.43 (1 H, dd, J_1 = 21 Hz, J_2 = 6 Hz, 17α-H), 4.97 (1 H, mm, *J* = 57 Hz, 16α-H), 6.62 (1 H, s, 4-H), 6.7 (1 H, d, *J* = 3 Hz, 2-H), 7.13 (1 H, d, *J* = 8 Hz, 1-H); mass spectrum, *m/e* 290 (M^+), 270 (M^+ – HF).

Reaction of 3-(Tetrahydropyran-2′-yloxy)estrone Enol Lithium 16 with Perchloryl Fluoride.[8] To a stirred (under argon) suspension of lithium diisopropylamide (302 mg, 2.82 mmol) in dry toluene (4 mL) was added dropwise a solution of estrone 3-THP ether (1 g, 2.82 mmol) in toluene (6 mL). The resulting yellowish-brown solution was concentrated to one-third of its original volume and dry THF (8 mL) added. Perchloryl fluoride was bubbled through the solution for 2 min at 0 °C. Excess perchloryl fluoride was then removed under reduced pressure (10 min), and the reaction mixture was poured into ice water (100 mL). The product was recovered with ether and processed in the conventional manner to give a gummy residue. Analytical TLC [silica gel, hexane–ethyl acetate (2:1)] indicated the presence of the starting material and of two more products. The THP moiety was cleaved [ethanol (3 mL), 0.4 M H_2SO_4 (1 mL), 70 °C, 20 min], and the resulting products were resolved by preparative TLC [silica gel, hexane–ethyl acetate (3:1)] to give estrone and 4-chloro-16α-fluoroestrone **17a** (50 mg): mp 140–143 °C; ^1H NMR δ 0.97 (3 H, s, 18-H), 5.13 (1 H, tt, J_1 = 54 Hz, J_2 = 6 Hz, 16β-H), 6.88 (1 H, d, *J* = 9 Hz, 2-H), 7.18 (1 H, d, *J* = 9 Hz, 1-H); mass spectrum, *m/e* 324, 322 (M^+ ions).

4-Chloro-16α-fluoroestra-1,3,5(10)-triene-3,17β-diol (17b). A solution of 4-chloro-16α-fluoroestrone **17a** (20 mg) in absolute ethanol (2 mL) was treated with $NaBH_4$ (10 mg) at 4 °C for 24 h. The mixture was diluted with water, neutralized with 1% H_2SO_4, and then extracted with ethyl acetate. The extract was washed, dried, and concentrated to give 4-chloro-16α-fluoroestradiol **17b** as a crystalline residue. The residue was purified by HPLC; mp 162–164 °C; ^1H NMR δ 0.81 (3 H, s, 18-H), 2.85 (1 H, dd, J_1 = 285 Hz, J_2 = 5 Hz, 17α-H), 4.97 (1 H, mm, *J* = 55.5 Hz, 16β-H), 6.85 (1 H, d, *J* = 9 Hz, 2-H), 7.16 (1 H, d, *J* = 9 Hz, 1-H); mass spectrum, *m/e* 324, 326 (M^+ ions), 304, 306 (M – HF).

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Quantitative Description of Steric and Electrical Effects of Planar π-Bonded Groups. 1. Variation of Dihedral Angle with the Size of an Adjacent Group

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The equation $1/\sin\theta = a_{30}/\sum r + a_{11}$, where θ is the dihedral angle and $\sum r$ the sum of the van der Waals r_V of a planar π-bonded substituent (Xpπ) and a nonplanar substituent (Xnp), has been derived. In this relationship, a_{30} is the slope and a_{11} the intercept. Data for 15 sets of compounds in which Xpπ and Xnp are vicinally bonded to a planar π-bonded skeletal group, G, have been correlated with this equation, generally with good results. In some cases, however, best results are obtained with the inclusions of a term for electrical effects in the correlation equation. These results are applicable to a wide range of Xpπ groups, including Ph, $CH{=}CH_2$, XC_6H_4, $CONH_2$, CO_2H, Ac, and NO_2, and to both ortho-substituted benzene and *cis*-vinylene skeletal groups.

It has been shown that the effect of ortho substituents on chemical reactivity or physical properties is well represented by the LDS equation (eq 1), where Q_X is the

$$Q_X = L\sigma_{IX} + D\sigma_{DX} + Sv_X + h \quad (1)$$

quantity of interest (pK_a, log *k*, μ, ν_{CO}, δ_H, etc.), σ_I and σ_D represent the localized (field and/or inductive) and delocalized (resonance) electrical effects. Available σ_D constants include σ_R, σ_R^+, σ_R^-, and σ_R°, the choice depending on whether or not π delocalization involving the substitutent X, the active site Y, and the skeletal group G (to which X and Y are bonded) is possible and on the electronic demand of Y. *v* is a steric parameter based on r_{VX}, the van der Walls radius of X ($v \equiv v_{vx} - 1.20$).

Planar π-Bonded Groups. The inclusion of planar π-bonded substituents, Xpπ, in a data set which is to be correlated with the LDS equation is difficult if a significant steric effect is present. Planar π–bonded groups have the

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