Oxidation of 1,1-Di(*p*-iodophenyl)ethane-2-^{14}C with Potassium Permanganate.—1,1-Di(*p*-iodophenyl)ethane-2-^{14}C, 1.06 g (2.44 mmol), and 1.45 g (9.18 mmol) of potassium permanganate were refluxed in 50 ml of glacial acetic acid for 4 hr. Water was added to the reaction mixture and the solution was filtered. The solid was extracted with 10 ml of a 10% solution of sodium hydroxide. The extract was acidified with concentrated hydrochloric acid, but no precipitate was formed. Since *p*-iodobenzoic acid is very insoluble in water, it can be concluded that no rearrangement can be detected on oxidation of the diarylethane with potassium permanganate. The remaining solid was repeatedly washed with water, dried, and recrystallized from toluene to yield 0.927 g (87%) of *p,p'*-diiodobenzophenone, mp 229–230°. Three more recrystallizations from toluene yielded a product melting at 240–241° whose activity was undistinguishable from background showing that the label was indeed at C-2.

Oxidation of *p,p'*-Diiodobenzophenone with Chromic Acid.—*p,p'*-Diiodobenzophenone, 1.01 g (2.33 mmol), and 2.61 g (26.1 mmol) of chromic acid were refluxed for 4 hr in 25 ml of acetic acid. The products were isolated according to the procedure described in the next paragraph. *p*-Iodobenzoic acid, 0.11 g, mp 268–268, was obtained in a 19% yield (0.112 g).

General Procedure for the Oxidation of 1,1-Di(*p*-iodophenyl)ethane with Chromic Acid.—1,1-Di(*p*-iodophenyl)ethane, 1.00 g (2.30 mmol), 2.60 g (26.0 mmol) of chromic acid, and 25 ml of glacial acetic acid were placed in a three-necked, round-bottomed flask fitted with a nitrogen inlet, a condenser, and either a magnetic stirrer for reactions at room temperature or boiling stones for reactions at reflux temperature. The condenser was connected to three traps containing 50 ml of 5% sodium hydroxide in each. Pure, dry nitrogen was bubbled through the system in order to sweep the carbon dioxide into the traps. Reflux time was 4 hr, while the reactions at room temperature were allowed to run for 24 hr. After the reaction time was completed, water was added to the mixture and it was filtered. The solid was extracted three times with 10% sodium hydroxide and the mother liquor was extracted with benzene. The benzene solution was also extracted with 10% sodium hydroxide. The combined sodium hydroxide extracts were acidified to precipitate the *p*-iodobenzoic acid. The benzene solution was washed with water, dried over calcium chloride, and taken to dryness. This residue was combined with the previously mentioned solid fraction and recrystallized from toluene to yield *p,p'*-diiodobenzophenone. The yields reported are for the crude precipitated acid and for the recrystallized benzophenone. For counting, the products were recrystallized until constant activity (zero, in the case of the ketone) and melting point [240–241° for the ketone, and 268–269° for the acid (lit.[5] mp 237–238° and 268–270°, respectively)] were attained. The contents of the traps were combined, 15 g of NH_4Cl was added, and then 90 ml of a 10% solution of $BaCl_2$. The carbonate was filtered on a tared, sintered glass funnel, dried in the oven at 100°, and kept in a desiccator.

Registry No.—Chromic acid, 7738-94-5; 1,1-di(*p*-iodophenyl)ethane, 5216-55-7; 1,1-di(*p*-iodophenyl)-ethane-2-^{14}C, 27067-11-4.

Synthesis of 6,6-Difluoronorethindrone[1]

GEORGE A. BOSWELL, JR.,* ALEXANDER L. JOHNSON, AND JOSEPH P. MCDEVITT

Contribution No. 1719 from the Central Research Department, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

Received July 31, 1970

Two syntheses of 6,6-difluoronorethindrone (**13**) are described, utilizing the reactions of NOF and SF_4 with steroids. The more direct approach from norethindrone (**20**) was less satisfactory than the longer route from 19-nortestosterone (**1**). Some of the chemistry of 6,6-difluoro-4-estrene-3,17-dione (**7**), a useful intermediate, is also discussed.

The enhancement of endocrine activity of steroids by fluorine substitution has been studied extensively.[2] We have recently described[3] the application of nitrosyl fluoride as a useful fluorinating agent for steroids, and, together with sulfur tetrafluoride,[3-5] it may be used in the key stages of a multistep steroid synthesis. In the present work, two synthesis of 6,6-difluoronorethindrone (**13**) are described, suitable starting materials being 19-nortestosterone (**1**) and norethindrone (**20**). The more direct route from norethindrone (Scheme III) was less satisfactory than the longer route from 19-nortestosterone (Scheme I) because the 17α-ethynyl group of **20** is sensitive both to NOF and to acidic oxidizing conditions.

The preferred synthesis (Scheme I) starts with the conversion of 19-nortestosterone to 3β,17β-dihydroxy-5-estrene-3,17-diacetate (**2**) by the procedure of Villotti, Djerassi, and Ringold.[6] This step protects the 3 and 17 positions and shifts the double bond from the 4 to the 5 position, for the introduction of 5 and 6 substituents by means of NOF and SF_4. Treatment of the Δ^5-diacetate **2** with NOF in dichloromethane[3] gave two major products in addition to unreacted starting material (Scheme II). When excess NOF was used, the major product was the 5α-fluoro-6-nitrimino steroid **17**, which was hydrolyzed to 3β,17β-dihydroxy-5α-fluoroestran-6-one-3,17-diacetate (**3**) on hydrated alumina chromatography.[3] The second product, which is more abundant when insufficient NOF is used, is 3β,17β-dihydroxy-5α-fluoro-6-nitrosoestrane-3,17-diacetate dimer[7] (**18**). **18** was also converted to ketone **3** in 70% overall yield by allowing it to tautomerize in methanol solution to 3β,17β-dihydroxy-5α-fluoro-6-oximinoestrane-3,17-diacetate[3f] (**19**), which was then deaminated to **3** with nitrous acid. The conversion of **2** to **3**, by combining the two procedures, was 40%.

(1) Presented in part at the Fifth Middle Atlantic Regional Meeting of the American Chemical Society, Newark, Del., April 2, 1970.

(2) (a) J. Fried and E. F. Sabo, *J. Amer. Chem. Soc.*, **76**, 1455 (1954); (b) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y. 1959, pp 593, 682–686; (c) C. Djerassi, "Steroid Reactions," Holden-Day, San Francisco, Calif., 1963, pp 155–177; (d) A. A. Akhrem, I. G. Reshetova, and Yu. A. Titov, *Russ. Chem. Rev.*, **34**, 926 (1965); (e) V. M. Khutoretskii, L. V. Okhlobystina, and A. A. Fainzilberg, *ibid.*, **36**, 145 (1967); (f) G. Schiemann and B. Cornils, "Chemie und Technologie Cyclischer Fluorverbindungen," Ferdinand Enke Verlag, Stuttgart, 1969, pp 114–127.

(3) (a) G. A. Boswell, Jr., *Chem. Ind. (London)*, 1929 (1965); (b) U. S. Patent 3,219,673 (1965); (c) *J. Org. Chem.*, **31**, 991 (1966); (d) U. S. Patent 3,235,571 (1967); (e) S. Andreades and G. A. Boswell, Jr., U. S. Patent 3,320,291 (1967); (f) G. A. Boswell, Jr., *J. Org. Chem.*, **33**, 3699 (1968).

(4) W. R. Hasek, W. C. Smith, and V. A. Engelhardt, *J. Amer. Chem. Soc.*, **82**, 543 (1960).

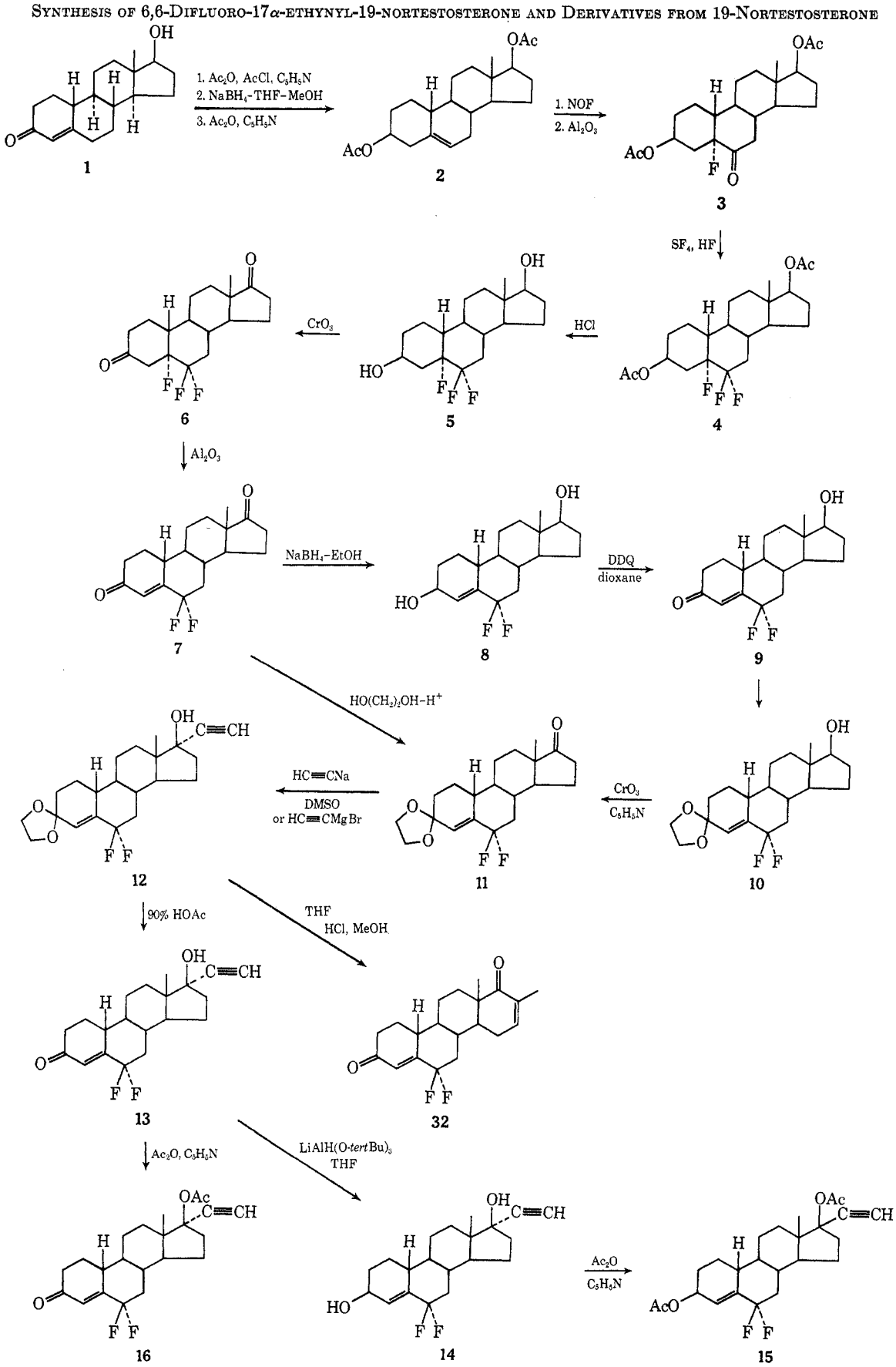
(5) (a) J. S. Tadanier and J. W. Cole, German Patent 1,183,077 (1961); (b) D. G. Martin and F. Kagan, *J. Org. Chem.*, **27**, 3164 (1962); (c) D. G. Martin and J. E. Pike, *ibid.*, **27**, 4086 (1962).

(6) R. Villotti, C. Djerassi, and H. J. Ringold, *J. Amer. Chem. Soc.*, **81**, 4566 (1959).

(7) In ref 3f, Table II, footnote 1, we stated that this product arose from excess NOF, but the reverse situation now appears to be true.

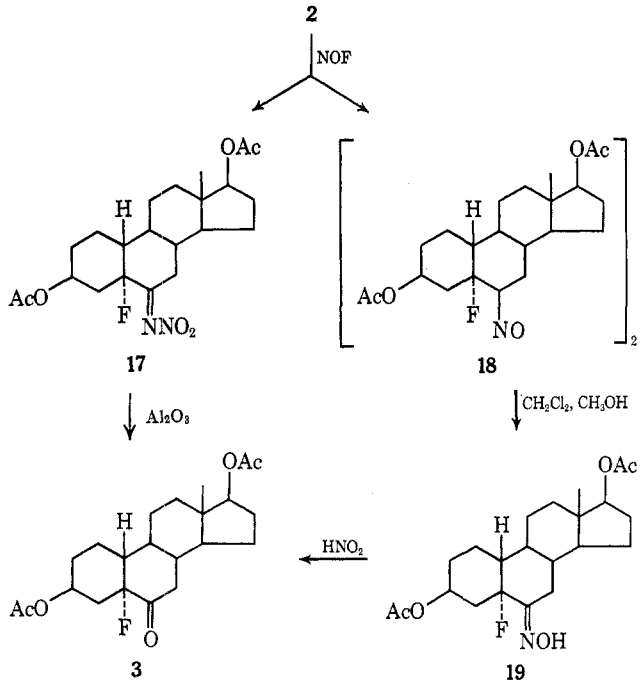
SCHEME I

SYNTHESIS OF 6,6-DIFLUORO-17α-ETHYNYL-19-NORTESTOSTERONE AND DERIVATIVES FROM 19-NORTESTOSTERONE



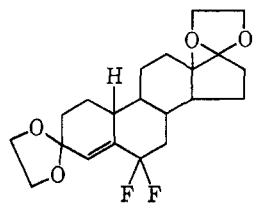
Treatment of the 5α-fluoro 6-ketone **3** with SF_4 under mild conditions[4,5] gave an 85% yield of 3β,17β-dihydroxy-5α,6,6-trifluoroestrane-3,17-diacetate (**4**). Inspection of Scheme I shows that all the necessary fluorine has been introduced into the steroid at an early stage; there are two reasons for this. These are (a)

SCHEME II
DETAILS OF THE REACTION OF NOF WITH 2



the *gem*-difluoro group in the 6 position is very stable toward hydrolysis and reduction under a variety of acidic and basic conditions, provided that there is no $\Delta^{5(10)}$ double bond; (b) because in compound **6** the 5α-fluorine substituent will be β to a carbonyl at position 3, the hydrogen atoms at position 4 are more acidic than the 10β-hydrogen atom, and the double bond produced by elimination of HF from **6** is found exclusively in the 4 position. Furthermore, the 5α-fluorine in **4** and **5** is stable to acidic conditions, so the hydrolysis of the acetate functions in **4** with methanolic HCl and the Jones oxidation[8] of the resulting diol (**5**) to the trifluorodione (**6**) can be readily carried out. The trifluorodione **6**, because of the activated methylene group with its acidic hydrogen atoms at position 4, readily underwent elimination on hydrated alumina to form the conjugated 6,6-difluoro-4-estrene-3,17-dione (**7**), an important intermediate in this synthesis. The alternative mode of elimination to form the unconjugated $\Delta^{5(10)}$ isomer (**26**) was not observed under these conditions, even though the 10β-hydrogen is in a trans-diaxial relationship to the 5α-fluorine. Treatment of the conjugated ketone **7** with a strong base such as sodium acetylide in DMSO caused isomerization to the unconjugated isomer **26**, presumably through protonation of the 3,5(10)-dienolate anion at position 4 during isolation. The stability of the geminal difluoro grouping during this isomerization is noteworthy.

The synthesis was completed by the preferential ethynylation of the 17-carbonyl group of **7**. The conjugated 3-carbonyl group was blocked as the ethylene ketal derivative. Originally, it was believed necessary to use the four-step sequence **7** → **8** → **9** → **10** → **11**, but it was subsequently shown that ketalization occurred more readily at position 3 than at position 17, with only minor amounts of the 3,17-bisketal (**25**)



25

being produced. Since the 3,17-bisketal was unaffected by the ethynylation step, was reconverted to dione **7** on acid hydrolysis, and could be separated chromatographically from the final product **13**, its presence was not a real disadvantage. Sodium borohydride reduction of dione **7** to the corresponding diol (**8**) was followed by preferential DDQ oxidation of the allylic hydroxyl in the 3 position to regenerate the Δ^4-3-ketone. 17β-Hydroxy-6,6-difluoro-4-estren-3-one (**9**) was converted to the ketal (**10**) using oxalic acid as the ketalization catalyst. The use of *p*-toluenesulfonic acid as a ketalization catalyst in this reaction causes extensive degradation of **9**. Furthermore, the normal course of *p*-toluenesulfonic acid catalyzed ketalization of a Δ^4-3-keto steroid is the formation of a Δ^5-3-ketal,[9] but the presence of the geminal difluoro group at position 6 prevents this isomerization from occurring. The formation of a steroid Δ^4-3-ketal is usually observed only with oxalic or adipic acid catalyzed ketalization.[10] A similar observation is also true for the direct conversion of **7** to **11**, oxalic acid again being the preferred catalyst. Sarett oxidation[11] of the 3-ketal 17-alcohol **10** produced 6,6-difluoro-4-estrene-3,17-dione 3-ethylene ketal (**11**).

The most satisfactory ethynylating agent was sodium acetylide in DMSO,[12] which reacted completely within 30 min. The crude ethynylated ketal (**12**) was usually hydrolyzed directly to the final product, 6,6-difluoronorethindrone (**13**), with 90% acetic acid. A pure sample of ketal **12** was prepared from **13** using the oxalic acid method. The reduction of **13** with lithium aluminum tri-*tert*-butoxy hydride gave the 3β,17β-diol (**14**), which was readily acetylated to 6,6-difluoroethynodiol diacetate (**15**). Direct acetylation of **13** gave 6,6-difluoronorethindrone acetate (**16**). Direct ethynylation of dione **7** with sodium acetylide in DMSO (Scheme IV), in addition to causing the isomerization to the unconjugated isomer **26**, described above, gave some of the 17α-ethynyl derivative, 6,6-difluoronorethynodrel (**27**). The treatment of **27** with dilute methanolic HCl caused hydrolysis of the allylic fluoride[13] to 17β-hydroxy-17α-ethynyl-5(10)-estrene-3,6-dione (**28**). Attempts to isomerize the $\Delta^{5(10)}$ isomer

(8) (a) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); (b) P. Bladon, J. M. Fabian, H. B. Henbest, H. P. Koch, and G. W. Wood, *ibid.*, 2402 (1951); (c) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *ibid.*, 2555 (1953); (d) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(9) (a) E. J. Salmi, *Ber.*, **71**, 1803 (1938); (b) J. W. Dean and R. G. Christiansen, *J. Org. Chem.*, **28**, 2110 (1963).

(10) J. J. Brown, R. H. Lenhard, and S. Bernstein, *Experientia*, **18**, 309 (1962).

(11) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

(12) C. H. Robinson, N. F. Bruce, and E. P. Oliveto, *J. Org. Chem.*, **28**, 975 (1963).

(13) For a discussion of difluoromethylene groups see the following sources: (a) M. Hudlický, "Chemistry of Organic Fluorine Compounds," MacMillan, New York, N. Y., 1962 pp 203–205; (b) ref 2f, pp 184–231; (c) W. A. Sheppard and C. M. Sharts, "Organic Fluorine Chemistry," W. A. Benjamin, New York, N. Y., 1969, pp 411–415.

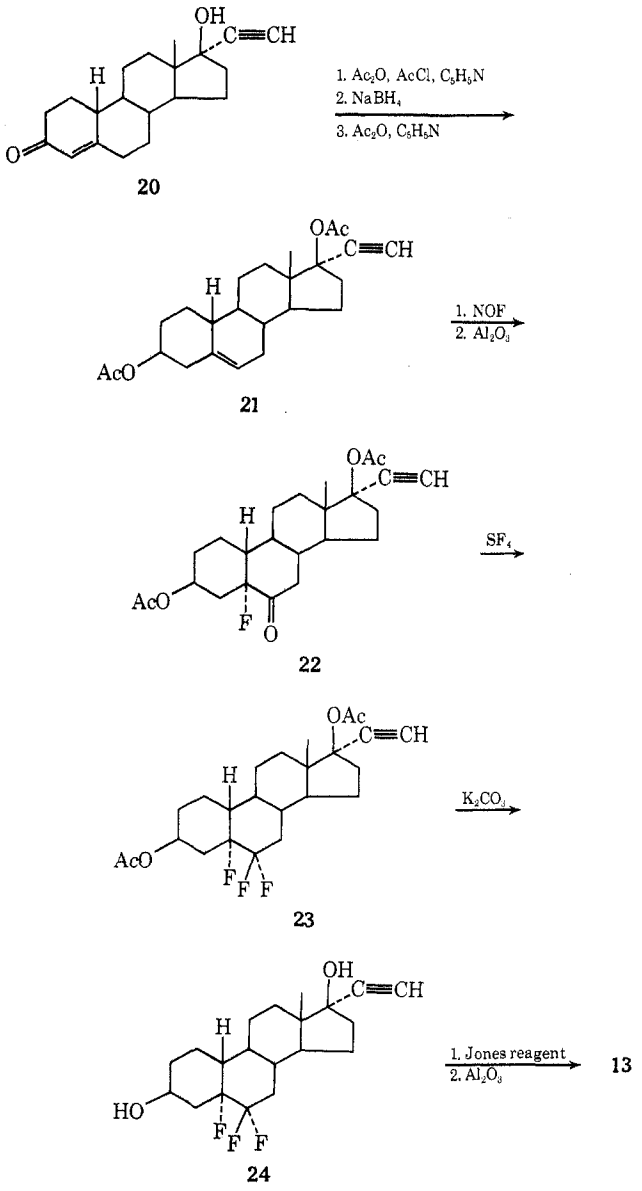
to the Δ^4 isomer fail in acidic media because of the hydrolysis of **27** to **28**, and in basic media no change is observed because the $\Delta^{5(10)}$ isomer is more stable to base than the Δ^4 isomer. A series of simple reactions can be used to convert dione **7** into some interesting 19-nor steroid derivatives, the remarkable feature of which is the stability of the Δ^4-6,6-*gem*-difluoro group to a variety of conditions, permitting a considerable amount of molecular modification once the fluorine atoms have been introduced.

An example of D homoannulation was observed during the isolation procedure in one synthesis of **13**. After ketal **11** had been treated with ethynylmagnesium bromide, hydrolysis of the Grignard complex with 5% methanolic HCl produced some 6,6-difluoronorethindrone, but the major product was 6,6-difluoro-17-methyl-4,16-*D*-homoestradiene-3,17a-dione (**32**) (Scheme I).

The second synthesis of 6,6-difluoronorethindrone (Scheme III) was more direct but less satisfactory.

SCHEME III

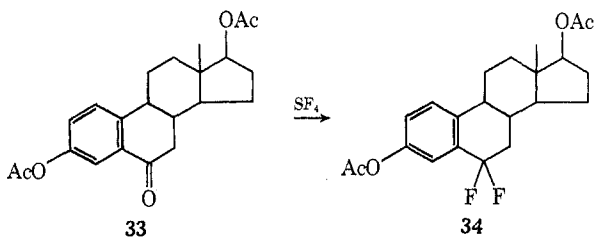
SYNTHESIS OF 6,6-DIFLUORO-17α-ETHYNYL-19-NORTESTOSTERONE FROM 17α-ETHYNYL-19-NORTESTOSTERONE



13

Norethindrone (**20**) was converted to 3β,17β-dihydroxy-17α-ethynyl-5-estrene-3,17-diacetate (**21**) by the literature procedure,[6,14] for reasons already discussed above. The treatment of **21** with NOF is complicated not only by dimerization of the 5α-fluoro-6-nitroso steroid, but by overreaction in which the ethynyl group reacts with NOF.[3f,15] It is essential to use only slight excess of NOF if a reasonable yield of 3β,17β-dihydroxy-5α-fluoro-17α-ethynylestran-6-one-3,17-diacetate (**22**) is to be obtained by hydrated alumina chromatography of the intermediate nitrimine. Treatment of this 5α-fluoro-6-ketone **22** with SF_4 gave the trifluorodiacetate (**23**), albeit in poorer yield than in the conversion of **3** to **4**. The sequence of hydrolysis of the acetate functions to diol **24**, Jones oxidation to the corresponding ketone, and dehydrofluorination of the latter on hydrated alumina to 6,6-difluoronorethindrone (**13**), identical with that obtained by the first synthesis, is similar to that described above for Scheme I. A considerable amount of degradation occurs in the Jones oxidation of **24**, so that, while fewer steps are involved in the second synthesis, yields in at least three of the steps are poorer, and the first synthesis is the preferred one.

Finally, dehydrogenation and dehydrofluorination both occurred when dione **7** was heated to 180° in the presence of 10% palladium on carbon (Scheme IV). The major product of this reaction is 6-fluoroequilenin (**29**), accompanied by lesser amounts of the completely dehydrofluorinated products equilenin (**30**) and 3ξ-hydroxy-5,7,9,(10)-estratrien-17-one (**31**). A-Ring aromatization is thus accompanied by spontaneous dehydrofluorination in the B ring. The initially formed benzylic fluoride would be expected to be unstable under these conditions.[3,16] An attempt to prepare a steroidal benzylic fluoride was unsuccessful. Treatment of 3,17β-estradiol-6-one-3,17-diacetate[17] (**33**) with SF_4 gave a dark residue from which no identifiable



product, such as 6,6-difluoro-3,17β-estradiol-3,17-diacetate (**34**), could be isolated.

The ^{19}F nmr spectra of various 5α,6,6-trifluoro and 6,6-difluoro steroids can be fairly readily interpreted. In compounds **3**, **4**, and **5** the 5α-fluorine appears as a triplet (J = 35 Hz) near +10,000 Hz the coupling being due to the neighboring axial protons at positions 4 and 10. In compounds **7**, **8**, **13**, **14**, **24**, and **32**, the geminal difluoride substituent at position 6 appears near +6000 Hz as a pair of doublets (J = 230–250 Hz) representing the axial and equatorial fluorine atoms. In compounds **7**, **8**, and **32**, the axial fluorine can be distinguished by the further splitting. (J = 30 Hz)

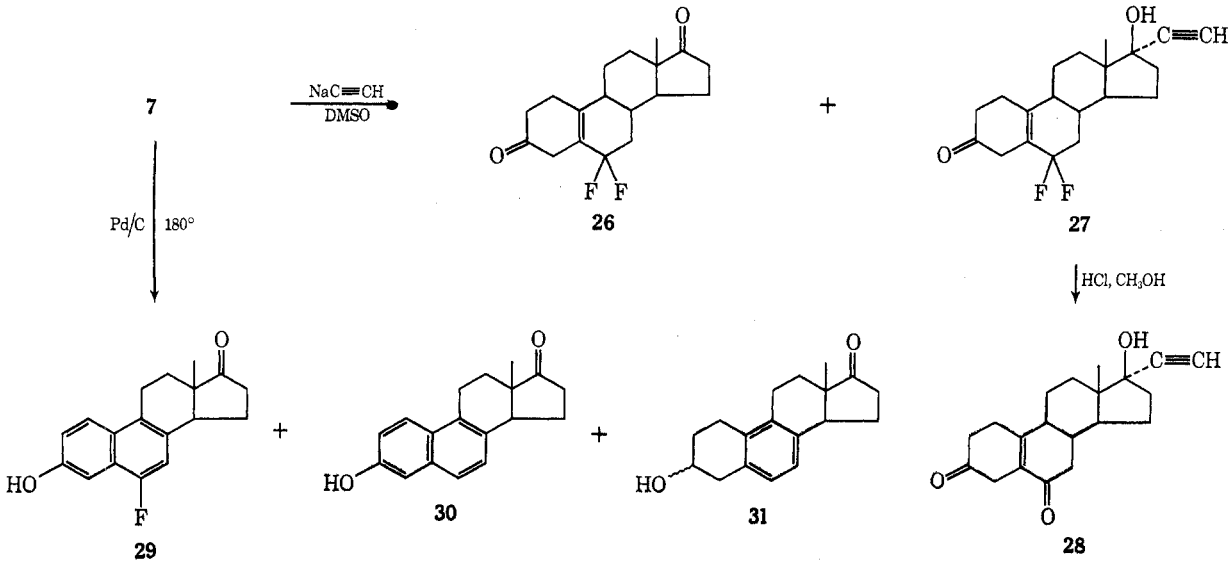
(14) (a) J. Iriarte, C. Djerassi, and H. J. Ringold, *J. Amer. Chem. Soc.*, **81**, 436 (1959); (b) L. H. Knox, J. A. Zderic, J. P. Ruelas, C. Djerassi, and H. J. Ringold, *ibid.*, **82**, 1230 (1960).

(15) This reaction is under study and will be reported in the near future.

(16) (a) Reference 13a pp 263–277; (b) ref 13c, p 349.

(17) B. Longwell and O. Wintersteiner, *J. Biol. Chem.*, **133**, 219 (1940).

SCHEME IV
REACTIONS OF 6,6-DIFLUORO-4-ESTRENE-3,17-DIONE (7)



of its member signals by the neighboring axial proton in the 7 position.

Experimental Section[18]

3β,17β-Dihydroxy-5-estrene-3,17-diacetate (**2**) was prepared from 19-nortestosterone (**1**) (1852 g) in 44% overall yield by the procedure of Villotti, Djerassi, and Ringold.[6]

3β,17β-Dihydroxy-5α-fluoroestran-6-one-3,17-diacetate (**3**) was prepared by Boswell's procedure[8] using 60-g batches of **2** and 20 g of nitrosyl fluoride in dichloromethane solution. A total of 470 g (33%) of the fluoro ketone **3** was obtained by chromatography of the intermediate nitrimine **17**, and a further 90 g of **3** was obtained from the 5α-fluoro-6-nitroso dimer[8,19] (**18**), which accompanies the nitrimine **17**, by the following procedure.

The crude dimer **18** (50.5 g) was dissolved in CH_2Cl_2 (350 ml) and filtered. The filtrate was diluted with MeOH (150 ml) and left for 3 days at 25°. The crude fluoro oxime (**19**), obtained by evaporating the solution, was redissolved in CH_2Cl_2 (250 ml) and treated at 25° with water (200 ml), glacial HOAc (25 ml), and a solution of sodium nitrite (33.0 g) in water (100 ml). The mixture was stirred for 2.5 hr, the layers were separated, and the aqueous layer was extracted with two 100-ml portions of CH_2Cl_2. The foamy residue of crude fluoro ketone **3**, isolated by evaporation of the dried extracts, was chromatographed on Woelm neutral activity III alumina (1000 g). Successive elution with hexane, hexane–benzene (3:1), and benzene, returned fluoro ketone **3**, which was recrystallized from a mixture of acetone (65 ml) and hexane (340 ml), recovery 33.7 g (70%), identified by comparison of melting point and infrared, ultraviolet, and nmr spectra with those of fluoro ketone obtained by chromatography of the nitrimine.

3β,17β-Dihydroxy-5α,6,6-trifluoroestrane-3,17-diacetate (**4**).—A mixture of 3β,17β-dihydroxy-5α-fluoroestran-6-one-3,17-diacetate (**3**) (7.0 g), CH_2Cl_2 (75 ml), water (1.0 ml), and sulfur tetrafluoride (160 g) was shaken at 20° for 10 hr in an autoclave.[4,5] The mixture was shaken successively with water, 5% $NaHCO_3$, water, and brine. The organic layer was dried over $MgSO_4$ and evaporated to leave a tan solid which was recrystallized from CH_2Cl_2–hexane to give pure 3β,17β-dihydroxy-5α,6,6-trifluoroestrane-3,17-diacetate (6.15 g, 83%): mp 188–190° $[\alpha]^{23}D$ ±0° (*c* 1.73, $CHCl_3$); ν_{max}^{Nujol} 1730 (OAc) and 1170 cm^{-1} (C–F); ^{19}F nmr δ +6330 (m) (6-F) and +10,017 Hz (t, *J* = 32) (5α-F); ^1H nmr δ 121 (s) (OAc) and 49 Hz (s) (18-H).

Anal. Calcd for $C_{22}H_{31}F_3O_4$: C, 63.44; H, 7.50; F, 13.69. Found: C, 63.40; H, 7.30; F, 13.28.

In larger scale runs, the crude trifluorodiacetate **4** was chromatographed on Florisil before recrystallization. The product **4** was eluted with 5–10% acetone in hexane, whereas unreacted **3** required 10–20% acetone in hexane. A total amount of 705.7 g of **3** was processed in batches to give 558.3 g (85%) of **4**.

3β,17β-Dihydroxy-5α,6,6-trifluoroestrane (**5**).—A solution of the trifluorodiacetate **4** (5.35 g) in MeOH (50 ml) and concentrated HCl (6 ml) was heated under reflux for 1 hr. The hot solution was carefully diluted with hot water and allowed to cool slowly to 25°, when long colorless needles of diol **5** appeared (4.28 g). Pure 3β,17β-dihydroxy-5α,6,6-trifluoroestrane (4.13 g, 97%) was obtained by recrystallization from acetone–hexane mixture. It had mp 170–171°; $[\alpha]^{23}D$ ±0° (*c* 1.04, $CHCl_3$); ν_{max}^{Nujol} 3590 cm^{-1} (OH); ^{19}F nmr δ +6297 (m) (6-F) and +1948 Hz (t, *J* = 38) (5α-F); ^1H nmr ($CDCl_3$, TMS) δ 45 Hz (s) (18-H).

Anal. Calcd for $C_{18}H_{27}F_3O_2$: C, 65.20; H, 8.18; F, 17.10. Found: C, 65.06; H, 8.07; F, 16.87.

5α,6,6-Trifluoroestrane-3,17-dione (**6**).—A mixture of the trifluorodiol **5** (3.5 g) and acetone was cooled to 15° and treated with Jones reagent[8d] (3.0 ml). The excess oxidizing agent was reduced with methanol, and the product was precipitated by the addition of water. The crude product was filtered, washed with water, air-dried, and recrystallized from acetone. Pure 5α,6,6-trifluoroestrane-3,17-dione (2.35 g, 65%), large colorless cubes, had mp 178–207° dec; $[\alpha]^{24}D$ +84° (*c* 1.30, $CHCl_3$); ν_{max}^{Nujol} 1720 (OAc) and 1140 cm^{-1} (C-F); ^1H nmr δ 56 Hz (s) (18-H).

Anal. Calcd for $C_{18}H_{23}F_3O_2$: C, 65.90; H, 7.06; F, 17.33. Found: C, 65.93; H, 7.08; F, 17.11.

6,6-Difluoro-4-estrene-3,17-dione (**7**).—A solution of 5α,6,6-trifluorodione **6** (2.35 g) in benzene (25 ml) was adsorbed onto Woelm neutral activity III alumina (80 g). After standing on the column for 30 min the product was eluted with benzene and recrystallized from a mixture of acetone and hexane. Pure 6,6-difluoro-4-estrene-3,17-dione formed colorless needles: mp 153.5–155.5°; $[\alpha]^{24}D$ +7° (*c* 1.38, $CHCl_3$); λ_{max}^{EtOH} 225 nm (ε 13,300), 298 (55), and 330 (40); ν_{max}^{Nujol} 1735 (17-CO), 1685 (3-CO) and 1170 cm^{-1} (C-F); ^{19}F nmr δ +5146 (d, *J* = 251, each member split *J* = 30), and +6020 Hz (d, *J* = 251); ^1H nmr δ 379 (m) (4-H), and 57 Hz (s) (18-H).

Anal. Calcd $C_{18}H_{22}F_2O_2$: C, 70.12; H, 7.19; F, 12.32. Found: C, 69.98, 70.00; H, 7.15, 7.22; F, 12.24, 12.34.

In larger batches, a total of 705.7 g of trifluorodiacetate **4** was processed without purification of intermediates **5** and **6**, to 342 g (61%) of pure **7**.

3β,17β-Dihydroxy-6,6-difluoro-4-estrene (**8**).—A mixture of 6,6-difluoro-4-estrene-3,17-dione (1.85 g), absolute ethanol (75

(18) Melting points (uncorrected) were determined in capillary tubes in a Mel-Temp apparatus or on a Kofler block. Infrared spectra were determined on Perkin-Elmer 21 or 221 instruments, ultraviolet spectra in 1-cm solution cells on a Cary Model 14 spectrophotometer, proton nmr spectra in $CDCl_3$ *vs.* TMS on a Varian Associates A-60 instrument, and fluorine nmr spectra in $CDCl_3$ *vs.* F11 on a modified Varian Associates HR-60 instrument. Mass spectra were determined by direct injection into Consolidated CEC-103 (low-resolution) or CEC-110B (high resolution) instruments, and optical rotations were determined in 1-dm tubes on a Zeiss instrument.

(19) The molecular ion of dimer **18** is not seen in the mass spectrometer because of cleavage into monomer: calcd for $C_{22}H_{32}O_5NF$, *m/e* 409.2264; found, 409.2267.

ml), and sodium borohydride (0.83 g) was stirred at 25° for 22 hr. The clear solution was stirred with ice water for 2 hr, and the coloress precipitate thus obtained was filtered and recrystallized from a mixture of acetone and hexane, recovery 1.48 g (79%) of colorless crystalline 3β,17β-dihydroxy-6,6-difluoro-4-estrene (**8**): mp 90–110°; $[\alpha]^{24}D$ −32° (*c* 1.26, $CHCl_3$); ν_{max}^{Nujol} 3450, 3340, 3200 (OH), and 1165 cm^{-1} (C-F); ^{19}F nmr δ +5028 (d, *J* = 241, each member split *J* = 32), and +5990 Hz (d, *J* = 241); ^1H nmr δ 368 (m) (4-H) and 48 Hz (s) (18-H). Yields of 98% were recorded in subsequent batches.

Anal. Calcd for $C_{18}H_{26}F_2O_2$: C, 69.20; H, 8.39; F, 12.16. Found: C, 69.21; H, 8.78; F, 11.86.

17β-Hydroxy-6,6-difluoro-4-estren-3-one, 6,6-Difluoro-19-nortestosterone (9).—A solution of 3β,17β-dihydroxy-6,6-difluoro-4-estrene (**8**) (1.38 g), DDQ (1.38 g), and dry dioxane was stirred at 25° for 3 days. The yellow precipitate was filtered and discarded, and the filtrate was diluted with benzene and washed successively with 5% $NaHCO_3$, 5% NaOH, water, and brine. The residue left on evaporation of the dried benzene extract was chromatographed on Woelm neutral activity III alumina (50 g). The product, 6,6-difluoro-19-nortestosterone (**9**), was eluted with (1:1) hexane–benzene and recrystallized from a mixture of acetone and hexane, recovery 0.745 g (53%) of colorless crystals: mp 156–158°; $[\alpha]^{24}D$ −61° (*c* 1.31, $CHCl_3$); λ_{max}^{EtOH} 225–230 nm (ε 12,000) and 333 (40); ν_{max}^{Nujol} 3400 (OH), 1680 (3-CO) and 1160 cm^{-1} (C-F); ^1H nmr δ 379 (m) (4-H), 222 (t, *J* = 7) (17α-H), 134 (s) (OH), and 50 Hz (s) (18-H).

Anal. Calcd for $C_{18}H_{24}F_2O_2$: C, 69.65; H, 7.79; F, 12.24. Found: C, 69.88; H, 7.83; F, 12.65.

17β-Hydroxy-6,6-difluoro-4-estren-3-one 3-Ethylene Ketal (10).—A mixture of 6,6-difluoro-19-nortestosterone (**9**) (1.0 g), benzene (50 ml), oxalic acid dihydrate (0.5 g), and redistilled ethylene glycol (5.0 ml) was heated under reflux with a Dean–Stark trap for 1.5 hr, at which time the reaction was judged to be complete by tlc (3:1 ethyl acetate–cyclohexane; **9**, R_f 0.40; **10**, R_f 0.50) and ir (disappearance of 1680-cm^{-1} band). The benzene solution was washed with 5% $NaHCO_3$ and water, dried over Na_2SO_4,[20] and evaporated to leave the pure ketal **10** as a colorless crystalline solid (1.1 g, 96%): mp 128–130°; ν_{max}^{KBr} 3530, 3460 (OH); $[\alpha]^{25}D$ +7° (*c* 1.32, $CHCl_3$); ^1H nmr δ 361 (d, *J* = 4) (4-H), 240 (d, *J* = 2) (ketal), 219 (t, *J* = 8) (17α-H), and 47 Hz (s) (18-H).

Anal. Calcd for $C_{20}H_{28}F_2O_3$: C, 67.78; H, 7.96; mol wt, 354. Found: C, 67.64, 67.84; H, 7.66, 7.82; mol wt, 354.

The use of *p*-toluenesulfonic acid to catalyze the ketalization was unsatisfactory and caused extensive degradation of **9**.

6,6-Difluoro-4-estrene-3,17-dione 3-Ethylene Ketal (11). A. From 10.—Ketal **10** (2.3 g) was dissolved in pyridine, cooled to 0°, and treated with solid CrO_3[10] (2.4 g). After the mixture had been stirred at 25° for 20 hr, it was diluted with ethyl acetate (150 ml) and filtered through Celite. The filtrate was washed with water and brine, dried, and evaporated to leave 2.3 g of crude **11**: ^1H nmr ($CDCl_3$, TMS) δ 360 (d, *J* = 4) (4-H), 240 (m) (ketal), and 54 Hz (s) (18-H).

B. From 7.—A mixture of 6,6-difluoro-4-estrene-3,17-dione (1.0 g), redistilled ethylene glycol (2.5 ml), oxalic acid dihydrate (1.0 g), and benzene (50 ml) was heated under reflux using a Dean–Stark trap for 2 hr, the preferential ketalization of the 3-carbonyl being followed by tlc (2:1 ethyl acetate–cyclohexane; **11**, R_f 0.65; **7**, R_f 0.70) and the disappearance of the 1685 cm^{-1} carbonyl band in the ir spectrum. The benzene solution was washed with 5% $NaHCO_3$ and water, dried over Na_2SO_4, and evaporated to leave a colorless solid (1.1 g, 98%), consisting of a 6:1 mixture of the 3-monoketal **11** and 3,17-bisketal **25**: ^1H nmr δ 361 (q, *J* = 4) (4-H), 239 (d, *J* = 2) (3-ketal), 233 (d, *J* = 2) (17-ketal), 53 and 52 Hz (singlets) (18-H of mono- and bisketals). This material is satisfactory because the 3,17-dione **7** may be recovered by chromatography after the ethynylation step.

17β-Hydroxy-6,6-difluoro-17α-ethynyl-4-estren-3-one 3-Ethylene Ketal (12). A. From 11.—A mixture of 6,6-difluoro-4-estrene-3,17-dione 3-ethylene ketal (33.0 g) and DMSO (400 ml) was stirred under N_2 at 25° and treated with a 20% suspension of sodium acetylide in xylene (250 ml). After 30 min, the mixture was poured into ice water, saturated with NaCl, and extracted with CH_2Cl_2. The extracts were washed with brine, dried, and evaporated to leave the crude product **12**. The same product was obtained when ketal **11** was treated with ethynylmagnesium bromide or acetylene and potassium *tert*-amylate, but the sodium acetylide method was the most convenient preparation.

B. From 13.—A pure sample of the final product 17β-hydroxy-6,6-difluoro-17α-ethynyl-4-estren-3-one (0.5 g) in a mixture of benzene (25 ml), oxalic acid dihydrate (0.5 g), and redistilled ethylene glycol (2.5 ml) was heated under reflux for 3 hr using a Dean–Stark trap, the progress of the reaction being followed by tlc (3:1 ethyl acetate–cyclohexane; **13**, R_f 0.57; **12**, R_f 0.62), and the disappearance of the 1680-cm^{-1} band in the ir spectrum. The benzene solution was washed with saturated $NaHCO_3$ and water, dried, and evaporated to leave the crude ketal **12** as a solid which was recrystallized from a mixture of $CHCl_3$ (5 ml), hexane (5 ml), and pyridine (1 drop). Pure ketal **12** formed colorless prisms (0.30 g): mp 170–171°; ν_{max}^{KBr} 3450 (OH) and 3310 cm^{-1} (C≡CH); $[\alpha]^{24}D$ −37° (*c* 0.65, $CHCl_3$); ^1H nmr δ 361 (d, *J* = 4) (4-H), 240 (d, *J* = 1) (ketal), 154 (s) (C≡CH), and 53 Hz (s) (18-H).

Anal. Calcd for $C_{22}H_{28}O_3F_2$: C, 69.71; H, 7.46; mol wt, 378. Found: C, 70.09; H, 7.58; mol wt, 378.

17β-Hydroxy-6,6-difluoro-17α-ethynyl-4-estren-3-one (13).—The ethynylated ketal **12** (from 33 g of **11**) was stirred with 90% acetic acid (500 ml) for 1 hr at 25°. The mixture was poured into water and extracted with chloroform. The extracts were washed with water and brine, dried over $MgSO_4$, and evaporated to leave crude **13**, two batches of which were combined and chromatographed on Woelm neutral alumina activity III (1000 g). The purified compound **13** was eluted with hexane and benzene mixtures and recrystallized from mixtures of acetone and hexane, yield 35.4 g (57% from **11**), mp 166–169°.

Pure samples of final product **13** were obtained on a small scale by preparative tlc on 2-mm silica gel plates[21] using 3:1 ethyl acetate–cyclohexane as the eluent, the product contained in the band R_f 0.50–0.70 being extracted with hot ethyl acetate; on a large scale, 10 g of **13** was dissolved in 2:1 cyclohexane–ethyl acetate and chromatographed on SilicAR CC-7 100–200 mesh silica gel[22] (400 g) using the same solvent mixture as eluent. The product (44.38 g), isolated from the early and middle fractions of several runs, was recrystallized from a mixture of cyclohexane (400 ml) and ethyl acetate (200 ml), recovery 36.99 g. The analytical sample formed colorless needles: mp 167–168°; ν_{max}^{KBr} 3475, 3265 (OH), and 1680 cm^{-1} (3-CO); λ_{max}^{EtOH} 330 nm (ε 37) and 228 (11,900); $[\alpha]^{24}D$ −113° (*c* 0.82, $CHCl_3$); ^1H nmr δ 383 (m), (4-H), 158 (s) (C≡CH), and 59 Hz (s) (18-H); ^{19}F nmr δ +5120 (d, *J* = 250) and +5965 Hz (d, *J* = 250).

Anal. Calcd for $C_{20}H_{24}F_2O_2$: C, 71.83; H, 7.23; mol wt, 334. found: C, 72.12, 71.96; H, 7.14, 7.24; mol wt, 334.

3β,17β-Dihydroxy-6,6-difluoro-17α-ethynyl-4-estrene (14).—A mixture of 17β-hydroxy-6,6-difluoro-17α-ethynyl-4-estren-3-one (**13**) (2.5 g), THF (100 ml), and lithium aluminum tri-*tert*-butoxide hydride (10.0 g) was stirred under N_2 at 25° for 3 days. The mixture was then stirred with 5% acetic acid (200 ml) for 4 hr at 25° and extracted continuously with chloroform. The crude diol was obtained as a colorless solid by evaporation of the dried extracts. It had ^1H nmr δ 368 (m) (4-H), 250 (m) (3α-H), 154 (s) (C≡CH), and 53 Hz (s) (18-H).

3β,17β-Dihydroxy-6,6-difluoro-17α-ethynyl-4-estrene-3,17-diacetate (15).—The crude diol **14** was acetylated by heating it in a mixture of pyridine (15 ml) and acetic anhydride (15 ml) at 100° for 20 hr. The crude product, isolated by pouring the reaction mixture into ice water followed by extraction with CH_2Cl_2, was chromatographed on Woelm neutral alumina activity III (70 g) using 2:1 hexane–benzene as the eluent. The diacetate product **15**, isolated from the early fractions, was recrystallized from hexane (5 ml), yield 1.47 g (47%). The analytical sample, obtained as colorless crystals after a further recrystallization, had mp 123–124°; ν_{max}^{KBr} 1745 cm^{-1} (OAc); $[\alpha]^{24}D$ −101° (*c* 0.37, $CHCl_3$); ^1H nmr δ 365 (m) (4-H), 157 (s) (C≡CH), 125, 123 (singlets) (3,17-OAc), and 55 Hz (s), (18-H); ^{19}F nmr δ +5131 (d, *J* = 230) and +6022 Hz (d, *J* = 230).

Anal. Calcd for $C_{24}H_{30}F_2O_4$: C, 68.55; H, 7.19; F, 9.03; mol wt, 420. Found: C, 68.79, 68.70; H, 6.80, 6.87; F, 9.10, 9.23; mol wt, 420.

17β-Hydroxy-6,6-difluoro-17α-ethynyl-4-estren-3-one-17-acetate (16).—A mixture of 17β-hydroxy-6,6-difluoro-17α-ethynyl-4-estren-3-one (**13**) (4.0 g), pyridine (40 ml), and acetic anhydride

(20) $MgSO_4$ has been used to cause deketalization; *e.g.*, see J. J. Brown, R. H. Lenhard, and S. Bernstein, *J. Amer. Chem. Soc.*, **86**, 2183 (1964).

(21) E. Merck AG, Darmstadt, Germany.

(22) Mallinckrodt Chemical Co.

(15 ml) was heated at 100° for 20 hr. The crude acetate, isolated by pouring the reaction mixture into ice water followed by dichloromethane extraction, was chromatographed on Woelm neutral alumina activity III (250 g), using 2:1 hexane–benzene as eluent. The product **16**, isolated from the middle fractions, was recrystallized from a mixture of acetone and hexane, yield 1.76 g (39%). After a further recrystallization, acetate **16** formed colorless prisms: mp 169–170°; ν_{max}^{KBr} 1745 (OAc) and 1690 cm^{-1} (3-CO); λ_{max}^{EtOH} 330 nm (ϵ 21) and 227 (9600); $[\alpha]^{24}D$ −111° (*c* 0.83, $CHCl_3$); ^1H nmr δ 378 (m) (4-H), 156 (s) (C≡CH), 122 (s) (17-OAc), and 55 Hz (s) (18-H).

Anal. Calcd for $C_{22}H_{26}F_2O_3$: C, 70.19; H, 6.96; mol wt, 376. Found: C, 70.91; H, 6.85; mol wt, 376.

3β,17β-Dihydroxy-17α-ethynyl-5-estrene-3,17-diacetate (21) was prepared in 54% yield from norethindrone (**20**) (125 g) by the literature procedure.[6,18]

3β,17β-Dihydroxy-5α-fluoro-17α-ethynylestran-6-one-3,17-diacetate (22) was prepared in 35% yield from 30 g of diacetate **21** according to Boswell.[3f]

3β,17β-Dihydroxy-5α,6,6-trifluoro-17α-ethynylestrane-3,17-diacetate (23).—A mixture of the 5α-fluoro 6-ketone **22** (1.0 g), dichloromethane (20 ml), water (0.5 ml), THF (3.5 ml), and SF_4 (46 g) was agitated at 18–22° for 10 hr in an autoclave. The organic layer was washed with water, 5% $NaHCO_3$, water, and brine, dried over $MgSO_4$, and evaporated to leave a residue which was chromatographed on Florisil (100 g). The trifluorodiacetate **23**, eluted with 10% acetone in hexane, was recrystallized from a mixture of acetone and hexane, yield 0.34 g (32%) of colorless crystals: mp 186.6–188.6°; ν_{max}^{Nujol} 1740 and 1210 cm^{-1} (OAc); $[\alpha]^{24}D$ −34° (*c* 1.48, $CHCl_3$); ^1H nmr δ 156 (s) (C≡CH), 122 (s) (OAc), and 53 Hz (s) (18-H); ^{19}F nmr δ +6339 (m) (6-F) and +10,025 Hz (m) (5α-F).

Anal. Calcd for $C_{24}H_{31}O_4F_3$: C, 65.60; H, 7.09; F, 12.95. Found: C, 65.69, 65.64; H, 7.30, 7.16; F, 13.32.

3β,17β-Dihydroxy-5α,6,6-trifluoro-17α-ethynylestrane (24).—A mixture of diacetate **23** (4.95 g), deaerated methanol (250 ml), anhydrous potassium carbonate (3.70 g), and deaerated water (70 ml) was stirred at 25° overnight. The product diol was precipitated with water and filtered, yield 3.56 g (88%). A pure sample was obtained by chromatography on Woelm neutral alumina activity III (75 g) using 10–20% ether in benzene as the eluent, followed by recrystallization from aqueous methanol. Compound **24** formed colorless crystals: mp 197–199°; ν_{max}^{Nujol} 3400 (OH) and 3300 cm^{-1} (C≡CH); ^1H nmr δ 154 (s) (C≡CH) and 52 Hz (s); ^{19}F nmr δ +6191 (d, J = 236), +6478 (d, J = 236) (6-F), and +9975 Hz (m) (5α-F).

Anal. Calcd for $C_{20}H_{27}F_3O_2$: C, 67.20; H, 7.60; F, 15.95. Found: C, 67.71; H, 7.82; F, 15.82, 16.00.

17β-Hydroxy-6,6-difluoro-17α-ethynyl-4-estren-3-one (13).—The trifluorodiol **24** (0.205 g) was oxidized with Jones' reagent,[8d] as described for compound **5**. The precipitated product (0.05 g, 23%), small colorless crystals, was taken up in benzene and passed down a column of Woelm neutral alumina, activity III, using benzene as the eluent. The product (0.04 g, 86%) was identified as **13** by comparison of melting point, infrared spectrum, and tlc behavior with those of the sample prepared by the first route.

6,6-Difluoro-5(10)-estrene-3,17-dione (26) and **17β-Hydroxy-6,6-difluoro-17α-ethynyl-5(10)-estren-3-one (27).**—A solution of 6,6-difluoro-4-estrene-3,17-dione (**7**) (1.0 g) in DMSO (20 ml) was treated under a nitrogen atmosphere with a 20% suspension of sodium acetylide in xylene (9 ml). After being stirred for 30 min at 25°, the reaction mixture was poured into ice water and extracted with dichloromethane. The dried extracts produced a residue which was chromatographed on Woelm neutral alumina activity III. Successive elution gave (a) 6,6-difluoro-5(10)-estrene-3,17-dione (**26**) (0.34 g) with 1:2 hexane–benzene and (b) 17β-hydroxy-6,6-difluoro-17α-ethynyl-5(10)-estren-3-one (**27**) (0.20 g) with benzene. Product **26** was recrystallized from hexane as a colorless solid: mp 196–197°; $\nu_{max}^{CHCl_3}$ 1740 (17-CO), 1720 (3-CO) and 1680 cm^{-1} (C=C); λ_{max} 287 nm (ϵ 140); $[\alpha]^{24}D$ +202° (*c* 1.30, dioxane); ^1H nmr δ 184 (m) (4-H) and 56 Hz (s) (18-H); ^{19}F nmr δ +2553 (d, J = 139) and +2815 Hz (d, J = 139).

Anal. Calcd for $C_{18}H_{22}F_2O_2$: C, 70.12; H, 7.19; F, 12.32. Found: C, 70.19; H, 7.20; F, 12.08.

Product **27** was recrystallized from hexane as colorless crystals: mp 166–168°; $\nu_{max}^{CHCl_3}$ 3600, 3400 (OH), 3300 (C≡CH), and 1720 cm^{-1} (3-CO); λ_{max}^{EtOH} 280 nm (ϵ 38); $[\alpha]^{24}D$ +109° (*c* 0.28, $CHCl_3$); ^1H nmr δ 182 (bm) (4-H) 156 (s) (C≡CH), 150 (s) (OH) and 54 Hz (s) (18-H).

Anal. Calcd for $C_{20}H_{24}F_2O_2$: C, 71.80; H, 7.23. Found: C, 71.99; H, 7.08.

17β-Hydroxy-17α-ethynyl-5(10)-estrene-3,6-dione (28).—A mixture of 17β-hydroxy-6,6-difluoro-17α-ethynyl-5(10)-estren-3-one **27** (0.10 g), methanol (100 ml), and concentrated HCl (0.5 ml) was stirred at 25° for 2 hr. The crude product, isolated by evaporation, was filtered through Florisil (25 g) using 10% acetone in hexane as eluent. Pure 3,6-dione **28** formed colorless crystals: mp 195–198°; $\nu_{max}^{CHCl_3}$ 3600 (OH), 3300 (C≡CH), 1715 (3-CO), and 1665 cm^{-1} (6-CO); λ_{max}^{EtOH} 248 nm (ϵ 9740) and 310 (90); $[\alpha]^{24}D$ +85° (*c* 0.33, $CHCl_3$).

Dehydrogenation–Dehydrofluorination of 6,6-Difluoro-4-estrene-3,17-dione (7).—A mixture of dione **7** (0.50 g) and 10% palladium on carbon (1.0 g) was sealed under N_2, and heated at 180° for 2 hr. The contents of the tube were extracted with dichloromethane (200 ml), evaporation of which left a gum (0.34 g). The principal components of this mixture were identified by high-resolution mass spectrometry as 6-fluoroequilenin (**29**) (62.5%), equilenin (**30**) (20.5%), and 3ξ-hydroxy-5,7,9(10)-estratrien-17-one (**31**) (17.0%).

6,6-Difluoro-17-methyl-4,16-*D*-homoestradiene-3,17a-dione (32).—6,6-Difluoro-4-estrene-3,17-dione 3-ethylene ketal (**11**) (4.0 g) was ethynylated in toluene with potassium *tert*-amylate and acetylene. The ethynylation mixture was hydrolyzed with 5% HCl in methanol (50 ml). The solvent was evaporated, and the residue was taken up in dichloromethane. The organic layer was washed with water, saturated $NaHCO_3$, and brine, dried, and evaporated to leave a residue which was chromatographed on Woelm neutral alumina activity III (125 g). Elution with (a) hexane and benzene mixtures gave the D-homo steroid **32**, and (b) benzene gave the expected ethynyl derivative **13** (0.10 g). Recrystallization of crude **32** from a mixture of acetone and hexane gave pure compound as colorless crystals: mp 181–186°; ν_{max}^{Nujol} 1690 (3,17a-CO), and 1635 cm^{-1}, (C=C); λ_{max}^{EtOH} 237 nm (ϵ 17,300) and 317 (194); $[\alpha]^{24}D$ −104°; ^1H nmr δ 377 (m) (4, 16-H), 110 (s) (17-CH_3), and 55 Hz (s) (18-H); ^{19}F nmr δ +5150 (d, J = 251, each member split J = 30), and +6021 Hz (d, J = 251).

Anal. Calcd for $C_{20}H_{24}O_2F_2$: C, 71.83; H, 7.23. Found: C, 72.51; H, 7.54.

Registry No.—**4**, 27150-58-9; **5**, 27150-59-0; **6**, 27150-60-3; **7**, 27150-61-4; **8**, 27150-62-5; **9**, 27150-63-6; **10**, 27150-64-7; **11**, 27150-65-8; **12**, 27150-66-9; **13**, 25450-33-3; **14**, 27150-68-1; **15**, 27150-69-2; **16**, 27189-18-0; **23**, 27150-70-5; **24**, 27189-19-1; **26**, 27141-92-0; **27**, 27141-93-1; **28**, 27141-94-2; **32**, 27141-95-3.

Acknowledgments.—We are indebted to Dr. R. I. Dorfman and Mr. Wendell Rooks of the Syntex Corporation, Palo Alto, Calif., for the biological evaluation of the compounds reported herein. Their results will appear in a separate publication.[23]

(23) W. H. Rooks II and R. I. Dorfman, *Contraception*, **1**, 403 (1970).