To isolate the isocaproaldehyde which results from treatment of the tetrols with tetraacetate, the oxidation was performed as stated above. After the acetic acid solution was allowed to stand for 48 hr, water was added and the suspension was extracted two times with methylene chloride. The organic extracts were washed with bicarbonate to remove all acetic acid and then shaken with water. The methylene chloride solution was cooled to 0° and dried over anhydrous sodium sulfate. After drying, the organic extract was decanted off, cooled to 0°, and evaporated to 0.1 ml in a stream of nitrogen. Identification of the isocaproaldehyde as the only volatile product resulting from tetraacetate oxidation of the tetrol side chain was performed gas chromatographically utilizing the conditions previously described by Burstein, *et al.*[11]

Registry No.—**4,** 34578-46-6; **5,** 34578-47-7; **6,** 34578-48-8; **7,** 34578-49-9; **8,** 34578-50-2; **9,** 34578-51-3; **10,** 34578-52-4; **11,** 34578-53-5; **16,** 34578-54-6; **21,** 34578-55-7; **22,** 34578-56-8; **23,** 34578-57-9; **24,** 34625-43-9; **27,** 34578-58-0; **28,** 21902-63-6; **30,** 34578-60-4; **31,** 34578-61-5; **32,** 34578-62-6; **33,** 21902-62-5.

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Synthesis of 14β-Fluoro Steroids

JOHN PATAKI* AND GABRIEL SIADE B.

The Ben May Laboratory for Cancer Research, The University of Chicago, Chicago, Illinois 60637

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14β-Fluoro-17α-hydroxy analogs of testosterone, estrone, and estradiol have been prepared from ring D unsaturated 17 ketones *via* perchloryl fluoride fluorination of the corresponding enol acetates. Small amounts of 14β-hydroxylated compounds were also isolated from the fluorination mixture.

For the use of steroid sex hormones in the chemotherapy of certain types of cancer, their primary hormonal activity is usually undesirable and may limit the applicable dose level or the duration of treatment. Consequently, efforts were directed toward the synthesis of such analogs of sex hormones that, ideally, would be hormonally inactive or at least have a favorable ratio of tumor inhibitory *vs.* hormonal activity. In the hope that substituting the strongly electronegative and somewhat larger fluorine atom for a hydrogen atom might suitably alter receptor site affinity of the resulting sex hormone analogs, we have synthesized compounds which are related to testosterone, estrone, and estradiol but are fluorinated in position 14β of the steroid nucleus differing from the normal steroid hormones in the cis juncture of rings C and D. This work reports the preparation and characterization of these compounds and of their synthetic intermediates.

The synthesis of the testosterone analog **10** is shown in Scheme I. Starting with dehydroepiandrosterone **1**, the bromo ketone **2** was prepared without attack upon the homoallylic group by direct bromination of **1** with cupric bromide in methanol.[1-3] Following dehydrobromination of the bromo ketone **2** with lithium bromide and lithium carbonate in dimethylacetamide,[3] compounds **3** and **4** were separated by fractional crystallization of the resulting equilibrium mixture. The nmr spectrum of the conjugated ketone **3** showed the vinylic protons at C_{15} and C_{16} as two doublets of doublets centered at 7.81 and 6.26 ppm (J = 6 and 2.5 Hz), and the vinyl proton at C_6 (unresolved) at 5.43 ppm. In the region corresponding to the n → π* transition, the ORD spectrum of **3** exhibited a positive Cotton effect. Sondheimer[4] reported the Cotton effect negative for 3β-hydroxyandrost-15-en-17-one but found it positive for the corresponding 14β-isomeric steroid. Recently, using circular dichroism measurements, Crabbé, Cruz, and Iriarte[5,6] found analogously oriented Cotton effects for a pair of epimeric 3-methoxyestra-1,3,5(10),15-tetraen-17-ones, *i.e.*, negative for the 14α and positive for the 14β isomer. The nmr spectrum of ketone **4** showed a broad peak at 5.53 ppm due to the two vinylic protons at C_6 and C_{15}. When **4** was acetylated, the product had the same melting point and opposite specific rotation of the same absolute value as the acetate described by St. André and coworkers.[7]

The enol diacetate **5** was prepared directly from the crude equilibrium mixture of **3** and **4**. Its nmr spectrum showed the vinyl proton resonances as an unresolved peak at 5.53 ppm (proton at C_6) and as a pair of doublets centered at 6 (J = 2.1 Hz) and 5.8 ppm (J = 2.1 Hz). Since the proton at C_{16} interacts with, and is also somewhat shielded by, the protons of the C_{17} acetoxy group, its signal is probably the less well defined doublet at higher field, while the sharper doublet at 6 ppm arises from the proton at C_{15} which only interacts with the proton at C_{16}. The ultraviolet absorption spectrum shows a maximum at 268 nm (ε 6700) due to the ring D chromophore of **5**.

Perchloryl fluoride treatment of the enol acetate **5** in aqueous tetrahydrofuran gave a mixture of fluorinated and hydroxylated products which were separated by column chromatography. The hydroxy ketone **7**, isolated in small amounts from the more polar fractions, was identified as androsta-5,15-diene-3β,14β-diol-17-one 3-acetate by its elementary analysis ($C_{21}H_{28}O_4$), presence of OH-stretching absorption at 2.88 μ, and by its nmr spectrum showing two doublets centered at 7.63 and 6.08 ppm (J = 6 Hz for both) indicating the C_{15} and C_{16} vinyl protons as well as the absence of a proton at C_{14} since further splitting was lacking. Nonreactivity of the product under acetylating conditions and observation of a positive Cotton

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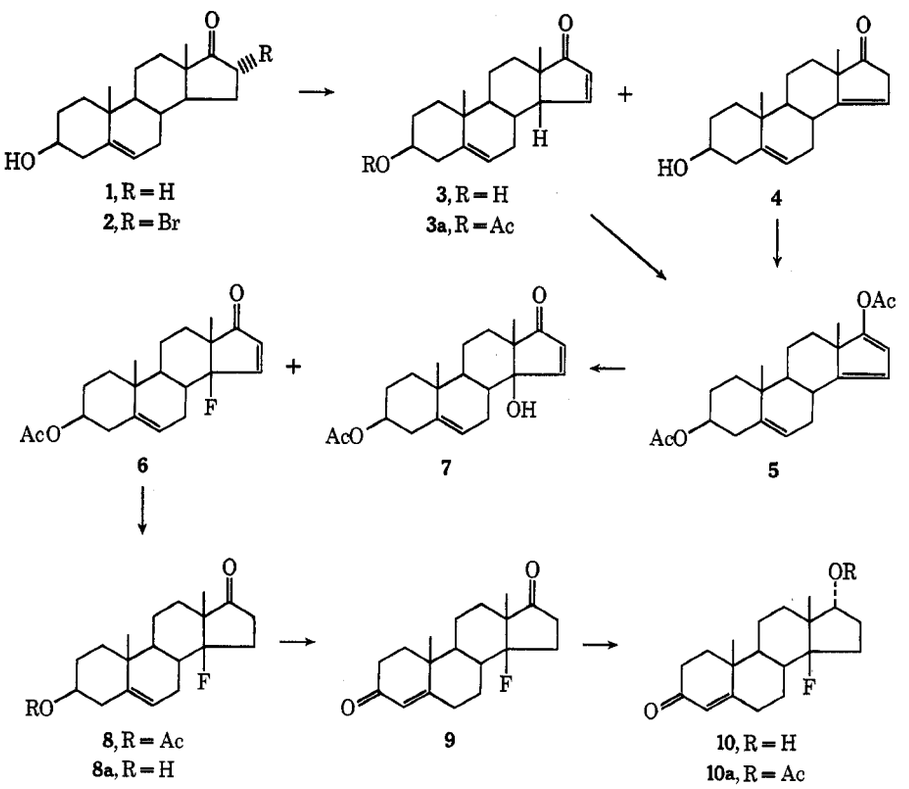
SCHEME I



effect in the ORD spectrum confirmed the presence of a 14β-oriented tertiary hydroxyl group.

The less polar main product was a fluoro ketone, $C_{21}H_{27}FO_3$, characterized as 14β-fluoroandrosta-5,15-dien-3β-ol-17-one acetate (**6**) based on the following evidence. Its ORD spectrum showed a positive Cotton effect in accord with the 14β configuration expected for products of addition across the 14,15 double bond.[4,8] In the nmr spectrum the vinyl protons on C_{15} and C_{16} resonated as a pair of doublets of doublets centered at 7.63 and 6.36 ppm, respectively, with a proton–proton coupling constant of J_{HH} = 6 Hz. The proton–fluorine coupling constants were the same both for the vicinal $C_{15}H$, and for the coplanar, allylic C_{16} H, with the value of J_{HF} = 2.5 Hz. This coupling constant would seem rather high for the dihedral angle of about 80–85° which appears between the 14β C–F bond and the 15 C–H bond when a Dreiding model of compound **6** is constructed with ring C in its usual chair form. However, a model with its ring C in the boat form shows a more acute angle approaching 60°. Taking into account the Karplus curve[9] the observed coupling constant might thus indicate a preferred boat conformation for ring C of **6**. Shoppee[10] reported similar conformational preferences for a number of 14β steroids. Due to interaction with the 14β fluorine, the protons of the C_{18} methyl group were split into a doublet centered at 1.13 ppm (J_{HF} = 4.5 Hz). Long-range proton–fluorine coupling through four σ bonds (or, conceivably, across space) involving the C_{18} methyl protons has been found in 12α- and 17α-fluoro 14α-steroids[11,12] but was not observed for the C_{19} methyl protons in 5α- or 9α-fluoro steroids.[11b]

The double bond in ring D of the fluoro ketone **6** was selectively reduced with palladium–calcium carbonate catalyst in dimethoxyethane. In the nmr spectrum of the saturated ketone **8** the vinylic proton signals at C_{15} and C_{16} disappeared, while the signal of the C_6 vinylic proton persisted at 5.4 ppm. The angular methyl protons at C_{18} again appear as a doublet centered at 1.1 ppm, due to 14β-fluorine coupling, but the constant (J_{HF} = 1.5 Hz) now reflects the change of geometry resulting from reduction of the Δ^{15} double bond.

The free alcohol **8a** was obtained by methanolysis and used to prepare the diketone **9** by Jones oxidation. After chromatographic purification, the ultraviolet spectrum of 14β-fluoroandrost-4-ene-3,17-dione (**9**) exhibited a maximum at 239 nm (ε 15,800) in agreement with the Δ^4-3-one chromophore. In the nmr spectrum, there was a signal centered at 5.8 ppm attributed to the vinylic proton at C_4. The C_{19} methyl signal had shifted to lower field (1.23 ppm) due to deshielding by the unsaturated ketone grouping, and the doublet corresponding to the angular C_{18} methyl appeared centered at 1.13 ppm (J = 1.5 Hz). Diketone **9** was reduced with sodium borohydride, and the crude allylic alcohol was reoxidized by the modified Oppenauer oxidation method described by Heusler and coworkers.[13] The product was purified by chromatography. Compound **10** showed in the infrared spectrum a hydroxyl band at 2.85 μ and carbonyl absorption at 6.01 μ (α,β-unsat-

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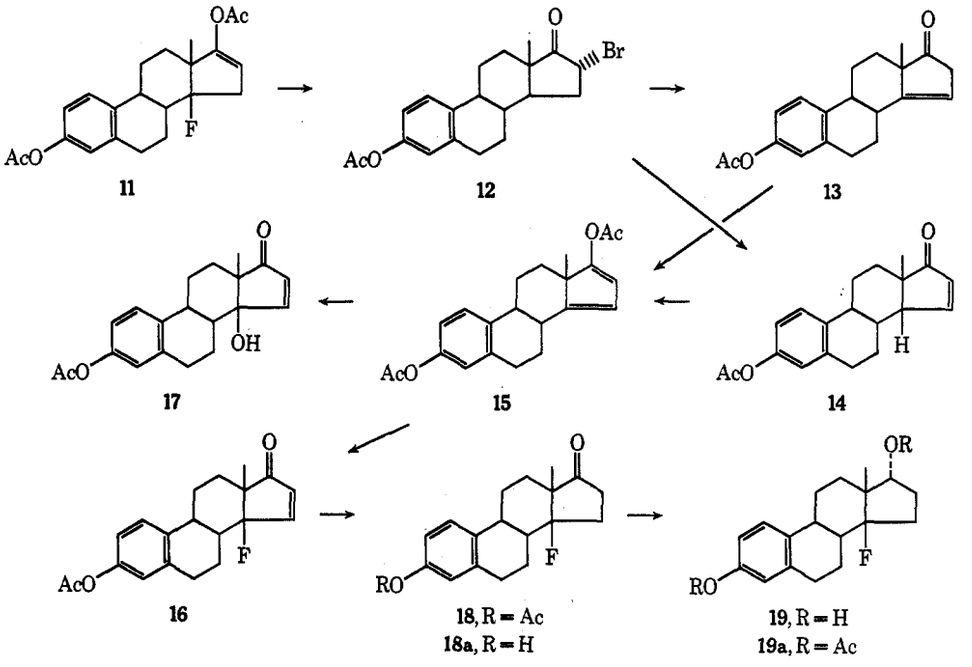
SCHEME II



urated ketone). The nmr spectrum is in agreement with the assigned structure: a broad singlet at 5.76 ppm corresponding to the C_4 proton, a singlet at 1.21 ppm belonging to the angular methyl at C_{19}, and a doublet at 1.1 ppm (J = 1.5 Hz) for the C_{18} methyl group were seen. The signal for the proton at C_{17} appeared as a not very well-defined triplet at 3.7 ppm. Configuration at C_{17} follows from the mode of preparation since hydride reduction of 17-keto steroids yields mainly 17α-hydroxy steroids if their C/D ring junction is cis.[7,14] Thus, the principal product of the above sequence is 17α-hydroxy-14β-fluoroandrost-4-en-3-one (**10**).

For the synthesis of the estrogen analogs the diacetate **11**[15] served as a starting material (Scheme II). It was brominated to give the bromo ketone **12**[16,17] which was dehydrobrominated[3] to the mixture of ketones **13** and **14**. The mixture could be separated by column chromatography. The nmr spectrum of **13** exhibited a broad signal at 5.65 ppm corresponding to the vinylic proton at C_{15}. The aromatic multiplet appeared centered at about 7.0 ppm. A singlet at 1.16 ppm with area equal to three protons was attributed to the methyl protons at C_{18}. Compound **14** showed in its nmr spectrum a doublet of doublets centered at 7.6 and 6.21 ppm with coupling constants of 6.0 and 2.5 Hz, respectively, representing the proton signals at C_{15} and C_{16}. The multiplet of the aromatic protons appeared at about 7 ppm, and the singlet for the C_{18} methyl was at 1.15 ppm. The ORD curve showed a positive Cotton effect, again indicating 14β configuration.

The preparation of estra-1,3,5(10),14,16-pentaene-3,17-diol diacetate (**15**) was similar to that of the enol acetate **5** of the androstane series. In the ultraviolet **15** showed a maximum at 268 nm, with the high extinction of ε 14,800, due to its ring D chromophore augmented by the presence of an aromatic ring in the molecule.[4] In the nmr spectrum, a doublet appeared centered at 6.13 ppm (J = 2.5 Hz); it was assigned to the C_{15} proton; the less well-defined doublet centered at 5.83 ppm corresponded to the C_{16} proton.

The fluorination of **15** was carried out under the same conditions as that of the enol acetate **5**. Pure 14β-fluoroestra-1,3,5(10),15-tetraen-17-one acetate (**16**) was obtained after chromatography on Florisil. In its nmr spectrum the C_{15} proton appeared as a doublet of doublets centered at 7.5 ppm (J = 6 and 3.5 Hz). The C_{16} proton signal was a doublet of doublets centered at 6.4 ppm (J = 6 and 2.4 Hz). The C_{18} protons appeared as a doublet centered at 1.17 ppm with J_{HF} = 3.5 Hz, due to fluorine–proton interaction. The compound showed a positive Cotton effect in its ORD curve.

From the more polar fractions estra-1,3,5(10),15-tetraene-3,14β-diol-17-one acetate (**18**) was isolated and identified by its analysis and spectroscopic properties. The ir spectrum showed hydroxyl absorption at 3.05 μ, the acetate carbonyl at 5.68 μ, and a carbonyl band for the α,β-unsaturated five-membered ring ketone at 5.87 μ. The nmr spectrum showed two doublets centered at 7.4 and 6.3 ppm (J = 6 Hz) due to the vinylic protons at C_{15} and C_{16}, respectively, a singlet at 2.03 ppm which disappeared upon treatment with D_2O (1H, 14β OH), and a singlet at 1.11 ppm pertaining to the C_{18} methyl group. The ORD spectrum showed positive Cotton effect indicating cis junction of rings C and D.

The reduction of **16** to **18** was effected with palladium on carbon catalyst. Treatment of **18** with sodium borohydride led directly to 14β-fluoroestra-1,3,5(10)-triene-3,17α-diol (**19**). Its nmr spectrum showed broad singlets at 5.4 ppm for the 3-hydroxyl and at 1.65 ppm for the 17α-hydroxyl. Both signals disappeared on treatment with D_2O. A triplet centered at 4.33 ppm and corresponding to one proton (J = 8 and 7 Hz) was

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assigned to the 17β hydrogen. The C_{18} methyl signal at 1.11 ppm was a doublet with a coupling constant of 1.6 Hz.

Experimental Section

Melting points were determined in open capillary tubes and are not corrected. Specific rotations were taken in chloroform solutions. Ultraviolet spectra were obtained in EtOH on a Cary 11 recording spectrophotometer. The nmr spectra were taken in $CDCl_3$ solution on a Varian 60 instrument; chemical shifts (δ) are expressed in parts per million downfield from internal tetramethylsilane. Optical rotatory dispersions were recorded on a Cary instrument. Microanalyses were performed by Mr. J. Alicino, Metuchen, N. J.

16α-Bromoandrost-5-en-3β-ol-17-one (2).—To a solution of 100 g of dehydroepiandrosterone in 1 l. of benzene and 2 l. of MeOH, 150 g of cupric bromide was added. The mixture was heated under reflux for 3.5 hr. The warm solution was filtered and concentrated to about $^2/_3$ volume under reduced pressure. The remainder was diluted with 2 l. of benzene and washed with H_2O. The dried solution was evaporated and the residue was crystallized from MeOH: first crop, 47.0 g, mp 172–175°; second crop, 30.6 g, mp 173–174°; third crop, 10.4 g, mp 172–175°; yield 69%.

14β-Androsta-5,15-dien-3β-ol-17-one (3) and Androsta-5,14-dien-3β-17-one (4).—The bromo ketone **2** (90.7 g) was dissolved in 1.8 l. of dimethylacetamide, and 133 g of lithium bromide and 115 g of lithium carbonate were added. The mixture was refluxed for 3.5 hr under nitrogen. The cooled mixture was poured into 2.7 l. of 20% acetic acid and extracted with a 1:1 mixture of benzene–ether. The organic layer was washed with a 5% $NaHCO_3$ solution and with H_2O. The dried solution left after evaporation of the solvents 77.9 g of a mixture of **3** and **4**. A portion of this mixture was fractionated by crystallization from acetone–hexane. The Δ^{15} ketone was the less soluble component. 14β-Androsta-5,15-dien-3β-ol-17-one (**3**) had mp 216–217°; $[\alpha]_D$ +329°; ir 2.88 and 5.9 μ; nmr δ 7.81 (d, d, 1, J = 6 and 2.5 Hz, H-15), 6.26 (d, d, 1, J = 6 and 2.5 Hz, H-16), 5.43 (s, 1, H-6), 1.1 (s, 3, CH_3-18), 1.0 (s, 3, CH_3-19); λ_{max} 228 nm (ε 8110).

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.50; H, 9.10. Found: C, 79.69; H, 9.15.

Androsta-5,14-dien-3β-ol-17-one (**4**) had mp 167–168°; ir 5.76 μ; nmr δ 5.53 (s, 2, H-6 and H_{15}), 1.15 (s, 3, CH_3-18), 1.1 (s, 3, CH_3-19). The compound was characterized as its acetate, mp 130–131°, $[\alpha]_D$ −55.40 (lit.[7] mp 130–132°, $[\alpha]_D$ +54°).

Androsta-5,14-triene-3β,17-diol Diacetate (5).—The solution of the crude dehydrobromination mixture (77.9 g) in 1060 ml of isopropenyl acetate and 1060 ml of acetic anhydride was refluxed with 31.5 g of *p*-toluenesulfonic acid. After 4 hr, the solution was poured on ice and the mixture was stirred for 1 hr. The oily product was taken up in ether, and the solution was washed with a 5% $NaHCO_3$ solution and with H_2O. After drying, the ether was removed *in vacuo*. The residue gave from MeOH 45.3 g of **5**, mp 151–154°. From the mother liquors an additional 14.2 g, mp 151–153°, was secured, yield 65% based on **2**. The analytical sample melted at 154.5–156.5°; $[\alpha]_D$ +19.1°; λ_{max} 268 nm (ε 6774); ir 5.71, 5.78, 8.02, 8.20 μ.

Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.47; H, 8.11.

14β-Fluoroandrosta-5,15-dien-3β-ol-17-one Acetate (6) and Androsta-5,15-diene-3β,14β-diol-17-one 3-Acetate (7).—Perchloryl fluoride was bubbled into a stirred solution of 15.0 g of **5** in 760 ml of tetrahydrofuran and 380 ml of H_2O for 50 min at room temperature. Most of the tetrahydrofuran and excess reagent were removed on the water pump and the residue was extracted with ether. The extract was washed with a 5% $NaHCO_3$ solution and with H_2O. The solvent was evaporated from the dried solution and the residue (15.5 g) was chromatographed on 450 g of Florisil. Petroleum ether containing 4–6% of acetone eluted 7.34 g of a partly crystalline material which gave, from hexane, 5.28 g of 14β-fluoroandrosta-5,15-dien-3β-ol-17-one acetate (**6**), mp 109–111°, yield 38%. The analytical sample melted at 113.5–114.5°: $[\alpha]_D$ +111.2°; ir 5.79, 5.83 μ; nmr δ 7.63 (d, d, 1, J = 6 and 2.5 Hz, H-15), 6.36 (d, d, 1, J = 6 and 2.5 Hz, H-16), 5.5 (s, 1, H-6), 4.6 (s, 1, H-3), 2.01 (5.3, CH_3CO), 1.13 (d, 3, J = 4.5 Hz, CH_3-18), 1.06 (s, 3, CH_3-19).

Anal. Calcd for $C_{21}H_{27}FO_3$: C, 72.80; H, 7.85; F, 5.48. Found: C, 72.96; H, 7.97; F, 5.55.

The petroleum ether–acetone (8:2) eluates (1.12 g) gave from MeOH–H_2O 0.37 g of androsta-5,15-diene-3β,14β-diol-17-one 3-acetate (**7**), mp 162–163.5°. One additional crystallization furnished the analytical sample: mp 165–166°; $[\alpha]_D$ +115.9°; ir 2.88, 5.77, 6.25 μ.

Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19, Found: C, 73.35; H, 8.26.

14β-Fluoroandrost-5-en-3β-ol-17-one Acetate (8).—VI (10.2 g) was hydrogenated in 250 ml of dimethoxyethane (freshly distilled from calcium hydride) in the presence of 2.0 g of 10% Pd/$CaCO_3$ catalyst. The hydrogen uptake ceased after 1.04 mol equiv was absorbed. The solution was filtered from the catalyst and the solvent was removed *in vacuo*. The crystalline residue was purified from hexane to afford 6.2 g of **8**, mp 134–135°; from the mother liquors 2.0 g of the compound, mp 121–126°, was recovered, yield 81%. The analytical sample had mp 139.5–141°; $[\alpha]_D$ +6°; ir 5.71, 5.76, 8.03 μ; nmr δ 5.4 (s, 1, H-6), 4.58 (3, 1, H-3), 2.01 (s, 3, CH_3CO), 1.1 (d, 3, J = 1.5 Hz, CH_3-18), 1.05 (s, 3, CH_3-19).

Anal. Calcd for $C_{21}H_{29}FO_3$: C, 72.38; H, 8.39; F, 5.45. Found: C, 72.14; H, 8.55; F, 5.61.

14β-Fluoroandrost-5-en-3β-ol-17-one (8a).—To a solution of 20.0 g of **8** in 750 ml of MeOH, 11.6 ml of concentrated HCl was added and the solution was kept for 23 hr at room temperature. Sodium acetate (12.0 g) in 180 ml of H_2O was added and about 500 ml of MeOH was distilled off under reduced pressure. After cooling, the crystalline product was filtered off, washed well with H_2O, and dried. The crude **8a** was recrystallized from MeOH, yield 11.03 g, mp 195–196.5°. From the mother liquors 5.43 g of product melting at 182–190° was obtained. The analytical sample had a melting point of 197.5–200°; $[\alpha]_D$ +9.60; ir 2.84, 5.73 μ.

Anal. Calcd for $C_{19}H_{27}FO_2$: C, 74.47; H, 8.88; F, 6.20. Found: C, 74.62; H, 9.18; F, 6.31.

14β-Fluoroandrost-4-ene-3,17-dione (9).—To a solution of 11.00 g of **8a** in 1640 ml of acetone (distilled from potassium permanganate), cooled in an ice bath, 7.4 ml of an 8 *N* chromium trioxide solution (Jones reagent) was added with stirring. After 2 min, 6 ml of EtOH was added and the reaction mixture was poured into 6 l. of ice water. The mixture was extracted with methylene chloride, and organic layer was washed with H_2O and saturated NaCl solution. After drying with Na_2SO_4, the solvent was evaporated. The crystalline residue (10.5 g) was suspended in 800 ml of MeOH and 9.5 ml of concentrated HCl was added. After the crystals had dissolved (about 3 min), the solution was stirred in a nitrogen atmosphere for 15 min at room temperature. Sodium acetate (12.75 g) was added and the MeOH was removed *in vacuo*. The residue was extracted with ether and washed with H_2O and with a 5% $NaHCO_3$ solution. The solution was dried and the ether was evaporated. The remaining product (9.47 g) was chromatographed on 275 g of florisil. The dione **9** (7.2 g) was eluted with petroleum ether containing 7% acetone. Crystallization from acetone–hexane gave 5.54 g, mp 153–156°. From the mother liquors 0.648 g, mp 149–151°, was obtained, yield 56.7%. The analytical sample melted at 158.5–160°; $[\alpha]_D$ +140.6°; ir 5.72, 5.98 μ; λ_{max} 239 nm (ε 15,801).

Anal. Calcd for $C_{19}H_{25}FO_2$: C, 74.96; H, 8.28; F, 6.24. Found: C, 75.17; H, 8.09; F, 6.20.

14β-Fluoroandrost-4-en-17α-ol-3-one (10).—To a solution of 5.47 g of diketone **9** in 650 ml of MeOH, 2.16 g of sodium borohydride was added. The solution was cooled in an ice bath during the addition, then kept at room temperature for 21 hr. Acetic acid (5 ml) was added and most of the solvent was removed under reduced pressure. The residue was dissolved in methylene chloride and the solution was evaporated. The residue (5.40 g) was dissolved in 270 ml of anhydrous benzene, and the solution of 5.5 g of aluminum isopropoxide in 20 ml of acetone was added. After standing for 24 hr at room temperature, the solution was washed with 2 *N* HCl solution and with H_2O and dried. Evaporation of the solvent left a semicrystalline residue (5.1 g) which was chromatographed on 150 g of Florisil. The fractions obtained with mixtures of petroleum ether containing 8–10% of acetone weighed 2.80 g and gave, after crystallization from acetone–hexane, 2.60 g of **10**, mp 150° dec, yield 47.2%. The analytical sample melted at 160–162° dec; $[\alpha]_D$ +98.7°; ir 2.85, 6.01 μ; λ_{max} 240 nm (ε 15,870); nmr δ 5.76 (s, 1, H-4), 1.21 (s, 3, CH_3-19), 1.1 (d, 3, J = 1.5 Hz, CH_3-18).

Anal. Calcd for $C_{19}H_{27}FO_2$: C, 74.47; H, 8.88; F, 6.20. Found: C, 74.41; H, 9.02; F, 6.12.

14β-Fluoroandrost-4-en-17α-ol-3-one Acetate (10a).—**10** (200 mg) was acetylated with acetic anhydride–pyridine. The solution was evaporated to dryness and the residue was recrystallized several times from ether–petroleum ether. The melting point of the analytical sample was 111.5–112.5°, ir 5.74, 5.98 μ.

Anal. Calcd for $C_{21}H_{29}FO_3$: C, 72.80; H, 7.88; F, 5.48. Found: C, 72.67; H, 7.79; F, 5.67.

16α-Bromoestra-1,3,5(10)-trien-3-ol-17-one Acetate (12).—A solution of 50 g of estra-1,3,5(10),16-tetraene-3,17-diol diacetate (**11**) (15) in 31 ml of carbon tetrachloride was stirred with 40 g of anhydrous K_2CO_3 at −8°. To the mixture, 27.37 g of bromine was added over a period of 30 min. The mixture was poured into ice water containing a small amount of $NaHSO_3$. The organic layer was washed with a 5% $NaHCO_3$ solution and with H_2O and dried with Na_2SO_4. After the solvent was evaporated, the residue crystallized from MeOH to yield 46.08 g of **12**, mp 164–163°. The mother liquors gave after acetylation and the usual work-up an additional 5.9 g of **12**, mp 161–169°, yield 78.5%

Estra-1,3,5(10),14-tetraen-3-ol-17-one Acetate (13) and 14β-Estra-1,3,5(10),15-tetraen-3-ol-17-one Acetate (14).—**12** (1 g) in 25 ml of dimethylacetamide was refluxed with 1.5 g of lithium bromide and 1.35 g of lithium carbonate under nitrogen for 3.5 hr. The mixture was poured into 25 ml of 20% acetic acid and extracted with ether. The ether solution was washed with 5% $NaHCO_3$ solution and with H_2O. The residue (0.879 g) left after evaporation of the solvent was chromatographed on 30 g of silica gel. Petroleum ether containing 3–4% acetone eluted 0.32 g of **13**, which was recrystallized from acetone–hexane to give 0.266 g of pure estra-1,3,5(10),14-tetraen-3-ol-17-one acetate (**13**): mp 141.5–142.5°; $[\alpha]D$ +255°; ir 5.68, 5.76 μ.

Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.41; H, 7.09. Found: C, 77.50; H, 7.09.

The fractions obtained with petroleum ether containing 5–6% acetone (0.310 g) gave from acetone–hexane 0.135 g of estra-1,3,5(10),15-tetraen-3-ol-17-one acetate (**14**), mp 123–125°. The purest sample had mp 125.5–126°: $[\alpha]D$ +420°; ir 5.68, 5.75 μ; λ_{max} 280 nm (ε 13,400).

On a preparative scale, 51 g of the bromo ketone **12** afforded 20.10 g of **13** (49.7%) and 9.8 g of **14** (24.2%).

Estra-1,3,5(10),14,16-pentaene-3,17-diol diacetate (15).—The solution of 20 g of crude **13** in 240 ml of isopropenyl acetate and 240 ml of acetic anhydride was refluxed with 8.0 g of *p*-toluenesulfonic acid for 4 hr. The reaction mixture was worked up a described in the preparation of **5**. The enol diacetate crystallized from MeOH, yield 18.6 g of **15**, mp 149–150.5°. A second crop of 2.14 g obtained from the mother liquors melted at 143–146°, yield 91.1%. The melting point of the analytical sample was 151–152.5°: $[\alpha]D$ +263°; λ_{max} 268 nm (ε 14,800); ir 5.68, 8.3 μ; nmr δ 2.26 (s, 3, CH_3CO-3), 2.20 (s, 3, CH_3CO-17), 1.1 (s, 3, CH_3-18).

Anal. Calcd for $C_{22}H_{24}O_4$: C, 75.00; H, 6.81. Found: C, 75.02; H, 6.88.

Starting with 9.8 g of **14**, the same reaction gave 9.4 g of **15**, mp 147–150°.

14β-Fluorestra-1,3,5(10),15-tetraen-3-ol-17-one Acetate (16) and Estra-1,3,5(10),15-tetraene-3,14β-diol-17-one 3-Acetate (17).—Perchloryl fluoride was bubbled into a stirred solution of 23.3 g of **15** in 1165 ml of tetrahydrofuran and 580 ml of H_2O for 50 min at room temperature. The work-up of the reaction mixture was essentially the same as in the androstane series. The crude reaction product was chromatographed on 650 g of Florisil.

Petroleum ether–acetone (3–5%) eluted 10.19 g of **16** which crystallized from acetone–hexane, yield 7.95 g (36.6%), mp 103–109°. The analytical sample of 14β-fluoroestra-1,3,5(10),-15-tetraen-3-ol-17-one acetate showed a melting point of 112.5–113.5°: $[\alpha]D$ +265°; ir 5.68, 5.81 μ; nmr δ 7.5 (d, d, 1, J = 6 and 3.5 Hz), *ca.* 7 (m, 3, aromatic H), 5.4 (d, d, 1, J = 6 and 2.4 Hz, H-16), 2.26 (s, 3, CH_3CO), 1.17 (d, 3, J = 3.5 Hz, CH_3-18).

Anal. Calcd for $C_{20}H_{21}FO_3$: C, 73.19; H, 6.39; H, 5.78. Found: C, 72.88; H, 6.34; F, 6.02.

The material eluted with petroleum ether–15% acetone gave from acetone–hexane 0.486 g of **17**, mp 170–170.5°. The analytical sample of estra-1,3,5(10),15-tetraene-3,14β-diol-17-one 3-acetate melted at 177.5–178°: $[\alpha]D$ +240°; ir 3.05, 5.65, 5.87 μ.

Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.64; H, 6.74. Found: C, 73.61; H, 6.82.

14β-Fluoroestra-1,3,5(10)-trien-3-ol-17-one Acetate (18).—**16** (5.3 g) was hydrogenated in 135 ml of freshly distilled dimethoxyethane in the presence of 1.05 g of 10% Pd/C catalyst. After the hydrogen uptake ceased, the mixture was filtered and the filtrate was evaporated to dryness. The residue was crystallized from acetone–hexane and yielded 3.66 g of **18**, mp 141–144°. From the mother liquors 0.66 g of the same compound was obtained, yield 81.5%. The analytical sample had mp 147–148°: $[\alpha]D$ +116°; ir 5.68, 5.75 μ; nmr δ *ca.* 7 (m, 3, aromatic H), 2.26 (s, 3, CH_3CO), 1.13 (d, 3, J = 1.5 Hz, CH_3-18).

Anal. Calcd for $C_{20}H_{23}FO_3$: F, 72.75; H, 6.96; H, 5.75. Found: C, 72.67; H, 7.00; F, 5.85.

14β-Fluoroestra-1,3,5(10)-trien-3-ol-17-one (18a).—A solution of 1.3 g of **18** in 40 ml of EtOH and 2.2 ml of concentrated HCl was refluxed for 1 hr. The solution was poured into H_2O and the mixture was extracted with ether. The ether solution was washed with a 5% $NaHCO_3$ solution and with H_2O and dried. The evaporation residue crystallized from benzene, first crop 0.88 g, mp 183° dec, second crop 0.155 g, mp 178° dec, yield 91%. The analytical sample melted at 183° with decomposition, $[\alpha]D$ +139°, ir 3.05, 5.75 μ.

Anal. Calcd for $C_{18}H_{21}FO_2$: C, 75.02; H, 7.28; F, 6.59. Found: C, 75.16; H, 7.47; F, 6.80.

14β-Fluoroestra-1,3,5(10)-triene-3,17α-diol (19).—To a cold solution of 2.18 g of 14β-fluoroestra-1,3,5(10)-trien-3-ol-17-one acetate in 300 ml of EtOH, 1.1 g of sodium borohydride was added. The solution was allowed to stand for 23 hr at room temperature. Acetic acid (2 ml) was added and most of the solvent was removed under diminished pressure. The residue was poured into H_2O and extracted with ether. After the usual work-up, 1.028 g of **19**, mp 151° dec, was obtained from MeOH, yield 53.8%. The analytical sample had mp 159° dec: $[\alpha]D$ +70.7°; ir 3.05 μ; nmr δ *ca.* 7 (m, 3, aromatic H), 5.4 (m, 1, HO-3), 4.33 (t, 1, J = 8 and 7 Hz, H-17), 1.15 (s, 1, HO-17), 1.11 (d, 3, J = 1.6 Hz, CH_3-18).

Anal. Calcd for $C_{18}H_{23}FO_2$: C, 74.50; H, 7.92; F, 6.54. Found: C, 74.35; H, 7.80; F, 6.80.

14β-Fluoroestra-1,3,5(10)-triene-3,17α-diol Diacetate (19a).—The mother liquors of **19** were evaporated to dryness and the residue (1.2 g) was acetylated with acetic anhydride–pyridine overnight. After the solvents were removed *in vacuo*, the residue was crystallized from acetone–hexane to give 0.564 g of **19a**, mp 127–130°. The analytical sample melted at 136–137°, $[\alpha]D$ +48°, ir 5.7, 5.81 μ.

Anal. Calcd for $C_{22}H_{27}FO_4$: C, 70.61; H, 7.21; F, 5.07. Found: C, 70.60; H, 7.40; F, 5.17.

Pure **19** (20 mg) was acetylated as above. The acetylated product displayed the same nmr as **19a** from the mother liquors of **19**, mmp 136–137°.

Registry No.—**2**, 1093-91-0; **3**, 34603-35-5; **4**, 34635-41-1; **5**, 34635-42-2; **6**, 34635-43-3; **7**, 19914-01-3; **8**, 34603-37-7; **8a**, 34603-38-8; **9**, 34603-39-9; **10**, 34603-40-2; **10a**, 34603-41-3; **12**, 1239-35-6; **13**, 34603-43-5; **14**, 34603-44-6; **15**, 34603-45-7; **16**, 34603-46-8; **17**, 34603-47-9; **18**, 34603-48-0; **18a**, 34603-49-1; **19**, 34603-50-4; **19a**, 34603-51-5.

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