Substituted Ring AB Aromatic Steroids

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Abstract: The synthesis of 6-methyl, 6-fluoro, 11β-hydroxy, Δ^{11}- and Δ^{14}-ring AB aromatic steroids is described. The facile elimination of a 6-fluoro substituent from a 9α,11β-dihalo-$\Delta^{1,4}$-3-one to form a $\Delta^{1,4,6,8,14}$-3-one is discussed.

The preceding publication[1] has delineated a procedure to prepare ring AB aromatic steroids from a nonaromatic precursor by an ionic process. This paper is designed to show the generality of the reaction to provide various substituted ring AB aromatic steroid compounds and also to reveal some unexpected complications.

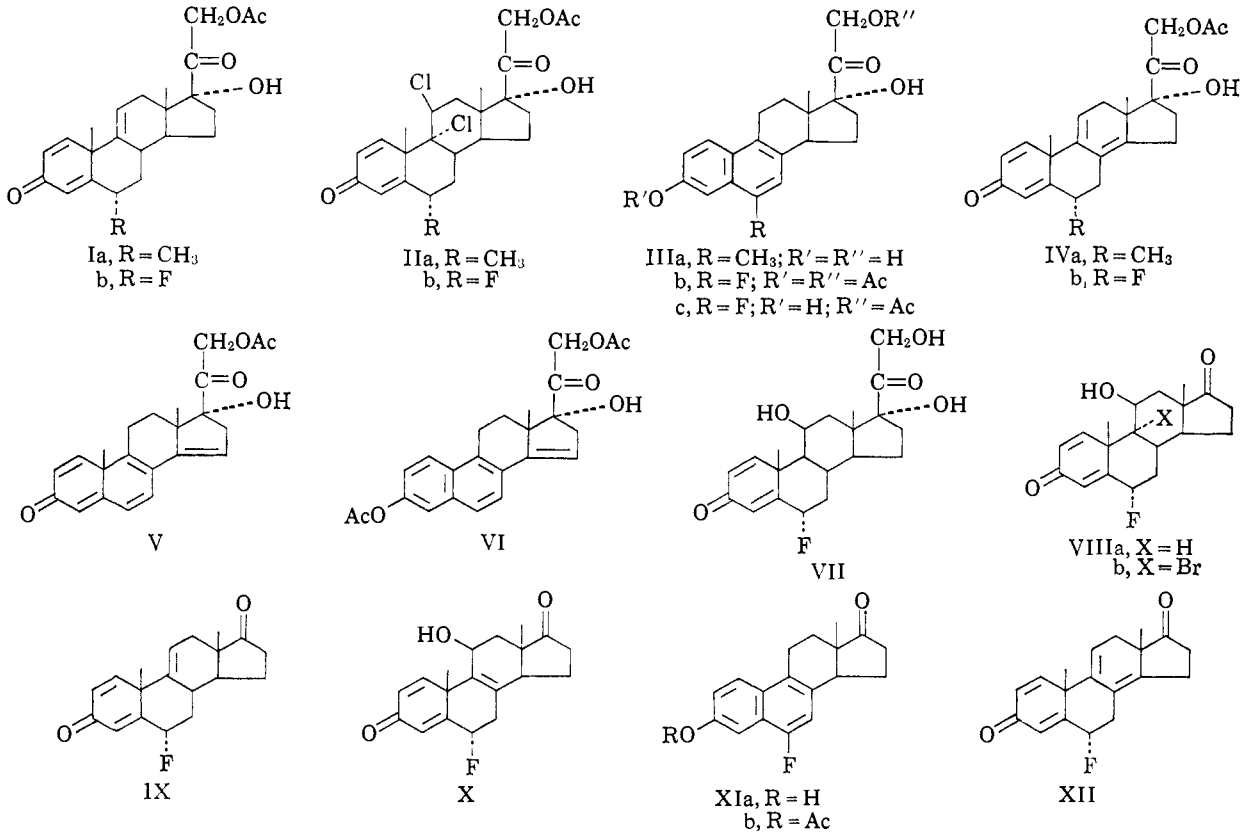
Treatment of 21-acetoxy-17α-hydroxy-6α-methylpregna-1,4,9(11)-triene-3,20-dione (Ia)[2] with N-chlorosuccinimide, lithium chloride, and acid[3] afforded the 9α,11β-dichloro compound IIa,[4] which was in turn aromatized in dimethylformamide, acetylated, and finally saponified to yield 3,17α,21-trihydroxy-6-methyl 19-norpregna-1,3,5(10),6,8-pentaen-20-one (IIIa). There was also isolated as a crude amorphous product 21-acetoxy-17α-hydroxy-6α-methylpregna-1,4,8(14),9(11)-tetraene-3,20-dione (IVa).[1] In the same manner, 21-acetoxy-6α-fluoro-17α-hydroxypregna-1,4,-9(11)-triene-3,20-dione (Ib)[5] was converted to the 9α,11β-dichloro compound IIb, which was in turn refluxed in dimethylformamide to give after acetylation 3,21-diacetoxy-6-fluoro-17α-hydroxy-19-norpregna-1,-3,5(10)6,8-pentaen-20-one (IIIb). It was also possible to isolate 21-acetoxy-6α-fluoro-17α-hydroxypregna-1,4,8(14),9(11)-tetraene-3,20-dione (IVb) from this reaction.

Since the yield of the 6-fluoro aromatic compound was somewhat lower (*ca.* 15%) than was expected from previous experience,[1] compound IIb was refluxed in pyridine in the hope that the yield might be improved. A very small amount of the 6α-fluoro-1,4,8(14),9(11)-tetraene IVb and, after acetylation, some 6-fluoro-1,3,5-(10),6,8-pentaene IIIb were recovered. The major portion of the material recovered, in accordance with its ultraviolet absorption spectrum, nmr spectrum, and elemental analysis, was assigned the structure 21-acetoxy-17α-hydroxypregna-1,4,6,8,14-pentaene-3,20-dione (V). The nmr spectrum (deuteriochloroform plus methanol-d_4) showed the vinyl hydrogen signal of C-1 at 7.49 ppm (J = 10.5 cps) and a multiplicity of signals at 6.18, 6.28, 6.62, and 6.80 ppm, with the correct quantitation representing overlapping of the hydrogens at C-2, C-4, C-6, and C-7, and a broad signal at 5.89 ppm for the C-15 hydrogen. The ultraviolet absorption spectrum with maxima at 234, 243, 262, 290–292, and 382 mμ is very reminiscent of that for a $\Delta^{4,6,8}$-3-one system. By application of the pertinent Woodward rules[6] and the bathochromic effect of a homoannular diene component,[7] the calculated maximum for a $\Delta^{4,6,8}$-3-one system is at 385 mμ, and is reported at 385–388 mμ.[7,8] Since the Δ^1 and Δ^{14} double bonds in V may be considered as cross-conjugated to the rest of the chromphoric system, they need not be used in the calculation of the maximum of the $\Delta^{1,4,6,8,14}$-3-one system. Thus, the actual value of 382 mμ is not far from the calculated value. It is also of interest that the intensity value at 382 mμ is only 11,800, again suggesting that this band is partially dependent upon a contribution from a homoannular diene (a cisoid form) such as in ring B.[9]

Further verification of the above proposed structure was obtained by treatment of V with lithium chloride and hydrochloric acid in dimethylformamide in the previously described fashion[1] to give after acetylation 3,21-diacetoxy-17α-hydroxy-19-norpregna-1,3,-5(10),6,8,14-hexaen-20-one (VI). The complex ultraviolet absorption spectrum is completely compatible with that reported for this system.[10] The nmr spectrum (deuteriochloroform) of VI is, of course, somewhat different from that of V, since the aromatic protons are now somewhat more deshielded (due to the ring current),[11] so that the C-1 hydrogen signal is at 7.94 ppm (J = 9 cps) and the C-2, C-4, C-6, and C-7 hydrogens form a complex of signals with peaks at 7.12, 7.18, 7.28, 7.33, 7.48, 7.57, 7.60, and 7.61 ppm. The C-15 hydrogen signal is at 6.03 ppm.

It is interesting to note that the formation of V must involve dehydrofluorination under refluxing pyridine conditions. It is likely that a postulated $\Delta^{1,4,8}$-3-one intermediate[1] might undergo this relatively unusual reaction to form the more highly conjugated $\Delta^{1,4,6,8}$-3-one system. The latter system might be considered the preferred arrangement of double bonds at or very close to the transition state for the aromatization reaction. It has never been isolated under those conditions, although possible indications of its presence have

(1) M. Heller, R. H. Lenhard, and S. Bernstein, *J. Am. Chem. Soc.*, **89**, 1911 (1967).
(2) G. B. Spero, J. L. Thompson, F. H. Lincoln, W. P. Schneider, and J. A. Hogg, *ibid.*, **79**, 1515 (1957).
(3) C. H. Robinson, L. Finckenor, E. P. Oliveto, and D. H. Gould, *ibid.*, **81**, 2191 (1959).
(4) The preparation of IIa has been reported by D. H. Gould, H. Reimann, and L. Finckenor, U. S. Patent 2,894,963 (1959), but no physical characterization was disclosed.
(5) G. B. Spero, B. J. Magerlein, W. P. Schneider, and J. A. Hogg, U. S. Patent 2,838,499 (1958).
(6) R. B. Woodward, *J. Am. Chem. Soc.*, **63**, 1123 (1941); **64**, 76 (1942).
(7) L. Dorfman, *Chem. Rev.*, **53**, 47 (1953).
(8) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957).
(9) H. P. Koch, *Chem. Ind.* (London), **61**, 273 (1942).
(10) A. L. Wilds, J. A. Johnson, Jr., and R. E. Sutton, *J. Am. Chem. Soc.*, **72**, 5524 (1950).
(11) N. S. Bhacca and D. H. Williams, "Applications of Nmr Spectroscopy in Organic Chemistry: Illustrations from the Steroid Field," Holden-Day, Inc., San Francisco, Calif., 1964, p 96.



been noted.[1] It is possible that the cross-conjugated Δ^{14} double bond materially aids the thermodynamic stability of this system.[12] In fact, an attempt to aromatize V to VI by treatment of V in acetone with hydrochloric acid at room temperature[1] failed. It is apparently necessary to provide more drastic conditions for this aromatization.

For other reasons it was felt necessary to develop a synthesis of a 6-fluoro aromatic system in reasonable yield. This may be illustrated by the following preparation of 6-fluoroequilenin (XIa). 6α-Fluoro-11β,-17α,21-trihydroxypregna-1,4-diene-3,20-dione (VII)[13] was oxidized with sodium bismuthate in aqueous acetic acid to give the 1,4-diene-3,17-dione (VIIIa).[14] Dehydration of this compound in dimethylformamide and collidine with a sulfur dioxide saturated solution of methanesulfonyl chloride[15] afforded the triene dione IX, which was in turn converted to the 9α-bromo-6α-fluoro-11β-hydroxy-$\Delta^{1,4}$-3,17-dione VIIIb by treatment with N-bromosuccinimide in *t*-butyl alcohol, methylene chloride, and perchloric acid.[16] Dehydrobromination of VIIIb in refluxing collidine yielded 6α-fluoro-11β-hydroxyandrosta-1,4,8-triene-3,17-dione (X) which on heating with hydrochloric acid in acetone gave 6-fluoroequilenin (XIa) and the expected $\Delta^{1,4,8(14),9(11)}$-tetraene by-product XII. It is to be noted that, in contrast to 21-acetoxy-11β,17α-dihydroxypregna-1,4,8-triene-3,20-dione,[1] refluxing conditions were required for the aromatization of X to XIa, and the yield (*ca.* 45%) of aromatic product was less than that obtained from the C-6-unsubstituted compound. The 3-acetate XIb was prepared from XIa in the usual manner. Reduction of 6-fluoroequilenin (XIa) with sodium borohydride afforded 6-fluoroestra-1,3,5(10),6,8-pentaene-3,17β-diol (XIIIa) which readily formed a diacetate XIIIb.

In order to further our investigation of the preparation of new aromatic compounds, 9α,11β,21-trichloro-16α,17α-isopropylidenedioxypregna-1,4,6-triene-3,20-dione (XIV)[17] was refluxed in dimethylformamide to give after acetylation 3-acetoxy-21-chloro-16α,-17α-isopropylidenedioxy-19-norpregna-1,3,5(10),6,8,14-hexaen-20-one (XV). From the mother liquors there was also obtained by chromatography on Florisil[18] the isomer 3-acetoxy-21-chloro-16α,17α-isopropylidenedioxy-19-norpregna-1,3,5(10),6,8,11-hexaen-20-one (XVI). The structure of compound XVI, whose ultraviolet absorption spectrum is quite similar to that of an identical system already reported,[19] depends mainly on its nmr spectrum (deuteriochloroform). In common with the previously discussed ring AB aromatic compounds, the aromatic protons at C-1, -2, -4, -6, and -7 form a complex signal of peaks which are, perhaps, even more deshielded than in the $\Delta^{1,3,5(10),6,8,14}$-hexaene detailed above, with the C-1 doublet isolated at 8.08 ppm (J = 9 cps). More important, how-

(12) The system $\Delta^{1,4,6,8}$-3,11-dione has been reported by K. Brückner, German Patent 1,046,042 (1958), and D. H. Gould, E. B. Hershberg, and E. Shapiro, U. S. Patent 2,864,835 (1958). The latter patent also disclosed the preparation of an 11β-hydroxy-$\Delta^{1,4,6,8}$-3-one system, but no physical characterization of this system was provided.

(13) J. A. Hogg, G. B. Spero, J. L. Thompson, B. J. Magerlein, W. P. Schneider, D. H. Peterson, O. K. Sebek, H. C. Murray, J. C. Babcock, R. L. Pederson, and J. A. Campbell, *Chem. Ind.* (London), 1002 (1958).

(14) R. L. Pederson, M. E. Herr, J. C. Babcock, J. A. Campbell, and J. A. Hogg, U. S. Patent 2,867,630 (1959), prepared VIIIa by microbiological oxidation of the corresponding Δ^4-3-one. No physical characterization was given.

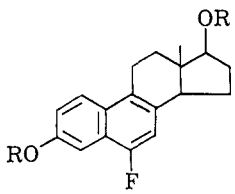
(15) G. G. Hazen and D. W. Rosenburg, *J. Org. Chem.*, **29**, 1930 (1964).

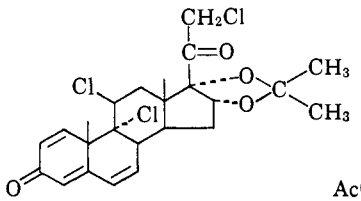
(16) G. B. Spero, B. J. Magerlein, W. P. Schneider, and J. A. Hogg, U. S. Patent 2,838,499 (1958).

(17) M. Heller, R. H. Lenhard, and S. Bernstein, *Steroids*, **5**, 615 (1965).

(18) Florisil (Floridin Co.), a synthetic magnesium silicate.

(19) M. M. Coombs, *J. Chem. Soc., Org.*, 955 (1966).


XIIIa, R = H
b, R = Ac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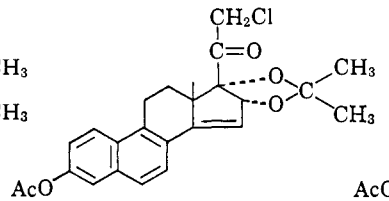
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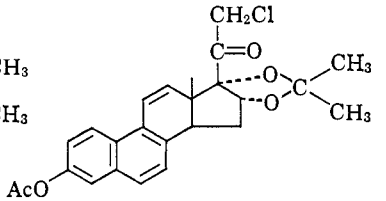
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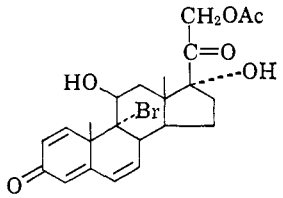
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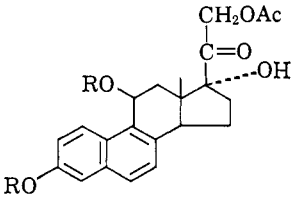
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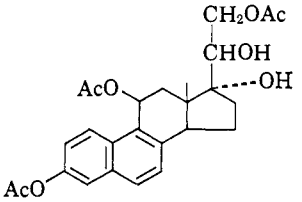
b, R = Ac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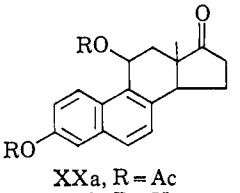
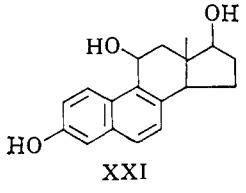

XXa, R = Ac
b, R = H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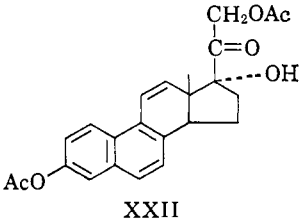
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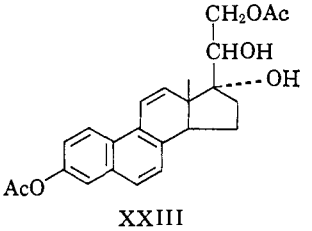
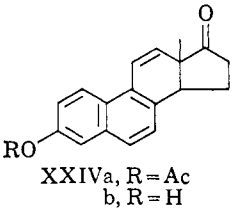

XXIII


XXIVa, R = Ac
b, R = H

ever, is that the C-12 proton can be seen as a distinct doublet centered at 6.51 ppm (J = 10 cps) and the C-11 proton is mixed in with the aforementioned complex of signals centered at 7.20 ppm. The latter position was confirmed by a spin decoupling experiment.[20] Some of the presumed 21-chloro-16α,17α-isopropylidenedioxypregna-1,4,6,8,14-pentaene-3,20-dione was also formed as indicated by the ultraviolet absorption spectrum.

These procedures appeared to be well adapted to prepare 11β-hydroxy ring AB aromatic compounds simply by providing the necessary double bonds so that elimination of an 11β-hydroxy group would not be necessary. Accordingly, 21-acetoxy-9α-bromo-11β,17α-dihydroxypregna-1,4,6-triene-3,20-dione (XVII)[21] was refluxed in pyridine to give 21-acetoxy-3,11β,17α-trihydroxy-19-norpregna-1,3,5(10),6,8-pentaen-20-one (XVIIIa) which was characterized as its 3,11β,21-triacetate (XVIIIb). Reduction of XVIIIb with sodium borohydride afforded the 17α,20ξ-diol 3,11β,21-triacetate XIX (presumably predominantly the 20β-alcohol) which was oxidized with sodium metaperiodate to give 3,11β-diacetoxyestra-1,3,5(10),6,8-pentaen-17-one (XXa). Saponification of XXa yielded 11β-hydroxyequilenin (XXb), which was further reduced to give estra-1,3,5(10),6,8-pentaene-3,11β,17β-triol (XXI).

It had been noticed that heating the bromohydrin XVII in pyridine showed indications of an elimination of the 11β-hydroxy function. Accordingly, prolonged heating (18 hr) of XVII in pyridine afforded after acetylation 3,21-diacetoxy-17α-hydroxy-19-norpregna-1,3,5(10),6,8,11-hexaen-20-one (XXII). This is presumed to occur by a routine β elimination under basic conditions. The nmr spectrum (deuteriochloroform) of XXII exhibited the same features described above in that of XVI. In this case, however, the C-12 proton signal was a doublet centering about 6.65 ppm. In the same manner as described above, sodium borohydride reduction of XXII afforded a crude sample of the 17α,20-diol XXIII, which without purification was oxidized to 3-acetoxyestra-1,3,5(10),6,8,11-hexaen-17-one (XXIVa). The latter compound was further saponified to the 3-ol-17-one XXIVb.

(20) This experiment was performed on a Varian DP-60 spectrometer by Dr. J. E. Lancaster of the Central Research Laboratories, American Cyanamid Co., Stamford, Conn.

(21) K. Brückner, German Patent 1,046,042 (1958).

Experimental Section[22]

21-Acetoxy-9α,11β-dichloro-17α-hydroxy-6α-methylpregna-1,4-diene-3,20-dione (IIa).[4] To a stirred cold solution of 21-acetoxy-17α-hydroxy-6α-methylpregna-1,4,9(11)-triene-3,20-dione[2] (Ia, 3.0 g) and lithium chloride (12.0 g) in glacial acetic acid (120 ml) was added N-chlorosuccinimide (1.11 g) followed by a saturated solution of anhydrous hydrogen chloride in tetrahydrofuran (3.0 ml). After standing at room temperature for 3 hr, the reaction mixture was poured into ice water. The resultant solid was filtered and washed with water. The residue was crystallized from acetone–hexane to give IIa (2.53 g, mp 214–221° dec). A portion was recrystallized four times from methylene chloride–ether to afford the analytical specimen, mp 227–231° dec; λ_{max} 237 mμ (ϵ 15,600) with an inflection at 264 mμ; $[\alpha]^{25}D$ +154° (chloroform).

Anal. Calcd for $C_{24}H_{30}O_5Cl_2$ (469.39): C, 61.41; H, 6.44; Cl, 15.11. Found: C, 61.51; H, 6.74; Cl, 15.26.

3,17α,21-Trihydroxy-6-methyl-19-norpregna-1,3,5(10),6,8-pentaen-20-one (IIIa) and 21-Acetoxy-17α-hydroxy-6α-methylpregna-1,4,8(14),9(11)-tetraene-3,20-dione (IVa). A solution of 21-acetoxy-9α,11β-dichloro-17α-hydroxy-6α-methylpregna-1,4-diene-3,20-dione (IIa, 1.0 g) in dimethylformamide (50 ml) was heated under reflux for 0.5 hr. The reaction mixture was evaporated *in vacuo*, and the residual oil was dissolved in a small amount of acetone. The addition of a large volume of water precipitated 855 mg of solid which was collected, triturated with ether, and filtered to afford the crude by-product IVa (105 mg), mp 171–180°; λ_{max} 240 mμ (ϵ 15,400). This material was not further investigated. The ether filtrate was evaporated and the residue dissolved in pyridine (5 ml) and acetic anhydride (2.5 ml). After standing at room temperature for 17 hr, methanol and benzene were added,

(22) All melting points are uncorrected. The infrared spectra, which were determined in a potassium bromide disk, and nmr spectra, all corroborated the proposed structures. The ultraviolet absorption spectra were done in methanol. The analyses were carried out by Louis M. Brancone and associates. The infrared, ultraviolet absorption, nmr (Varian A-60 spectrometer, tetramethylsilane internal reference) and optical rotational data were supplied by William Fulmor and associates.

and the reaction mixture was evaporated *in vacuo* to dryness. The residue was dissolved in methylene chloride (5 ml) and adsorbed on Florisil (40 g). Elution with 7% acetone–hexane (nine 100-ml fractions) afforded 235 mg of the 3,21-diacetate. Elution with 9% acetone–hexane (nine 100-ml fractions) gave an additional 204 mg of the by-product IVa which was not further investigated. The diacetate (obtained as an amorphous solid) was dissolved in methanol (20 ml) and treated with 10% aqueous potassium carbonate (2.5 ml) while under an atmosphere of argon. After 30 min at room temperature the reaction mixture was neutralized with glacial acetic acid and evaporated under reduced pressure to dryness. The residue was triturated with water to afford the triol IIIa (118 mg), mp 202–210°. Two recrystallizations from acetone–hexane gave 61 mg, mp 222.5–225° red melt. One additional crystallization from aqueous methanol afforded the analytical sample of IIIa solvated with water, mp 216.5–219.5° red melt; λ_{max} 231 mμ (ε 51,000), 273 (4450), 285 (5580), 297 (4620), 331 (2620), and 344 (3060); $[\alpha]^{25}D$ +35° (acetone); nmr, 0.52 (18 CH_3, singlet) and 2.52 ppm (6 CH_3, singlet) (acetone-d_6).

Anal. Calcd for $C_{21}H_{24}O_4 \cdot 0.5H_2O$ (349.41): C, 72.18; H, 7.21. Found: C, 72.57, 72.86; H, 7.29, 6.81.

21-Acetoxy-9α,11β-dichloro-6α-fluoro-17α-hydroxypregna-1,4-diene-3,20-dione (IIb). To a stirred cold solution of 21-acetoxy-6α-fluoro-17α-hydroxypregna-1,4,9(11)-triene-3,20-dione[5] (Ib, 0.25 g) and lithium chloride (1.0 g) in glacial acetic acid (10 ml) was added N-chlorosuccinimide (91 mg) followed immediately by a saturated solution of anhydrous hydrogen chloride in tetrahydrofuran (0.25 ml). The reaction mixture was allowed to remain at room temperature for 3 hr and then was poured into ice water. The resultant solid was filtered and washed with water. A methylene chloride solution of the moist product was dried over magnesium sulfate and evaporated *in vacuo*. The residue (0.27 g) was crystallized from methylene chloride–methanol to afford IIb (163 mg, mp 248–249.5° dec). One additional crystallization from the same solvents did not appreciably alter the melting point, 248–250° dec; λ_{max} 234 mμ (ε 15,500) (methyl cellosolve–methanol); $[\alpha]^{25}D$ +121° (pyridine).

Anal. Calcd for $C_{23}H_{27}O_5Cl_2F$ (473.36): C, 58.36; H, 5.75; Cl, 14.98; F, 4.01. Found: C, 58.62; H, 6.07; Cl, 15.26; F, 4.16.

3,21-Diacetoxy-6-fluoro-17α-hydroxy-19-norpregna-1,3,5(10),6,8-pentaen-20-one (IIIb) and 21-Acetoxy-6α-fluoro-17α-hydroxypregna-1,4,8(14),9(11)-tetraene-3,20-dione (IVb). A solution of 21-acetoxy-9α,11β-dichloro-6α-fluoro-17α-hydroxypregna-1,4-diene-3,20-dione (IIb, 1.0 g) in dimethylformamide (50 ml) was heated under reflux for 0.5 hr. The orange solution was evaporated under reduced pressure to a brown gum. Trituration with acetone produced colorless crystals which were filtered and washed with acetone. The extremely hygroscopic crystals (positive Beilstein test) were soluble in dilute alkali (liberating an ammonia-like odor), and an infrared spectrum proved identity with dimethylamine hydrochloride. The acetone filtrate was concentrated to near dryness, water (*ca.* 100 ml) was added, and the resultant brown oil was worked with a glass rod to give 0.76 g of solid (negative Beilstein test), mp 110–198°; λ_{max} ($E^{1\%}_{1cm}$) 229 mμ (640) and a shoulder at 240 mμ (564). The solid was triturated with warm ether and filtered to afford the by-product IVb (0.28 g), mp 228–230° dec. Recrystallization from acetone–hexane and methylene chloride–ether gave 216 mg of IVb, mp 229° dec; λ_{max} 239 mμ (ε 17,300); $[\alpha]^{25}D$ +206° (chloroform).

Anal. Calcd for $C_{23}H_{25}O_5F$ (400.43): C, 68.98; H, 6.29; F, 4.74. Found: C, 69.45; H, 6.00; F, 4.50.

The initial ether filtrate and the acetone–hexane mother liquor were combined and evaporated. The residue was dissolved in methylene chloride (*ca.* 20 ml) and adsorbed on Florisil (36 g). Elution with 10% acetone–hexane (four 100-ml fractions) afforded 21-acetoxy-6-fluoro-3,17α-dihydroxy-19-norpregna-1,3,5(10),6,8-pentaen-20-one (IIIc, 107 mg). Further elution (12 100-ml fractions) with the same solvent mixture gave a pale yellow solid (0.28 g) which consisted mainly of the by-product IVb and a small amount of IIIc. This material was not further investigated. The above 107 mg of IIIc was dissolved in pyridine (2 ml) and acetic anhydride (1 ml) and allowed to stand at room temperature overnight. The addition of ice precipitated a solid (100 mg, mp 183.5–189°) which was collected, dissolved in methylene chloride (3 ml), and adsorbed on Florisil (10 g). Elution with 7% acetone–hexane (four 50-ml fractions) afforded 77 mg of the diacetate IIIb. Three crystallizations from acetone–hexane gave the analytical sample (59 mg), mp 203–205.5°; λ_{max} 212 mμ (ε 35,400), 234 (62,000), 283 (4900), 316 (2140), and 330 (2350); $[\alpha]^{25}D$ +92° (chloroform).

Anal. Calcd for $C_{24}H_{25}O_6F$ (428.44): C, 67.28; H, 5.88; F, 4.43. Found: C, 67.55; H, 6.33; F, 4.41.

21-Acetoxy-17α-hydroxypregna-1,4,6,8,14-pentaene-3,20-dione (V). A solution of 21-acetoxy-9α,11β-dichloro-6α-fluoro-17α-hydroxypregna-1,4-diene-3,20-dione (IIb, 0.949 g) in pyridine (50 ml) was refluxed 17.5 hr. The solvent was removed *in vacuo*. The residue was dissolved in a small amount of acetone and precipitated with water to give 0.769 g of amorphous solid. This solid was triturated with 20–25 ml of hot ether and filtered. The ether was removed from the filtrate to give a residue (0.18 g) which was acetylated in pyridine (2 ml) with acetic anhydride (1.0 ml) for 16 hr at room temperature. Addition of ice water gave an oil which was extracted with ethyl acetate to afford a yellow glass after removal of the solvent. This was chromatographed on Florisil (18 g). The 7% acetone–hexane eluates gave crystals, which yielded upon crystallization from acetone–hexane 3,21-diacetoxy-6-fluoro-17α-hydroxy-19-norpregna-1,3,5(10),6,8-pentaen-20-one (IIIb, 0.027 g), mp 194–199°. The infrared spectrum was identical with that of the previously prepared sample.

About 100 mg of the once-crystallized residue (0.58 g) from the original ether trituration was placed on a preparative thin layer chromatography plate (silica gel, 20 × 20 cm × 0.5 mm) and developed *ca.* 5.5 hr in the system benzene–acetone–water (2:1:2) (upper phase). The less polar compound forming a band 10–13 cm from the origin was scraped from the plate and eluted from the silica gel with acetone. This gave after removal of the solvent 21-acetoxy-6α-fluoro-17α-hydroxypregna-1,4,8(14),9(11)-tetraene-3,20-dione (IVb, 0.014 g), mp 225° dec; λ_{max} 239–240 mμ (ε 18,800). The infrared spectrum was identical with that of the previously prepared material. The more polar band of material on the plate was eluted, rerun on a thin-layer plate (1 mm in thickness), and eluted to give 0.031 g of the pentaene V described below.

The remainder of the residue from the ether trituration was recrystallized several times from acetone–hexane to give 21-acetoxy-17α-hydroxypregna-1,4,6,8,14-pentaene-3,20-dione (V, 0.057 g), mp 259–261° dec; λ_{max} 234 mμ (ε 11,600) (I), 243 (12,600), 262 (10,700) (I), 290–292 (9900), and 382 (11,800); $[\alpha]^{25}D$ +321° (chloroform–methanol). The analysis for fluorine was zero.

Anal. Calcd for $C_{23}H_{24}O_5$ (380.42): C, 72.61; H, 6.36. Found: C, 72.72; H, 6.73.

3,21-Diacetoxy-17α-hydroxy-19-norpregna-1,3,5(10),6,8,14-hexaen-20-one (VI). A solution of the 1,4,6,8,14-pentaene-3,20-dione V (0.075 g) and lithium chloride (0.075 g) in dimethylformamide (2 ml) was treated with one drop of concentrated hydrochloric acid and refluxed 0.5 hr. The solvent was removed *in vacuo*, the residue was dissolved in a small amount of acetone, and a large quantity of water was added. The resultant viscous oil was worked up to an amorphous solid (0.062 g). This was placed on a thin-layer preparative plate and developed as described in the preparation of V. After 1.75 hr, the least polar band (10–11.5 cm from the origin) was removed and eluted with acetone. Removal of the solvent gave 0.039 g of a yellow solid which was treated in pyridine (1.0 ml) with acetic anhydride (0.5 ml) for 15.5 hr. Addition of ice water gave a solid (0.028 mg), mp 119–129°. Crystallization from acetone–hexane afforded the hexaene VI, mp 138.5–141.5°; λ_{max} 237 mμ (ε 28,400) (I), 246 (34,600), 254 (44,300), 263 (42,800), 282 (14,000), 293 (17,200), and 305 (14,700). There was insufficient material to characterize this compound completely.

6α-Fluoro-11β-hydroxyandrosta-1,4-diene-3,17-dione[14] (VIIIa). A solution of 6α-fluoro-11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione[13] (VII, 20.0 g) in glacial acetic acid (500 ml) and water (500 ml) was stirred with sodium bismuthate (160 g) at room temperature for 24 hr. The reaction mixture was filtered and washed with methylene chloride. The filtrate was diluted with water and extracted several times with methylene chloride. The washed and dried extract was evaporated and the residue dissolved in ethyl acetate. The solution was extracted with saturated sodium bicarbonate solution, washed with water, dried, and evaporated to afford a crystalline solid (14 g), mp 207.5–211°. Crystallization from acetone–hexane gave VIIIa (12.33 g), mp 210–212.5°. In a smaller similar run the analytical sample had mp 210.5–212.5°; λ_{max} 240 mμ (ε 14,900); $[\alpha]^{25}D$ +107° (chloroform).

Anal. Calcd for $C_{19}H_{23}O_3F$ (318.37): C, 71.67; H, 7.28; F, 5.97. Found: C, 71.91; H, 7.49; F, 5.53.

6α-Fluoroandrosta-1,4,9(11)-triene-3,17-dione (IX). A solution of 6α-fluoro-11β-hydroxyandrosta-1,4-diene-3,17-dione (VIIIa, 12.0 g) in dimethylformamide (100 ml) and *s*-collidine (33 ml) was cooled to 10°. The cooling bath was removed and methanesulfonyl chloride (saturated with anhydrous sulfur dioxide at room temperature for 5 min) (10.0 ml) was added to the stirred reaction mixture

over a 2-min period. The temperature rose to 33° and cooling was employed to lower the reaction temperature to approximately 27°. After 5 min the ice bath was replaced and water (25 ml) was slowly added to decompose the excess methanesulfonyl chloride. The reaction mixture was then poured into cold water (*ca.* 1 l.), and the precipitated product was filtered and washed with water to afford 9.67 g, mp 183.5–192°. The crude product was dissolved in methylene chloride and filtered through Magnesol.[23] The filtrate was evaporated and the residual solid was crystallized from acetone–hexane to give IX (8.28 g, mp 199.5–202.5°). In another run the product was further crystallized from the same solvents to give the analytical specimen, mp 201–204°; λ_{max} 236 mμ (ε 16,300); $[\alpha]^{25}D$ +94° (chloroform).

Anal. Calcd for $C_{19}H_{21}O_2F$ (300.36): C, 75.97; H, 7.05; F, 6.33. Found: C, 75.60; H, 7.16; F, 6.09.

9α-Bromo-6α-fluoro-11β-hydroxyandrosta-1,4-diene-3,17-dione (VIIIb). A stirred solution of 6α-fluoroandrosta-1,4,9(11)-triene-3,17-dione (IX, 0.50 g) in methylene chloride (10 ml) and *t*-butyl alcohol (20 ml) was treated at room temperature with N-bromoacetamide (285 mg) in *t*-butyl alcohol (5 ml) and 72% perchloric acid (1.55 ml) in water (12 ml). After 15 min a solution of sodium sulfite (285 mg) in water (15 ml) was added, and the reaction mixture was concentrated under reduced pressure (bath temperature not over 45°) until crystals appeared. Water was added, and the product was filtered and washed with water to afford VIIIb (631 mg, mp 186–188° dec). Three crystallizations from acetone–hexane gave the analytical sample, mp 197.5–198.5° dec; λ_{max} 240 mμ (ε 12,700); $[\alpha]^{25}D$ +130° (chloroform).

Anal. Calcd for $C_{19}H_{22}O_3BrF$ (397.28): C, 57.44; H, 5.58; Br, 20.12; F, 4.78. Found: C, 57.94; H, 5.82; Br, 20.08; F, 4.69.

6α-Fluoro-11β-hydroxyandrosta-1,4,8-triene-3,17-dione (X). A solution of 9α-bromo-6α-fluoro-11β-hydroxyandrosta-1,4-diene-3,17-dione (VIIIb, 2.53 g) in *s*-collidine (10 ml) was refluxed for 10 min. The reaction mixture was cooled to room temperature and the precipitated collidine hydrobromide (1.26 g) was filtered and washed with ether. The filtrate (*ca.* 150 ml) was cooled, and the precipitated product was filtered and washed with ether. The crude product (1.54 g) was slurried with water to remove any residual collidine hydrobromide, filtered, and washed with water to afford X (1.52 g, mp 223.5–224.5° dec). Crystallization from acetone–hexane gave 1.12 g, mp 233° dec. A portion was recrystallized from the same solvents to afford the analytical specimen, mp 237° dec; λ_{max} 238 mμ (ε 15,500); $[\alpha]^{25}D$ +55° (pyridine).

Anal. Calcd for $C_{19}H_{21}O_3F$ (316.36): C, 72.13; H, 6.69; F, 6.01. Found: C, 72.00; H, 6.95; F, 5.96.

6-Fluoro-3-hydroxyestra-1,3,5(10),6,8-pentaen-17-one (6-Fluoroequilenin) (XIa) and 6α-Fluoroandrosta-1,4,8(14),9(11)-tetraene-3,17-dione (XII). A. A suspension of 6α-fluoro-11β-hydroxyandrosta-1,4,8-triene-3,17-dione (X, 0.38 g) in acetone (8 ml) and concentrated hydrochloric acid (0.2 ml) was refluxed for 3 hr (complete solution was attained). The cooled reaction mixture was poured into ice water, and the resultant soft solid, after being worked with a glass rod, was filtered and washed with water to afford a mixture of XIa and XII (257 mg, mp *ca.* 175–197°). The mixture was heated with methylene chloride, cooled, filtered, and washed with cold methylene chloride to give XIa (124 mg, mp 237–241° red melt). The analytical specimen was obtained by crystallization from acetone–hexane and from methylene chloride, mp 242–246° red melt; λ_{max} 227 mμ (ε 51,700), 241 (31,800) (I), 272 (4520), 282 (5010), 293 (3370), 314 (1350), 330 (2200), and 343 (2560); $[\alpha]^{25}D$ +80° (acetone).

Anal. Calcd for $C_{18}H_{17}O_2F$ (284.32): C, 76.03; H, 6.03; F, 6.68. Found: C, 75.67; H, 6.16; F, 6.28.

B. A suspension of X (4.38 g) in acetone (90 ml) and concentrated hydrochloric acid (2.25 ml) was refluxed and worked up as in A above to give 3.66 g of solid, mp *ca.* 180–200°. Trituration of the mixture with hot methylene chloride followed by cooling and filtration afforded XIa (1.76 g, mp 235–240° red melt). Two crystallizations from acetone–hexane gave pure XIa (1.15 g, mp 242–246° red melt). The initial methylene chloride filtrate containing crude XII was evaporated to a brown gum which was dissolved in pyridine (5 ml) and acetic anhydride (2.5 ml) and allowed to stand at room temperature overnight. Methanol and benzene were added and the reaction mixture was evaporated to a viscous reddish brown oil. The residue was dissolved in benzene (*ca.* 100 ml) and adsorbed on a column of silica gel (100 g). Elution with 10% ethyl acetate–benzene (12 100-ml fractions) gave 0.785 g of a mixture of 6-fluoroequilenin acetate (XIb) and 6α-fluoroandrosta-1,4,8(14),9(11)-tetraene-3,17-dione (XII) as indicated by thin layer chromatography. Further elution (five 100-ml fractions) with the same solvent mixture gave 0.43 g of the by-product XII as indicated by ultraviolet and infrared absorption spectra and thin layer chromatography. Five crystallizations from acetone–hexane afforded the analytical sample, mp 193.5–196° (melt), 202° dec; λ_{max} 238 mμ (ε 19,800); $[\alpha]^{25}D$ +437° (chloroform).

Anal. Calcd for $C_{19}H_{19}O_2F$ (298.34): C, 76.49; H, 6.42; F, 6.37. Found: C, 76.41; H, 6.98; F, 6.47.

3-Acetoxy-6-fluoroestra-1,3,5(10),6,8-pentaen-17-one (6-Fluoroequilenin Acetate) (XIb). A solution of 6-fluoro-3-hydroxyestra-1,3,5(10),6,8-pentaen-17-one (XIa, 0.15 g) in pyridine (2 ml) and acetate anhydride (1 ml) was treated in the usual manner to afford XIb (171 mg, mp 143–147°). Two crystallizations from methanol–water gave the analytical sample (136 mg), mp 145–148°; λ_{max} 212 mμ (ε 33,300) (I), 234 (58,600), 273 (3940) (I), 283 (4830), 296 (4050) (I), 315 (1910), and 329 (2150); $[\alpha]^{25}D$ +63° (chloroform).

Anal. Calcd for $C_{20}H_{19}O_3F$ (326.35): C, 73.60; H, 5.87; F, 5.82. Found: C, 73.52; H, 5.83; F, 6.08.

6-Fluoroestra-1,3,5(10),6,8-pentaene-3,17β-diol (6-Fluoro-17β-dihydroequilenin) (XIIIa). A suspension of 6-fluoro-3-hydroxyestra-1,3,5(10),6,8-pentaen-17-one (XIa, 439 mg) and sodium borohydride (439 mg) in absolute ethanol (10 ml) and water (1 ml) was swirled at room temperature for 30 min. The reaction mixture was neutralized with 1 *N* sulfuric acid and diluted with water, and the precipitated product was filtered and washed with water to give XIIIa (0.40 g, mp 221.5–228°). Two crystallizations from ethanol–water and one from methanol–water afforded the analytical specimen, mp 226–230°; λ_{max} 228 mμ (ε 50,500), 240 (34,700) (I), 272 (4200), 283 (4680), 295 (3360), 316 (1990), 333 (2320), and 345 (2830); $[\alpha]^{25}D$ +42° (acetone).

Anal. Calcd for $C_{18}H_{19}O_2F$ (286.33): C, 75.50; H, 6.69; F, 6.64. Found: C, 75.37; H, 6.75; F, 5.81.

6-Fluoroestra-1,3,5(10),6,8-pentaene-3,17-diol Diacetate (6-Fluoro-17β-dihydroequilenin Diacetate) (XIIIb). A solution of 6-fluoroestra-1,3,5(10),6,8-pentaene-3,17β-diol (XIIIa, 125 mg) in pyridine (2 ml) and acetic anhydride (1 ml) was treated in the usual fashion to give XIIIb (151 mg, mp 96–101°). Five crystallizations from methanol–water afforded the analytical specimen (75 mg), mp 113.5–115°; λ_{max} 215 mμ (ε 34,400) (I), 234 (61,500), 273 (3680) (I), 285 (4510), 298 (3850) (I), 316 (2050), and 330 (2380); $[\alpha]^{25}D$ −14° (chloroform).

Anal. Calcd for $C_{22}H_{23}O_4F$ (370.40): C, 71.33; H, 6.26; F, 5.13. Found: C, 70.99; H, 6.39; F, 5.01.

3-Acetoxy-21-chloro-16α,17α-isopropylidenedioxy-19-norpregna-1,3,5(10),6,8,14-hexaen-20-one (XV) and 3-Acetoxy-21-chloro-16α,17α-isopropylidenedioxy-19-norpregna-1,3,5(10),6,8,11-hexaen-20-one (XVI). A solution of 9α,11β,21-trichloro-16α,17α-isopropylidenedioxypregna-1,4,6-triene-3,20-dione (XIV, 1.0 g) in dimethylformamide (50 ml) was refluxed for 30 min and evaporated. A small amount of acetone was added and then a large amount of water. The resultant precipitate was worked with a glass rod to afford a yellow solid (0.88 g) which was dissolved in pyridine (5 ml) and acetic anhydride (2.5 ml). After standing at room temperature for 2 hr, the reaction mixture was poured into ice water, and the precipitate was filtered and washed with water to give 0.89 g, mp 152–210°. Crystallization from acetone afforded XV (232 mg, mp 228–232°). Three additional crystallizations from acetone gave the analytical sample, mp 238.5–240°; λ_{max} 244 mμ (ε 37,700) (shoulder), 252 (54,700), 261 (55,700), 282–283 (13,800), 293 (16,800), and 305 (13,300).

Anal. Calcd for $C_{25}H_{25}O_5Cl$ (440.91): C, 68.10; H, 5.62; Cl, 8.04. Found: C, 68.34; H, 5.70; Cl, 8.09.

The mother liquor from the initial acetone crystallization above was evaporated and the residue dissolved in methylene chloride. Filtration through Magnesol afforded 0.59 g of solid which was adsorbed on Florisil (30 g). Elution with 4% acetone–hexane (seven 100-ml fractions) gave in the first fraction reasonably pure XVI as indicated by the infrared and ultraviolet absorption spectra while subsequent fractions consisted of a mixture of XV and XVI. Crystallization of the first fraction from acetone–hexane afforded 73 mg of XVI, mp 165–168° with loss of solvent on insertion at 150°. Recrystallization from the same solvents gave XVI as an acetone solvate[24] (46 mg, mp 160–164°) while one additional crystallization afforded the analytical specimen as a hexane solvate,[24] 39 mg, mp

(23) Magnesol (Food Machinery Chemical Corp.), a hydrous magnesium silicate.

(24) The solvents of crystallization were confirmed by nmr spectra.

157–161°; λ_{max} 240 mμ (ε 60,750), 303 (6520), 316 (7260), 328 (4600) (shoulder), and 342 (4120); $[\alpha]^{25}D$ +142° (chloroform).

Anal. Calcd for $C_{25}H_{25}O_5Cl \cdot 0.5C_6H_{14}$ (483.99): C, 69.48; H, 6.66; Cl, 7.33. Found: C, 69.30; H, 6.72; Cl, 7.53.

Further elution of the column with 6% acetone–hexane provided a small amount of the 21-chloro-16α,17α-isopropylidenedioxypregna-1,4,6,8,14-pentaene-3,20-dione as indicated by its ultraviolet absorption spectrum [λ_{max} 242 mμ (ε 15,200), 262 (13,600) (I), 293 (12,600), and 375 (14,800)], but the amount and behavior of the compound precluded characterization.

3,11β,21-Triacetoxy-17α-hydroxy-19-norpregna-1,3,5(10),6,8-pentaen-20-one (XVIIIb). A solution of 21-acetoxy-9α-bromo-11β,17α-dihydroxypregna-1,4,6-triene-3,20-dione[21] (XVII, 4.89 g) in pyridine (50 ml) was refluxed for 20 min. The cooled reaction mixture was poured into ice water (*ca.* 2 l.), aged overnight at 5°, filtered, and washed with water to afford 21-acetoxy-3,11β,17α-trihydroxy-19-norpregna-1,3,5(10),6,8-pentaen-20-one (XVIIIa, 2.97 g). The crude product (2.87 g) in pyridine (10 ml) and acetic anhydride (5 ml) was allowed to stand at room temperature for 20 hr. The reaction mixture was poured into ice water and the precipitated solid (3.4 g) was collected, dissolved in methylene chloride (*ca.* 30–40 ml), and adsorbed on Florisil (300 g). Elution with 20% acetone–petroleum ether (bp 30–60°) (two 500-ml fractions) gave 2.35 g of the triacetate XVIIIb as a pale yellow glass. A portion (100 mg) was placed on a thin layer chromatography plate (silica gel, 20 × 20 cm × 0.5 mm) and developed for 50 min in the system benzene–acetone–water (2:1:2) (upper phase). The band containing the product (*ca.* 9.5–11 cm from the origin) still contained the yellow color, and after elution with acetone and evaporation, the residue was rechromatographed in the system cyclohexane–ethyl acetate (70:30). After developing for 1 hr the plate was removed, dried, redeveloped for 55 min. The now colorless band (*ca.* 4–5 cm from the origin) after elution and evaporation afforded 3,11β,21-triacetoxy-17α-hydroxy-19-norpregna-1,3,5(10),6,8-pentaen-20-one (XVIIIb) as a white amorphous solid (63 mg, mp *ca.* 90–130°); λ_{max} 231 mμ (ε 81,200), 268 (4900) (I), 280 (6240), 292 (4900) (shoulder), 312 (1430), and 326 (1560); $[\alpha]^{25}D$ +94° (chloroform). The compound resisted crystallization and was analyzed as an amorphous solid.

Anal. Calcd for $C_{26}H_{28}O_8$ (468.48): C, 66.65; H, 6.02. Found: C, 66.85; H, 6.35.

3,11β,21-Triacetoxy-19-norpregna-1,3,5(10),6,8-pentaene-17α,-20ξ-diol (XIX). A solution of 3,11β,21-triacetoxy-17α-hydroxy-19-norpregna-1,3,5(10),6,8-pentaen-20-one (XVIIIb, 1.51 g) in tetrahydrofuran (40 ml) was reduced with sodium borohydride (51 mg) in water (0.4 ml). After standing at room temperature for 1.25 hr, the reaction mixture was acidified with glacial acetic acid (ten drops) and evaporated. The residue was triturated with water to afford a solid (1.34 g, mp 93–108° with effervescence) which dissolved in methanol (*ca.* 5 ml) and precipitated as a crystalline solid (0.56 g, mp 168.5–176.5°). Recrystallization from methanol gave XIX (0.44 g, mp 153–168°). One additional crystallization did not alter the wide range melting point; λ_{max} 231 mμ (ε 77,000), 270 (4470) (I), 280 (5500), 291 (4330) (shoulder), 312 (960), and 326 (1240); $[\alpha]^{25}D$ +18° (chloroform). A satisfactory analysis was not obtained.

Anal. Calcd for $C_{26}H_{30}O_8$ (470.50): C, 66.37; H, 6.43. Found: C, 68.31, 68.65; H, 6.53, 6.52.

3,11β-Diacetoxyestra-1,3,5(10),6,8-pentaen-17-one (11β-Hydroxyequilenin Diacetate) (XXa). To a solution of 3,11β,21-triacetoxy-19-norpregna-1,3,5(10),6,8-pentaene-17α,20ξ-diol (XIX, 0.30 g) in methanol (10 ml) was added a solution of sodium metaperiodate (0.445 g) in water (5 ml). The reaction mixture was allowed to stand at room temperature for 22 hr, water was added, and the product was filtered and washed with water to afford a solid (0.18 g), mp 163–173°. The crude product was dissolved in benzene and adsorbed on silica gel (10 g). Elution with 5% ethyl acetate–benzene (seven 50-ml fractions) gave 118 mg of XXa which after crystallization from ether and several crystallizations from acetone–hexane afforded pure XXa, mp 186–189.5°; λ_{max} 231 mμ (ε 81,200), 271 (5020) (I), 281 (6100), 293 (4500) (I), 311 (980), and 325 (1050); $[\alpha]^{25}D$ +25° (chloroform).

Anal. Calcd for $C_{22}H_{22}O_5$ (366.40): C, 72.11; H, 6.05. Found: C, 72.38; H, 6.39.

3,11β-Dihydroxyestra-1,3,5(10),6,8-pentaen-17-one (11β-Hydroxyequilenin) (XXb). A solution of 3,11β-diacetoxyestra-1,3,5,(10),6,8-pentaen-17-one (XXa, 278 mg) in 5% potassium hydroxide–methanol (10 ml) was purged with argon and refluxed for 20 min. The blue solution was cooled and neutralized with 5% hydrochloric acid (pink at end point). Water was added, and the product was filtered and washed with water to afford XXb (197 mg, mp 217.5–218° red melt). Two crystallizations from methanol and three from acetone–hexane gave the analytical sample, mp 253–255° red melt; λ_{max} 234 mμ (ε 64,000), 260 (3140), 270 (4390), 280 (5260), 292 (3690), 328 (2070), and 340 (2390); $[\alpha]^{25}D$ +55° (pyridine).

Anal. Calcd for $C_{18}H_{18}O_3$ (282.32): C, 76.57; H, 6.43. Found: C, 76.53; H, 6.53.

Estra-1,3,5(10),6,8-pentaene-3,11β,17β-triol (11β-Hydroxy-17β-dihydroequilenin) (XXI). A suspension of 3,11β-dihydroxyestra-1,3,5(10),6,8-pentaen-17-one (XXb, 133 mg) and sodium borohydride (133 mg) in absolute ethanol (5 ml) and water (0.5 ml) was swirled at room temperature for 30 min. The reaction mixture was neutralized with 1 *N* sulfuric acid, diluted with water, cooled, filtered, and washed with water to give 48 mg of product, mp 185.5–191°. The filtrate was salted out, and the precipitated product was filtered and washed with saturated saline. Trituration with hot acetone (*ca.* 15 ml), followed by filtration and evaporation, afforded an additional 69 mg of crude product. Both fractions were combined and placed on a preparative thin layer chromatography plate (silica gel, 20 × 20 cm × 1 mm) and developed 1 hr in the system benzene–acetone–water (1:2:2) (upper phase). The band containing the desired product (*ca.* 4.5–10 cm from the origin) was scraped from the plate and eluted from the silica gel with acetone. This gave after removal of the solvent 107 mg of the triol XXI. Crystallization from acetone–hexane afforded 79 mg of solvated product, mp 177–180° with effervescence. One additional crystallization from the same solvents did not alter the melting point. After drying *in vacuo* at 80° overnight the compound melted at 179.5–180°, solidifying at 185°, and remelting at 207.5–212°; λ_{max} 233 mμ (ε 76,300), 259 (3840), 269 (5160), 280 (5950), 291 (4380), 328 (2500), and 341 (2900); $[\alpha]^{25}D$ +88° (pyridine).

Anal. Calcd for $C_{18}H_{20}O_3 \cdot 0.5C_3H_6O^{25}$ (313.38): C, 74.73; H, 7.40. Found: C, 74.48, 74.94, 74.35; H, 6.84, 7.57, 7.35.

3,21-Diacetoxy-17α-hydroxy-19-norpregna-1,3,5(10),6,8,11-hexaen-20-one (XXII). A solution of 21-acetoxy-9α-bromo-11β,17α-dihydroxypregna-1,4,6-triene-3,20-dione (XVII, 1.53 g) in pyridine (25 ml) was refluxed for 18 hr. After the addition of benzene, the reaction mixture was evaporated, and the residue was triturated with water, filtered, and washed with water to afford 1.14 g of solid, mp, 110–125°. The crude solid in pyridine (5 ml) and acetic anhydride (2.5 ml) was acetylated at room temperature for 20 hr. Methanol and benzene were added and after evaporation of solvents the residual glass was chromatographed on Florisil (75 g). The product was eluted with 12% acetone–petroleum ether (bp 30–60°), and pure XXII was obtained by crystallization from ether–hexane, mp 170–172.5°; λ_{max} 241 mμ (ε 61,400), 291 (4360) (I), 304 (6550), 317 (7530), 328 (4950), and 343 (4650); $[\alpha]^{25}D$ +147° (chloroform).

Anal. Calcd for $C_{24}H_{24}O_6$ (408.43): C, 70.57; H, 5.92. Found: C, 70.82; H, 5.81.

3-Acetoxyestra-1,3,5(10),6,8,11-hexaen-17-one (11-Dehydroequilenin Acetate) (XXIVa). A solution of 3,21-diacetoxy-17α-hydroxy-19-norpregna-1,3,5(10),6,8,11-hexaen-20-one (XXII, 0.50 g) in tetrahydrofuran (15 ml) was treated with sodium borohydride (19.3 mg) in water (0.2 ml). After standing at room temperature for 1 hr, the reaction mixture was acidified with glacial acetic acid (four drops) and evaporated. Water was added, and the resultant pasty solid was worked with a glass rod, filtered, and washed with water to afford crude XXIII (456 mg, mp 120–130°). The crude reduction product was dissolved in methanol (15 ml) and oxidized with sodium metaperiodate (0.77 g) in water (7 ml). After standing at room temperature for 19 hr, the reaction mixture was diluted with water and cooled; the product was filtered and washed with water to give 312 mg of yellow solid. The solid was dissolved in ether and filtered through silica gel (3 g) in a futile attempt to remove the yellow color. Evaporation of the ether filtrate, followed by crystallization from methanol, afforded colorless crystals of XXIVa (201 mg, 164–166.5°). Further recrystallization from methanol gave the analytical sample, mp 167.5–170°; λ_{max} 237 mμ (ε 59,500), 289 (4590) (I), 302 (7200), 314 (8300), 324 (5250), and 340 (4160); $[\alpha]^{25}D$ +183° (chloroform).

Anal. Calcd for $C_{20}H_{16}O_3$ (306.34): C, 78.41; H, 5.92. Found: C, 78.14; H, 6.10.

3-Hydroxyestra-1,3,5(10),6,8,11-hexaen-17-one (11-Dehydroequilenin) (XXIVb). A solution of 3-acetoxyestra-1,3,5,(10),6,8,11-hexaen-17-one (XXIVa, 0.13 g) in methanol (10 ml) was treated with 10% aqueous potassium carbonate solution (1 ml). After 5 min at room temperature the blue solution was acidified slightly with 5% hydrochloric acid, diluted with water, cooled, filtered, and

(25) The presence of acetone was confirmed in the nmr spectrum.

washed with water to give 104 mg, mp 229–234° dark red melt. The crude product was placed on two preparative thin layer chromatography plates (silica gel, 20 × 20 cm × 0.5 mm) and developed in the system benzene–acetone–water (2:1:2) (upper phase). After 55 min the plates were removed, dried, and redeveloped for 50 min. The bands containing the product (*ca.* 12.5–15 cm from the origin) were scraped from the plates and eluted with acetone to afford 80 mg of crystalline solid. Crystallization from acetone–hexane and methanol–water gave an analytical specimen of XXIVb, mp 233.5–238° red melt; λ_{max} 240 mμ (ε 54,000), 291 (4490), 302 (6600), 316 (8170), 343 (3680), and 356 (3720); $[\alpha]^{25}D$ +229° (acetone).

Anal. Calcd for $C_{18}H_{16}O_2$ (264.31): C, 81.79; H, 6.10. Found: C, 81.30, 82.15, 81.73; H, 6.41, 6.46, 6.83.

Hydroboration of Terpenes. III. Isomerization of (+)-3-Carene to (+)-2-Carene. Hydroboration of (+)-2-Carene (Δ^4-Carene). Nuclear Magnetic Resonance Spectra with Absolute Configurational and Conformational Assignments for the 2-Caranols and 2-Caranones

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Abstract: (+)-3-Carene (**1**) isomerizes to an equilibrium mixture of 40% (+)-2-carene (**2**) and 60% (+)-3-carene (**1**) under the influence of potassium *t*-butoxide in dimethyl sulfoxide. This unfavorable equilibrium is attributed to steric congestion present in both of the possible conformations (**2A**) and (**2B**) for (+)-2-carene. (+)-2-Carene on hydroboration–oxidation gives (−)-2-isocaranol (**10**), which on oxidation gives (−)-2-isocaranone (**7**). In the presence of base, this ketone epimerizes readily to an equilibrium mixture containing (−)-2-caranone (**8**) predominantly (83%). The recent assignment of the absolute configuration for (−)-dihydrocarvone, previously converted into (+)-2-caranone, permits assignment of the absolute configuration of (+)-2-carene and all other derivatives examined in this study. The reduction of (−)-2-isocaranone (**7**) with lithium trimethoxyaluminohydride gives (+)-2-neoisocaranol (**9**) of 96% purity. The other two epimeric alcohols, (−)-2-caranol (**11**) and (+)-2-neocaranol (**12**), have been prepared from (−)-2-caranone by reductions with lithium aluminum hydride and aluminum isopropoxide, respectively. The nmr spectra of the four alcohols and two ketones were subjected to detailed examination. This study revealed that the major alcohol obtained in the lithium aluminum hydride reduction of 2-caranone is 2-caranol (**11**) and not 2-neocaranol (**12**) as reported in the literature. (+)-2-Carene (**2**), like (+)-3-carene (**1**), gives on hydrogenation mainly *cis*-carane (**3**), which is readily distinguishable from the *trans*-carane (**4**) obtained by the Huang-Minlon reduction of (−)-2-caranone. These two hydrocarbons can be distinguished by glpc as well as nmr. Attempts to protonolyze the organoborane from (+)-2-carene (**2**) both in acidic and basic media or by the reduction of the tosylhydrazones from (−)-2-isocaranone and (−)-2-caranone failed to yield pure caranes. The ketones and alcohols have been characterized through their tosylhydrazones and *p*-nitrobenzoates, respectively. It is concluded that 2-carene resembles α-pinene in undergoing hydroboration practically exclusively from the side away from the *gem*-dimethyl groups to provide an entry into the 2-isocaranone series, with a ready entry into the carane series by epimerization of the (−)-2-isocaranone. In the latter respect 2-carene differs markedly from 3-carene, where the 4-isocaranone obtained *via* hydroboration–oxidation is the more stable isomer and cannot be epimerized into 4-caranone.

The report in 1960 that the hydroboration–oxidation of 3-carene (**1**) (Δ^3-carene) yields 4-neocaranol (**15**),[2] with a *trans* addition of the elements of water to the double bond, was startling and prompted an investigation[3] of this proposed exception to the stereochemical characteristics of this hydration procedure.[4,5] In the course of this investigation we came to the conclusion that the assigned configurations[6] of the 4-caranols (**13**, **14**, and **15**) and 4-caranones (**16** and **17**) were in error. However, the unusual stability of 4-isocaranone (**16**) in the epimerization reaction[3] and the flexibility of (+)-3-carene (**1**)[7] introduced a measure of uncertainty into our conclusion that hydroboration was proceeding on the side of the molecule away from the *gem*-dimethyl group (A, Figure 1). It was conceivable that the hydroboration would involve the alternate conformation and takes place preferentially on the side of the *gem*-dimethyl group (B, Figure 1). This ambiguity had been absent in our previous study of the hydroboration of α-pinene.[8] The greater rigidity of the 2-carene (**2**) (C, Figure 1) suggested the essential absence of such an ambiguity in this derivative. Consequently, we undertook a study of the hydroboration of

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