Molecular Weight Determinations.—The molecular weights of 2-chlorocyclohexanone, 2-chloro-4-*t*-butylcyclohexanone and *n*-heptane (used as a standard to check the experimental procedure) in purified cyclohexane (see above) were determined as described previously.[8] Compound III (52% IIa) gave an experimental molecular weight that was 10% too large, while with IV the experimental value was too large by a factor of 3.3 (all at about 0.1*M* which was the concentration used for the infrared studies). Clearly considerable association occurred with IV.

Dipole Moments.—The dipole moments were obtained using the apparatus described earlier,[28] and the calculations were carried out with an IBM 650 computer.[29] Experimental error was about 0.02 D. The data are summarized in Table VII.

Theoretical Calculations.—The energy of the electrostatic interaction of the dipoles was calculated for the chloroketone by the same method used earlier for the bromoketone,[6,4] using the appropriate constants from Table VIII. The bond dipole moments used for the equatorial isomers were those justified earlier[6,10] for C=O and C—Br. The C—Cl moment was taken as the same as the C—Br. For the axial isomers induction is certainly less important, so it has been ignored and the bond moments for the isolated bonds have been used. Justification for this treatment comes from the fact that the calculated moments of the axial isomers are in better agreement with the experimental ones when this is done. These energies are inversely proportional to the effective dielectric constant of the medium.

The energy lowering due to an induced dipole was calculated from equation 4. The distance between the oxygen and halogen was measured on a model.[30] This energy is also inversely proportional to the effective dielectric constant.

The energy, E, of the van der Waals interaction for a pair of atoms is given[22] by

$$E/\epsilon = -2.25/\alpha^6 + 8.28 \times 10^5\, e^{-\alpha/0.0736} \qquad (5)$$

where α is the distance between atomic centers (in units of the sum of their van der Waals radii), and ϵ is a constant which is dependent on the pair of atoms involved. For the interactions of interest ϵ has the following values (in cal./mole) where hydrogen is interacting with the second atom: hydrogen, 42.0; chlorine, 115; bromine, 135.8. For the interactions involving oxygen, it was necessary to first calculate ϵ for the interaction of two oxygen atoms. This calculation was carried out using the method outlined by Hill.[22] The value found was 7.77×10^{-15} erg. From this quantity then it was possible to find the ϵ for interaction of oxygen with other atoms as follows (in units of 10^{-15} erg./molecule): hydrogen, 4.77; chlorine, 13.0; bromine, 15.4. To calculate the difference in van der Waals energy between the axial and equatorial halide, the interactions were considered between oxygen–halogen, and oxygen–C_2 hydrogen. The equatorial halogen was considered to interact with the C_3 hydrogens, while the C_2 hydrogen interacted with the axial hydrogens at C_4 and C_6 and the equatorial hydrogen at C_3. When the halogen was axial, the analogous interactions were considered. The distances between atoms were found by direct measurement on models.[30] In a few cases these values were also checked by vector analysis using the cyclohexylidene model of Corey and Sneen[31] with the appropriate modifications.

TABLE VIII

NUMERICAL CONSTANTS USED FOR CALCULATIONS

Bond lengths, Å.	
C=O	1.22
C—Cl	1.76
C—Br	1.94
C—H	1.09

van der Waals radii, Å.	
O	1.40
Cl	1.80
Br	1.95
H	1.20

	Dipole moments, D: Eq. halogen	Axial halogen
C=O	2.83	3.00
C—Br	1.91	2.24
C—Cl	1.91	2.24

	Oxygen–halogen distances, Å.: Axial	Eq.
Cl	3.56	2.81
Br	3.68	2.91

	Polarizability × 10^{+24} cm.^{3}
Cl	2.28
Br	3.34
=O	0.84

(28) M. T. Rogers, THIS JOURNAL, **77**, 3681 (1955).

(29) N. L. Allinger and J. Allinger, *J. Org. Chem.*, **24**, 1613 (1959).

(30) Dreiding stereomodels were found to be satisfactory for such measurements (see A. S. Dreiding, *Helv. Chim. Acta*, **42**, 1339 (1959)).

(31) E. J. Corey and R. A. Sneen, THIS JOURNAL, **77**, 2505 (1955).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A., MEXICO, D. F., MEX.]

Steroids. CL.[1] 10β-Halo Steroids[2]

BY J. S. MILLS, JULIA BARRERA, EUGENIA OLIVARES AND HILDELISA GARCIA

RECEIVED MAY 31, 1960

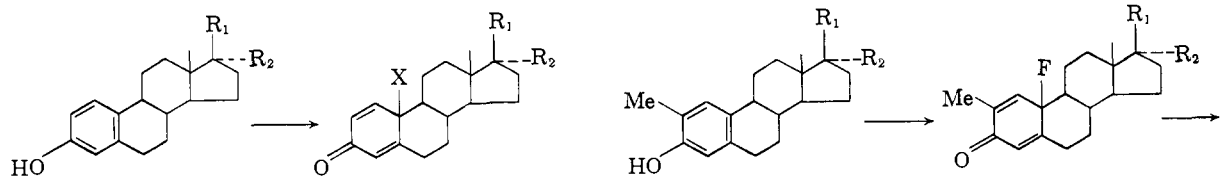
Chlorination of steroidal ring A phenols with N-chlorosuccinimide affords the 10β-chloro-$\Delta^{1,4}$-3-ones in about 25% yield together with a smaller proportion of the 10β-(2 or 4)-dichloro-$\Delta^{1,4}$-diene-3-ones. Analogous 10β-fluoro dienones are formed on treatment of ring A phenols with perchloryl fluoride in dimethylformamide solution. Both the 10β-chloro and 10β-fluoro compounds are readily reducible to the original phenols; however, the 10β-fluoro dienones may also be hydrogenated in rather low yields to the saturated 10β-fluoro-5β-3-ketones. Dehydrochlorination of the 10β-chlorodienones affords the $\Delta^{9,11}$-phenols. 10β-Fluoro-Δ^1-dehydro-19-nortestosterone readily undergoes dienone–phenol rearrangement with acetic anhydride–sulfuric acid to yield the *p*-fluorophenol diacetate (XVIa).

The halogenation of steroidal phenols with "positive halogen" reagents such as the N-halo amides and imides has been little investigated. Woodward[3] treated estradiol with N-bromoacetamide in ethanol and obtained 2,4-dibromoestradiol in high yield. We have now examined the reaction of estradiol with N-chlorosuccinimide in a variety of solvents and obtained after chromatography on deactivated alumina two compounds which both showed the characteristic bands at 6.00, 6.15 and 6.25 mμ of the 1,4-diene-3-one system. The first compound eluted and obtained in smaller quantity showed an ultraviolet maximum at 251 mμ, log ε 4.14, and its analysis agreed well with its formulation as 2 (or 4), 10-dichloro-Δ^1-dehydro-19-nortestosterone. The second compound obtained showed an ultraviolet maximum at 243 mμ, log ε 4.13, and its analysis indicated it to be 10-chloro-Δ^1-dehydro-19-nortestosterone (IIa). Recently a publication has appeared by

(1) Part CXLIX, J. A. Zderic and A. Bowers, *Ciencia*, **20**, 23 (1960).

(2) A preliminary account of part of this work has already appeared; J. S. Mills, THIS JOURNAL, **81**, 5515 (1959).

(3) R. B. Woodward, *ibid.*, **62**, 1625 (1940).

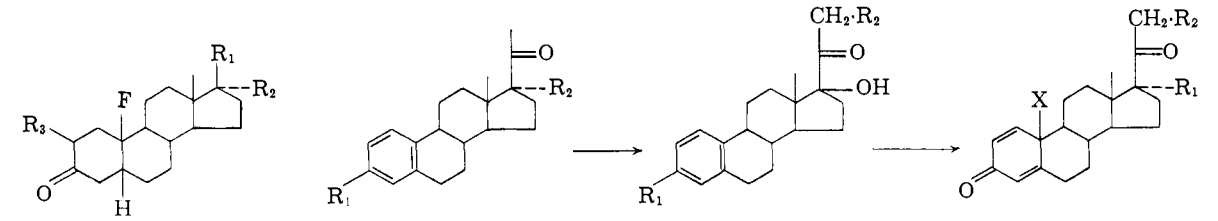


Ia, R_1 = OH, R_2 = H
b, R_1 = OH, R_2 = Me
c, R_1 = OH, R_2 = C≡CH
d, R_1 + R_2 = >O

IIa, X = Cl, R_1 = OH, R_2 = H
b, X = Cl, R_1 = OH, R_2 = Me
c, X = F, R_1 = OH, R_2 = H
d, X = F, R_1 = OH, R_2 = Me
e, X = F, R_1 = OAc, R_2 = H
f, X = F, R_1 = OH, R_2 = C≡CH
g, X = F, R_1 + R_2 = >O

IIIa, R_1 + R_2 = >O
b, R_1 = OH, R_2 = H
c, R_1 = OH, R_2 = Me

IVa, R_1 = OH, R_2 = H
b, R_1 = OH, R_2 = Me

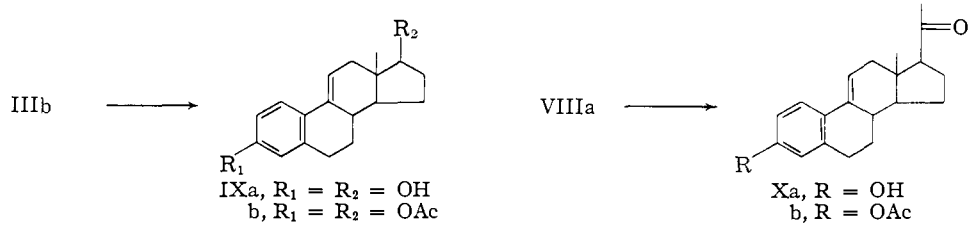


Va, R_1 = OH, R_2 = R_3 = H
b, R_1 = OH, R_2 = Me, R_3 = H
c, R_1 + R_2 = >O, R_3 = H
d, R_1 = OH, R_2 = H, R_3 = Me
e, R_1 = OH, R_2 = R_3 = Me

VIa, R_1 = R_2 = OH
b, R_1 = OH, R_2 = H
c, R_1 = R_2 = OAc
d, R_1 = OH, R_2 = OAc
e, R_1 = OAc, R_2 = OH

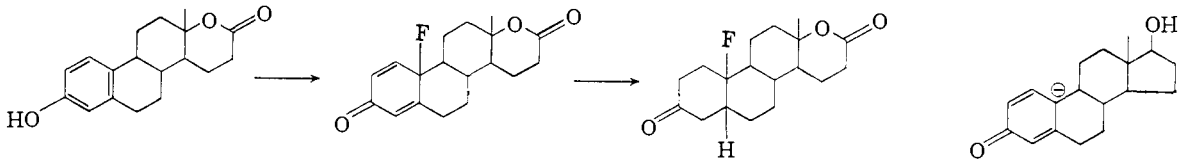
VIIa, R_1 = OAc, R_2 = Br
b, R_1 = OH, R_2 = Br
c, R_1 = OH, R_2 = OAc
d, R_1 = R_2 = OH

VIIIa, X = Cl, R_1 = R_2 = H
b, X = Cl, R_1 = OH, R_2 = H
c, X = Cl, R_1 = OAc, R_2 = H
d, X = F, R_1 = R_2 = H
e, X = F, R_1 = OH, R_2 = H
f, X = F, R_1 = OAc, R_2 = H
g, X = F, R_1 = OH, R_2 = OAc
h, X = F, R_1 = R_2 = OH



IXa, R_1 = R_2 = OH
b, R_1 = R_2 = OAc

Xa, R = OH
b, R = OAc

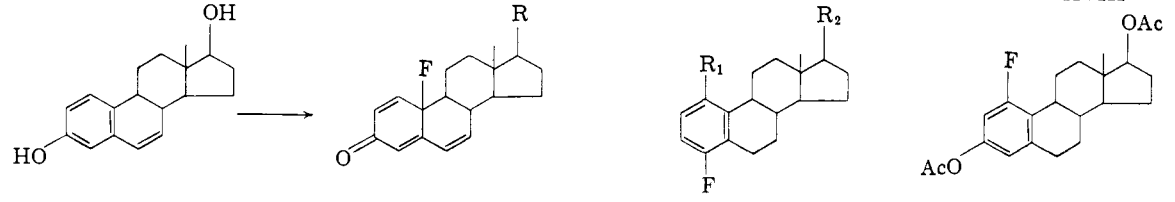


XI

XII

XIII

XVIII

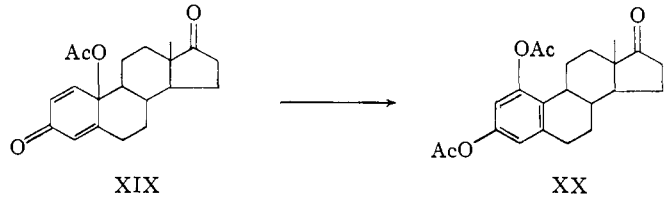


XIV

XVa, R = OH
b, R = OAc

XVIa, R_1 = R_2 = OAc
b, R_1 = R_2 = OH
c, R_1 = OMe, R_2 = OH

XVI



XIX

XX

Mukawa[4] describing an analogous reaction of estradiol 17-monoacetate with isocyanuric chloride, and the isolation of a monochloro and a trichloro $\Delta^{1,4}$-diene-3-one. Mukawa reports the ultraviolet maximum of the monochloro compound to

(4) F. Mukawa, *Tetrahedron Letters*, **14**, 17 (1959).

be at 248 mμ and of the trichloro compound at 258 mμ.

The reaction was initially carried out in aqueous dioxane containing a small proportion of perchloric acid and afterward in aqueous acetic acid and aqueous dimethylformamide–acetic acid. Better yields however were obtained finally with acetonitrile without acids, though at best the yield of the monochlorodienone did not exceed about 25%. It is very probable that chlorinated estradiols were also formed in the reaction but no attempt to isolate these was made.

The configuration of the 10-chlorine atom has already been shown by Mukawa to be β by virtue of the similarity of the rotatory dispersion curves of 10β-chloro-Δ¹-dehydro-19-nortestosterone acetate and cholesta-1,4-diene-3-one, and our findings confirm this, the curve of the 17β-ol and of the compounds described below being of similar shape. In view of the possible interesting biological activities of such compounds other 10-chlorodienones were prepared by means of this reaction. Thus 17α-methylestradiol[5] (Ib) afforded 10β-chloro-17α-methyl-Δ¹-dehydro-19-nortestosterone (IIb), 3-hydroxy-17β-acetyl-1,3,5(10)-estratriene (aromatic progesterone)[6a,b,c] (VIb) gave 10β-chloro-Δ¹-dehydro-19-norprogesterone (VIIIa), and 3,17α-dihydroxy-17β-acetyl-1,3,5(10)-estratriene[6b] (VIa) yielded 10β-chloro-17α-hydroxy-Δ¹-dehydro-19-norprogesterone (VIIIb). The 17-acetate of the last-named compound was prepared as follows. Acetylation of VIa with acetic anhydride and *p*-toluenesulfonic acid yielded the 3,17-diacetate VIc, which on brief saponification with 1.1 equivalents of potassium hydroxide gave the 17-monoacetate VId. This with N-chlorosuccinimide gave 10β-chloro-17α-acetoxy-Δ¹-dehydro-19-norprogesterone (VIIIc). Hydrogenation of 10β-chloro-Δ¹-dehydro-19-norprogesterone gave back aromatic progesterone in high yield. Dehydrochlorination with dimethylformamide and calcium carbonate yielded the Δ⁹⁽¹¹⁾-dehydro aromatic progesterone Xa. The double bond is assigned the Δ⁹⁽¹¹⁾- rather than the Δ⁸-position by virtue of the ultraviolet maximum at 264 mμ. The Δ⁹⁽¹¹⁾- and Δ⁸-derivatives of 14-isoestrone have ultraviolet maxima at 264 and 275 mμ, respectively.[7] Δ⁹⁽¹¹⁾-Estrone also shows an ultraviolet maximum at 263 mμ.[8] Dehydrochlorination of 10β-chloro-Δ¹-dehydro-19-nortestosterone (IIa) similarly gave Δ⁹⁽¹¹⁾-estradiol (IXa) in good yield.

The 10β-chlorodienones are unstable compounds and decompose in the light in a day or two. Analogous 10β-fluoro compounds would be expected to be more stable and this, and their intrinsic interest, made the preparation of such compounds an attractive goal. In view of the probable mechanism of the formation of the 10β-chlorodienones, involving attack of electrophilic chlorine on the carbanion XVIII, consideration was given to reagents which might give rise to electrophilic fluorine. It seemed to us *a priori* that perchloryl fluoride (ClO_3F)[9] might be such a reagent, and its known reaction with diethyl malonate in the presence of sodium methoxide to yield the difluoro derivative[10] gave support to this idea. Subsequently other reactions of perchloryl fluoride, notably with enol ethers,[11] have been described and indicate that in basic media the fluorine atom does have an electrophilic character. We first tried brief reaction of perchloryl fluoride with the sodium salt of estradiol suspended in dioxane, and a small amount (2%) of a dienone was isolated as evidenced by its ultraviolet maximum at 240 mμ. More prolonged reaction with the free compound in dioxane gave about 10% of the same product while replacement of dioxane with dimethylformamide raised the yield to about 70%. Use of 50% pyridine–dimethylformamide gave a similar yield. The structure of the product as 10β-fluoro-Δ¹-dehydro-19-nortestosterone follows from its ultraviolet and infrared spectra (bands at 6.0, 6.12 and 6.21 μ), from its elemental analysis and from its reactions described below. The β-configuration of the fluorine atom is assigned on the basis of the similarity of the rotatory dispersion curve to that of cholesta-1,4-diene-3-one (Fig. 1). It is noteworthy that in contrast to the formation of dichloro as well as monochloro dienones in the reaction of estradiol with N-chlorosuccinimide, no difluoro compound was isolated from the reaction with perchloryl fluoride.

By means of this reaction a variety of 10β-fluoro steroid analogs were prepared: 17α-Methylestradiol (Ib) gave 10β-fluoro-17α-methyl-Δ¹-dehydro-19-nortestosterone (IId), aromatic progesterone (VIb) gave 10β-fluoro-Δ¹-dehydro-19-norprogesterone (VIIId), 17α-hydroxy aromatic progesterone (VIa) gave 10β-fluoro-17α-hydroxy-Δ¹-dehydro-19-norprogesterone (VIIIe), 17α-acetoxy aromatic progesterone (VId) gave 10β-fluoro-17α-acetoxy-Δ¹-dehydro-19-norprogesterone (VIIIf), 17α-ethynylestradiol[12] (Ic) gave 10β-fluoro-17α-ethynyl-Δ¹-dehydro-19-nortestosterone (IIf), estrololactone[13a,b] (XI) gave 10β-fluoro-Δ¹-dehydro-19-nortestolactone (XII), 2-methylestradiol[14a,b] (IIIb) gave 10β-fluoro-2-methyl-Δ¹-dehydro-19-nortestosterone (IVa), 2,17α-dimethylestradiol (IIIc, see below) gave 10β-fluoro-2,17α-dimethyl-Δ¹-dehydro-19-nortestosterone (IVb), and 3,17α,-21-trihydroxy-19-norpregna-1,3,5(10)-triene-3-one 21-monoacetate (aromatic substance "S" 21-monoacetate) (VIIc, see below) gave 10β-fluoro-

(5) B. C. Bocklage, W. J. Nicholas, E. A. Doisy, Jr., W. H. Elliott, S. A. Thayer and E. A. Doisy, *J. Biol. Chem.*, **202**, 27 (1953).

(6) (a) L. Velluz and G. Muller, *Bull. soc. chim. France*, 166 (1950); (b) C. Djerassi, G. Rosenkranz, J. Iriarte, J. Romo and J. Berlin, THIS JOURNAL, **73**, 1523 (1951); (c) J. S. Mills, H. J. Ringold and C. Djerassi, *ibid.*, **80**, 6118 (1958).

(7) D. Banes, J. Carol and J. Haenni, *J. Biol. Chem.*, **187**, 557 (1950).

(8) B. J. Magerlein and J. A. Hogg, THIS JOURNAL, **79**, 1508 (1957); **80**, 2220 (1958).

(9) Pennsylvania Salt Manufacturing Co., Philadelphia 2, Pa.

(10) C. E. Inman, E. A. Tyczkowski, R. E. Oesterling and F. L. Sott, *Experientia*, **14**, 355 (1958); C. E. Inman, R. E. Oesterling and E. A. Tyczkowski, THIS JOURNAL, **80**, 6533 (1958).

(11) S. Nakanishi, K. Marita and E. V. Jensen, *ibid.*, **81**, 5259 (1959).

(12) H. H. Inhoffen, W. Logemann, W. Hohervey and A. Serini, *Ber.*, **71**, 1024 (1938).

(13) (a) W. W. Westerfeld, *J. Biol. Chem.*, **143**, 177 (1942); (b) R. P. Jacobsen, *ibid.*, **171**, 61 (1947); H. Levy and R. P. Jacobsen, *ibid.*, **171**, 71 (1947); R. P. Jacobsen, G. M. Picha and H. Levy, *ibid.*, **171**, 81 (1947).

(14) (a) J. Iriarte and H. J. Ringold, *Tetrahedron*, **3**, 28 (1958); (b) T. L. Patton, *Chemistry & Industry*, 923 (1959).

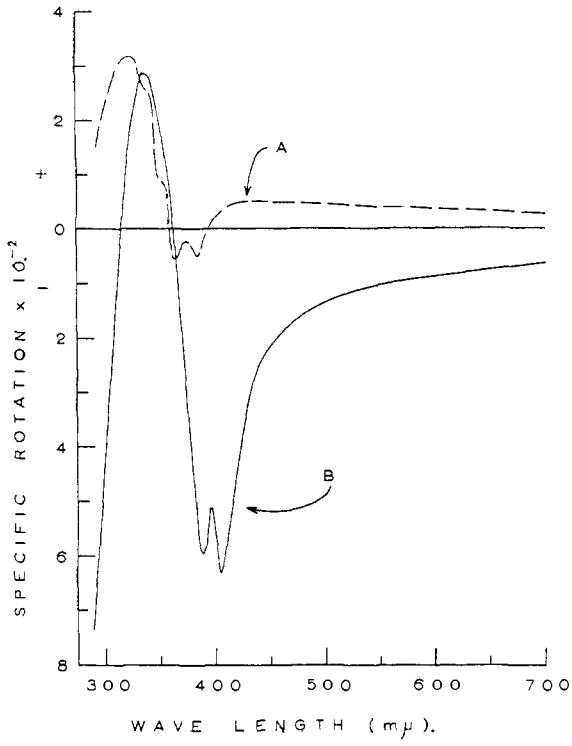


Fig. 1.—Rotatory dispersion curves in dioxane of cholesta-1,4-diene-3-one (A) (*cf.* C. Djerassi, R. Riniker and B. Riniker, THIS JOURNAL, **78,** 6362 (1956)) and 10β-fluoro-17α-ethynyl-Δ¹-dehydro-19-nortestosterone (B).

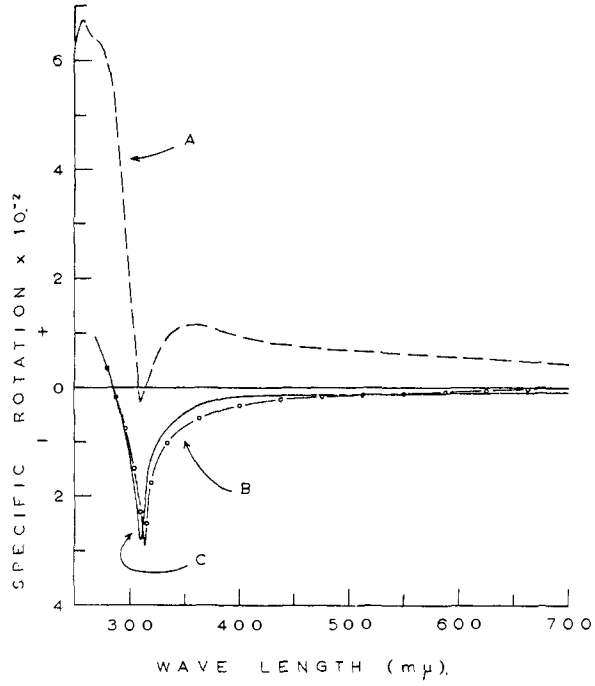


Fig. 2.—Rotatory dispersion curves in dioxane of coprostane-3-one (A) (*cf.* C. Djerassi and W. Closson, THIS JOURNAL, **78,** 3761 (1956)), 10β-fluoro-2β,17α-dimethyl-5β-19-norandrostane-3-one-17β-ol (B) and 10β-fluoro-17α-methyl-5β-19-norandrostane-3-one-17β-ol (C).

17α,21-dihydroxy-19-norpregna-1,4-diene-3,20-dione 21-monoacetate (VIIIg), which was saponified to the free compound VIIIb. 2,17α-Dimethylestradiol was synthesized by refluxing 2-methylestrone[14a,b,15] with methylmagnesium bromide in tetrahydrofuran for a prolonged period (3 days). Shorter reaction time gave much recovered starting material. Aromatic substance "S" 21-monoacetate (VIIc) was prepared as follows. Bromination of 17α-hydroxy aromatic progesterone 3-monoacetate[6b] (VIe) afforded the 21-bromo derivative VIIa which was hydrolyzed by methanolic hydrochloric acid to the free compound VIIb. Refluxing with potassium acetate in acetone then gave VIIc. Free aromatic "S" (VIId) was prepared by mild alkaline hydrolysis. This compound has already been described.[16]

Reduction of 10β-fluoro-Δ¹-dehydro-19-nortestosterone with sodium borohydride in methanol or with Raney nickel in refluxing methanol gave back estradiol. Hydrogenation in pyridine, dioxane or ethanol over palladium–barium sulfate afforded a rather low yield of a saturated ketone showing infrared absorption at 5.86 μ and no strong ultraviolet maximum, the remainder of the product being estradiol. Even lower yields of saturated ketone were given by 10β-fluoro-19-norandrosta-1,4-diene-3,17-dione (IIg) but higher yields were obtained with compounds of the 17β-hydroxy-17α-methyl series, as also with 10β-fluoro-2-methyl-Δ¹-dehydro-19-nortestosterone (IVa) and 10β-fluoro-Δ¹-dehydro-19-nortestolactone (XII). Only one (C_5) isomer was isolated in each case and the rotatory dispersion curves of these compounds show a negative Cotton effect characteristic of 10β,-5β-steroids (Fig. 2). In the case of the 2-methyl compounds (Vd and Ve) the 2-methyl group is assigned the 2β (equatorial) configuration since the compound Vd was recovered unchanged after prolonged contact with 1% methanolic potassium hydroxide solution. Moreover the intensity of the Cotton effect is almost the same as in the compounds without the 2-methyl group whereas the Octant rule[17] would predict a more strongly negative Cotton effect than the parent compounds for a 2α (axial) methyl substituted derivative.

10β-Fluoro-Δ¹-dehydro-19-nortestosterone (IIc) on treatment with acetic anhydride containing a little sulfuric acid readily underwent dienone-phenol rearrangement to give a high yield of a fluoro-phenol diacetate which could be either of the *meta* (XVII) or *para* (XVIa) structure. 10-Methyl-1,4-diene-3-ones under these conditions normally give products of the *para* type as in XVIa (fluorine replaced by methyl)[18a,b] while 10-methyl-1,4,6-triene-3-ones give Δ⁶-phenols of the *meta* type.[6b,19a,b] However, 10-acetoxy-1,4-diene-3-ones (XIX)[20] yield *meta* type products (XX) though

(15) 2-Methylesterone was prepared by the convenient procedure of T. L. Patton.[14b] We are very grateful to Dr. Patton for providing us with experimental details before their full publication.

(16) M. Nishikawa and H. Hagiwara, *Chem. Pharm. Bull. Japan*, **6,** 226 (1958).

(17) Carl Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960.

(18) (a) R. B. Woodward and T. Singh, THIS JOURNAL, **72,** 494 (1950); (b) A. S. Dreiding and A. Voltman, *ibid.*, **76,** 537 (1954).

(19) (a) C. Djerassi, G. Rosenkranz, J. Romo, J. Pataki and St. Kaufmann, *ibid.*, **72,** 4540 (1950); (b) J. Romo, C. Djerassi and G. Rosenkranz, *J. Org. Chem.*, **15,** 896 (1950).

(20) A. M. Gold and E. Schwenk, THIS JOURNAL, **80,** 5683 (1958).

this can be explained by their ability to form 1,10-cyclic intermediates.[20] In the present case a decision was made in favor of the *para* structure XVIa by means of n.m.r. spectroscopy.[21]

The spectrum of the free diol XVIb was run in $CDCl_3$ with added tetramethylsilane as internal standard and the signal pattern due to the two aromatic hydrogens showed both HH and HF spin couplings. The alternative structure XVII would not have a large HH spin coupling since the protons are *meta* rather than *ortho* to each other. We tried also to effect dienone-phenol rearrangement of 10β-fluoro-$\Delta^{1,6}$-bisdehydro-19-nortestosterone (XVa) which was prepared by the action of perchloryl fluoride on Δ^6-estradiol (XIV),[22] but no homogeneous product could be isolated from this reaction.

Preliminary biological assay data[23] on the above compounds indicate that 10β-fluoro-17α-methyl-5β-19-norandrostane-3-one-17β-ol and 10β-fluoro-5β-19-norandrostalactone-3-one are potent antiandrogens, inhibiting the effect of simultaneously administered testosterone in the rat.

Experimental[24]

10β-Chloro-Δ^1-dehydro-19-nortestosterone (IIa).—To a solution of estradiol (Ia, 10 g.) in hot acetonitrile (400 cc.) was added N-chlorosuccinimide (7.3 g.) in one portion and the hot solution allowed to stand. After approximately 2 hours the reaction was complete (neg. starch–KI) and the solution was poured into ice-water and the product isolated with methylene chloride. The resulting oil was chromatographed over 300 g. of neutral alumina deactivated with 5 cc. of water. Elution with benzene gave a series of crystalline fractions, the ultraviolet λ_{max} of which ranged down from 252 to 243 mμ. The first three fractions (λ_{max} above 248 mμ) were combined and crystallized from acetone to yield 750 mg. of **10β, (2 or 4)-dichloro-Δ^1-dehydro-19-nortestosterone**, m.p. 180–184° dec. Recrystallization afforded an analytical sample, m.p. 183–187° dec., $[\alpha]_D$ −23°, λ_{max}^{EtOH} 250–252 mμ, log. ε 4.14; λ_{max}^{KBr} 2.87, 6.00 6.10-(sh.) and 6.25 μ.

Anal. Calcd. for $C_{18}H_{22}O_2Cl_2$: C, 63.33; H, 6.50; O, 9.38; Cl, 20.79. Found: C, 63.29; H, 6.74; O, 9.51; Cl, 20.90.

The later fractions (λ_{max}^{EtOH} below 245 mμ) were combined and crystallized from acetone to yield 2.9 g. of **10β-chloro-Δ^1-19-nor-testosterone (IIa)**, m.p. 158–161° dec. Recrystallization afforded the analytical sample, m.p. 159–164° dec. (variable), $[\alpha]_D$ −6°, λ_{max}^{EtOH} 242–244 mμ, log ε 4.13; λ_{max}^{KBr} 287, 6.00, 6.15 and 6.25 μ.

Anal. Calcd. for $C_{18}H_{23}O_2Cl$: C, 71.39; H, 7.32; O, 10.10; Cl, 11.19. Found: C, 70.95; H, 7.76; O, 10.20; Cl, 11.42.

Both of the above compounds and the succeeding 10-chloro compounds decomposed in the light and more slowly in the dark.

10β-Chloro-Δ^1-dehydro-19-norprogesterone (VIIIa).—Aromatic progesterone (18 g.) dissolved in dimethylformamide (600 cc.), acetic acid (40 cc.) and water (40 cc.) was treated with N-chlorosuccinimide (12.6 g.) with warming at *ca.* 60°. After about 2 hours reaction was complete and the mixture was poured into ice-water and the product isolated with methylene chloride. The resulting oil was chromatographed on alumina (500 g.), elution with benzene yielding a series of crystalline fractions all but the first of which were combined and crystallized from acetone to yield 5.05 g. of **10β-chloro-Δ^1-dehydro-19-norprogesterone (VIIIa)**, m.p. *ca.* 160–165° dec. Several recrystallizations afforded an analytical sample, m.p. 165–168° dec. (variable), $[\alpha]_D$ +77°, λ_{max}^{EtOH} 242–244 mμ, log ε 4.14; λ_{max}^{KBr} 5.90, 6.00, 6.15 and 6.23 μ.

Anal. Calcd. for $C_{20}H_{25}O_2Cl$: C, 72.16; H, 7.57; O, 9.61; Cl, 10.65. Found: C, 71.77; H, 7.56; O, 10.2; Cl, 10.89.

10β-Chloro-17α-hydroxy-Δ^1-dehydro-19-norprogesterone (VIIIb).—3,17α-Dihydroxy-17β-acetyl-1,3,5(10)-estratriene (VIa, 1 g.) in dimethylformamide (40 cc.), acetic acid (2 cc.) and water (2 cc.) was warmed with N-chlorosuccinimide (0.65 g.) on the steam-bath at *ca.* 60°. When the reaction was complete the products were isolated as above and chromatographed over alumina (30 g.) deactivated with water (0.5 cc.). Elution with benzene gave oily fractions which crystallized with methanol, all but the first of which were combined and crystallized from methanol to yield 110 mg. of **10β-chloro-17α-hydroxy-Δ^1-dehydro-19-norprogesterone (VIIIb)** decomposing between 170–180°, $[\alpha]_D$ −6°, λ_{max}^{EtOH} 242, log ε 4.15; λ_{max}^{KBr} 2.88, 5.87, 6.01, 6.15 and 6.23 μ.

Anal. Calcd. for $C_{20}H_{25}O_3Cl$: C, 69.01; H, 7.22; O, 13.76; Cl, 10.17. Found: D, 68.54; H, 7.22; O, 13.86; Cl, 10.17.

3,17α-Diacetoxy-17β-acetyl-1,3,5(10)-estratriene (VIc).—3,17α-Dihydroxy-17β-acetyl-1,3,5(10)-estratriene (VIa, 4 g.), *p*-toluenesulfonic acid (1.2 g.) and acetic anhydride (50 cc.) were left overnight at room temperature. The solution was poured into water and stirred for 1 hour whereupon the product was filtered and crystallized from methanol to yield the **diacetate VIc** (3.6 g.), m.p. 191–194°. Recrystallization afforded the analytical sample, m.p. 194–195°, $[\alpha]_D$ +34°.

Anal. Calcd. for $C_{24}H_{30}O_5$: C, 72.33; H, 7.59; O, 20.08. Found: C, 72.24; H, 7.65; O, 19.92.

3,17α-Dihydroxy-17β-acetyl-1,3,5(10)-estratriene-17-monoacetate (VId).—To a solution of the foregoing diacetate (3.375 g.) in methanol (300 cc.) was added methanolic potassium hydroxide solution (33.75 cc., 1.2%) and the solution allowed to stand at room temperature for 10 min. Acetic acid (1 cc.) was added and the solution concentrated to yield the **17-monoacetate VId** (2.79 g.), m.p. 240–243°. Recrystallization from methanol gave the analytical sample, m.p. 242–244°, $[\alpha]_D$ +49°, λ_{max} 280–282 mμ, log ε 3.27.

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92; O, 17.95. Found: C, 74.22; H, 7.59; O, 17.96.

10β-Chloro-17α-acetoxy-Δ^1-dehydro-19-norprogesterone (VIIIc).—The foregoing compound (1 g.) in acetic acid (100 cc.) and water (5 cc.) was warmed with N-chlorosuccinimide (0.45 g.) on the steam-bath at 70° for 2.5 hr., by which time reaction was almost complete. The product, isolated in the usual way, was chromatographed on 30 g. of alumina. Benzene eluted oils which crystallized from methanol. All but the first of these were combined and crystallized from methanol to yield 220 mg. of **10β-chloro-17α-acetoxy-Δ^1-dehydro-19-norprogesterone (VIIIc)**, m.p. 170–175° dec. Recrystallization afforded an analytical sample, m.p. 176–178° dec., $[\alpha]_D$ −9°, λ_{max}^{EtOH} 242–244 mμ, log ε 4.12; λ_{max}^{KBr} 5.8, 5.85(sh.), 6.00, 6.15, 6.24μ.

Anal. Calcd. for $C_{22}H_{27}O_4Cl$: C, 65.47; H, 7.42; O, 17.44; Cl, 9.66. Found: C, 65.92; H, 7.01; O, 16.67; Cl, 10.31.

10β-Chloro-17α-methyl-Δ^1-dehydro-19-nortestosterone (IIb).—17α-Methylestradiol (Ib, 2 g.) in dioxane (40 cc.) and water (5 cc.) was treated with N-chlorosuccinimide (1.2 g.) and perchloric acid (70%, 6 drops) and the solution left overnight at room temperature. The product was isolated in the usual way and chromatographed on alumina (60 g.) deactivated with water (1 cc.). Benzene eluted oils,

(21) We are indebted to Drs. J. N. Shoolery and LeRoy F. Johnson of Varian Associate, 611 Hansen Way, Palo Alto, Calif., for measuring and interpreting this spectrum.

(22) St. Kaufmann, J. Pataki, G. Rosenkranz, J. Romo and C. Djerassi, THIS JOURNAL, **72**, 4531 (1950).

(23) Biological assay by Dr. R. I. Dorfman, Worcester Foundation for Experimental Biology, Shrewsbury, Mass.

(24) Melting points were determined on a Fisher–Johns block and are uncorrected. Rotations were measured in chloroform unless otherwise stated. Ultraviolet light absorption spectra were determined in 95% ethanol solution. The rotatory dispersion measurements were obtained with a Rudolph spectropolarimeter using a xenon arc lamp (250–320 mμ) and a zirconium arc lamp (320–700 mμ). We are grateful to Dr. J. Matthews and his staff for these measurements. The alumina used had been neutralized by suspension in ethyl acetate and reactivated by drying at 100° *in vacuo*. The elemental analysis were carried out by Dr. A. Bernhardt, Mulheim, Ruhr, Germany.

those with ultraviolet λ_{max} below 245 being combined. The material crystallized with considerable difficulty from aqueous methanol as a solvate, m.p. 65–75° (280 mg.). Recrystallization from methanol gave long solvated needles of IIb, m.p. 75–80°, which would not crystallize from other solvents; $[\alpha]_D$ −25°, λ_{max}^{EtOH} 242–244 mμ log ε 4.10; λ_{max}^{KBr} 3.18, 6.00, 6.13, 6.22 μ. Drying at room temperature did not raise the m.p. Drying at 60° gave opaque, partially decomposed crystals, m.p. 121–123° dec.

Anal. Calcd. for $C_{19}H_{25}O_2Cl$ H_2O: C, 67.34; H, 8.03; Cl, 10.46. Found: (dried at room temp.) C, 67.32; H, 8.10; Cl, 10.51.

Hydrogenation of 10β-Chloro-Δ¹-dehydro-19-norprogesterone.—10β-Chloro-Δ¹-dehydro-19-norprogesterone (255 mg.) in ethanol–ethyl acetate (1:1, 10 cc.) was hydrogenated over pre-reduced $Pd/BaCO_3$ (40 mg.). One mole (24.1 cc.) of hydrogen was absorbed in 12 minutes and at this point the product crystallized. Acetone was added and the solution filtered from catalyst and concentrated to crystallization to yield, in two crops, 195 mg. of 3-hydroxy-17β-acetyl-1,3,5(10)-estratriene (VIb), m.p. and mixed m.p. 243–247°, λ_{max}^{EtOH} 282 mμ, log ε 3.33.

3-Hydroxy-17β-acetyl-1,3,5(10),9(11)-estratetraene (Xa).—10β-Chloro-Δ¹-dehydro-19-norprogesterone (2 g.) and calcium carbonate (4 g.) in dimethylformamide (100 cc.) were refluxed under nitrogen for 1 hour. The mixture was filtered through Celite and poured into water and the product isolated by filtration. Crystallization from ethyl acetate afforded the Δ⁹⁽¹¹⁾-dehydro-phenol (Xa, 1.45) g., m.p. 240–245°. The analytical sample had m.p. 245–247°, $[\alpha]_D$ +156°, λ_{max}^{EtOH} 264 mμ, log ε 4.24.

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16; O, 10.80. Found: C, 81.46; H, 8.21; O, 10.49.

Acetylation of this compound with pyridine–acetic anhydride overnight at room temperature yielded the 3-acetate Xb, m.p. 141–142° (from methanol), $[\alpha]_D$ +189°, λ_{max}^{EtOH} 258–260 mμ, log ε 4.28.

Anal. Calcd. for $C_{22}H_{26}O_3$: C, 78.07; H, 7.74; O, 14.19. Found: C, 78.68; H, 7.87; O, 13.60.

Δ⁹⁽¹¹⁾-Dehydro-estradiol (IXa).—10β-Chloro-Δ¹-dehydro-19-nortestosterone (1 g.) and calcium carbonate (2 g.) in dimethylformamide (50 cc.) were refluxed for 1 hr. under nitrogen and worked up as in the preceding section. Crystallization from aqueous acetone gave, in two crops 0.82 g. of Δ⁹⁽¹¹⁾-dehydro-estradiol (IXa), m.p. 166–169°. The analytical sample had m.p. 174–175°, $[\alpha]_D$ +127°, λ_{max}^{EtOH} 264 mμ, log ε 4.23.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20; O, 11.84. Found: C, 79.48; H, 7.95; O, 12.27.

Acetylation of this compound with acetic anhydride–pyridine overnight at room temperature yielded the **diacetate IXb**, m.p. 134–135° (from methanol), $[\alpha]_D$ +79°, λ_{max}^{EtOH} 258–260 mμ, log ε 4.26.

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.38. Found: C, 74.03; H, 6.99.

10β-Fluoro-Δ¹-dehydro-19-nortestosterone (IIc).—Estradiol (1 g.) in dimethylformamide (50 cc.) was treated at room temperature with a rapid stream of perchloryl fluoride for 0.5 hr., and then with a very slow stream of the gas to maintain a saturated solution overnight (*ca.* 16 hr.). The solution was poured into dilute aqueous sodium bicarbonate and the product, isolated with methylene chloride, was chromatographed over alumina (30 g.). Elution with benzene and one crystallization from acetone–hexane afforded almost pure **10β-fluoro-Δ¹-dehydro-19-nortestosterone (IIc**, 680 mg.), m.p. 152–154°. The analytical sample had the same m.p. $[\alpha]_D$ −27°, λ_{max}^{EtOH} 240 mμ, log ε 4.06; λ_{max}^{KBr} 2.9, 6.0, 6.12, 6.21 μ.

Anal. Calcd. for $C_{18}H_{23}O_2F$: C, 74.46; H, 7.98; F, 6.54. Found: C, 74.20; H, 7.60; F, 6.20.

Acetylation of the compound with pyridine–acetic anhydride overnight at room temperature afforded the **17-acetate IIe** (from hexane), m.p. 73.5–75°, $[\alpha]_D$ −21°, λ_{max}^{EtOH} 240 mμ, log ε 4.06.

Anal. Calcd. for $C_{20}H_{25}O_3F$: C, 72.26; H, 7.58; F, 5.72. Found: C, 72.66; H, 7.71; F, 5.35.

10β-Fluoro-19-norandrosta-1,4-diene-3,17-dione (IIg).—Estrone (10 g.) in dimethylformamide (500 cc.) was treated with perchloryl fluoride for 20 hours at room temperature. After working up in the usual way, chromatography on alumina, elution with benzene and crystallization from acetone–hexane gave the 10β-fluoro dienone IIg (7.0 g.), m.p. 138–140°. Recrystallization gave a sample, m.p. 143–144°, $[\alpha]_D$ +52°, λ_{max}^{EtOH} 238 mμ, log ε 4.05.

Anal. Calcd. for $C_{18}H_{21}O_2F$: C, 74.98; H, 7.34; F, 6.59. Found: C, 74.72; H, 7.40; F, 6.23.

10β-Fluoro-17α-methyl-Δ¹-dehydro-19-nortestosterone (IId).—17α-Methylestradiol (Ib, 1 g.) in dimethylformamide (500 cc.) was treated with perchloryl fluoride and worked up as in the preceding section. Chromatography over alumina (30 g.) and elution with benzene gave an oil which crystallized from slightly aqueous methanol with considerable difficulty to give solvated needles of IId (540 mg.), m.p. 65–70°. Recrystallization from acetone–hexane gave material which was solvent free, m.p. 100–102°, $[\alpha]_D$ −52°, λ_{max}^{EtOH} 240 mμ, log ε 4.01; λ_{max}^{KBr} 2.85, 6.00, 6.15 and 6.20 μ.

Anal. Calcd. for $C_{19}H_{25}O_2F$: C, 74.97; H, 8.28; F, 6.24. Found: C, 75.10; H, 8.33; F, 6.4.

10β-Fluoro-17α-ethynyl-Δ¹-dehydro-19-nortestosterone (IIf).—17α-Ethynylestradiol (Ic, 1 g.) in dimethylformamide (50 cc.) was treated with perchloryl fluoride and worked up as above. Chromatography over alumina (30 g.), elution with benzene and crystallization from acetone–hexane yielded 520 mg. of **10β-fluoro-17α-ethynyl-Δ¹-dehydro-19-nortestosterone (IIf)**, m.p. 156–159°. The analytical sample had m.p. 160–162°, $[\alpha]_D$ −80°, λ_{max}^{EtOH} 240 mμ, log ε 4.05; λ_{max}^{KBr} 3.00, 3.15, 6.00 6.15 and 6.22 μ; rotatory dispersion curve (*c* 0.0665 in dioxane): $[\alpha]_{700}$ −62°, $[\alpha]_{589}$ − 111°, $[\alpha]_{405}$ −637°, $[\alpha]_{395}$ −539°, $[\alpha]_{390}$ −596°, $[\alpha]_{335}$ +285°, $[\alpha]_{290}$ −736°.

Anal. Calcd. for $C_{20}H_{23}O_2F$: C, 76.40; H, 7.38; F, 6.04. Found: C, 76.65; H, 7.71; F, 5.59.

10β-Fluoro-Δ¹-dehydro-19-norprogesterone (VIIId).—3-Hydroxy-17β-acetyl-1,3,5(10)-estratriene (VIb, 1 g.) in dimethylformamide (50 cc.) was treated with perchloryl fluoride and worked up and chromatographed as above. Elution with benzene and crystallization from acetone–hexane afforded 660 mg. of **10β-fluoro-Δ¹-dehydro-19-norprogesterone (VIIId)**, m.p. 101–103°. The analytical sample had m.p. 108–109.5° $[\alpha]_D$ +62°, λ_{max}^{EtOH} 241 mμ, log ε 4.04; λ_{max}^{KBr} 5.89, 6.00, 6.13 and 6.20 μ.

Anal. Calcd. for $C_{20}H_{25}O_2F$: C, 75.92; H, 7.97; F, 6.00. Found: C, 76.06; H, 8.17; F, 5.54.

10β-Fluoro-17α-hydroxy-Δ¹-dehydro-19-norprogesterone (VIIIe).—3,17α-Dihydroxy-17β-acetyl-1,3,5(10)-estratriene (VIa, 1 g.) in dimethylformamide (50 cc.) was treated with perchloryl fluoride and worked up as above. Crystallization of the product from methylene chloride–methanol gave 630 mg. of **10β-fluoro:17α-hydroxy-Δ¹-dehydro-19-norprogesterone (VIIIe)**, m.p. 181–184° dec. The analytical sample had m.p. 188–190° dec., $[\alpha]_D$ −22°, λ_{max}^{EtOH} 239 mμ, log ε 4.06; λ_{max}^{KBr} 2.85, 5.91, 6.00, 6.13 and 6.20 μ.

Anal. Calcd. for $C_{20}H_{25}O_3F$: C, 72.26; H, 7.58; F, 5.72. Found: C, 72.66; H, 7.65; F, 6.09.

10β-Fluoro-17α-acetoxy-Δ¹-dehydro-19-norprogesterone (VIIIf).—3,17α-Dihydroxy-17β-acetyl-1,3,5(10)-estratriene-17-monoacetate (VId, 1 g.) in dimethylformamide (50 cc.) was treated with perchloryl fluoride, worked up and chromatographed as above. Elution with benzene and crystallization from acetone–hexane gave 540 mg. of **10β-fluoro-17α-acetoxy-Δ¹-dehydro-19-norprogesterone (VIIIf)**, m.p. 144–146°. The analytical sample had the same m.p., $[\alpha]_D$ −33°, λ_{max}^{EtOH} 240 mμ, log ε 4.06; λ_{max}^{KBr} 5.81, 5.86(sh.), 6.11 and 6.21 μ.

Anal. Calcd. for $C_{22}H_{27}O_4F$: C, 70.56; H, 7.12; F, 5.07. Found: C, 70.48; H, 7.12; F, 4.70.

3,17α-Dihydroxy-17β-bromoacetyl-1,3,5(10)-estratriene 3-Monoacetate (VIIa).—3,17α-Dihydroxy-17β-acetyl-1,3,5(10)-estratriene 3-monoacetate (VIe, 2.54 g.), in chloroform (50 cc.) was brominated by addition of a solution of bromine in chloroform (58 cc., 2%) at room temperature. After a few minutes the solution was poured into dilute aqueous sodium bicarbonate and worked up in the usual way. Crystallization of the product from acetone–hexane yielded 2.55 g. of the 21-bromo derivative VIIa, m.p. 160–162°. The analysis of a further purified sample, m.p. 161–163°, $[\alpha]_D$ +56°, indicated that it probably still contained unbrominated material.

Anal. Calcd. for $C_{22}H_{27}O_4Br$: C, 60.69; H, 6.25; O, 14.70; Br, 18.36. Found: C, 61.47; H, 6.28; O, 14.58; Br, 17.52.

3,17α-Dihydroxy-17β-bromoacetyl-1,3,5(10)-estratriene (VIIIb).—The foregoing 21-bromo compound (2.48 g.) in methanol (120 ml.) was treated with concentrated hydrochloric acid (3 cc.) and the solution left at room temperature for 24 hours. The product, isolated in the usual way, was crystallized from acetone–hexane to give 1.99 g. of the free 3-hydroxy compound VIIb, m.p. 181–183°, $[\alpha]_D$ +81°, λ_{max}^{EtOH} 281 mμ, log ε 3.2, which still appeared to contain unbrominated material.

Anal. Calcd. for $C_{20}H_{25}O_3Br$: C, 61.06; H, 6.41; O, 12.20; Br, 20.32. Found: C, 62.05; H, 6.42; O, 11.97; Br, 19.58.

3,17α-21-Trihydroxy-1,3,5(10)-pregnatriene-20-one 21-Monoacetate (VIIc).—The foregoing bromo-ketone (1.52 g.), potassium acetate (2.2 g.) and sodium iodide (1.2 g.) in acetone (60 cc.) were refluxed for 20 hr. Most of the acetone was removed by evaporation, water was added and the product collected. Crystallization from methylene chloride–methanol yielded 1.03 g. of "**aromatic substance S**" **21-monoacetate (VIIc)**, m.p. 179–183°. Recrystallization from the same solvent pair and from acetone–hexane gave an analytical sample, m.p. 187–190° (after drying at 130°), $[\alpha]_D$ +124°, λ_{max}^{EtOH} 282 mμ, log ε 3.29.

Anal. Calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58; O, 21.48. Found: C, 71.16; H, 7.52; O, 21.29.

Saponification of this compound with methanolic potassium hydroxide at 0° under nitrogen, and crystallization of the product from ethyl acetate yielded free "**aromatic substance S**" **(VIId)**, m.p. 229–231°, $[\alpha]_D$ +80°.

Anal. Calcd. for $C_{20}H_{26}O_4$: C, 73.14; H, 7.37; O, 19.49. Found: C, 72.67; H, 7.77; O, 19.48.

10β-Fluoro-17α,21-dihydroxy-19-norpregna-1,4-diene-3,20-dione 21-Monoacetate (VIIIg).—3,17α,21-Trihydroxy-1,3,5(10)-pregnatriene-20-one 21-monoacetate (VIIc, 1 g.) in dimethylformamide (50 cc.) was treated with perchloryl fluoride and worked up as in previous experiments. Chromatography over alumina (30 g.), elution with benzene and crystallization from methanol gave 620 mg. of the 10β-fluoro-dienone VIIIg, 191–193°. The analytical sample had m.p. 197–199° dec., $[\alpha]_D$ +49°, λ_{max}^{EtOH} 238 mμ, log ε 4.06; λ_{max}^{KBr} 2.85, 5.8(broad), 6.00, 6.13 and 6.21 μ.

Anal. Calcd. for $C_{22}H_{27}O_5F$: C, 67.67; H, 6.97; F, 4.87. Found: C, 68.13; H, 6.82; F, 4.64.

Hydrolysis of this compound with one-tenth of its weight of potassium hydroxide in methanol at 0° for 1 hour under nitrogen and crystallization of the product from acetone gave the free compound VIIIh, m.p. 212–214°, $[\alpha]_D$ +26°, λ_{max}^{EtOH} 239 mμ, log ε 4.06; λ_{max}^{KBr} 2.9, 5.86, 6.00, 6.13 and 6.21μ.

Anal. Calcd. for $C_{20}H_{25}O_4F$: C, 68.94; H, 7.23; F, 5.45. Found: C, 69.09; H, 7.10; F, 5.18.

Estradiol from 10β-Fluoro-Δ¹-dehydro-19-nortestosterone. (a) **With Sodium Borohydride.**—10β-Fluoro-Δ¹-dehydro-19-nortestosterone (500 mg.) in methanol (30 cc.) was treated with sodium borohydride (1 g.) in four portions during 1 hour. After standing, for a further 1 hour at room temperature, excess acetic acid was added and the solution evaporated to dryness *in vacuo*. Water was added and the product filtered. Crystallization from aqueous methanol gave 370 mg. of estradiol (Ia), m.p. and mixed m.p. 169–171°, λ_{max}^{EtOH} 282 mμ, log ε 3.27.

(b) **With Raney Nickel.**—10β-Fluoro-Δ¹-dehydro-19-nortestosterone (500 mg.) in methanol (20 cc.) was refluxed for 0.5 hour with excess Raney nickel. After filtering from the nickel the solution was evaporated to dryness and the residue crystallized from aqueous methanol to yield 405 mg. of estradiol, m.p. and mixed m.p. 170–172°, λ_{max}^{EtOH} 282 mμ, log ε 3.32.

10β-Fluoro-Δ¹,⁶-bisdehydro-19-nortestosterone (XVa).—Δ¹-Dehydro-estradiol (XIV, 910 mg.) in dimethylformamide (45 cc.) was treated with perchloryl fluoride, worked up and chromatographed as in previous experiments. Elution with benzene and crystallization from acetone–hexane yielded 220 mg. of **10β-fluoro-Δ¹,⁶-bisdehydro-19-nortestosterone (XVa)**, m.p. 165–168°. The analytical sample had m.p. 167–168°, $[\alpha]_D$ +60°; λ_{max} 229, 282 and 318 mμ; log ε 4.36, 3.45 and 3.80; λ_{max}^{KBr} 6.01, 6.11, 6.21(strong), 6.28(sh).

Anal. Calcd. for $C_{18}H_{21}O_2F$: C, 74.97; H, 7.34; F, 6.59 Found: C, 74.75; H, 7.50; F, 5.80.

Acetylation of this compound with pyridine–acetic anhydride at room temperature overnight yielded the 17-acetate XVb, m.p. 127–128° (from methanol), $[\alpha]_D$ +10°; λ_{max}^{KBr} 5.8, 6.01, 6.11, 6.21(strong), 6.29(sh.).

Anal. Calcd. for $C_{20}H_{23}O_2F$: C, 72.70; H, 7.01; F, 5.75. Found: C, 72.73; H, 7.08; F, 6.44.

10β-Fluoro-5β,19-norandrostane-3,17-dione (Vc).—10β-Fluoro-19-norandrosta-1,4-diene-3,17-dione (IIg, 2 g.) in ethanol (80 cc.) was hydrogenated over 10% Pa/$BaSO_4$ (1 g.) until no further hydrogen was absorbed. After filtering from catalyst, the solution was evaporated to dryness. The residue was warmed with benzene cooled and filtered from estrone (0.9 g.), m.p. 260°, and the solution chromatographed on alumina. Elution with benzene and crystallization from acetone–hexane gave **10β-fluoro-5β,19-norandrostane-3,17-dione (Vc**, 150 mg.), m.p. 164–167°. The analytical sample had m.p. 167–169°, $[\alpha]_D$ +98°.

Anal. Calcd. for $C_{18}H_{25}O_2F$: C, 73..94; H, 8.62. Found: C, 73.84; H, 8.36.

10β-Fluoro-17β-hydroxy-5β,19-norandrostane-3-one (Va)—10β-Fluoro-Δ¹-dehydro-19-nortestosterone (500 mg.) in pyridine (15 cc.) was hydrogenated over palladium/$BaSO_4$ (10%, 250 mg.) until no further hydrogen was absorbed. After filtering from catalyst and working up in the usual way the product was chromatographed on 15 g. of alumina. Elution with benzene and crystallization from acetone–hexane gave 130 mg. of **10β-fluoro-17β-hydroxy-5β,19-norandrostane-3-one (Va)**, m.p. 167–172°. Recrystallization afforded an analytical sample, m.p. 181–182.5°, $[\alpha]_D$ +8°, no strong absorption in the ultraviolet, λ_{max}^{KBr} 2.8 and 5.86 μ.

Anal. Calcd. for $C_{18}H_{27}O_2F$: C, 73.44; H, 9.24; F, 6.45. Found: C, 73.78; H, 9.16; F, 61.7.

Further elution of the column with benzene–ether 9:1 gave estradiol, m.p. and mixed m.p. 171–172°. When the hydrogenation was conducted in dioxane or in ethanol a similar yield (145 mg. from 500 mg.) of the saturated compound, m.p. 168–173°, was obtained.

10β-Fluoro-17α-methyl-17β-hydroxy-5β,19-norandrostane-3-one (Vb).—10β-Fluoro-17α-methyl-Δ¹-dehydro-19-nortestosterone (2.2 g.) in dioxane (65 cc.) was hydrogenated over Pa/$BaSO_4$ (1.1 g.) until no further hydrogen was absorbed. After filtering from catalyst and working up in the usual way the product was chromatographed on alumina (66 g.). Elution with benzene and crystallization from acetone–hexane yielded **10β-fluoro-17α-methyl-17β-hydroxy-5β,19-norandrostane-3-one (Vb)** (850 mg.), m.p. 157–159°. The analytical sample had m.p. 159–160°, $[\alpha]_D$ −12°, no strong absorption in the ultraviolet λ_{max}^{KBr} 5.86 μ; rotatory dispersion curve (*c* 0.071, dioxane); $[\alpha]_{700}$ −20°, $[\alpha]_{584}$ −28°, $[\alpha]_{310}$ −280°, $[\alpha]_{270}$ +99°.

Anal. Calcd. for $C_{19}H_{29}O_2F$: C, 73.82; H, 9.54; F, 6.20. Found: C, 73.98; H, 9.39; F, 6.39.

10β-Fluoro-Δ¹-dehydro-19-nortestolactone (XII).—Estrololactone (XI, 9 g.) was suspended in dimethylformamide (450 cc.) with magnetic stirring and treated with a slow stream of perchloryl fluoride at room temperature for 18 hours by which time all the material had dissolved. The solution was poured into ice-water and the product isolated with methylene chloride. Chromatography in benzene on neutral alumina (300 g.) and crystallization from acetone–hexane afforded 4.18 g. of the 10β-fluoro-dienone XI, m.p. 164–167°. The analytical sample had m.p. 169–171°, $[\alpha]_D$ −84°, λ_{max}^{EtOH} 237 mμ, log ε 4.1.

Anal. Calcd. for $C_{18}H_{21}O_3F$: C, 71.03; H, 6.96; D, 6.24. Found: C, 70.94; H, 6.77; F, 5.69.

10β-Fluoro-5β,19-norandrostalactone-3-one (XIII).—The preceding dienone (1 g.) in dioxane (30 cc.) was hydrogenated over 10% Pa/$BaSO_4$ (500 mg.) until no further hydrogen was absorbed. After filtering from catalyst the dioxane was removed *in vacuo* and the residue chromatographed on 30 g. of neutral alumina. Elution with benzene and crystallization from acetone–hexane afforded 450 mg. of the saturated ketone XIII, m.p. 187–191°. The analytical sample had m.p. 195–196°, $[\alpha]_D$ −39°; rotatory dispersion curve (*c* 0.071, dioxane): $[\alpha]_{700}$ −42°, $[\alpha]_{589}$ −53.5°, $[\alpha]_{315}$ −538°, $[\alpha]_{280}$ +13°.

Anal. Calcd. for $C_{18}H_{25}O_2F$: C, 70.1; H, 8.17; F, 6.16. Found: C, 70.32; H, 8.39; F, 6.05.

10β-Fluoro-2-methyl-Δ¹-dehydro-19-nortestosterone (IVa).—2-Methylestradiol (IIIb, 9 g.) in dimethylformamide (450 cc.) was treated with perchloryl fluoride for 20 hours. After working up in the usual way the product was chromatographed on 270 g. of alumina. Elution with benzene and crystallization from acetone–hexane gave **10β-fluoro-2-methyl-Δ¹-dehydro-19-nortestosterone** (IVa, 3.4 g.), m.p 169–173°. The analytical sample had m.p. 173–174°, $[\alpha]_D$ −51°, λ_{max}^{EtOH} 246 mμ, log ε 4.14.

Anal. Calcd. for $C_{19}H_{25}O_2F$: C, 74.96; H, 8.28; F, 6.24. Found: C, 74.44; H, 8.35; F, 5.79.

10β-Fluoro-2β-methyl-5β-19-norandrostane-3-one-17β-ol (Vd).—The preceding dienone (2.5 g.) in dioxane (80 cc.) was hydrogenated over 10% Pd/$BaSO_4$ until no further hydrogen was absorbed. After filtering from catalyst on 75 g. of alumina, elution with benzene and crystallization from acetone–hexane gave the saturated ketone (Vd, 1.2 g.) m.p. 194–197°. The analytical sample had m.p. 202–204°, $[\alpha]_D$ +0.5°.

Anal. Calcd. for $C_{19}H_{29}O_2F$: C, 73.99; H, 9.48; F, 6.16. Found: C, 74.22; H, 9.36; F, 5.71.

This m.p. compound (100 mg., m.p. 200–202°) was dissolved in methanolic potassium hydroxide solution (1%, 5 cc.) and allowed to stand for 72 hours at room temperature. The alkali was then neutralized with acetic acid and the solution evaporated to give a crystalline residue, which, after addition of water, was isolated by filtration (98 mg.). This proved to be starting material and had m.p. and mixed m.p. 196–198°, $[\alpha]_D$ 0°. The infrared spectrum was identical with that of the starting material.

2,17α-Dimethylestradiol (IIIc).—2-Methylestrone (IIIa, 22 g.) was dissolved in dry tetrahydrofuran (1.5 l.) and treated with a large excess of ethereal methylmagnesium bromide (4 *N*, 300 cc.), the ether was distilled off and the residue refluxed with good stirring for 3 days. Most of the tetrahydrofuran was then distilled off and the residue treated with ice-water and excess hydrochloric acid and extracted with methylene chloride. Crystallization of the product from acetone–hexane afforded 15.2 g. of **2,17α-dimethylestradiol** (no carbonyl band in the infrared), m.p. 202–204°. Recrystallization from acetone–hexane gave an analytical sample, m.p. 208–210°, $[\alpha]_D$ +53°, λ_{max}^{EtOH} 283 mμ, log ε 3.42.

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39; O, 10.65. Found: C, 79.89; H, 9.47; O, 10.50.

10β-Fluoro-2,17α-dimethyl-Δ¹-dehydro-19-nortestosterone (IVb).—2,17α-Dimethylestradiol (15 g.) in dimethylformamide (750 cc.) was treated with perchloryl fluoride for 18 hours. After working up in the usual way the product was chromatographed on 450 g. of alumina. Elution with benzene and crystallization from acetone–hexane gave the 10β-fluorodienone (IVb, 7.8 g.), m.p. 165–167°. Recrystallization gave a sample with m.p. 176–177°, $[\alpha]_D$ −64°, λ_{max} 246 mμ, log ε 4.17.

Anal. Calcd. for $C_{20}H_{27}O_2F$: C, 75.44; H, 8.55; F, 5.96. Found: C, 75.06; H, 8.56; F, 6.17.

10β-Fluoro-2β,17α-dimethyl-5β-19-norandrostane-3-one-17β-ol (Ve).—The preceding dienone (7.7 g.) in dioxane (230 cc.) was hydrogenated over 10% Pa/$BaSO_4$ (3.75 g.) until no further hydrogen was absorbed. After filtering from catalyst the solvent was removed *in vacuo* and the residue chromatographed on 270 g. of alumina. Elution with benzene and crystallization from methanol gave 3.2 g. of the saturated ketone Vb. m.p. 92–94°, apparently with solvent loss. The substance would not crystallize from other solvents. Recrystallization from methanol gave an analytical sample, m.p. 92–94° (97–99° after drying for 2 days at 60°), $[\alpha]_D$ −18°; rotatory dispersion curve (*c* 0.0763, dioxane); $[\alpha]_{700}$ +4°, $[\alpha]_{584}$ −10.5°, $[\alpha]_{315}$ −292.5°, $[\alpha]_{280}$ +38°.

Anal. Calcd. for $C_{20}H_{31}O_2F.{}^1/_2\ H_2O$ C, 72.47; H, 9.73. Found: C, 72.59; H, 9.93.

Further elution with 5% ether–benzene and crystallization from acetone–hexane gave 0.7 g. of 2,17α-dimethylestradiol, m.p. 199–201°.

Dienone–Phenol Rearrangement of 10β-Fluoro-Δ¹-dehydro-19-nortestosterone.—10β-Fluoro-Δ¹-dehydro-19-nortestosterone (400 mg.) in acetic anhydride (4 ml.) was treated with concentrated sulfuric acid (3 drops) and the solution allowed to stand at room temperature for 3 hours. Ice was then added and the crystalline product filtered. Crystallization from methylene chloride–methanol afforded the fluorophenol diacetate (XVIa) (360 mg.), m.p. 129–132°, $[\alpha]_D$ +149°, λ_{max}^{EtOH} 268 and 274 mμ, log ε 2.85.

Anal. Calcd. for $C_{22}H_{27}O_4F$: C, 70.56; H, 7.09. Found: C, 70.54; H, 7.16.

Saponification of this diacetate with 5% methanolic potassium hydroxide for 18 hours at room temperature afforded the free diol XVIb, m.p. 193–194° (from acetone), $[\alpha]_D$ +183°, λ_{max}^{EtOH} 284 mμ, log ε 3.45.

Anal. Calcd. for $C_{18}H_{23}O_2F$: C, 74.45; H, 7.98. Found: C, 74.29; H, 8.31.

Methylation of the free diol with dimethyl sulfate and potassium hydroxide in the usual way afforded the **methyl ether XVIc**, m.p. 119–120° (from aqueous acetone), $[\alpha]_D$ +202°, λ_{max}^{EtOH} 281 mμ, log ε 3.42.

Anal. Calcd. for $C_{19}H_{25}O_2F$: C, 74.97; H, 8.27; F, 6.24. Found: C, 74.95; H, 7.98; F, 6.34.

[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE, THE WEIZMANN INSTITUTE OF SCIENCE, REHOVOTH, ISRAEL]

The Synthesis of the Steroidal Sapogenins[1,2]

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Isoandrosterone (V) is converted by an eighteen-stage process to a mixture of tigogenin (LXIII) and neotigogenin (LXIV). Each of these steroidal sapogenins is obtained in the pure state and is identified with an authentic sample. The synthesis leads to other steroidal sapogenins (smilagenin, gitogenin, diosgenin, chlorogenin, hecogenin) as well as to certain steroidal alkaloids (tomatidine, solasodine).

The steroidal sapogenins are an important group of substances occurring in nature in the form of their glycosides (the steroidal saponins), from which they can be obtained by acid treatment.[5a] Although the chemistry of these compounds has been investigated extensively since the end of the last century, it was only in 1939 that the correct structure of a typical member was proposed.[6] More

(1) For preliminary communications, see N. Danieli, Y. Mazur and F. Sondheimer, *Chemistry & Industry*, 1724, 1725 (1958); Y. Mazur and F. Sondheimer, THIS JOURNAL, 81, 3161 (1959).

(2) Presented in part before the Organic Chemistry Division at the 136th Meeting of the American Chemical Society, Atlantic City, N. J., September, 1959 (Asbtracts of Papers, p. 85-P).

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(4) Part of the material described in this paper has been taken from a Ph.D. thesis presented by Naftali Danieli to the Hebrew University, Jerusalem, June, 1958.

(5) For a review, see L. F. Fieser and M. Fieser, "Steroids," 3rd Edition, Reinhold Publishing Corp., New York, N. Y., 1959; (a) chapter 21; (b) chapter 10; (c) pp. 343–344; (d) pp. 533–538.

(6) R. E. Marker and E. Rohrmann, THIS JOURNAL, 61, 846 (1939).