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Synthesis of 5α,6,6-Trifluoro-3-keto and 6,6-Difluoro-Δ⁴-3-keto Steroids

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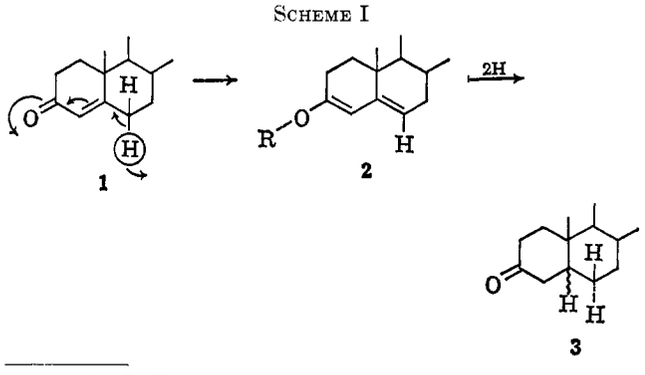
Reaction of 5α-fluoro-6-keto steroids with sulfur tetrafluoride containing hydrogen fluoride at room temperature afforded the corresponding 5α,6,6-trifluoro derivatives in moderate to good yields. The latter system was found to be a convenient precursor to 6,6-difluoro steroid hormone analogs. Some fluorine and proton nmr data are given.

Modification of steroid hormones at the C-6 position by the introduction, for example, of a 6α-methyl group[1] or 6α-halogen atom[1] has resulted, in some instances, in remarkable enhancement as well as favorable separation of biological activities.

The enhanced biological activity of the 6α-methyl- and 6α-halogen-substituted progestational agents has been explained as possibly being the result of increased resistance of the C-6-substituted analogs toward metabolic inactivation by either hydroxylation[2] at C-6 or reduction[3] of the biologically necessary α,β-unsaturated ketone system. Ringold[3] has suggested that enzymatic reduction of a Δ⁴-3-keto steroid (**1**) may proceed *via* the enol form **2** which is formed by preferential abstraction of a 6α-hydrogen (Scheme I). Thus, the introduction of a 6α substituent would block or at least delay enol formation and reduction.[4] Regardless of which pathway may predominate in the metabolic inactivation of Δ⁴-3-keto steroid hormones, C-6 appears to be vitally involved and the presence of a C-6 hydrogen leaves this site vulnerable to attack. Since replacement of one of the C-6 hydrogen atoms by a methyl group or a halogen atom has provided analogs of greatly enhanced biological activity, it was of interest to ascertain the effect on biological activity of replacing both C-6 hydrogen atoms of a model Δ⁴-3-keto steroid hormone by an appropriate grouping so as to preclude both formation of enol **2** and oxidation at C-6.

SCHEME I



The selection of a *gem*-difluoro modification at C-6 as a blocking group and 17α-acetoxyprogesterone as a model Δ⁴-3-keto steroid hormone appeared to be suitable for the following reasons. First, 6β- and 6α-fluoro-17α-acetoxyprogesterone are both active progestational agents.[5] Secondly, since the fluorine atom is not much larger than the hydrogen atom,[6] a C-6 *gem*-difluoro group should not cause undue distortion of ring B or otherwise decrease biological activity owing to steric reasons. Finally, methods have been developed for the introduction of *gem*-difluoro groups into the steroid nucleus under mild conditions using sulfur tetrafluoride.[7] Accordingly, the preparation of 6,6-difluoro-17α-acetoxyprogesterone (**14a**, Chart I) was undertaken.

The preparation of 6,6-difluoro-Δ⁴-3-keto steroids was built around two reactions. First, the discovery

(1) *Cf.* L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp 564, 565, 685, 686.

(2) A. David, F. Hartley, D. R. Millson, and V. Petrow, *J. Pharm. Pharmacol.*, **9**, 929 (1957).

(3) H. J. Ringold, "Mechanism of Action of Steroid Hormones," C. A. Villee and L. I. Engel, Ed., Pergamon Press Inc., New York, N. Y., 1961, pp 222–225.

(4) After this work had been well underway, Ringold reported that, while 6β- and 6α-methyl-Δ⁴-3-keto steroid hormones underwent enzymatic reduction only slowly compared with the unsubstituted parent compounds, 6β- and 6α-fluoro Δ⁴-3-ketones were reduced considerably faster than the unsubstituted parent and followed an abnormal reduction pathway. Furthermore, it was not possible to establish a general relationship between the rate of enzymatic reduction *in vitro* and the biological activity of this series of modified steroid hormones. *Cf.* H. J. Ringold, "Hormonal Steroids: Biochemistry, Pharmacology and Therapeutics," Vol. 1, L. Martini and E. Pecile, Ed., Academic Press Inc., New York, N. Y., 1964, pp 305–316.

(5) See ref 3, p 223.

(6) The van der Waals radii of hydrogen and fluorine are 1.2 and 1.4 A, respectively. *Cf.* E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., Inc., New York, N. Y., 1959, pp 50–53.

(7) (a) D. G. Martin and F. Kagan, *J. Org. Chem.*, **27**, 3164 (1962); (b) J. Tadanier and W. Cole, *ibid.*, **26**, 2436 (1961).

CHART I

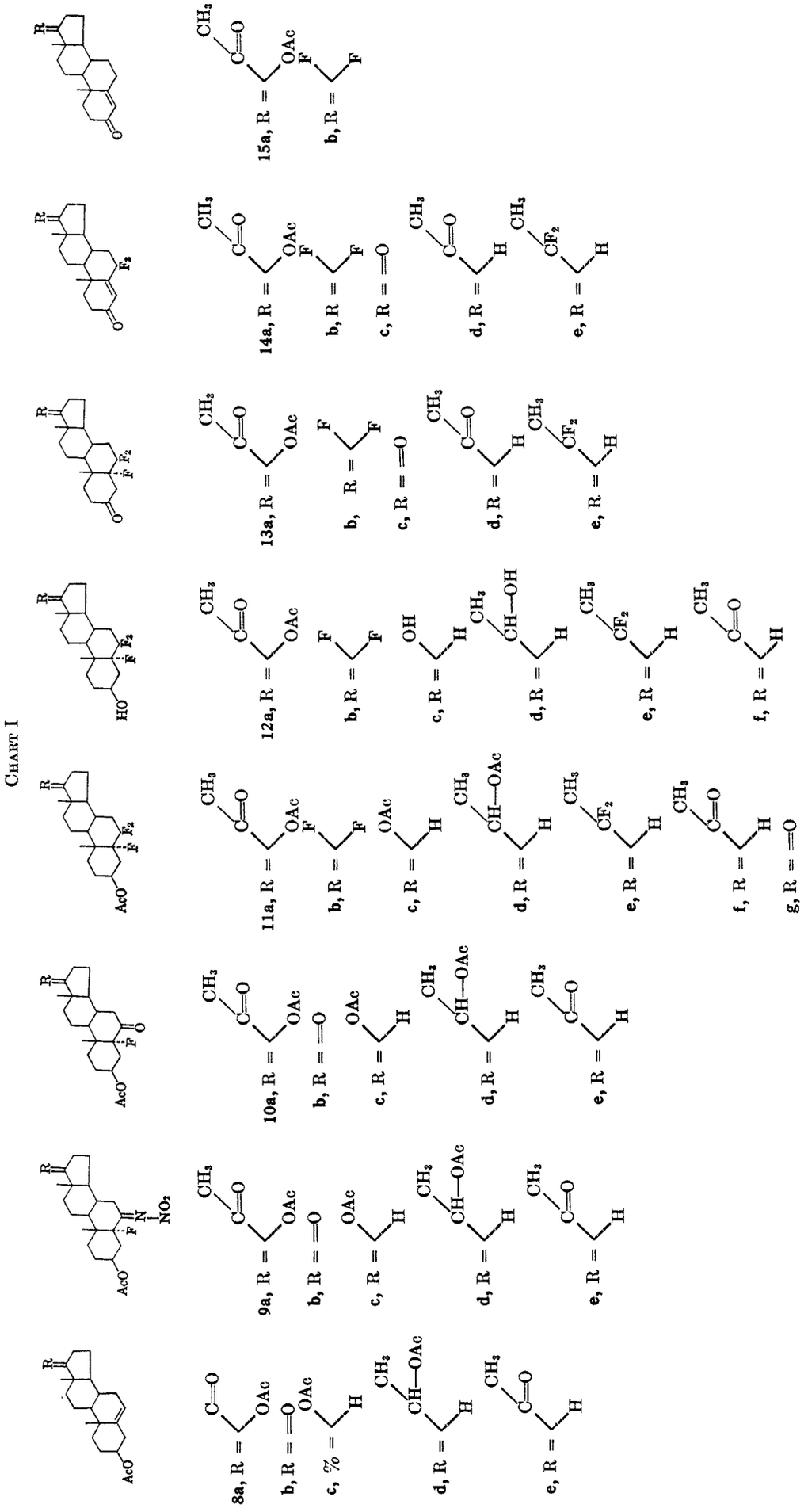

8a, R = C=O, OAc
b, R = =O, OAc
c, % = OAc, H
d, R = CH—OAc, H
e, R = C=O, H
9a, R = C=O, OAc
b, R = =O
c, R = OAc, H
d, R = CH—OAc, H
e, R = C=O, H
10a, R = C=O, OAc
b, R = =O
c, R = OAc, H
d, R = CH—OAc, H
e, R = C=O, H
11a, R = C=O, OAc, F, F
b, R = F, F
c, R = OAc, H
d, R = CH—OAc, H
e, R = CF2, H
f, R = C=O, H
g, R = =O
12a, R = C=O, OAc
b, R = F, F
c, R = OH, H
d, R = CH—OH, H
e, R = CF2, H
f, R = C=O, H
13a, R = C=O, OAc
b, R = F, F
c, R = =O
d, R = CH3, H
e, R = CF2, H
14a, R = C=O, OAc, F, F
b, R = F, F
c, R = =O
d, R = CH3, H
e, R = CF2, H
15a, R = C=O, OAc, F, F
b, R = F, F

TABLE I

CHARACTERIZATION DATA ON 5α,6,6-TRIFLUORO AND 5α,6,6,17,17- AND 5α,6,6,20,20-PENTAFLUORO 3-ACETATES

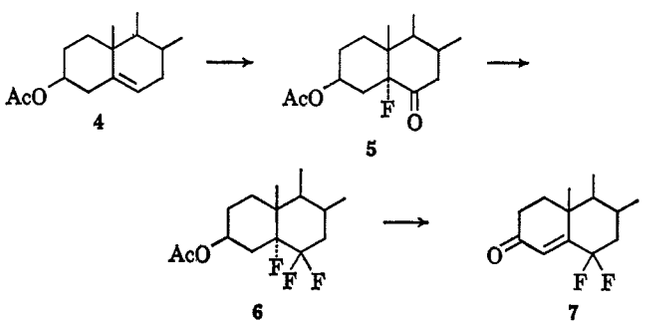
Starting material	Product[a]	Yield,[b] %	Mp, °C[c]	[α]D, deg[d]	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Fluorine, % Calcd	Fluorine, % Found
5α-Fluoropregnane-3β,-17α-diol-6,20-dione diacetate (10a)	5α,6,6-Trifluoropregnane-3β,17α-diol-20-one diacetate (11a)	61[e,f]	249–250 (E)	−13	$C_{25}H_{35}F_3O_5$	63.54	63.51	7.47	7.43	12.06	12.00
5α-Fluoroandrostan-3β-ol-6,17-dione acetate (10b)	5α,6,6,17,17-Pentafluoroandrostan-3β-ol acetate (11b)	52[g]	137–137.5 (F)	−12	$C_{21}H_{28}F_5O_2$	61.90	61.82	7.04	7.28	23.31	23.18
	5α,6,6-Trifluoroandrostan-3β-ol-17-one acetate (11g)	6[g]	188–187 (A–B)	+47	$C_{21}H_{29}F_3O_3$	65.26	65.48	7.56	7.61	14.75	14.38
5α-Fluoroandrostane-3β,-17β-diol-6-one diacetate (10c)	5α,6,6-Trifluoroandrostane-3β,17β-diol diacetate (11c)	82[e,f]	161–162 (B)	−10	$C_{23}H_{33}F_3O_4$	64.16	64.17	7.73	7.74	13.24	13.11
5α-Fluoropregnane-3β,-20β-diol-6-one diacetate (10d)	5α,6,6-Trifluoropregnane-3β,20β-diol diacetate (11d)	68[e,h]	157–160 (B)	+10 (dioxane)	$C_{25}H_{37}F_3O_4$	65.48	65.38	8.13	8.04	12.43	12.20
5α-Fluoropregnan-3β-ol 6,20-dione acetate (10e)	5α,6,6,20,20-Pentafluoropregnan-3β-ol acetate (11e)	29[i]	130–132 (B–F)	±0	$C_{23}H_{33}F_5O_2$	63.29	63.03	7.62	7.45	21.76	20.72
	5α,6,6-Trifluoropregnan-3β-ol-20-one acetate (11f)	58[f,i]	114–115 (B–F)	+54	$C_{23}H_{33}F_3O_3$	66.64	66.44	8.02	8.03	13.75	13.72

[a] The infrared spectra exhibited a number of medium intensity absorptions in the 8.5–9.0-μ region. [b] Yield of recrystallized product. [c] Analytical melting point. Recrystallization solvents: A, acetone; B, hexane; C, methylene chloride; D, ethanol; E, methanol; and F, petroleum ether (bp 37–56°). [d] Unless otherwise noted, rotations were measured at 24° in chloroform at a concentration of 1.5–2.5%. [e] Chromatography was not required. The crude product was recrystallized to afford the stated yield. [f] Sulfur tetrafluoride containing approximately 11 mole % of hydrogen fluoride and a 10-hr reaction period at 20 ± 2° were employed. [g] The total crude product was chromatographed on Florisil and recrystallized to afford the stated yields. Sulfur tetrafluoride containing approximately 47 mole % of hydrogen fluoride and a 20-hr reaction period at 20 ± 2° were employed. Florisil is a synthetic magnesia–silica gel made by the Floridin Co., Warren, Pa. [h] Sulfur tetrafluoride containing approximately 7 mole % of hydrogen fluoride and a 10-hr reaction period at 20 ± 2° were employed. [i] Sulfur tetrafluoride containing approximately 24 mole % of hydrogen fluoride and a 16-hr reaction period at 20 ± 2° were employed. The total crude reaction product was chromatographed on neutral alumina (activity III). Elution with petroleum ether and recrystallization in the solid fractions afforded **11e** in the stated yield. Elution with benzene–petroleum ether (1:1) and benzene afforded crystalline material which was recrystallized to give **11f** in 49% yield. [j] The crude product was chromatographed on neutral alumina (activity III) and recrystallized to afford the stated yield.

that reaction of nitrosyl fluoride with steroid 5-enes **4** affords the corresponding 5α-fluoro-6-nitrimines which are readily converted to 5α-fluoro 6-ketones[8] **5** by chromatography on neutral alumina containing 6% water (activity III) provided, in essentially one step and in an acceptable yield, a suitable intermediate for reaction with sulfur tetrafluoride. Secondly, the finding that sulfur tetrafluoride reacts preferentially with the 6-keto group of 5α-fluoro 6-ketones **5** in the presence of additional carbonyl groups at C-17 or C-20 to afford the corresponding 5α,6,6-trifluoro 3β-acetates **6** in good yield reduced the synthesis of 6,6-difluoro Δ^4-3-ketones **7** from readily available steroid 5-enes to a relatively straightforward task. By employing longer reaction times and larger amounts of hydrogen fluoride in the sulfur tetrafluoride reaction, additional carbonyl groups at C-17 or C-20 could be converted to the corresponding *gem*-difluoro groups (see Table I). The 5α,6,6-trifluoro 3β-acetates **6** were readily converted to the desired 6,6-difluoro Δ^4-3-ketones **7** by means of standard steroid transformations (Scheme II).

Preparation of 6,6-difluoro-17α-acetoxyprogesterone (**14a**) was achieved in six steps in an over-all yield of 25% from the commercially available 17α-acetoxypregnenolone acetate (**8a**). Treatment of **8a** with nitrosyl fluoride followed by hydrolysis of the total crude fluoronitrimine **9a** by chromatography on neutral alumina (activity III) afforded the corresponding fluoro ketone **10a** in 76% yield.[9] Fluorination of fluoro ketone **10a** with sulfur tetrafluoride[7a] at 20°

SCHEME II



for 10 hr gave selective reaction with the 6-carbonyl group to afford 5α,6,6-trifluoropregnane-3β,17α-diol-20-one diacetate (**11a**) in 61% yield.[9]

Selective hydrolysis of the 3-acetate **11a** in methanol containing hydrochloric acid on a steam bath then led to the trifluoro-3β-ol **12a** which, in turn, was oxidized to the dione **13a** with 8 *N* chromic acid[10] in acetone solution. Dehydrofluorination of trifluorodione **13a** was conveniently accomplished by passing it as a benzene solution through a column of neutral alumina. Recrystallization of the crude, crystalline product afforded pure 6,6-difluoro-17α-acetoxyprogesterone (**14a**). The elemental analyses and infrared, ultraviolet, and proton nmr spectra, the latter showing C-4 proton resonance as a doublet[11] centered at δ 6.10 with J = 3 cps and the C-19 methyl resonance as a doublet[12] centered at δ 1.30 with $J_{6\beta\text{-F},19\text{-H}}$ = 2.2 cps,

(8) (a) G. A. Boswell, Jr., *Chem. Ind.* (London), 1929 (1965). (b) For a review of the literature on nitrosyl fluoride, *cf.* S. Andreades, *J. Org. Chem.*, **27**, 4157, 4163 (1962).

(9) Pure recrystallized product.

(10) (a) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); (b) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *ibid.*, 2548 (1953).

(11) T. A. Wittstruck, S. K. Malhotra, H. T. Ringold, and A. D. Cross, *J. Am. Chem. Soc.*, **85**, 3038 (1963).

(12) *Cf.* A. D. Cross and P. H. Landis, *ibid.*, **86**, 4005 (1964), and references therein.

TABLE II

CHARACTERIZATION DATA ON 6,6-DIFLUORO- AND 6,6,17,17- AND 6,6,20,20-TETRAFLUORO-Δ^4-3-ONES

Starting material	Product	Yield,[a] %	Mp, °C[b]	$[\alpha]_D$, deg[c]	λ_{max}, μ[d]	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Fluorine, % Calcd	Fluorine, % Found
5α,6,6-Trifluoropregnan-17α-ol-3,20,-dione 17-acetate (**13a**)	6,6-Difluoro-4-pregnen-17α-ol-3,20-dione acetate (**14a**)	90	219–219.5 (E)	−26 (dioxane)	5.77 5.84 5.92 5.97 (sh) 7.90 8.60	$C_{23}H_{30}F_2O_4$	67.63	67.52	7.40	7.40	9.30	9.28
5α,6,6,17,17-Pentafluoroandrostan-3-one (**13b**)	6,6,17,17-Tetrafluoro-4-androsten-3-one (**14b**)	79	109–110 (B–F)	−12	5.94 8.63 8.83	$C_{19}H_{24}F_4O$	66.26	66.27	7.02	7.06	22.07	22.05
5α,6,6-Trifluoroandrostane-3,17-dione (**13c**)	6,6-Difluoro-4-androstene-3,17-dione (**14c**)	83	200–202 (A–B)	+69	5.75 5.90 8.65	$C_{19}H_{24}F_2O_2$	70.78	70.84	7.50	7.54	11.79	11.70
5α,6,6-Trifluoropregnane-3,20-dione (**13d**)	6,6-Difluoro-4-pregnene-3,20-dione (**14d**)	80	147–148[e] (B–D) 135–135.5[e] (B–C)	+48 (dioxane)	5.85 (sh) 5.95 8.62	$C_{21}H_{28}F_2O_2$	71.97	71.82	8.05	7.86	10.84	10.66
5α,6,6,20,20-Pentafluoropregnan-3-one (**13e**)	6,6,20,20-Tetrafluoro-4-pregnen-3-one (**14e**)	78	97.5–99 (B–F)	±0	5.92 8.58	$C_{21}H_{28}F_4O$	67.72	67.92	7.58	7.10	20.41	20.00

[a] Yield of chromatographed and recrystallized product. [b] Analytical melting point. Recrystallization solvents: A, acetone; B, hexane; C, methylene chloride; D, ethanol; E, methanol; and F, petroleum ether (bp 37–56°). [c] Unless otherwise noted, rotations were measured at 24° in chloroform solution at a concentration of 0.5–2.5%. These have λ_{max}^{EtOH} 227–228 mμ (ϵ 12,000–13,200). [d] The infrared spectra were determined in micro KBr wafers. The positions of carbonyl, acetate, and fluorine peaks are listed. Only in the case of **14a** was the conjugated double-bond band noted and this appeared as a shoulder (sh). [e] The compound was dimorphic; rapid crystallization gave the lower melting form (needles) while slow crystallization afforded the higher melting form (prisms). The choice of crystallization solvent appeared to play a role in determining the crystalline form.

TABLE III

CHARACTERIZATION DATA ON 5α,6,6-TRIFLUORO- AND 5α,6,6,17,17- AND 5α,6,6,20,20-PENTAFLUORO-3-OLS

Starting material	Product	Yield, %[a]	Mp, °C[b]	$[\alpha]_D$, deg[c]	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Fluorine, % Calcd	Fluorine, % Found
5α,6,6-Trifluoropregnane-3β,17α-diol-20-one diacetate (**11a**)	5α,6,6-Trifluoropregnane-3β,17α-diol-20-one 17-acetate (**12a**)	69	225–225.5 (E)	−26 (dioxane)	$C_{25}H_{33}F_3O_4$	64.17	64.20	7.73	7.59	13.25	12.75
5α,6,6,17,17-Pentafluoroandrostan-3β-ol acetate (**11b**)	5α,6,6,17,17-Pentafluoroandrostan-3β-ol (**12b**)	94	145–145.5 (B)	−21	$C_{19}H_{27}F_5O$	62.28	62.07	7.43	7.66	25.9	25.99
6α,6,6-Trifluoroandrostane-3β,17β-diol diacetate (**11c**)	5α,6,6-Trifluoroandrostane-3β,17β-diol (**12c**)	95	155–156 (A–B)	−14 (dioxane)	$C_{19}H_{29}F_3O_2$	65.87	65.53	8.44	8.87	16.45	16.01
5α,6,6-Trifluoropregnane-3β,20β-diol diacetate (**11d**)	5α,6,6-Trifluoropregnane-3β,20β-diol (**12d**)	96	201–202 (B)	−20 (dioxane)	$C_{21}H_{33}F_3O_2$	67.35	67.09	8.88	8.71	15.22	14.82
5α,6,6,20,20-Pentafluoropregnan-3β-ol acetate (**11e**)	5α,6,6,20,20-Pentafluoropregnan-3β-ol (**12e**)	86	132–133 (B)	±0	$C_{21}H_{31}F_5O$	63.94	63.60	7.92	8.13	24.08	23.27
5α,6,6-Trifluoropregnan-3β-ol-20-one acetate (**11f**)	5α,6,6-Trifluoropregnan-3β-ol-20-one (**12f**)	92	165–168 (A–B)	+54	$C_{21}H_{31}F_3O_2$	67.72	67.65	8.39	8.39	15.31	15.28

[a] Yield of recrystallized product. [b] Analytical melting point. Recrystallization solvents: A, acetone; B, hexane; C, methylene chloride; D, ethanol; E, methanol; and F, petroleum ether (bp 37–56°). [c] Unless otherwise mentioned, rotations were measured at 24° in chloroform solution at a concentration of 1.5–2.5%.

were consistent with structure **14a**. The 6,6-difluoro Δ^4-3-ketone **14a** was further characterized by reductive removal of the fluorine atoms with zinc to give 17α-acetoxyprogesterone (**15a**).[13]

Ringold and Bowers[14] have investigated the influence of C-6 substituents on the principal ultraviolet maximum of Δ^4-3-keto steroids and found that the hypsochromic effect of a 6β-fluorine is −5 to −8 mμ and that of a 6α-fluorine is −4 to −5 mμ. The 6,6-difluoro-Δ^4-3-keto steroids reported here (see Table II) all have λ_{max}^{EtOH} 228–229 mμ, which represents a hypsochromic effect of −12 to −14 mμ. Thus, it appears that the hypsochromic effect of the individual 6α- and 6β-fluorines are additive. The infrared spectra of the 6,6-difluoro-3-keto steroids, with the exception of **14a** which shows a partially resolved band at 5.95 μ, fail to show the conjugated double-bond absorption which apparently falls under the carbonyl peak. The infrared absorptions of the C-6 fluorines appear as overlapping bands at 8.55–8.65 μ.

Additional examples of 5α,6,6-trifluoro- and 6,6-difluoro-4-ene 3-ketones were prepared using the same general procedure from the appropriate starting materials (see Tables I–IV). Reductive removal of the C-6 *gem*-difluoro group of **14b** gave 17,17-difluoro-4-androsten-3-one (**15b**).[7]

Reduction of 6,6-difluoro-4-androstene-3,17-dione (**14c**) with sodium borohydride followed by oxidation of the allylic hydroxyl group using 2,3-dichloro-5,6-dicyanobenzoquinone[15] in dioxane at room temperature led to 6,6-difluorotestosterone (**17a**).

The 17-ethynyl derivative of **17a** was prepared using a procedure patterned after that described by Ringold,

(13) R. B. Turner, *J. Am. Chem. Soc.*, **75**, 3489 (1953).
(14) H. J. Ringold and A. Bowers, *Experientia*, **17**, 65 (1961).
(15) D. Burn, V. Petrow, and G. O. Weston, *Tetrahedron Letters*, **No. 9**, 14 (1960).

TABLE IV

CHARACTERIZATION DATA ON 5α,6,6-TRIFLUORO- AND 5α,6,6,17,17- AND 5α,6,6,20,20-PENTAFLUORO-3-ONES

Starting material	Product	Yield, %[a]	Mp, °C[b]	[α]D, deg[c]	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Fluorine, % Calcd	Fluorine, % Found
5α,6,6-Trifluoropregnane-3β,17α-diol-20-one 17-acetate (**12a**)	5α,6,6-Trifluoropregnan-17α-ol-3,20-dione 17-acetate (**13a**)	87	220–227[d] (A–E)	−7	$C_{23}H_{31}F_3O_4$	64.47	64.55	7.29	7.31	13.30	12.95
5α,6,6,17,17-Pentafluoroandrostan-3β-ol (**12b**)	5α,6,6,17,17-Pentafluoroandrostan-3-one (**13b**)	88	155–160[d] (A–B)	−6	$C_{19}H_{23}F_5O$	62.62	62.95	6.92	6.91	26.07	26.01
5α,6,6-Trifluoroandrostane-3β,17β-diol (**12c**)	5α,6,6-Trifluoroandrostane-3,17-dione (**13c**)	91	213–215 (A–B)	+66	$C_{19}H_{25}F_3O_2$	66.65	66.76	7.36	7.38	16.65	16.50
5α,6,6-Trifluoropregnane-3β,20β-diol (**12d**)	5α,6,6-Trifluoropregnane-3,20-dione (**13d**)	83	200–207[d] (A)	+61 (dioxane)	$C_{21}H_{29}F_3O_2$	68.08	68.13	7.86	7.90	15.39	15.09
5α,6,6,20,20-Pentafluoropregnan-3β-ol (**12e**)	5α,6,6,20,20-Pentafluoropregnan-3-one (**13e**)	97	138–141[d] (B–F)	±0	$C_{21}H_{29}F_5O$	64.27	64.42	7.45	7.72	24.21	23.22

[a] Chromatography was not required. The reaction product was crystallized to afford the stated yield. [b] Analytical melting point. Recrystallization solvents: A, acetone; B, hexane; C, methylene chloride; D, ethanol; E, methanol; and F, petroleum ether (bp 37–56°). [c] Unless otherwise noted, rotations were measured at 24° in chloroform solution at a concentration of 1.5–2.5%. [d] Sharp melting points could not be obtained for these compounds. Repeated recrystallization and drying *in vacuo* did not raise or sharpen the melting points.

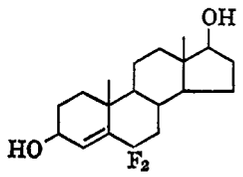
TABLE V

CHARACTERIZATION DATA ON 6,6-DIFLUORO- AND 6,6,17,17-TETRAFLUORO-$\Delta^{1,4}$-3-ONES

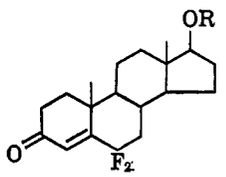
Starting material	Product	Yield, %	Mp, °C[a]	[α]D, deg[b]	λ_{max}, μ[c]	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Fluorine, % Calcd	Fluorine, % Found
6,6,17,17-Tetrafluoro-4-androsten-3-one (**14b**)	6,6,17,17-Tetrafluoro-1,4-androstadien-3-one (**23b**)	64[d]	102–103 (B–F)	−57	6.00 6.10 8.60	$C_{19}H_{22}F_4O$	66.65	66.82	6.48	6.82	22.20	21.70
6,6-Difluoro-4-androstene-3,17-dione (**14c**)	6,6-Difluoro-1,4-androstadiene-3,17-dione (**23c**)	72[e]	183–184 (E)	−48	5.96 6.07 8.58	$C_{19}H_{22}F_2O_2$	71.23	71.26	6.92	6.93	11.86	11.53
6,6-Difluoro-4-androsten-17β-ol-3-one acetate (**17b**)	6,6-Difluoro-1,4-androstadien-17β-ol-3-one acetate (**23a**)	43[d]	162–163 (B–C)	−29	5.97 6.09 8.53	$C_{21}H_{26}F_2O_3$	69.20	69.04	7.19	7.42	10.43	10.32
6,6-Difluoro-17α-ethynyl-4-androsten-17β-ol-3-one acetate (**21b**)	6,6-Difluoro-17α-ethynyl-1,4-androstadien-17β-ol-3-one acetate (**22d**)	40[d]	142–143 (B–D)	−74	5.98 6.10 8.56	$C_{23}H_{26}F_2O_3$	71.11	71.18	6.75	6.81	9.78	9.78

[a] Analytical melting point. Recrystallization solvents: A, acetone; B, hexane; C, methylene chloride; D, benzene; E, methanol; and F, petroleum ether (bp 37–56°). [b] The rotations were measured at 24° in chloroform solution at concentration of 0.5–2.5%. The compounds show λ_{max}^{EtOH} 238–240 mμ (ε 12,700–15,800). The infrared spectra were determined on micro KBr wafers. [c] The positions of carbonyl, double-bond, and fluorine peaks are listed. [d] The total crude product was chromatographed on neutral alumina (activity III) and recrystallized to afford the product in the stated yield. [e] Chromatography was not required. The total crude product was recrystallized to afford the stated yield.

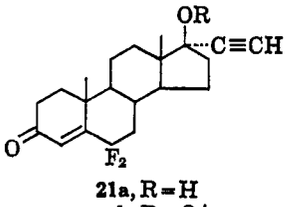
Rosencranz, and Sondheimer[16] for the preparation of 17α-ethynyl-19-nortestosterone from 19-nortestosterone.



16

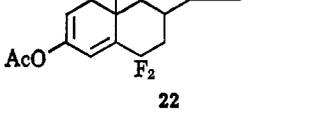


17a, R = H
b, R = OAc



21a, R = H
b, R = OAc

Acetylation of 6,6-difluoro-17α-ethynyl-4-androsten-17β-ol-3-one (**21a**) with acetic anhydride and pyridine gave, in addition to the expected 17-acetate **21b**, a less polar material which on the basis of elemental analyses and infrared and ultraviolet spectra appears to be the enol acetate **22**. Insufficient material prevented complete characterization.



22

Dehydrogenation of the 6,6-difluoro Δ^4-3-ketone with 2,3-dichloro-5,6-dicyanobenzoquinone[17] in refluxing toluene with *p*-toluenesulfonic acid as catalyst afforded the corresponding 6,6-difluoro $\Delta^{1,4}$-3-ketones **23a–d** (see Table V).

The C-6 *gem*-difluoro group of 6,6-difluoro Δ^4-3-ketones is remarkably resistant to dehydrofluorination or hydrolysis. 6,6,17,17-Tetrafluoro-4-androsten-3-one (**14b**) was recovered unchanged after being heated to reflux in collidine solution for 90 min or after treatment with anhydrous lithium chloride in dimethylformamide solution[18] at 130° for 24 hr. Furthermore, 6,6-difluoro-4-en-3-one **14b** was recovered unchanged after treatment with aqueous sulfuric acid in dioxane on a steam bath for 2 hr.

Fluorine and Proton Nmr Spectra.—Although considerable attention has been given to the proton nmr

(16) H. J. Ringold, G. Rosencranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **78**, 2477 (1956).

(17) D. Burn, D. N. Kirk, and V. Petrow, *Proc. Chem. Soc.*, 14 (1960).

(18) R. P. Holysz, *J. Am. Chem. Soc.*, **75**, 4432 (1953).

TABLE VI

F^{19} NMR SPECTRA[a]

Position	Chemical shifts, cps							
	10b	11g	11b	12b	13b	14c	14b	23b
5α	+8984 (doublet, J = 50)	+9493[b] (doublet, J = 44)	+9492[b] (doublet, J = 40)	+9468[b] (doublet, J = 40)	+9254[b] (doublet, J = 45)			
6,6		+6037[c]	+6038[c]	+6041[c]	+6038[c]	+4741, +4993, +5631, +5884 } AB quartet[d]	+4759, +5013, +5643, +5896 } AB quartet[d]	+5067, +5316, +5704, +5952 } AB quartet[e]
17,17			5657, 5878, 6403, 6623 } AB quartet[f]	5657, 5876, 6403, 6622 } AB quartet[f]	5660, 5879, 6404, 5623 } AB quartet[g]		+5668, +5886, +6406, +6626 } AB quartet[f]	+5668, +5889, +6405, +6625 } AB quartet[h]

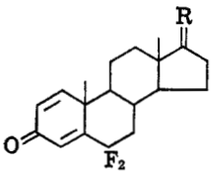
[a] Fluorine nmr spectra were obtained on a Varian HR-60 spectrometer operating at 56.4 Mc/sec in deuteriochloroform solution and were calibrated against internal trichlorofluoromethane. The spectra were calibrated in cycles per second above trichlorófluoromethane (trichlorofluoromethane = 0.0 cps). J values are given in cycles per second. The author is grateful to Dr. H. Foster for the determination and interpretation of these spectra. [b] Evidence for further splitting, but resolution was not possible. [c] This peak is probably a triplet, but it is broad and the centers are poorly defined (J = *ca.* 12–15 cps). [d] An AB quartet with the low-field peaks being split into doublets, J = 33 cps. There is evidence for further splitting of the doublets, but further resolution was not possible. [e] An AB quartet with the low-field peaks being split into doublets, J = 33 cps, and the high-field peaks being unsplit. [f] An AB quartet with the low-field pair being split into riplets, J = 24 cps, and the high-field pair being unsplit. [g] Same as footnote *f* with J = 21 cps. [h] Same as footnote *f* with J = 25 cps.

TABLE VII

H NMR SPECTRA[a]

Proton	Chemical shifts, ppm							
	10b[b]	11g	11b	12b	13b	14c	14b	23b
CH_3—C—O (O above C)	2.00	2.00	2.00					
C-19	0.88[c]	1.11 (triplet, J = 2.80)	1.08 (triplet, J = 2.85)	1.06 (triplet, J = 2.80)	1.24[d] (doublet, J = 3.2)	1.30 (doublet, J = 2.2)	1.28 (doublet, J = 2.4)	1.32 (doublet, J = 3.0)
C-18	0.88[c]	0.90 (singlet)	0.90 (doublet, J = 2)	0.90 (doublet, J = 2)	0.95[d] (doublet, J = 2.4)	0.95 (singlet)	0.96 (doublet, J = 2)	0.97 (doublet, J = 2.0)
C-4						6.23 (doublet, J = 4.1)	6.24 (doublet, J = 4.0)	6.54[e] (unresolved multiplet)

[a] Spectra were determined in dilute deuteriochloroform solution on a Varian A-60 spectrometer and were calibrated against internal tetramethylsilane. Chemical shifts are reported in parts per million measured from tetramethylsilane (0.0 ppm) in the direction of decreasing field. J values are given in cycles per second. The author is grateful to Dr. H. Foster for the determination and interpretation of these spectra. [b] The method of preparation and characterization of **10b** will be given in a forthcoming publication. *Cf.* ref 8. [c] The positions of the C-18 and C-19 absorption bands coincide. [d] Evidence for further splitting, but resolution was not possible. [e] The C-1 and C-2 protons appear as an AB quartet at 6.17, 6.33, 5.96, and 7.13 ppm with each band being further split into doublets with J = 2 cps due to coupling with the C-4 proton.



23a, R = 

b, R = 

c, R = =O

d, R = 

spectra of fluorinated steroids,[19] particularly coupling between fluorine and angular methyl protons, a cursory examination of the literature failed to reveal any reports on the fluorine nmr spectra of fluorinated steroids. In Table VI are listed the fluorine chemical shifts at 56.4 Mc/sec of the 5α-fluoro, 6,6-difluoro, and 17,17-difluoro groups of **10b**, **11b**, **11g**, **12b**, **13b**, **14b**, **14c**, and **23b**. The 5α-fluorine of **10b** appears as a doublet at +8984 cps with $J_{F\text{-}H}$ = 50 cps. It was surprising to find that the introduction of C-6 *gem*-difluoro group did not appear to cause additional splitting of the 5α-fluorine which remains a doublet in **11g**, **11b**, **12b**, and **13b** with J = 40–55 cps. The C-6 difluoro resonance in the examples having a 5α,6,6-trifluoro grouping appears as a strong peak at +6037–6041 cps, which is clearly a triplet but is broad and its centers are ill defined. The C-6 difluoro resonances of the 6,6-difluoro Δ^4-ketones and 6,6-difluoro $\Delta^{1,4}$-3-ketones are exemplified by **14c**, **14b**, and **23b** and appear as AB quartets at the indicated positions with the low-field peaks being split into doublets with J = 20–33 cps. There is evidence of further splitting of the low-field peaks, but resolution was not possible. The C-17 *gem*-difluoro group also appears as an AB quartet at the indicated positions with the low-field pair being split into triplets with J = 21–25 cps.

The chemical shifts of the C-18 and C-19 protons and C-4 vinyl protons of representative examples are summarized in Table VII. In keeping with the "converging vector rule" of Cross and Landis,[12] the C-19 resonance of the 6,6-difluoro Δ^4- and $\Delta^{1,4}$-3-ketones occurs as a doublet at 1.28 to 1.32 ppm with $J_{H\text{-}F}$ = 2.2–3.0 cps as exemplified by **14b**, **14c**, and **23b**. In those examples having a 5α,6,6-trifluoro grouping and a C-3 acetate or hydroxyl (**11a**, **11b**, and **12b**), the C-19 resonance appears as a triplet (W-S-W) at 1.06–1.11 ppm with J = 2.80–2.85 cps. The C-19 resonance of **13b** occurs as a doublet at 1.24 ppm with J = 3.2 cps. The C-18 protons of the 17,17-difluoro compounds occur as doublets at 0.90–0.97 ppm with $J_{H\text{-}F}$ = 2 cps which is in keeping with the report[12] that the C-18 protons of C/D-*trans* 17α-fluoro steroids appear as a doublet with J = 2.1 cps and those of 17β-fluoro steroids appear as a broadened singlet. Finally, the C-4 vinyl proton of the 6,6-difluoro Δ^4-3-ketones appears as a doublet centered at 6.23–6.24 ppm with $J_{6\beta\text{-}F\text{-}4H}$ = 4.0–4.1 cps.[11]

Biological Assays.—Preliminary biological assays[20] have been run on several of the 6,6-difluoro-Δ^4-3-keto steroids reported here. 6,6-Difluoro-17α-ethynyltestosterone (**21a**) showed oral progestational activity in the rabbit intermediate to that of 17α-ethynyltestosterone and 17α-ethynyl-19-nortestosterone; administered subcutaneously, the ethynyltestosterone analog **21a** was about equal in potency to progesterone. 6,6-Difluoroprogesterone (**14e**) was slightly less potent than progesterone as a progestational and antiovulatory agent in the rabbit by subcutaneous administration. The hormone analog **17a** showed only a small percentage of the androgenic activity of testosterone but still retained appreciable myotrophic activity and was a potent gonadotrophic inhibitor in the 7-day parabiotic rate assay. The tetrafluoroenone **14b** showed mild antigonadotrophic activity in the parabiotic rat test. 6,6-Difluoro-17α-acetoxyprogesterone (**14a**) was about equal to progesterone and to 17α-ethynyltestosterone in potency as a progestational agent by the subcutaneous and oral routes, respectively. It showed considerably less antiovulatory activity in the rabbit by the subcutaneous route than progesterone. It was inactive as an inhibitor of ovulation in the rabbit by the oral route. The 1(2)-dehydro derivatives of **14b**, **17a**, and **21a** were less active than their parent compounds.

Experimental Section[21]

The sulfur tetrafluoride fluorinations were carried out using conditions described by Martin and Kagan.[7a] A 400-ml, 316 stainless steel lined shaker tube equipped with a 1200-atm stainless steel lined shaker tube equipped with a 1200-atm backhead rupture disk covered with a 316 stainless steel plate was employed. Hydrogen fluoride was generated *in situ* by the hydrolysis of sulfur tetrafluoride ($SF_4 + H_2O \rightarrow SOF_2 + 2HF$). Sulfur tetrafluoride was measured by distilling into a shaker tube containing all other reactants, which was cooled in Dry Ice–acetone and mounted on a balance so the increase in weight due to sulfur tetrafluoride could be determined. The procedure is illustrated by the preparation of 5α,6,6-trifluoropregnane-3β,17α-diol-20-one diacetate (**11a**). Other sulfur tetrafluoride reactions were carried out under similar conditions (see Table I).

The details of the reaction of nitrosyl fluoride with steroid 5-enes will be described in a forthcoming publication.[8a] However, the reaction of 5-pregnene-3β,17α-diol-20-one diacetate (**8a**) with nitrosyl fluoride to give 5α-fluoro-6-nitrimine **9a** and its subsequent hydrolysis to give 5α-fluoropregnane-3β,17α-diol-6,20-dione diacetate (**10a**) will be described here for illustrative purposes, since the 5α-fluoro 6-ketones are the key intermediates in the preparation of 5α,6,6-trifluoro-3-keto and 6,6-difluoro-Δ^4-3-keto steroids.

5α-Fluoropregnane-3β,17α-diol-6,20-dione Diacetate (10a).—In a dry, 500-ml polyethylene bottle equipped with a magnetic stirring bar and gas inlet and exit tubes was placed 17α-acetoxypregnenolone acetate (**8a**, 19.0 g) and carbon tetrachloride (200 ml). The exit tube was protected by a drying tube containing calcium chloride, and the system was swept with a slow stream of nitrogen to remove moisture and air. The reactor was cooled in ice bath while a slow stream of (*ca.* 14 g) nitrosyl fluoride[22]

(19) 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, pp 123–132.

(20) The biological assays were conducted by Dr. Elva G. Shipley of the Endocrine Laboratories, Madison, Wis.

(21) Melting points were recorded as observed on a Kofler block unless otherwise designated. Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrometer from Nujol mulls or micro KBr wafers. Ultraviolet spectra were taken in absolute ethanol using a Cary Model 14 spectrometer. The F^{19} and proton nmr spectra were obtained on Varian HR-60, operating at 56.4 Mc/sec, and A-60 spectrometers. Optical rotations were measured in chloroform solution unless noted otherwise.

(22) Nitrosyl fluoride was purchased from the Ozark-Mahoning Co., Tulsa, Okla.

was passed into the stirred solution for 7 hr. During this time, after an induction period of 1 hr, the reaction solution became deep blue. The final blue-green solution was washed with water and saturated salt solution. The carbon tetrachloride solution was dried over magnesium sulfate and concentrated to dryness under reduced pressure to afford a thick syrup which partially solidified on standing. Without further purification, the crude fluoronitrimine was adsorbed onto a column of neutral alumina (600 g, activity III) from benzene solution. Elution with benzene afforded crystalline material. The crystalline fractions were combined and recrystallized from methanol–methylene chloride to give **10a** (15.6 g in two crops, 75% yield), mp 270–273° (Fisher-Johns apparatus). Two recrystallizations from methanol–methylene chloride afforded the analytical sample: mp 268.5–269.5°; $[\alpha]^{24}D$ −28° (*c* 2.29), $[\alpha]^{22}D$ −32° (*c* 2.14 dioxane); λ_{max}^{KBr} 5.75, 8.0, and 8.63 μ.

Anal. Calcd for $C_{25}H_{35}FO_6$: C, 66.64; H, 7.83; F, 4.22. Found: C, 66.73; H, 7.81; F, 4.26.

5α,6,6-Trifluoropregnane-3β,17α-diol-20-one Diacetate (11a).—A mixture of 5α-fluoropregnane-3β,17α-diol-6,20-dione diacetate (**10a**, 13.7 g), water (1.5 ml), and methylene chloride (100 ml) was placed in a 400-ml shaker tube. The reactor was sealed and frozen in a bath of Dry Ice and acetone. Sulfur tetrafluoride (160 g) was then condensed into the reactor, and the reactor was allowed to warm to 20°, at which temperature it was agitated for 10 hr. The shaker tube was vented, and the contents were poured with caution into ice–water. The phases were separated, and the methylene chloride solution was washed with water, 5% sodium bicarbonate solution, water, and saturated salt solution. The methylene chloride solution was dried over magnesium sulfate and then evaporated under reduced pressure to leave a tan, crystalline residue. Recrystallization from methanol–methylene chloride afforded **11a**, (8.75 g in two crops) as thick colorless blades, mp 249–250° (Fisher-Johns apparatus), $[\alpha]^{24}D$ −13° (*c* 1.31).

Anal. Calcd for $C_{25}H_{35}F_3O_5$: C, 63.54; H, 7.47; F, 12.06. Found: C, 63.51; H, 7.43; F, 12.00.

The other 5α,6,6-trifluoro 3-acetates given in Table I were prepared similarly, with the exception that in those cases where a C-17 or C-20 carbonyl group was to be converted to the corresponding *gem*-difluoride, an increased reaction time and larger ratio of hydrogen fluoride to sulfur tetrafluoride were employed.[23]

5α,6,6-Trifluoropregnane-3β,17α-diol-20-one Acetate (12a).—A solution of 5α,6,6-trifluoropregnane-3β,17α-diol-20-one diacetate (**11a**, 9.20 g) in methanol (150 ml) containing concentrated hydrochloric acid (15 ml) was heated to reflux for 1 hr. The reaction mixture was cooled and diluted with water to precipitate the product. The product was extracted into methylene chloride, and the organic extract was washed with water and saturated salt solution, dried over magnesium sulfate, and then evaporated to dryness under reduced pressure. The residue was crystallized from methanol to afford **12a** (5.78 g), mp 225–226°. The analytical sample was crystallized from methanol once again to give colorless leaflets, mp 225–225.5°, $[\alpha]^{24}D$ −26° (*c* 0.50, dioxane).

Anal. Calcd for $C_{23}H_{33}F_3O_4$: C, 64.17; H, 7.73; F, 13.25. Found: C, 64.20; H, 7.59; F, 12.75.

The other examples given in Table III were prepared in the same manner.

5α,6,6-Trifluoropregnan-17α-ol-3,20-dione Acetate (13a).—To a stirred solution of 5α,6,6-trifluoropregnane-3β,17α-diol-20-one acetate (**12a**, 3.90 g) in acetone (75 ml) cooled in an ice bath was added an excess of 8 *N* chromic acid[10] (permanent orange color). The reaction mixture was allowed to stir for 15 min at 5–10°, after which time a few milliliters of methanol was added to consume the excess oxidizing agent. The mixture was filtered to remove chromium salts, and the filtrate was diluted with water. The product crystallized as short colorless needles, yield 3.37 g, mp 225–230° (softens at 220°) (Fisher-Johns apparatus). The analytical sample was recrystallized from acetone–methanol to give **13a** as thick, colorless needles, mp 220–227°, $[\alpha]^{24}D$ −7° (*c* 1.04).

Anal. Calcd for $C_{23}H_{31}F_3O_4$: C, 64.47; H, 7.29; F, 13.30. Found: C, 64.55; H, 7.31; F, 12.95.

The additional examples given in Table IV were prepared in the same manner.

6,6-Difluoro-4-pregnen-17α-ol-3,20-dione Acetate (14a). A. Dehydrofluorination by Alumina.—A solution of 5α,6,6-trifluoropregnan-17α-ol-3,20-dione acetate (**13a**, 5.68 g) in benzene was adsorbed onto a column of neutral alumina (125 g, activity III) and then eluted with benzene as a white crystalline solid. Recrystallization from methylene chloride–hexane gave **14a** (4.86 g in two crops): mp 216–218°; $[\alpha]^{23}D$ −26° (*c* 2.33, dioxane); λ_{max} 228 mμ (ε 12,100), 285 (84), and 340 (33); λ_{max}^{KBr} 5.77, 5.84, 5.92, 5.97, 7.90, and 9.60 μ.

Anal. Calcd for $C_{23}H_{30}F_2O_4$: C, 67.63; H, 7.40; F, 9.30. Found: C, 67.52; H, 7.40; F, 9.28.

B. Dehydrofluorination with Sodium Acetate in Methanol.[24]—A solution of 5α,6,6-trifluoropregnan-17α-ol-3,20-dione acetate (**13a**, 2.43 g) and sodium acetate (6.76 g) in methanol (85 ml) was heated to reflux for 3 hr in a nitrogen atmosphere. Water was added to the hot solution which was then allowed to cool to room temperature. The product crystallized as long, colorless blades, yield 1.98 g, mp 216–219°. Recrystallization from methanol afforded **14a** (1.48 g), mp 219–219.5°.

The other 6,6-difluoro Δ^4-3-ketones listed in Table II were prepared in the same manner from the corresponding 5α,6,6-trifluoro derivatives.

4-Pregnen-17α-ol-3,20-dione Acetate (15a).—Zinc dust (1.33 g) was added to a solution of 6,6-difluoro-17α-acetoxyprogesterone (**14a**, 0.50 g) in glacial acetic acid (25 ml). The reaction mixture was heated to reflux for 12 hr and then was filtered hot to remove insoluble, inorganic material. The filtrate and washings were diluted with methylene chloride and washed with water, 5% sodium bicarbonate solution, water, and saturated salt solution, dried ($MgSO_4$), and evaporated under reduced pressure to give a light yellow, crystalline residue (374 mg), which was adsorbed from benzene–hexane onto a column of neutral alumina (20 g, activity III). Elution with benzene and one recrystallization from methylene chloride–petroleum ether (bp 37–56°) afforded **15a** (172 mg): mp 246–248°; $[\alpha]^{24}D$ +58° (*c* 2.23, dioxane); λ_{max} 238 mμ (ε 16,100) and 285 mμ (ε 44); λ_{max}^{Nujol} 5.80, 5.85, 6.05, 6.21, and 8.0 μ [lit.[13] mp 243–244.5°, $[\alpha]D$ +56° (*c* 1.28 dioxane)].

6,6-Difluoro-4-androsten-17β-ol-3-one (17a).—A solution of 6,6-difluoro-4-androstene-3,17-dione (**14c**, 6.5 g), sodium borohydride (3.0 g), and absolute ethanol (300 ml) was allowed to stir for 10 hr at room temperature. The reaction mixture was then carefully diluted with cold 5% hydrochloric acid (50 ml), followed by water. Extraction with methylene chloride followed by drying the methylene chloride solution ($MgSO_4$) and evaporation of the solvent under reduced pressure gave a white crystalline solid, λ_{max}^{Nujol} 3.0 μ, which was used in the next step without further purification.

The crude diol **16** from above was dissolved in dry benzene and the solution was heated to reflux, allowing a few milliliters of solvent to distil, to dry the reaction. The benzene solution was cooled, and a solution of dichlorodicyanobenzoquinone (6.5 g) in dry dioxane (50 ml) was added. The reaction mixture was allowed to stir for 3 days at room temperature. During this time copious amounts of the hydroquinone precipitated. The reaction mixture was diluted with water (300 ml) and extracted thoroughly with benzene. The benzene extract was washed successively with water, 5 % sodium bicarbonate solution, water, and saturated salt solution. The benzene solution was dried over magnesium sulfate and then evaporated to dryness to leave an oil which was adsorbed from benzene onto a column of neutral alumina (150 g, activity III). Elution with petroleum ether–benzene (1:1) and benzene and two recrystallizations from hexane–ether afforded 6,6-difluorotestosterone (**17a**, 5.0 g): mp 130.5–132.5°; $[\alpha]^{22}D$ −5° (*c* 2.02, dioxane); λ_{max} 229 mμ (ε 12,100); λ_{max}^{Nujol} 2.8, 2.95, 5.95, 8.60, 8.70, and 8.95 μ.

Anal. Calcd for $C_{19}H_{26}F_2O_2$: C, 70.34; H, 8.07; F, 11.71. Found: C, 70.72, 70.32; H, 8.16, 8.03; F, 11.66, 11.64.

6,6-Difluoro-4-androsten-17β-ol-3-one Acetate (17b).—Acetylation of 6,6-difluorotestosterone (**17a**, 1.13 g) with acetic anhydride (50 ml) at reflux for 1 hr gave the 17-acetate **17b** (769 mg) from methanol: mp 161–163°; $[\alpha]^{24}D$ −4° (*c* 2.17); λ_{max} 228 mμ (ε 12,600) and 333 mμ (ε 30); λ_{max}^{KBr} 5.77, 5.92, 8.05, 8.15, and 8.53 μ.

Anal. Calcd for $C_{21}H_{28}F_2O_3$: C, 68.83; H, 7.70; F, 10.35. Found: C, 68.65; H, 7.81; F, 10.46.

6,6-Difluoro-17α-ethynyl-4-androsten-17β-ol-3-one (21a).—A solution of 6,6-difluorotestosterone (**17a**, 5.00 g), *p*-toluenesulfonic acid (1.0 g), and ethylene glycol (25 ml) in dry benzene (100 ml) was heated to reflux with stirring for 24 hr using a

(23) See footnotes of Table I and ref 7a.

(24) A. Bowers, *et al.*, *J. Am. Chem. Soc.*, **84**, 1050 (1962).

Sterling–Bidwell trap to remove water of reaction. The reaction mixture separated into two phases with the bottom phase being a dark purple. The reaction mixture was shaken with 5% sodium bicarbonate solution, water, and saturated salt solution. The benzene phase was dried over magnesium sulfate and evaporated to dryness under reduced pressure to leave the ketal **18** as a crude, crystalline solid whose infrared spectrum showed only a trace amount of Δ^4-3-ketone.

The crude ketal **18** was dissolved in pyridine (50 ml) and then cooled in an ice bath while sweeping with a slow stream of nitrogen. To the stirred solution cooled in an ice bath was added portionwise chromium trioxide (5.10 g).[25] A yellow solid separated. The reaction mixture was stirred at room temperature for 20 hr. The mixture was at first quite thick and red-brown, but later became thin and turned dark. The reaction mixture was diluted with ethyl acetate and filtered through Celite to give a clear yellow solution which was washed with water and saturated salt solution. The ethyl acetate solution was dried over magnesium sulfate and evaporated under reduced pressure to afford the 17-ketone **19**, λ_{max}^{Nujol} 5.78 μ.

To a stirred solution of 17-ketone **19** in dry toluene (100 ml) was added a solution prepared from potassium (4.5 g) and *t*-amyl alcohol (45 ml). A slow stream of acetylene gas was bubbled through the resultant dark solution for 20 hr with stirring at room temperature. The reaction mixture was diluted with benzene and washed with water and 5% hydrochloric acid. The organic phase was mixed with 5% hydrochloric acid (50 ml) and then steam distilled. The resultant residue was dissolved in methylene chloride, and the methylene chloride solution was washed with water and saturated salt solution and dried over magnesium sulfate. The solvent was evaporated *in vacuo* to leave a brown amorphous solid (4.0 g) which was absorbed onto neutral alumina (150 g, activity III) from benzene. Elution with benzene and benzene–ether (1:1) returned colorless, crystalline solid. Recrystallization from methylene chloride containing a few milliliters of hexane afforded **21a** (1.582 g) as well-formed, colorless prisms, mp 217–218° (Fisher-Johns apparatus). The analytical sample was recrystallized from methylene chloride: mp 212–212.5°; $[\alpha]^{22}D$ −57° (*c* 1.90, pyridine); λ_{max} 229 mμ (ϵ 12,350) and 332 mμ (ϵ 35); λ_{max}^{KBr} 2.92, 3.05, 4.75, 5.94, 8.53, and 8.62 μ.

Anal. Calcd for $C_{21}H_{26}F_2O_2$: C, 72.39; H, 7.52; F, 10.91. Found: C, 72.49, 72.35; H, 7.70, 7.56; F, 11.03, 10.97.

In an alternative preparation of 6,6-difluoroethisterone (**21a**) ketone **19** was ethynylated using sodium acetylide[26] in dimethyl sulfoxide. To a stirred solution of ketone **19** (8.0 g of crude product) in dimethyl sulfoxide (150 ml) at room temperature under nitrogen was added a solution of sodium acetylide in dimethyl sulfoxide, prepared by centrifuging 75 ml of a 19% suspension of sodium acetylide in xylene, decanting the supernatant liquid, and dissolving the residue in dimethyl sulfoxide (200 ml). The resultant dark mixture was stirred at room temperature for 24 hr and then was carefully diluted with ice–water. The diluted reaction mixture was thoroughly extracted with ethyl acetate. The ethyl acetate solution was washed with water and saturated salt solution, dried over magnesium sulfate, and evaporated to dryness under reduced pressure to leave a dark residue. This was dissolved in methanol (75 ml) containing concentrated hydrochloric acid (10 ml), and the solution was heated to reflux for 1 hr. The cooled solution was diluted with water and extracted with methylene chloride. The methylene chloride extract was washed with water and saturated salt solution, dried over magnesium sulfate, and evaporated *in vacuo* to give a red-brown syrup which slowly solidified. The crude product was chromatographed on neutral alumina (activity III). Elution with benzene gave white crystalline solids which were combined and crystallized from hot methylene chloride containing a little hexane to give 6,6-difluoroethisterone (**21a**, 2.18 g) as well-formed, colorless prisms, mp 212–213°. The infrared spectrum was identical with that of material prepared above.

6,6-Difluoro-17α-ethynyl-4-androsten-17β-ol-3-one Acetate (21b) and 6,6-Difluoro-17α-ethynyl-2,4-androstadiene-3,17β-diol Diacetate (22).—A solution of 6,6-difluoro-17α-ethynyl-4-androsten-17β-ol-3-one (**21a**, 1.50 g) in dry pyridine (30 ml) containing acetic anhydride (10.5 ml) was heated under nitrogen at 100° for 48 hr. The dark reaction mixture was poured into ice–water (150 ml), and the resulting mixture was allowed to stir for 15 min, after which it was extracted with methylene chloride. The organic extract was washed with water and saturated salt solution, dried over magnesium sulfate, and evaporated to dryness under reduced pressure to afford an oil which was chromatographed on neutral alumina (50 g, activity III). Elution with petroleum ether (seven 50-ml fractions) gave a colorless oil (0.43 g) which crystallized when triturated with cold hexane. A second chromatography of the solid on neutral alumina (activity III) followed by crystallization from methylene chloride–hexane afforded **22** as colorless rosettes: mp 138–143°; $[\alpha]^{24}D$ +57° (*c* 0.70); λ_{max} 265 mμ (ϵ 4750); λ_{max}^{Nujol} 3.08, 5.69, 5.76, 5.97, 6.01 (doublet), 7.95, 8.10, 8.21, 8.32, and 8.65 μ.

Anal. Calcd for $C_{25}H_{30}F_2O_4$: C, 69.42; H, 6.99; F, 8.79. Found: C, 70.20; H, 7.28; F, 8.83.

Elution with petroleum ether–benzene (1:1) gave crystalline material which was recrystallized from methylene chloride–hexane to afford 6,6-difluoro-17α-ethynyl-4-androsten-17β-ol-3-one acetate (**21b**, 0.442 g) as pale yellow rosettes: mp 164°; $[\alpha]^{23}D$ −55° (*c* 2.17); λ_{max}^{KBr} 229 mμ (ϵ 12,900) and 335 mμ (ϵ 28.5); λ_{max}^{KBr} 3.08, 4.75, 5.73, 5.92, 7.97, 8.12, 8.52, and 8.62 μ.

Anal. Calcd for $C_{23}H_{28}F_2O_3$: C, 70.72; H, 7.23; F, 9.73. Found: C, 70.45; H, 7.20; F, 9.65.

6,6-Difluoro-17α-ethynyl-1,4-androstadien-17β-ol-3-one Acetate (23d).—A solution of 6,6-difluoro-17α-ethynyl-4-androsten-17β-ol-3-one acetate (**21b**, 2.25 g), dichlorodicyanobenzoquinone (1.75 g), and *p*-toluenesulfonic acid (60 mg) in dry toluene (36 ml) was heated to reflux under nitrogen with stirring for 7 hr, after which stirring was continued for an additional 36 hr at room temperature. The reaction mixture was diluted with water and thoroughly extracted with methylene chloride. The organic extracts were washed with water, 5% sodium bicarbonate solution, water, and saturated salt solution, dried over magnesium sulfate, and evaporated under reduced pressure to leave a dark gum. This was purified by chromatography on neutral alumina (75 g, activity III). Elution with petroleum ether–benzene (1:1) gave crystalline solids which were combined and recrystallized from benzene–hexane to afford **23d** (611 mg), mp 144–145°, as long, jagged, white crystals. The analytical sample was recrystallized from benzene–hexane to give material with mp 142–143°; $[\alpha]^{24}D$ −74° (*c* 0.74); λ_{max} 238 mμ (ϵ 14,400); λ_{max}^{KBr} 3.07, 4.75, 5.72, 5.98, 6.10, 8.02, 8.09, 8.14, 8.55, and 11.0 μ.

Anal. Calcd for $C_{23}H_{26}F_2O_3$: C, 71.11; H, 6.75; F, 9.78. Found: C, 71.18; H, 6.81; F, 9.78.

The 6,6-difluoro $\Delta^{1,4}$-3-ketones listed in Table V were prepared from the corresponding 6,6-difluoro Δ^4-3-ketones in the same way.

17,17-Difluoro-4-androsten-3-one (15b).—A solution of 6,6-17,17-tetrafluoro-4-androsten-3-one (**14b**, 2.0 g) in glacial acetic acid (40 ml) containing suspended zinc dust (1.0 g) was heated to reflux with stirring. After 1 hr at reflux, the mixture developed a deep blue color. At this point, the colored solution was decanted from the zinc into ice water. The zinc was washed with additional acetic acid and the washings were added to the above mixture. The product was extracted with methylene chloride and the methylene chloride extracts were washed with water, 5% sodium bicarbonate solution, water, and saturated salt solution, dried over magnesium sulfate, and evaporated *in vacuo* to leave a clear, tan syrup. The total crude product was adsorbed from hexane–benzene (1:1) onto a column of neutral alumina (60 g, activity III). Elution with hexane–benzene (1:1) returned solid material (0.50 g), mp 180–182°. This was recrystallized from acetone–hexane to give **15b** (0.429 g): mp 186–187°; λ_{max} 238 mμ (ϵ 15,400); λ_{max}^{Nujol} 6.0 (C-3 C=O) and 6.16 μ (C=C) [lit.[7a] mp 185–187°, ν_{max} 1660 and 1615 cm^{-1}, λ_{max} 240 mμ (ϵ 16,750)].

Attempted Dehydrofluorination of 14b. A. With Lithium Chloride in Dimethylformamide.—A solution of 6,6,17,17-tetrafluoro-4-androsten-3-one (**14b**, 200 mg) in redistilled dimethylformamide (11 ml) containing anhydrous lithium chloride (100 mg) was heated to 130° for 24 hr under nitrogen. The reaction product was isolated with methylene chloride as a tan syrup which was adsorbed from hexane onto neutral alumina (activity III). Elution with hexane–benzene (1:1) and crystallization of the solid fractions from hexane afforded a crystalline product (162 mg) which was identical in every respect with starting material.

B. With Collidine.—A solution of 6,6,17,17-tetrafluoro-4-androsten-3-one (**14b**, 1.0 g) in collidine (30 ml) was heated to

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reflux under nitrogen for 90 min. The nearly colorless solution was cooled to room temperature and then poured into ice–water. The mixture was extracted with methylene chloride and the methylene chloride extracts were washed with water followed by 5% hydrochloric acid solution (three 100-ml portions) and saturated salt solution, and dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure afforded a crystalline residue whose infrared spectrum was identical with that of **14b**. Recrystallization from acetone gave 0.70 g of colorless crystalline material which was identical with **14b** (melting point, mixture melting point, and infrared spectrum).

The Conformational Preferences in Diastereomers. I

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Nmr data are reported for a series of diastereomers involving a substituted phenylethyl skeleton. When the alkyl groups substituted at each asymmetric center are small, *i.e.*, methyl, both *gauche* and *trans* rotamers have substantial populations. When the alkyl groups are large, *i.e.*, isopropyl, these groups strongly prefer a *trans* orientation which allows the vicinal protons to be *trans* in the *erythro* but *gauche* in the *threo* isomer. In all cases but one, the *erythro* isomer exhibits the larger vicinal coupling constant.

The study of the mechanism of certain reactions involving *erythro* and *threo* pairs of diastereomers frequently has involved attempts to predict conformational preferences of each diastereomer.[1-3] These attempts frequently utilize molecular models to aid in deciding which rotamer was the most stable.

In other cases conformational preferences were decided from Newman projections. In simplified terms, the most stable rotamer was taken as the one in which nonbonded repulsions were minimized.[1,4-6] *gauche* interactions between large groups were considered particularly unfavorable.

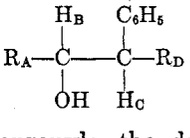
Although these ideas were logical and their application was fairly straightforward, they frequently were not based on physical or chemical evidence.

In recent years, nmr spectral evidence has been used to determine conformational preferences. Originally the main interest was in sugars and other cyclic molecules,[7,8] but more recently acyclic molecules have been investigated.[9-14]

In diastereomers which contain a proton at each asymmetric center, the vicinal coupling constant, J, should give an indication of the preferred conformation of the molecule. Unfortunately, the frequency of rotation about the central carbon is large compared to the nmr frequency separations between the vicinal protons,[15] and the vicinal coupling constant is a weighted average derived from contributions from several conformations. Nevertheless, a knowledge of the average conformation is still valuable, particularly where other information is lacking. Thus, if the vicinal protons are *trans* to one another, a coupling constant approaching 10–12 cps might be expected. If the vicinal protons are *gauche*, a coupling constant of 1–3 cps will be found. A mixture of *trans* and *gauche* conformers will give rise to intermediate values of J. A freely rotating structure such as an ethyl group, which presumably has no conformational preferences, often exhibit vicinal coupling constants of 6–7 cps.[15]

Electronegative groups substituted at the asymmetric centers will give rise to slightly lower values for J.[13,16] Snyder has recently shown that vicinal coupling constants vary with concentration of substrate[17] and type of solvent as much as ±1 cps; thus it probably is not worthwhile trying to interpret small differences in J values.

It seemed worthwhile to determine the effect of systematically increasing the hindrance at each asymmetric center on the conformational preferences of a set of diastereomers of the same basic skeleton, given in the formula. In this study, R_A and R_D were varied



from methyl to isopropyl; the data concerning the relevant chemical shifts, the coupling constants, and the multiplicity of peaks are given in Table I. The spectra were relatively easy to interpret. The most deshielded alkyl proton is almost certainly H_B, while H_C (also considerably deshielded by phenyl) was also usually far removed from the resonance absorptions of the remainder of the molecule. The vicinal coupling constant J_{BC} could usually be determined by inspection. Spin decoupling was utilized in cases where ambiguity existed. The individual compounds are discussed below.

In *erythro*-3-phenyl-2-butanol (I) (R_A, R_D = CH_3), both proton B and proton C are quintets. Thus the R_A–H_B coupling constant and the H_B–H_C coupling constant are very similar, namely *ca.* 7 cps; proton B basically sees a sum of four magnetically similar protons, giving a quintet pattern. Considering the

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