Registry No.—**2**, 17392-96-0; **3**, 17392-89-1; **4**, 17414-38-9; **5**, 2233-71-8; **6**, 17392-90-4; **7**, 17414-39-0; **8**, 17393-00-9; **9**, 17392-91-5; **10**, 17393-01-0; **11**, 17392-92-6; **12**, 17397-48-7; **13**, 17392-93-7; **14**, 17392-94-8; **15**, 17392-95-9; **16**, 17448-07-6; **17**, 17392-97-1; **18**, 17392-98-2; **20**, 1239-33-4; 3β-acetoxy-17α-hydroxy-6-methyl-16-methylene-5-pregnen-20-one, 5618-32-6; 3β,15α-diacetoxy-5-pregnen-20-one, 17397-50-1.

Acknowledgments.—The authors wish to thank Dr. W. Charney and Miss C. Federbush for performing the microbiological transformations.

Reaction of Nitrosyl Fluoride and Selected Steroid Enes.[1] A New Synthesis of Δ5-4-Keto Steroids

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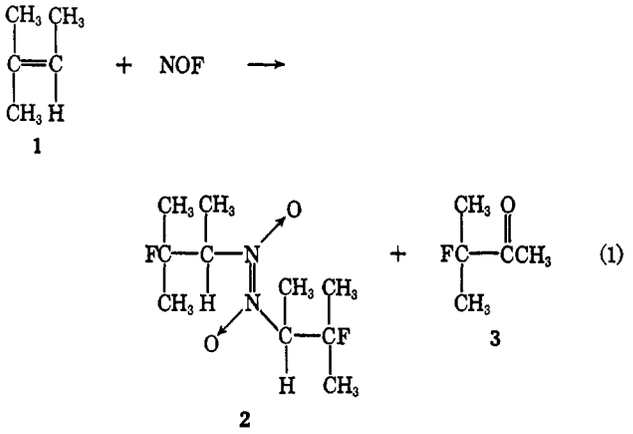
Reaction of steroid 4- and 5-enes with nitrosyl fluoride gave 5α-fluoro-4- and -6-nitrimines which on chromatography on alumina containing 6% water were converted into 5α-fluoro-4 and -6 ketones in high yield. Steroid 5-en-3β-ols were converted into Δ4-3,6-diones in moderate yield. Dehydrofluorination of 5α-fluoro-4 ketones gave Δ5-4 ketones, a relatively inaccessible class of steroids. Transformations of these products are discussed. Reactions of nitrosyl fluoride with various steroid olefins are described.

Since Fried and Sabo discovered that introduction of fluorine[2] at C-9 (α) of cortisone and cortisol significantly enhanced antiinflammatory activity of the parent adrenal hormones, a prodigious effort has been made to prepare fluoro steroid hormones[3] and to develop new methods for introducing fluorine at key positions throughout the steroid nucleus.[4] Although much work has been done in this area, new methods are needed for selectively fluorinating steroids with sensitive functional groups.

There are many examples of nitrosyl chloride addition to carbon–carbon double bonds, particularly in terpenes, to give dimeric chloronitroso compounds or isomeric chloro oximes.[5] However, this reaction with steroid olefins was described only recently; three different groups[6] reported that steroid 5-enes react with excess nitrosyl chloride to give 5α-chloro-6β-nitro steroids in good yield. These reports and the ready availability of nitrosyl fluoride[7,8] suggested its evaluation as a steroid fluorination agent.

Addition of nitrosyl fluoride (NOF) to a simple olefin, 2-methylbut-2-ene (**1**), in carbon tetrachloride, gave as a major product a white crystalline adduct, which, on the basis of its ultraviolet spectrum[9] [λ_{max}^{EtOH} 300 mμ (ε 7100)], was clearly the fluoronitroso dimer **2**. This is analogous to reaction of 2-methylbut-2-ene (**1**) with nitrosyl chloride.[10,11a]



When fluoronitroso dimer **2** was chromatographed on alumina III or refluxed briefly in 2-propanol containing water, it isomerized to the oxime, lost hydrogen fluoride, and finally, hydrated to give 3-methyl-3-hydroxybutan-2-one oxime (**4**)[11] in high yield (eq 2). A second, volatile product was isolated by vpc; structure **3** is suggested from mass and infrared spectra (see Experimental Section).

Reaction of Nitrosyl Fluoride and Steroid 5-Enes.—Cholesteryl acetate (**5a**) underwent reaction with excess NOF at 0° in methylene chloride or carbon tetrachloride to give a crystalline product (72% yield) which was assigned 5α-fluoro-6-nitrimine structure **6a** on the basis of elemental analysis, molecular weight determinations, characteristic imine (6.08 μ) and nitro absorption bands

(1) Preliminary reports of portions of this research have been published: (a) G. A. Boswell, Jr., *Chem. Ind.* (London), 1929 (1965); (b) G. A. Boswell, *J. Org. Chem.*, **31**, 991 (1966); and (c) S. Andreades and G. A. Boswell, U. S. Patent 3,320,291 (1967), and G. A. Boswell, Jr., U. S. Patent 3,235,571 (1967).

(2) J. Fried and E. F. Sabo, *J. Amer. Chem. Soc.*, **76**, 1455 (1954).

(3) *Cf.* L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp 593 and 682–686.

(4) *Cf.* C. Djerassi, "Steroid Reactions," Holden-Day, Inc., San Francisco, Calif., 1963, pp 155–177.

(5) (a) For a review of nitrosyl chloride chemistry, see L. J. Beckham, W. A. Fessler, and M. A. Kise, *Chem. Rev.*, **48**, 319 (1951); (b) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds," Vol. II, W. A. Benjamin, Inc., New York, N. Y., 1966, pp 382, 383.

(6) (a) K. Tanabe and R. Hayashi, *Chem. and Pharm. Bull. Jap.*, **10**, 1177 (1962); (b) W. A. Harrison, R. N. Jones, G. D. Meakins, and P. A. Wilkinson, *J. Chem. Soc.*, 3210 (1964); (c) A. Hassner and C. Heathcock, *J. Org. Chem.*, **29**, 1350, 1964; (d) similar experiments were underway in these laboratories about the time of the appearance of the first report.

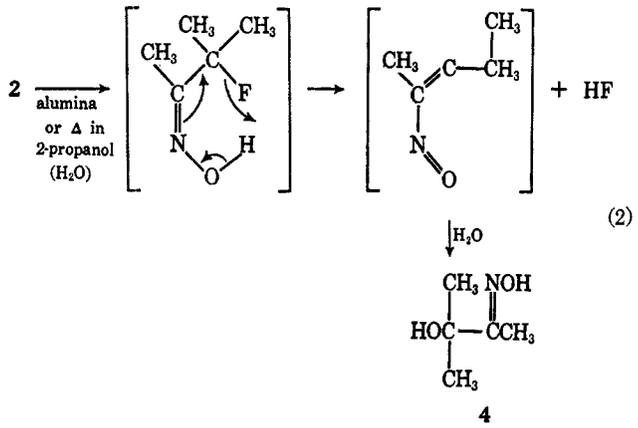
(7) (a) For a review of the literature covering nitrosyl fluoride, see A. Andreades, *J. Org. Chem.*, **27**, 4157 (1962); **27**, 4163 (1962).

(8) Nitrosyl fluoride may be purchased from the Ozark-Mahoning Co., Tulsa, Okla.

(9) (a) A. E. Gilliam and E. S. Stern, "Electronic Absorption Spectroscopy," Edward Arnold (Publishers) Ltd., London, 1960, pp 64–65; (b) H. Batt, B. G. Gowenlock, and J. Trotman, *J. Chem. Soc.*, 2222 (1960).

(10) N. Thorne, *ibid.*, 2587 (1956).

(11) (a) *Cf.* S. N. Danilov and K. A. Oglobin, *Zh. Obshch. Khim.*, **22**, 2113 (1952); *Chem. Abstr.*, **48**, 1945 (1954). (b) *Cf.* M. S. Newman, *J. Amer. Chem. Soc.*, **75**, 4740 (1953).



(2)

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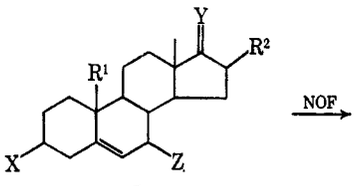
(6.35 and 7.65 μ) in the infrared, and characteristic nitrimine absorption [λ_{max} 267 mμ (480)] in the ultraviolet.[12] 5α-Fluoro-6-nitrimines were similarly prepared from a variety of steroid 5-enes; those cases in which 5α-fluoro-6-nitrimines were isolated and characterized are summarized in Table I. In general, intermediate 5α-fluoro-6-nitrimines were subsequently used without purification.



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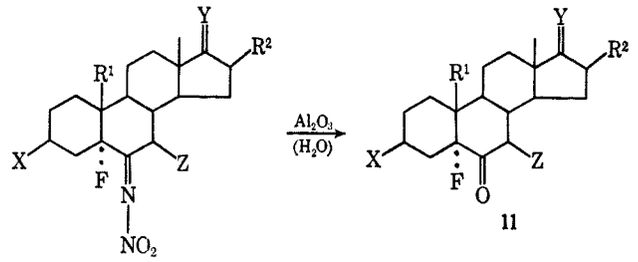
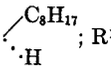
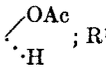


6 11

a, X = OAc; Y =  ; $R^1 = CH_3$; $R^2 = Z = H$

b, X = Cl; Y =  ; $R^1 = CH_3$; $R^2 = Z = H$

c, X = OAc; Y =  ; $R^1 = CH_3$; $R^2 = Z = H$

d, X = OAc; Y =  ; $R^1 = CH_3$; $R^2 = Z = H$

e, X = OAc; Y =  ; $R^1 = CH_3$; $R^2 = -CH_3$; Z = H

f, X = OAc; Y =  ; $R^1 = CH_3$; $R^2 = Z = H$

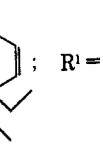
g, X = OH; Y =  ; $R^1 = CH_3$; $R^2 = Z = H$

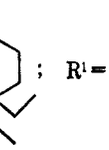
h, X = OAc; Y = =O; $R^1 = CH_3$; $R^2 = Z = H$

i, X = OAc; Y =  ; $R^1 = CH_3$; $R^2 = Z = H$

j, X = OH; Y =  ; $R^1 = CH_3$; $R^2 = Z = H$

k, X = OAc; Y =  ; $R^1 = CH_3$; $R^2 = Z = H$

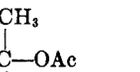
l, X = OAc; Y =  ; $R^1 = CH_3$; $R^2 = Z = H$

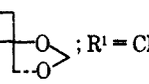
m, X = OH; Y =  ; $R^1 = CH_3$; $R^2 = Z = H$

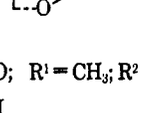
n, X = OAc; Y =  ; $R^1 = R^2 = Z = H$

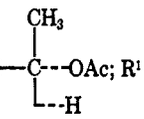
o, X = OAc; Y =  ; $R^1 = R^2 = Z = H$

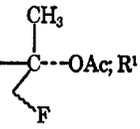
p, X = OAc; Y =  ; $R^1 = CH_3$; $R^2 = H$; Z = OAc

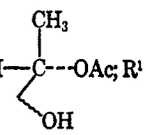
q, X = OAc; Y =  ; $R^1 = CH_3$; $R^2 = \cdots CH_3$; Z = H

r, X = OAc; Y =  ; $R^1 = CH_3$; $R^2 = Z = H$ (11-one)

s, X = OAc; Y =  ; $R^1 = CH_3$; $R^2 = Z = H$, Δ^{16}

t (5), X = OAc; Y =  ; $R^1 = CH_3$; $R^2 = Z = H$, Δ^{16}

t (6), X = OAc; Y =  ; $R^1 = CH_3$; $R^2 = =NNO_2$; Z = H

t (11), X = OAc; Y =  ; $R^1 = CH_3$; $R^2 = =O$; Z = H

Until recently, the structure of aliphatic nitrimines, from reaction of *t*-alkyl ketoximes and nitrosating agents and referred to as pernitroso compounds in the older literature, was controversial. Freeman[12] has established that these are, in fact, N-nitrimines, and this work completely agrees with his findings.

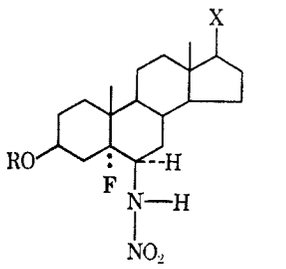
(12) For leading references and a proof of structure of nitrimines, see J. P. Freeman, *J. Org. Chem.*, **27**, 1309 (1962); **26**, 4190 (1961); *Chem. Ind.* (London), 1624 (1960).

TABLE I
CHARACTERIZATION DATA FOR 5α-FLUORO-6-NITRIMINES

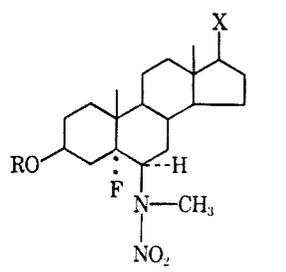
Steroid reactant	Product[a]	Yield,[b] %	Mp,[c] °C	[α]D, deg[d]	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	F, % Calcd	F, % Found	N, % Calcd	N, % Found
Cholesteryl acetate (**5a**)	5α-Fluoro-3β-hydroxycholestane-6-nitrimine acetate (**6a**)	72	158–163 (C–B) (D–G)	−68	$C_{29}H_{47}FN_2O_4$	68.79	68.74	9.35	9.58	3.78	3.85	5.53	5.41
Cholesteryl chloride (**5b**)	3β-Chloro-5α-fluorocholestane-6-nitrimine (**6b**)	69	123 (F)	−59	$C_{27}H_{44}ClFN_2O_2$	67.01	67.46	9.16	9.23	3.93	3.73	5.80	5.72
Androst-5-ene-3β,17β-diol diacetate (**5c**)[e]	5α-Fluoro-3β,17β-dihydroxyandrostane-6-nitrimine diacetate (**6c**)	52	128–130 (E)	−97	$C_{23}H_{33}FN_2O_6$	61.05	61.14	7.35	7.42	4.20	4.35	6.19	5.84
3β,17α-Dihydroxypregn-5-en-20-one diacetate (**5d**)	5α-Fluoro-3β,17α-dihydroxy-6-nitriminopregnan-20-one diacetate (**6d**)	68	185–187 (C–E)	−97 (dioxane)	$C_{25}H_{35}FN_2O_7$	60.71	60.70	7.13	7.29	3.84	3.86	5.66	5.37
Pregn-5-ene-3β,20β-diol diacetate (**5f**)[f]	5α-Fluoro-3β,20β-dihydroxypregnane-6-nitrimine diacetate (**6f**)	70	165–168 (A–F)	−63	$C_{25}H_{37}FN_2O_6$	62.48	62.48	7.76	7.53	3.96	3.98	5.83	5.86
16α-Methylpregn-15-ene-3β,20ξ-diol diacetate (**5q**)[g]	5α-Fluoro-16α-methyl-3β,20ξ-dihydroxypregnane-6-nitrimine diacetate (**6q**)[h]	67	189–191 (A–B)	−76	$C_{26}H_{39}FN_2O_6$	63.13	63.41	7.95	7.69	3.84		5.66	5.08
Estr-5-ene-3β,17β-diol diacetate (**5h**)	5α-Fluoro-3β,17β-dihydroxyestrane-6-nitrimine diacetate[i] (**6n**)	23	168–180 dec (B–C)	−93	$C_{22}H_{31}FN_2O_6$	60.26	59.92	7.12	7.23	4.33	4.76	6.39	5.99

[a] The infrared spectra show characteristic absorptions at 6.1 (C=N), 6.35 and 7.65 (NO_2), and 8.55–8.65 μ (F). The ultraviolet spectra show a maximum absorption in the region 267 mμ (ε *ca.* 500). The F^{19} nmr spectra (56.4 Mc/sec) show two peaks of equal intensity in the +9000- to +9100-cps region with a separation varying from 40 to 50 cps. (10β-methyl series) (*cf.* ref 34). The F^{19} chemical shifts for **6a** were uncorrectly reported to be +8660 and +9160 cps (external trichlorofluoromethane) in ref 1a. The actual values are +9008 and +9056 cps (internal trichlorofluoromethane). [b] Yield of recrystallized product and in general not optimum. [c] Analytical melting point. Recrystallization solvents: A, acetone; B, hexane; C, methylene chloride; D, ethanol; E, methanol; F, petroleum ether (bp 30–60°); G, ether. [d] Unless noted otherwise, rotations were measured at 24° in chloroform at a concentration of 1 to 1.5%. [e] Reference 18. [f] H. Hirshmann, M. A. Davis, and F. B. Hirshmann, *J. Biol. Chem.*, **192**, 115 (1951). [g] A mixture of 20 epimers was used for this experiment prepared by reducing 16α-methyl-3β-hydroxypregn-5-en-20-one acetate (**5e**) [R. E. Marker and Harry M. Crooks, Jr., *J. Amer. Chem. Soc.*, **64**, 1280 (1942)] with excess sodium borohydride and acetylation of the resultant diol with acetic anhydride and pyridine. [h] The author is indebted to Dr. W. C. Ripka for this experiment. [i] The F^{19} nmr spectrum (56.4 Mc/sec) shows three peaks (w, s, w,) at +9367, +9407, and +9447 cps relative to internal trichlorofluoromethane.

Reduction of **6a** with lithium hydrotri-*t*-butoxyaluminate[13] in tetrahydrofuran or with sodium borohydride in ethanol and dioxane gave 5α-fluoro-6β-nitramine **7a** [λ_{max} 235 mμ (ε 7600)].[14,15]



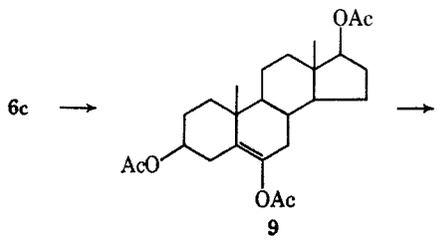
7a, R = Ac; X = C_8H_{17}
b, R = Ac; X = OAc
c, R = H; X = HC(CH3)OH



8a, R = Ac; X = OAc
b, R = H; X = HC(CH3)OH

Reduction with lithium aluminum hydride in ether or tetrahydrofuran results in cleavage of acetates to alcohols and gives lower yields of fluoronitramines.

5α,6β Configuration of 5-fluoro-6-nitramines was determined as follows. Fluoronitrimine **6c** was reduced with zinc dust in acetic acid to give androst-5-ene-3β,6,17β-triol triacetate (**9**) which was then hydrolyzed to the known 3β,17-β-dihydroxyandrostan-6-one (**10**).[16] This fixes the position of the nitrogen moiety at C-6. Reaction of nitrosyl chloride and steroid 5-enes has



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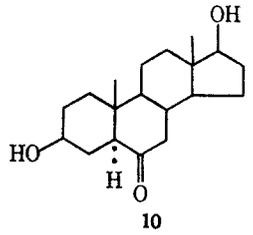

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previously been shown to give 5α-chloro-6β-nitro substitution,[6] and, since reaction of NOF with 5-enes parallels nitrosyl chloride reaction up to a point (see below),

(13) H. C. Brown and R. F. McFarlin, *J. Amer. Chem. Soc.*, **80**, 5372 (1958); J. Fajkos, *Collect. Czech. Chem. Commun.*, **24**, 2284 (1959).

(14) Infrared spectra of 5α-fluoro-6β-nitramine **7a** and other 5α-fluoro-6β-nitramines (Nujol) show carbonyl absorption of the 3β-acetate at 5.87 μ considerably outside the expected range for saturated steroid acetates, 5.73–5.77 μ. The NH bands are at 3.13 and 3.20 μ. However, when the spectrum is taken in chloroform, acetate carbonyl absorption is at 5.79 μ and NH absorptions are at 2.96 and 3.05 μ. The magnitude and direction of the carbonyl absorption shifts are similar to those of β-amino α,β-unsaturated esters, salicylates, and related compounds, and are ascribed to chelation of the ester carbonyl and the hydrogen atom of the nitramine moiety. Conversion of nitramine **7b** into the N-methyl derivative **8a** of nitramine **7b** has normal carbonyl absorption [$\lambda_{max}^{KBr\ or\ Nujol}$ 5.75 μ]. Also, 5α-fluoroandrostane-3β,6β,17β-triol 3,17-diacetate (**16b**) exhibits analogous behavior: $\lambda_{max}^{CCl_4}$ 2.77, 2.87 (OH), 5.77 (C-3 and C-17 acetate carbonyls); λ_{max}^{Nujol} 2.89 (OH, sharp), 5.76 (C-17 acetate carbonyl), 5.85 μ (hydrogen bonded C-3 acetate carbonyl). A Dreiding model of the 3β-acetoxy-5α-fluoro-6β-nitramine **7a** shows that, if ring A assumes a boat conformation, the 3β-acetate carbonyl and the 6β-nitramino hydrogen are in perfect proximity for hydrogen bonding. *Cf.* L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 1960, pp 181, 184.

(15) Nitramines show a λ_{max} 230–250 mμ (ε 6000–8000). *Cf.* R. N. Haszeldine and J. Jander, *J. Chem. Soc.*, 691 (1954).

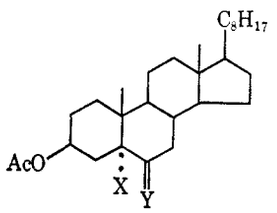
(16) H. B. MacPhillamy and C. R. Scholz, *J. Amer. Chem. Soc.*, **74**, 5512 (1952).

the fluorine should be 5α. Reduction of 5α-6-keto steroids with lithium hydrotri-*t*-butoxyaluminate in tetrahydrofuran has been shown to give the 6β-hydroxy epimer,[17] and it is reasonable to expect the same for the reduction of a 5α-fluoro-6-nitrimino steroid. Reductive elimination of the elements of $FNHNO_2$ from fluoronitramine **7b** with zinc dust in acetic acid to give androst-5-ene-3β,17β-diol diacetate[18] (**5c**) along with 5α-fluoroandrostane-3β-17β-diol diacetate (**13**) agrees with a *trans*-diaxial orientation. The H nmr ($CDCl_3$) of fluoronitramine **7b** shows the 3α proton to be geminal to the C-3 acetoxyl group as a broad band at 5.11 ppm with a band width at half-height of 24 cps, showing it to be axial and, therefore, the A–B ring juncture *trans*[6c] and the fluorine 5α. The 6α proton geminal to the nitramino moiety is a triplet at 4.53 ppm (J = *ca.* 7 cps); C-19 resonance is at 1.19 ppm which corresponds to a deshielding of approximately 0.25 ppm conforming to that expected for a 6β but not for a 6α substituent.[19] Additional evidence presented below corroborates these structural and stereochemical assignments.

Primary nitramines are weak acids and form water-soluble salts.[20] 5α-Fluoro-6β-nitramine **7a** was converted into the salt by treatment with sodium hydroxide in ethanol followed by precipitation of product with water. It was crystallized from aqueous N,N-dimethylformamide. It is soluble in hot water and acts as a surfactant. Because steroid nitramines form salts, they can be isolated from reaction mixtures by extraction with dilute sodium bicarbonate or sodium hydroxide and then recovered by acidification with acetic acid.

Steroid nitramines are decomposed by dilute mineral acids with complete loss of the nitrogen moiety;[21] the fate of the steroid nucleus is under investigation. 5α-Fluoro-6β-nitramines can be alkylated[22] in high yield with methyl iodide. Spectral evidence shows that alkylation takes place on nitrogen and not on oxygen as occurs with aromatic nitramines.[23] In the infrared, 5α-fluoro-6β-(N-methylnitramine) **8a** shows a strong, sharp band characteristic of a nitramino group (6.43 and 7.95 μ).[24] The ultraviolet spectrum exhibits λ_{max} 216 mμ (ε 8050), which is similar to the parent 5α-fluoro-6β-nitramine **7b** but is shifted to shorter wavelength by 19 mμ. The H nmr spectrum shows a sharp singlet at 3.98 ppm ($N-CH_3$). Attempts to alkylate intramolecularly, *i.e.*, form the anion of **7a** and displace fluoride ion to form 5β,6β-(N-nitroaziridine) **12**, were unsuccessful.[25]

5α-Fluoro-6-ones.—Percolation of a benzene solution of 5α-fluoro-6-nitrimine **6a** through a neutral alumina (activity III) column[26] resulted in quantitative hydrolysis to give 5α-fluoro-3β-hydroxycholestan-6-one acetate (**11a**)[27] further characterized as the oxime **14a**. The fluorine was reductively eliminated with zinc dust in acetic acid to give 3β-hydroxycholestan-6-one 3-acetate (**14b**).[28] A variety of 5α-fluoro-6-nitrimines re-



14a, X = F; Y = =NOH
b, X = H; Y = =O

act smoothly with neutral alumina (activity III) to give 5α-fluoro-6-ones (Table II). In every case the alumina became quite warm during the hydrolysis, particularly in large-scale runs. Alternatively, 5α-fluoro-6-nitrimine **6b** was hydrolyzed to 5α-fluoro-6-one **11b** by refluxing in aqueous dioxane for 30 hr; shorter periods resulted in partial conversion into fluoro ketone. In general, when fluoro ketone is desired, the steroid olefin is treated with NOF and the crude product is absorbed onto alumina and immediately eluted. Since the yield of 5α-fluoro-6-nitrimine from steroid olefin is about 70% (in the absence of complicating factors such as functional groups reactive to NOF), the over-all yield from 5-enes to 5α-fluoro-6-ones is about 70%.

Henbest and Wrigley[27] reported that 5β,6β-oxidocholestan-3β-ol acetate (**15a**) reacts with boron trifluoride etherate to give a fluorohydrin which they assigned 5α-fluoro-6β-hydroxy structure **16a** (Scheme I); when treated with potassium *t*-butoxide in *t*-butyl alcohol, **16a** gave 5β,6β-oxidocholestan-3β-ol (**15b**). Fluorohydrin **16a** was oxidized with 8 *N* chromic acid[29] in acetone to give a fluoro ketone with properties very similar to fluoro ketone **11a**. To substantiate these structures, fluoro ketone **11a** was reduced with lithium hydrotri-*t*-butyoxyaluminate to a fluorohydrin having the same properties as reported by Henbest and Wrigley for **16a**. Fluorohydrin **16a** was treated with potassium *t*-butoxide in *t*-butyl alcohol at room temperature for 16 hr to give partial conversion into 5β,6β-oxidocholestan-3β-ol (**15b**).[30] Fluorohydrin **16b** was hydrolyzed with methanol and hydrochloric acid to give fluorodiol **17**[27] which was oxidized with excess 8 *N* chromic acid in acetone[29] to give fluorodione **18**. Treatment of **18** with sodium acetate in refluxing meth-

(17) H. Bowers, E. Denot, L. Cúellar Ibañez, Ma. Elena Cabezas, and G. J. Ringold, *J. Org. Chem.*, **27**, 1862 (1962).

(18) L. Ruzicka and A. Wettstein, *Helv. Chim. Acta*, **18**, 1264 (1935).

(19) (a) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day Inc., San Francisco, Calif., 1964, pp 13–24, 29–31. (b) Observations made in this laboratory show that the deshielding effect of 5α-F on the 10β-methyl is about 5 cps.

(20) See ref 5b, p 494.

(21) See ref 5b, p 491.

(22) See ref 5b, p 495.

(23) E. D. F. Degering, "An Outline of Organic Nitrogen Compounds," University Lithoprinters, Ypsilanti, Mich., 1945, p 316.

(24) See ref 14, p 302.

(25) Reaction of potassium salts of primary nitramines with small alkyl iodides gives mostly N,N-dialkylnitramines, but the proportion of O,N-dialkyl isomer increases with the bulk of the alkyl group; *cf.* ref 22. Although treatment of 5α-fluorocholestane-3β,6β-diol 3-acetate with potassium *t*-butoxide in *t*-butyl alcohol gives β-oxide **15b**, stereochemically a situation analogous to formation of 5β,6β-(N-nitroaziridine) (**12**) from 5α-fluoro-6β-nitramine (**7a**), treatment of **7a** with potassium *t*-butoxide in *t*-butyl alcohol, potassium or sodium hydroxide in methanol, or potassium carbonate in dioxane at elevated temperatures gave no aziridine. This agrees with earlier observations that bulky alkyl groups give mainly O alkylation of the ambident anion, a course which is probably sterically precluded for steroid 5α-fluoro-6β-nitramines.

(26) Neutral Woelm alumina (activity grade III). Activity grade I gave no hydrolysis and the fluoronitrimine was recovered unchanged.

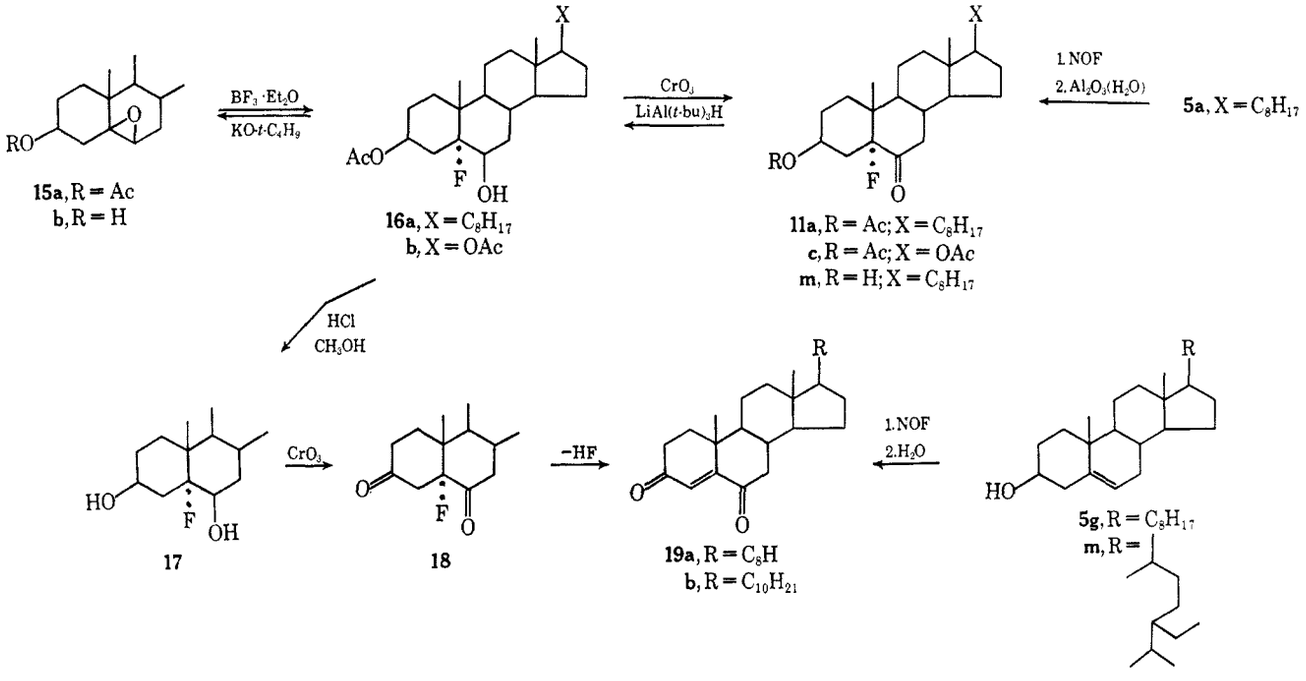
(27) H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 4765 (1957).

(28) R. M. Dodson and B. Riegel, *J. Org. Chem.*, **13**, 424 (1948).

(29) (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).

(30) (a) A. T. Rowland and H. R. Nace, *J. Amer. Chem. Soc.*, **82**, 2833 (1960); (b) R. A. Baxter and F. S. Spring, *J. Chem. Soc.*, 613 (1943).

SCHEME I



anol resulted in loss of hydrogen fluoride[31] to give known cholest-4-ene-3,6-dione (**19a**).[32] Interestingly, reaction of cholesterol (**5g**) with NOF followed by chromatography of the total crude product on neutral alumina furnished cholest-4-ene-3,6-dione (**19a**) as the major product (21% yield) along with 5α-fluoro-3β-hydroxycholestan-6-one (**11g**) (10% yield). In its infrared spectrum, ketone **11g** shows strong carbonyl absorption at 5.81 μ which represents a 6-carbonyl hypsochromic shift of 0.05 μ (20 cm^{-1}) as would be expected from a 5α-fluorine substituent.[33] The ultraviolet spectrum shows λ_{max}^{EtOH} 300 mμ (ε 76), which represents a bathochromic shift of about 13 mμ compared to the nonfluorinated 5α-6-keto parent [λ_{max}^{EtOH} 287 mμ (ε 21)], and is that expected for a ketone bearing an α-halo substituent in an axial conformation.[34] The F^{19} nmr (56.4 Mc/sec) shows the 5α-fluorine as an apparent doublet at +8950 and +8997 cps from internal trichlorofluoromethane.[35] In the H nmr, 19-H's absorb at 0.90 ppm. Similarly, β-sitosterol (**5m**) gave enedione **19b** as well as 5α-fluoro-6-one **11m** (see Table II).

Reaction of NOF and 19-nor steroid 5-enes is more complicated because it parallels both reaction of NOF with trimethylethylene (1) and C-10-methyl steroid 5-enes. Estr-5-ene-3β,17β-diol diacetate[36] (**5n**) reacted with NOF to give a green oil (Scheme II) which on trituration with benzene gave a 20% yield of a white solid (see Table II). The solid dissolved in methylene chloride to give a clear blue solution. Dilution with acetone and cooling deposited well-formed colorless crystals which were assigned fluoronitroso dimer structure **20a** [λ_{max} 297 mμ (ε 8650)].[9] On standing in methanol–methylene chloride solution at room temperature, fluoronitroso dimer **20a** dissociated to monomer and isomerized[37] to 5α-fluoro-6 oxime **21a**. When the crude reaction mixture from **5n** and NOF was chromatographed on alumina without isolating **20a**, 5α-fluoro-3β,17β-dihydroxyestran-6-one diacetate (**11n**, see Table II) was first obtained and then a substance,[38] $C_{22}H_{33}NO_6$, assigned 5α-hydroxy-6-oximino structure **22**. Since in the H nmr the 3α proton is a broad band at 5.0 ppm with a band width at half-width of about 25 cps, it is axial and the A–B ring juncture is *trans;* the hydroxyl group is then 5α.[6c] Similarly, 17α-ethynyl derivative **5o** afforded 5α-fluoro-17α-ethynyl-6-one **11o** along with the fluoronitroso dimer **20b**[39] (see Table II).

The 5α-fluoro-3β-acetate 6-ones are very useful for synthesizing 6,6-difluoro-4-ene-3-keto steroid hormone analogs.[1b,c]

5α-Fluoro-4-nitrimines and 5α-Fluoro-4-ones.—Reaction of androst-4-en-17β-ol acetate[40] (**23a**) with NOF gave 5α-fluoro-4-nitriminoandrostan-17β-ol acetate (**24a**) in 67% yield. The infrared and ultraviolet spectra show essentially the identical characteristic peaks and maxima as those of the 5α-fluoro-6-nitrimines. Adsorption of 5α-fluoro-4-nitrimine **24a** onto neutral alumina and delayed elution[41] of the product gave 5α-fluoro-

(31) A. Bowers, *et al.*, *J. Amer. Chem. Soc.*, **84**, 1050 (1962).
(32) L. Fieser, *ibid.*, **75**, 4386 (1953).
(33) (a) See ref 14, pp 139, 140; (b) A. H. Nathan, B. J. Magerlein, and J. A. Hogg, *J. Org. Chem.*, **24**, 1517 (1959); (c) R. Deghenghi and R. Gaudry, *Can. J. Chem.*, **39**, 1553 (1961).
(34) Reference 9a, p 57.
(35) All 5α-fluoro-6-ones prepared in the 10β-methyl series have similar F^{19} nmr spectra, *i.e.*, a broad doublet with peaks of equal intensity at +8900 to +9050 cps with a separation from 40 to 50 cps. Although this separation was attributed to J_{HaxFax} (see ref 1b), Dr. R. F. Merritt and Dr. F. A. Johnson have pointed out in a private communication that such an interpretation is an incorrect oversimplification and the observed spectrum represents the X portion of an ABX system; the spread between peaks then represents the sum of J_{AX} and J_{BX}. This point is receiving further attention.
(36) J. Hartman, *J. Amer. Chem. Soc.*, **77**, 5151 (1956).
(37) For another example of formation of a steroid nitroso dimer and isomerization of nitroso monomer to the corresponding oxime, see D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *ibid.*, **83**, 4076 (1961).
(38) This compound was first isolated by Dr. W. C. Ripka of this laboratory.
(39) The ethynyl group is slowly attacked by NOF under conditions used for addition to the 5,6 double bond. However, with excess NOF at 25° the ethynyl group does react. This reaction will be the subject of a future report.
(40) R. E. Marker, E. L. Wittle, and B. F. Tullar, *ibid.*, **62**, 123 (1940).
(41) Elution of the reaction products before 1 hr resulted in only partial conversion of nitrimine **24a**.

TABLE II

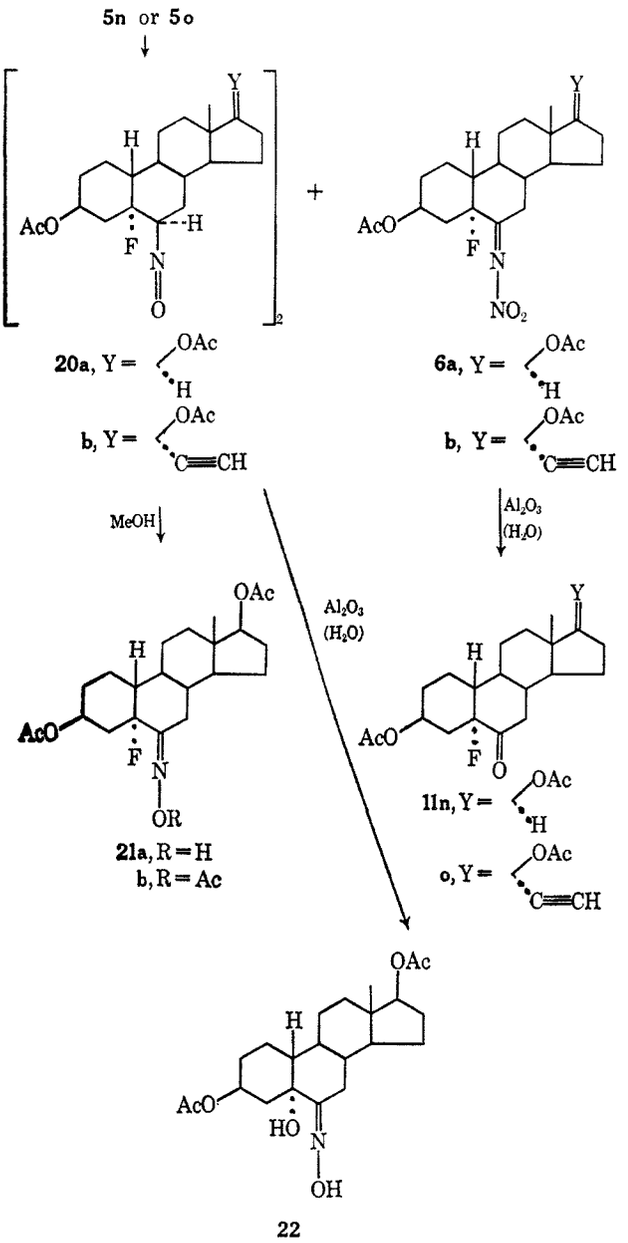
CHARACTERIZATION DATA FOR 5α-FLUORO-6-ONES

Steroid reactant	Product[a]	Yield, %[b]	Mp, °C[c]	[α]D, deg[d]	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	F, % Calcd	F, % Found
Cholesteryl acetate (**5a**)	5α-Fluoro-3β-hydroxycholestan-6-one acetate (**11a**)[e]	63	121–122	−7	$C_{29}H_{47}FO_3$	75.28	75.59	10.24	10.13	4.11	4.13
Cholesteryl chloride (**5b**)	3β-Chloro-5α-fluorocholestan-6-one (**11b**)[f]	74	113–115	−5	$C_{27}H_{44}ClFO$	73.85	73.75	10.10	9.97	4.33	4.26
Androst-5-ene-3β,17β-diol diacetate (**5c**)	5α-Fluoro-3β,17β-dihydroxyandrostan-6-one diacetate (**11c**)	68	185–186	−27	$C_{23}H_{33}FO_5$	67.62	67.51	8.14	8.18	4.66	4.70
3β,17α-Dihydroxypregn-5-en-20-one diacetate (**5d**)	5α-Fluoro-3β,17α-dihydroxypregnane-6,20-dione diacetate (**11d**)[g]	75	268.5–269.5	−28	$C_{25}H_{35}FO_6$	66.64	66.73	7.83	7.81	4.22	4.26
3β-Hydroxy-16α-methylpregn-5-en-20-one acetate (**5e**)[h]	5α-Fluoro-3β-hydroxy-16α-methylpregnane-6,20-dione acetate (**11e**)	53	183–187	+30	$C_{24}H_{35}FO_4$	70.91	71.16 71.00	8.68	8.74	4.67	5.05
Pregn-5-ene-3β,20β-diol diacetate (**5f**)	5α-Fluoro-3β,20β-dihydroxypregnan-6-one diacetate (**11f**)	65	160–162	±0	$C_{25}H_{37}FO_5$	68.78	69.09	8.54	8.70	4.36	4.58
Cholesterol (**5g**)	5α-Fluoro-3β-hydroxycholestan-6-one (**11g**)[i]	17	75–78 121–122	+9	$C_{27}H_{45}FO_2$	77.09	77.23	10.78	10.66	4.51	4.28 5.12
3β-Hydroxyandrost-5-en-17-one acetate (**5h**)	5α-Fluoro-3β-hydroxyandrostane-6,17-dione acetate (**11h**)	71	188–190.5	+55	$C_{21}H_{29}FO_4$	69.21	69.58 69.11	8.02	8.04 8.09	5.22	5.15
3β-Hydroxypregn-5-en-20-one acetate (**5i**)	5α-Fluoro-3β-hydroxypregnane-6,20-dione acetate (**11i**)	71	155–157	+42	$C_{23}H_{33}FO_4$	70.38	70.26 70.13	8.48	8.43 8.51	4.83	4.83
3β,17α-Dihydroxypregn-5-en-20-one 17-acetate (**5j**)	5α-Fluoro-3β,17α-dihydroxypregnane-6,20-dione 17-acetate (**11j**)	28[j]	223–225	−35 (dioxane)	$C_{23}H_{33}FO_5$	67.62		8.14	8.22	4.66	4.63
17α-Methylandrost-5-ene-3β,17β-diol diacetate (**5k**)	5α-Fluoro-3β,17β-dihydroxy-17α-methylandrostan-6-one diacetate (**11k**)	63	182–183	−24	$C_{24}H_{35}FO_5$	68.38	68.33	8.13	8.37	4.50	4.49
Stigmasterol acetate (**5l**)	5α-Fluoro-3β-hydroxystigmast-22-en-6-one acetate (**11l**)	73	163–164	±0	$C_{31}H_{49}FO_3$	76.18	76.65	10.11	10.17	5.88	5.81
β-Sitosterol (**5m**)	5α-Fluoro-3β-hydroxystigmastan-6-one (**11m**)[k]	34	114.5–115.5	−4	$C_{29}H_{49}FO_2 \cdot {}^1/_2H_2O$	76.10	76.29	11.01	11.05	4.15	4.55
Estr-5-ene-3β,17β-diol diacetate (**5n**)	5α-Fluoro-3β,17β-dihydroxyestran-6-one diacetate (**11n**)[l]	35	173–175 (A–B)	−18	$C_{22}H_{31}FO_5$	66.98	67.44	7.92	7.96	4.82	4.90
17α-Ethynylestr-5-ene-3β,17β-diol diacetate (**5o**)[m]	5α-Fluoro-3β,17β-dihydroxy-17α-ethynyl estran-6-one (**11o**)	20[n]	187–194 (E)	−40	$C_{24}H_{31}FO_5$	68.67	68.65	7.47	7.68	4.54	5.16
Cholest-5-ene-3β,7ξ-diol diacetate (**5p**)[o]	5α-Fluoro-3β,7ξ-dihydroxycholestan-6-one diacetate (**11p**)	10	166–168 (E)	−42	$C_{31}H_{49}FO_5$	71.50	71.12	9.48	9.54	3.66	3.65
16α-Methylpregn-5-ene-3β,20ξ-diol diacetate (**5q**)[p]	5α-Fluoro-3β,20ξ-dihydroxy-16α-methylpregnan-6-one diacetate (**11q**)[q]	65	166–176	+2	$C_{26}H_{39}FO_5$	69.30	69.56	8.73	8.71	4.21	4.69
17,20;20,21-Bismethylenedioxy-3β-hydroxypregn-5-en-11-one acetate (**5r**)[r]	5α-Fluoro-17,20;20,21-bismethylenedioxy-3β-hydroxypregnane-6,11-dione acetate (**11r**)	50	213–215	−60	$C_{28}H_{33}FO_8$	62.48	62.72	6.93	7.03	3.96	4.09
3β-Hydroxypregna-5,16-dien-20-one acetate (**5s**)[s]	5α-Fluoro-3β-hydroxypregn-16-ene-6,20-dione acetate (**11s**)	41	206–207 (A–B)	+10 (dioxane)	$C_{23}H_{31}FO_4$	70.74	70.56	8.00	8.23	4.87	4.10
	5α-Fluoro-16-nitro-3β-hydroxypregn-16-ene-6,20-dione acetate (**49**)[t]	9	253–258 (A–B)	+4 (dioxane)	$C_{23}H_{30}FNO_6$	63.43	63.35	6.95	7.06	4.37	4.06
Pregna-5,16-diene-3β,-20α-diol diacetate (**5t**)[u]	5α-Fluoro-3β,17ξ-trihydroxypregnane-6,16-dione 3,20-diacetate (**11t**)										
	a	21	228–230 (A–B) (C–E)	−118 (dioxane)	$C_{29}H_{35}FO$	64.36	64.23	7.56	7.51	4.08	4.25
	b	7	288 (A)	−121 (dioxane)			64.37		7.36		4.87

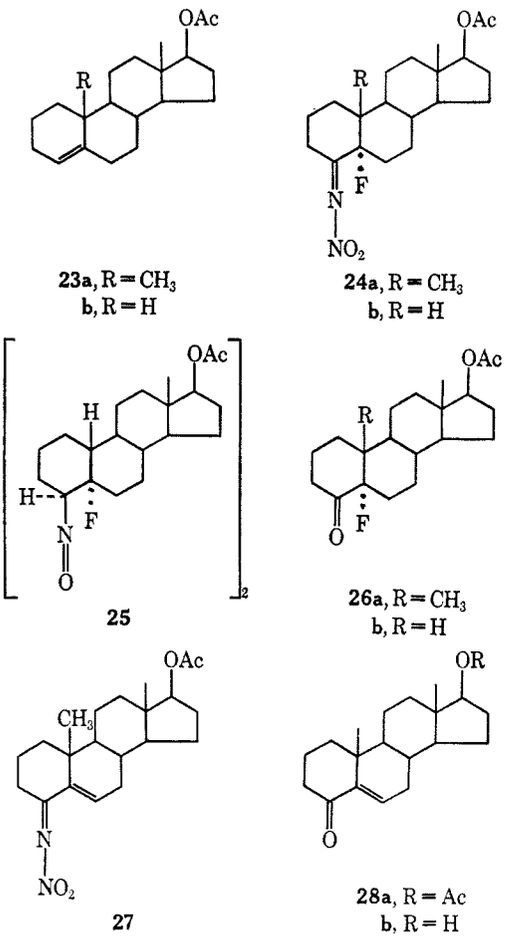
[a] The infrared spectra showed a sharp, medium intensity absorption in the 8.5–8.6-μ region and the ultraviolet violet spectra for those compounds not having interfering chromophores display a maximum in the 295- to 300-mμ region (ε 25 to 80). The F^{19} nmr (56.4 cps) spectra show two peaks of equal intensity in the +8800- to +9000-cps region (relative to internal trichlorofluoromethane) with a separation varying from approximately 40 to 50 cps with the exception of the estrane derivatives which display a triplet (w, s, w) with an apparent *J* of *ca.* 35 cps centered at +9270 for **11n**. [b] Yield of recrystallized product; in general not optimum yield. [c] Analytical melting point. Recrystallization solvents: A, acetone; B, hexane; C, methylene chloride; D, ethanol; E, methanol; F, petroleum ether (bp 37–56°); G, ether; and H, water. [d] Unless noted otherwise, rotations were measured at 23 to 24° in chloroform at a concentration of 1 to 2.5%. [e] Reference 28. [f] **6b** was also hydrolyzed to **11b** in nearly quantitative yield by heating under reflux in water–dioxane for 30 hr in the presence of an excess of urea. *Cf.* S. G. Brooks, *et al.*, *J. Chem. Soc.*, 4614 (1958). [g] Reference 35. [h] R. E. Marker and H. M. Crooks, Jr., *J. Amer. Chem. Soc.*, **64**, 1280 (1942). [i] The major product isolated was cholest-4-ene-3,6-dione (**19a**); *cf.* Experimental Section. D. L. Labler, Czechoslovak Academy of Science Institute of Organic Chemistry and Biochemistry (private communication) reports the following physical constants for **11g** prepared by another route: mp 68–70, 103–104, 120° (Kofler block); $[\alpha]^{20}D$ −8° (chloroform). The infrared spectra of Dr. Labler's sample and that for the material prepared here were entirely identical. [j] The low yield of product in this run was due to inadvertent loss of products during work-up. [k] β-Sitosterol (**5m**) was treated with excess nitrosyl fluoride and the crude nitrimine mixture was heated to reflux for 30 hr in dioxane–water in the presence of excess urea to afford a mixture of **11m** and Δ^4-sitostene-3,6-dione (**14b**) [E. Fernholz, *Ann.*, **508**, 215 (1934)]. Separation by chromatography on neutral alumina (activity III) followed recrystallization afforded **11m** and enedione **30b**: mp 112–115, 145° dec; $[\alpha]D$ −37°; λ_{max} 252 mμ (ε 10,400) and 320 (22). *Anal.* Calcd for $C_{29}H_{46}O_2$: C, 81.63; H, 10.87. Found: C, 81.54; H, 10.92. [l] Bis(5α-fluoro-6β-nitrosoestrane-

3β,17β-diol diacetate) (**20a**) was isolated by direct crystallization in 20% yield from reaction mixture of **5n** and excess nitrosyl fluoride. Recrystallization from acetone–methylene chloride afforded an analytical sample having the following properties: mp 166–169°; $[\alpha]_D$ −42°; λ_{max} 297 mμ (ε 8650). *Anal.* Calcd for $(C_{22}H_{32}FNO_5)_2$: C, 64.50; H, 7.88; F, 4.64; N, 3.42; mol wt, 818.96. Found: C, 64.72; H, 7.95; F, 4.79; N, 3.35; mol wt, 791 (osmotic pressure in ethylene dichloride). [m] **5o** was prepared from 17α-ethynylestr-5-ene-3β,17β-diol 17-acetate [L. H. Knox, *et al.*, *J. Amer. Chem. Soc.*, **82**, 1230 (1960)], acetic anhydride, and pyridine. An analytical sample crystallized from methanol showed mp 195–200° and $[\alpha]_D$ −63°. *Anal.* Calcd for $C_{24}H_{32}O_4$: C, 75.00; H, 8.33. Found: C, 75.00; H, 8.47. [n] The formation of fluoronitrimine **6p** was accompanied by some of fluoronitroso dimer **20b**, the characterization of which remains incomplete. [o] The configuration of the hydroxyl group at C-7 is not known with certainty but is most likely β; *cf.* O. Wintersteiner and W. L. Ruigh, *J. Amer. Chem. Soc.*, **64**, 2453 (1942). [p] See footnote *h*, Table I. [q] The author is indebted to Dr. W. C. Ripka for this result. [r] **5r** was prepared from 17,20;20,21-bismethylenedioxy-3β-hydroxyprena-3,5-dien-11-one acetate [J. H. Fried, A. N. Nutile, and G. E. Arth, *J. Org. Chem.*, **26**, 976 (1961)] by reduction with sodium borohydride in methanol and tetrahydrofuran to the Δ^5-3β,11β-diol, followed by acetylation at C-3 with acetic anhydride and pyridine, and oxidation of the 11β-ol with excess Jones reagent to the corresponding ketone **5r**: mp 146–150°; $[\alpha]_D$ −110°; λ_{max} 293 mμ (ε 27); λ_{max} 5.76, 5.88, 8.04 μ. *Anal.* Calcd for $C_{25}H_{34}O_7$: C, 67.24; H, 7.68. Found: C, 67.21; H, 7.76. [s] Reference 49. [t] λ_{max} 266 mμ (ε 5760). *Anal.* Calcd for $C_{23}H_{30}FNO_6$: N, 3.21. Found: N, 3,19. [u] Reference 50.

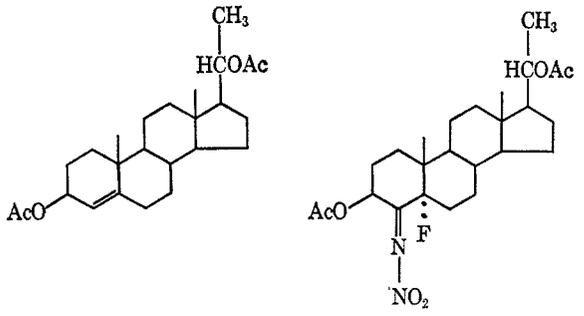
SCHEME II



17β-hydroxyandrostan-4-one acetate (**26a**) and a trace amount (*ca.* 0.5%) of 4-nitriminoandrost-5-en-17β-ol acetate (**27**). The F^{19} nmr was essentially identical with that of 5α-fluoro-4-nitrimine **24a**. Moreover, reaction of 5α-fluoro-4-one **26a** with lithium bromide and lithium carbonate in N,N-dimethylformamide[42] at reflux gave known 17β-hydroxyandrost-5-en-4-one acetate (**28a**)[43] which was hydrolyzed to 17β-ol **28b**.



The presence of a 3β-acetoxyl group on the steroid 4-ene did not seriously hinder the formation of the



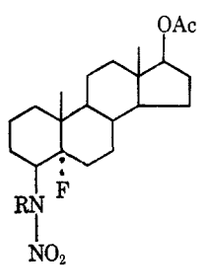
(42) See ref 33c.

(43) A. Butenandt and H. Danneberg, *Chem. Ber.*, **71**, 1681 (1938); A. Butenandt and G. Ruhenstroth-Bauer, *ibid.*, **77**, 397 (1944).

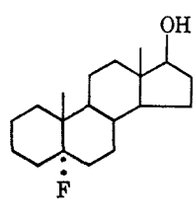
fluoronitrimine. Treatment of pregn-4-ene-3β,20β-diol diacetate[44] (**29**) with NOF gave 5α-fluoro-4-nitrimine **30**.

Like 19 nor steroid 5-enes, estr-4-en-17β-ol acetate (**23b**)[45] undergoes reaction with nitrosyl fluoride to give both 5α-fluoro-4-nitrimine **24b** and 5-fluoro-4β-nitrosoestran-17β-ol acetate dimer (**25**). Nitroso dimer **25** [λ_{max}^{EtOH} 300 mμ (ϵ 5120)] crystallized directly from the crude reaction mixture in 23% yield. 5α-Fluoro-4-nitrimine **24b** in the filtrate was converted into 5α-fluoro-17β-hydroxyestran-4-one acetate (**26b**) by alumina chromatography. Structural assignments for **24b**, **25**, and **26b** are based on the same considerations used for **24a**, **20a**, **11a**, and **26a**.[46]

Reduction of 5α-fluoro-4-nitrimine **24a** with sodium borohydride in dioxane and ethanol solution gave 5α-fluoro-4β-nitramine **31a** [λ_{max}^{EtOH} 236 mμ (ϵ 7800)]. When nitramine **31a** was treated with excess methyl iodide in acetone, it gave 5α-fluoro-4β-(N-methyl nitramino)androstan-17β-ol acetate (**31b**). 4β configuration in **31a** and **31b** was assigned in analogy with the reduction of 5α-fluoro-6-nitrimines and because the H-19 resonances are located at 1.00 and 1.15 ppm, respectively, corresponding to deshielding of the C-19 methyl of about 0.14 and 0.30 ppm, respectively, as expected for a 4β substituent but not for a 4α substituent.[19] Attempted reduction of 5α-fluoro-4β-(N-methylnitramine) **31b** with excess lithium aluminum hydride in ether at room temperature for 3 days was unsuccessful; the nitramino moiety remained intact. However, when **31b** was treated with excess lithium aluminum hydride in refluxing tetrahydrofuran for 15 hr, the carbon–nitrogen bond was cleaved as well as the 17β-acetate to afford 5α-fluoroandrostan-17β-ol (**32**).



31a, R = H
b, R = CH_3



32

Reaction of NOF with cholest-2-ene (**33**)[47] proceeded sluggishly even at 25° to give after chromatography of the crude reaction low yields of a nitro olefin (**34**)[48] and known 2α-fluorocholestan-3-one (**35**).[49] See Scheme III. Reduction with zinc dust and acetic acid transformed **34** into the known cholestan-3-one (**36**)[50] indicating that the nitro group is at C-3.

(44) B. Camerino and C. G. Alberti, *Gazz. Chim. Ital.*, **85**, 51 (1955).

(45) M. S. de Winter, C. M. Siegmann, and S. A. Szpifogel, *Chem. Ind.* (London), 905 (1959).

(46) The ultraviolet and infrared spectra of the 5α-fluoro-4- and -6-ones and 5α-fluoro-4- and -6-nitrimines of the 10β-methyl and 19-nor series, respectively, are essentially identical with respect to the positions of the pertinent absorption bands. Moreover, the [α]D's of corresponding pairs of fluoro ketones in the two series are very similar in magnitude and sign.

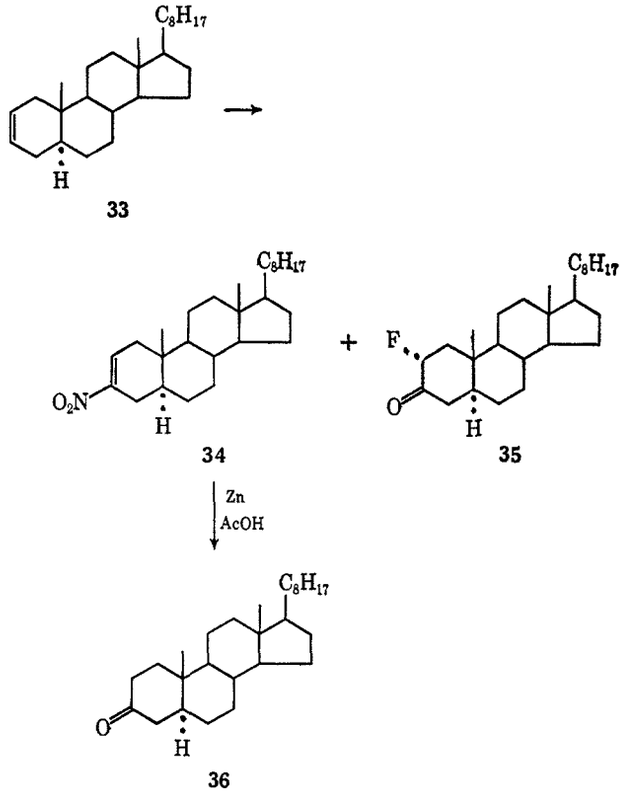
(47) L. Fieser, *J. Amer. Chem. Soc.*, **79**, 4122 (1957).

(48) The spectral data agree with those reported for steroid 6-nitro-6-enes except that ϵ is much greater and the double bond adsorption is very intense in the infrared spectrum; *cf.* C. E. Anagnostopoulos and L. F. Fieser, *ibid.*, **76**, 532 (1954).

(49) E. Jensen, *J. Org. Chem.*, **23**, 1406 (1958).

(50) L. F. Fieser, *J. Amer. Chem. Soc.*, **75**, 4386 (1953).

SCHEME III
REACTION OF NITROSYL FLUORIDE AND STEROID 2-ENES



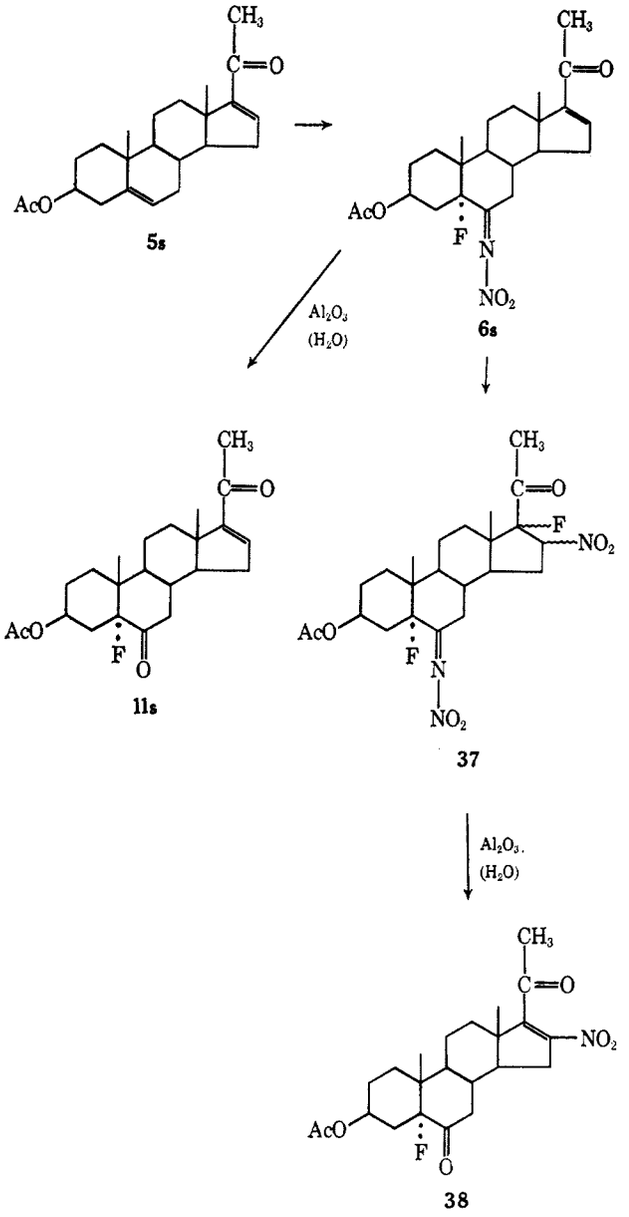
Reaction of NOF with 3β-hydroxypregna-5,16-dien-20-one acetate (**5s**)[51] followed by chromatography gave 5α-fluoro-3β-hydroxypregn-16-ene-6,20-dione acetate (**11s**) and 5α-fluoro-16-nitro-3β-hydroxypregn-16-ene-6,20-dione acetate (**38**). See Scheme IV. Similarly, pregna-4,16-diene-3,20-dione (**39**) gave 16-nitropregna-4,16-diene-3,20-dione (**41**) in 16% yield (based on converted **39**). See Scheme V.

Reaction of NOF with 16-en-20α-ol acetates differs from that with 16-en-20-ones. Pregna-5,16-diene-3β,20α-diol diacetate (**5t**)[52] treated with NOF followed by chromatography gave two isomers, $C_{25}H_{35}FO_7$ (Scheme VI), which were assigned the tentative structures **11t** (a and b) with isomer a having mp 228–230° and [α]D −118°, and isomer b having mp 288° and [α]D −121°. Each was homogeneous by thin layer chromatography with the b epimer migrating ahead of the a epimer. Tentative structural assignments rest on the elemental analysis and spectral characteristics. In the infrared spectrum **11t** (b) shows absorption characteristics of a hydroxyl group (2.85), a five-ring ketone (5.73 μ), six-ring ketone and acetates (5.78, 7.95 and 8.15 μ), and 5α-fluorine (8.65 μ). The infrared spectrum of **11t** (a) was very similar except the five-ring ketone band was not resolved from the intense overlapping acetate and α-fluoro six-ring carbonyl bands. Dione **11t** (a) exhibits λ_{max} 302 (ϵ 102) in the ultraviolet and in the H nmr shows sharp singlets for 18 and 19 protons at 0.82 and 0.87, respectively, a doublet for 21 protons at 1.47 (J = 7 cps) and a corresponding doublet for the 20 proton at 5.12 (J = 7 cps), a sharp singlet for the 3β,20α-acetates at 2.05,

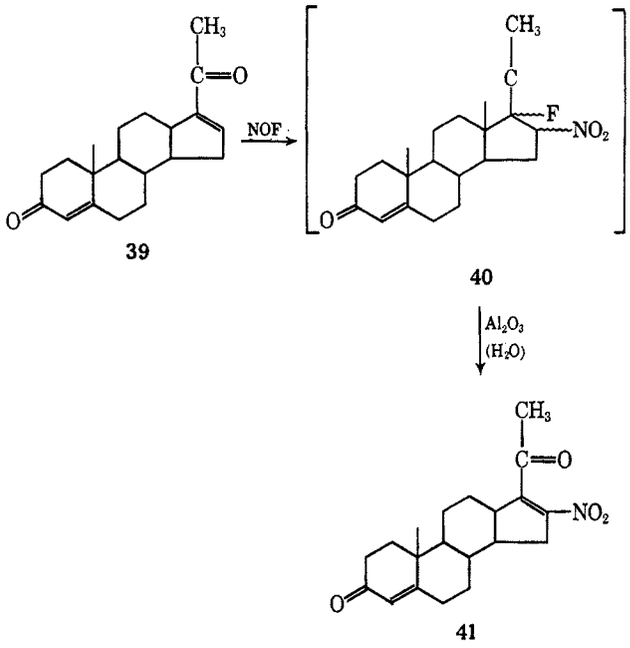
(51) A. Butenandt and J. Schmidt-Thome, *Chem. Ber.*, **72**, 182 (1939).

(52) E. L. Shapiro, D. Gould, and E. B. Hirshberg, *J. Amer. Chem. Soc.*, **77**, 2912 (1955).

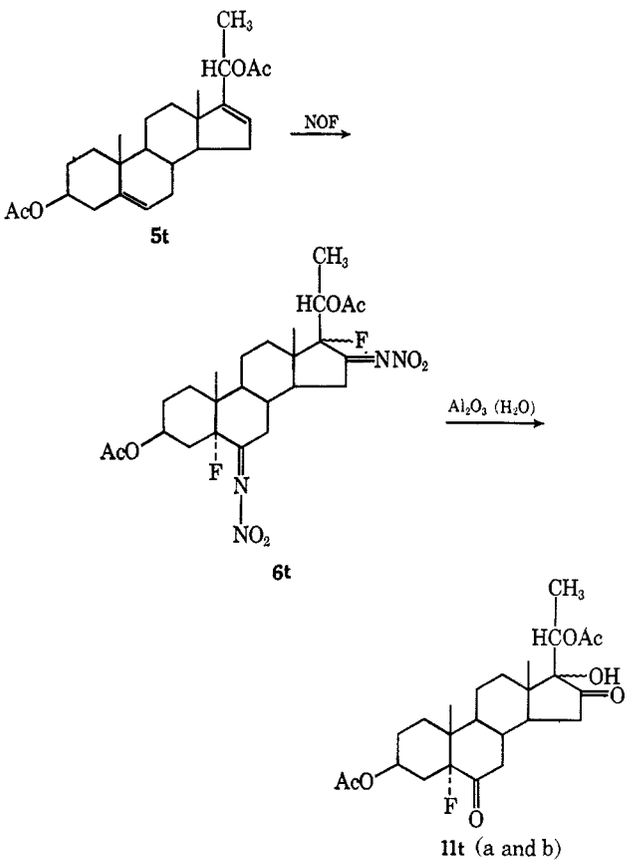
SCHEME IV
REACTION OF NITROSYL FLUORIDE AND STEROID 16-EN-20-ONES



SCHEME V

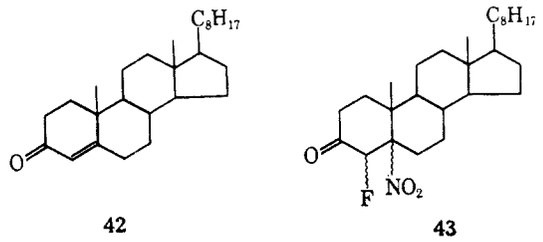


SCHEME VI



and a peak for the 17ξ-hydroxyl at 2.82 ppm (removed by the addition of D_2O). For epimer b, the 18 and 19 protons are at 0.87 as overlapping peaks, the 21 protons are a doublet at 1.25 (J = 7 cps), the 20 proton also is a doublet at 5.17 (J = 7 cps), and the 17ξ-hydroxyl group is at 3.06 ppm.

Reaction of Nitrosyl Fluoride and 4-Ene-3-keto Steroids.—Using reaction conditions described under general procedures in the Experimental Section, 4-en-3-ones are recovered unchanged. However, cholest-4-en-3-one (**42**) was treated with NOF under autogenous



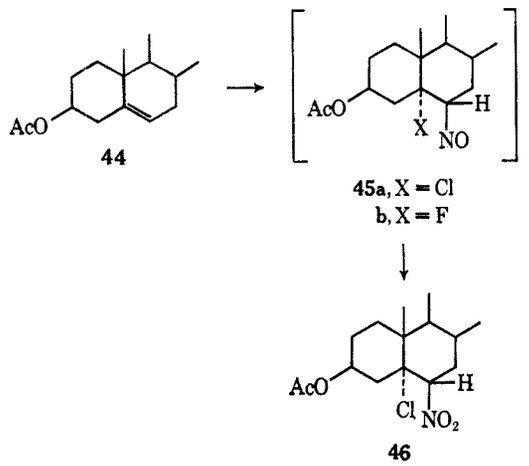
pressure in a shaker tube at 25° to give, after chromatography on neutral alumina (activity III), a 4.2% yield of crystalline ketone, $C_{27}H_{44}FNO_3$, which was assigned 4ξ-fluoro-5ξ-nitro-3-one structure **43**. In the infrared spectrum, ketone **43** shows absorptions characteristic of a six-ring ketone having an equatorial fluorine on the α carbon (5.68 μ)[33] and a nitro group (6.30 and 7.65 μ). The ultraviolet spectrum shows maximum absorption at 282 mμ (ϵ 126), in accord with a compound having a tertiary aliphatic nitro sub-

stituent[53] and a saturated six-ring carbonyl bearing an equatorial α fluorine.[54] Since **43** is stable to chromatography on alumina, *i.e.*, does not eliminate HF, it follows that the nitro group is at C-5 and therefore the fluorine is at C-4. Thus, addition of NOF to 4-ene-3-keto steroids follows the same course as with 16-ene-20-keto steroids. From the available evidence, it is not possible to assign fluorine and nitro group configurations.

Discussion

Although the addition of nitrosyl chloride to steroid 5-enes **44** has been conclusively shown to give 5α-chloro-6β-nitro substitution products **46** (Scheme VII),

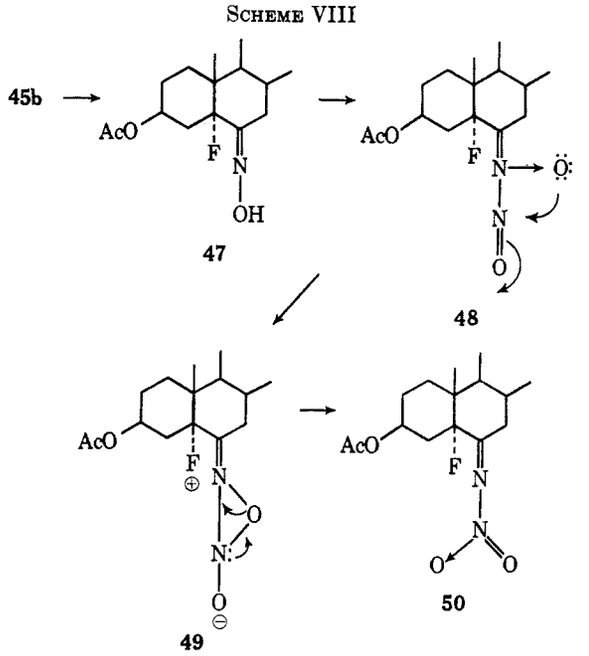
SCHEME VII



44 46

the exact mode of addition is unclear because certain evidence favors a *trans* ionic addition[6c] whereas other evidence favors a *trans* free-radical addition.[6b,c] Nevertheless, the reaction gives *trans* substitution whether carried out in ether,[6b] carbon tetrachloride,[6a,c] or methylene chloride.[4c,55] Since nitroso alkanes are oxidized to nitro compounds by nitrosyl chloride,[5] it is believed[6] that 5α-chloro-6β-nitro steroids **57** are formed by oxidation of initially formed 5α-chloro-6β-nitroso adduct **45a**.[56] Addition of NOF to carbon–carbon double bonds parallels that of nitrosyl chloride up to a point, *i.e.*, formation of nitroso fluoride. However, here the two reactions take different courses if formation of nitroso dimer is sterically prevented. For 10β-methyl-5-ene **44**, intermediate nitroso halide **45a,b** is sterically prevented from dimerizing and can therefore react further. Nitroso chloride **45a** is oxidized to nitro chloride **46** before it tautomerizes to the oxime.[57] NOF, on the other hand, does not seem to be as effective an oxidizing agent as nitrosyl chloride, thus allowing nitroso fluoride **45b** to tautomerize to fluoro oxime **47**[58] (Scheme VIII). The transient fluoro oxime **47** is then nitrosated by NOF to give N-nitrosonitrone **48** which rearranges spontaneously to nitrimine **50**.[59] The following observations support this. When cholesteryl acetate (**5a**) was treated with 1 molar equiv of NOF and the crude reaction mixture was chromatographed, only starting olefin and fluoro ketone **11a** were obtained. After an initiation period, the solution turned deep blue, then gradually faded to a straw color. Moreover, 5α-fluoro-6 oxime **14a** reacts with NOF to give 5α-fluoro-6-nitrimine **6a** as expected from the proposed reaction scheme. Steroid 4- and 5-enes react with NOF very rapidly; when two reactors are attached in series so that a stream of NOF passes into the first reactor containing a typical steroid 5-ene in methylene chloride and then into the second containing the same solution, no reaction takes place in the second reactor until all the olefin in the first has been converted.

SCHEME VIII



Absence of the 10β-methyl in the 19-nor-4- and -5-ene series allows dimerization of the initially formed adduct to compete with tautomerization and nitrosation, and nitroso fluoride dimer and α-fluoronitrimine therefore are formed in comparable amounts. With α,β-unsaturated carbonyl compounds **39** and **42**, however, reaction proceeds slowly with only partial conversion into nitro compounds **41** and **43**. The products are probably formed by a radical process[60] similar to that observed in the reaction of impure nitrosyl chloride and steroid 5-enes,[6b] since NOF does not readily add to electron-deficient olefins.[7a] Disubstituted olefins such as cholest-2-ene (**33**) react slowly with NOF[61] to give

(53) Reference 9a, p 65.

(54) If the fluorine were axial the maximum in the uv spectrum would be expected to appear at 300 mμ as seen for 5α-fluoro-6- and -4-ones.

(55) This is somewhat surprising since addition of nitrosyl chloride to cyclohexene in chlorinated hydrocarbon solvents affords 2-chloro-1-nitrosocyclohexane *cis* dimer, whereas in liquid sulfur dioxide it yields the *trans* dimer [*cf.* M. Ohno, M. Okamoto, and K. Nukada, *Tetrahedron Lett.*, 4047 (1965)].

(56) However, when nitrosyl chloride contains nitrogen dioxide, it is postulated (*cf.* ref 6b) that nitro chloride **46** is formed rapidly by free-radical attack of NO_2 on the olefin to give the C-5 radical which, in turn, reacts with NOCl to give observed product.

(57) Since it is well known that oximes are generally converted into α-chloronitroso or α-chloronitro compounds by NOCl, it follows that 6-nitroso steroids must be oxidized directly to 5-nitro compounds (*cf.* ref 5).

(58) That some oxidation to the corresponding 5α-fluoro-6β-nitro compound may occur is evidenced by the observation of characteristic vinyl nitro bands in the infrared spectra of impure fractions from the chromatographed reaction product of NOF and steroid 5-enes.

(59) This is Freeman's mechanism for formation of pernitroso compounds derived by reaction of *t*-alkyl ketoximes and nitrosating agents (*cf.* ref 12).

(60) Under conditions employed for reaction of **39** and **42** with NOF, considerable amounts of N_2O_4 were observed to form. The origin of this is uncertain.

(61) Reaction of NOF and steroid 9(11)-enes is not straightforward and is still under investigation. Under certain conditions nitro-substituted products are formed.

2-fluoro-3-nitro derivatives probably by a radical process,[6b,60] and 2α-fluoro-3-keto derivatives. Chromatography of intermediate nitro fluorides results in dehydrofluorination and isolation of vinyl nitro derivative **34**. The observation that the crude reaction product, before chromatography on alumina, showed a sharp carbonyl absorption (5.78 μ) and characteristic nitro bands (6.40 and 7.60 μ) in the infrared spectrum suggests that fluoro ketone **35** was formed directly from reaction of olefin **33** and nitrosyl fluoride rather than *via* hydrolysis of a transient 2-fluoro-3-nitrimine. This parallels the reaction of excess nitrosyl fluoride and trimethylene (**1**) which gave appreciable amounts of fluoro ketone **3** in addition to nitroso fluoride dimer **2**. Direct conversion of certain olefins into fluoro ketones without hydrolysis of an intermediate suggests that for "less-hindered" fluoro oximes, in contrast to steroid 5α-fluoro-6 oximes, nitrosation by NOF leads directly to fluoro ketone. This is reminescent of the reaction of ketoximes with nitrosating agents to regenerate the parent ketone.[62,63]

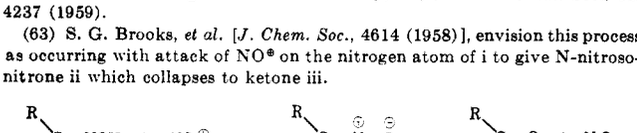
Experimental Section[64]

Nitrosyl Fluoride Addition to Steroid 4- and 5-Enes. General Procedure.—In a dry, 500-ml polyethylene bottle equipped with a magnetic stirring bar and polyethylene gas inlet and exit tubes was placed a solution of the steroid olefin (1–60 g) in methylene chloride or carbon tetrachloride (100–250 ml). The exit tube was protected by a drying tube containing calcium chloride, and the system was swept with a stream of nitrogen to remove moisture and air. The reactor was cooled in an ice bath while a slow stream of nitrosyl fluoride[8] (0.33 to 0.5 times the weight of steroid olefin charged) was passed into the stirred solution over 3 to 7 hr. After an initial induction period of 0.25–2 hr depending on the rate of flow, the reaction solution became deep blue, gradually turned green, and finally took on a straw color. The reaction mixture was washed with water and saturated salt solution, dried over magnesium sulfate, and evaporated under reduced pressure. The viscous residue was either crystallized from the appropriate solvent system to furnish the fluoronitrimine or chromatographed on neutral alumina (20–30 g/g of starting olefin, activity III). The eluted solids were crystallized from the appropriate solvent system to furnish the fluoro ketone.

5α-Fluoro-6-nitriminochlolestan-3β-ol Acetate (6a).—Reaction of cholesteryl acetate (**5a**, 40.0 g) with nitrosyl fluoride (15.0 g) as described above afforded 34.0 g of fluoronitrimine **6a**, mp 160–162° (capillary). Recrystallization from methylene chloride–hexane gave 31.55 g of material. After a final recrystalliza-

(62) D. T. Manning and H. A. Stansbury, Jr., *J. Amer. Chem. Soc.*, **81**, 4237 (1959).

(63) S. G. Brooks, *et al.* [*J. Chem. Soc.*, 4614 (1958)], envision this process as occurring with attack of $NO^{\oplus}$ on the nitrogen atom of i to give N-nitrosonitrone ii which collapses to ketone iii.



i ii iii

(64) Melting points were recorded as observed on a Kofler block unless designated otherwise. 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. Proton nmr spectra were recorded for dilute solutions (*ca.* 10% by weight) in deuteriochloroform containing tetramethylsilane as an internal reference (0.0 ppm) on a Varian A-60 spectrometer, unless noted otherwise. Chemical shifts are quoted in parts per million (ppm) downfield from the reference signal and are accurate to ±0.01 ppm. Coupling constants and band half-widths are quoted in cycles per second. The F^{19} nmr spectra were recorded for dilute solutions in deuteriochloroform (*ca.* 10% by weight), unless noted otherwise, containing a small amount of trichlorofluoromethane as an internal reference (0.0 cps) on a Varian HR-60 spectrometer operating at 56.4 Mc/sec. Chemical shifts are quoted in cycles per second downfield from the reference signal. Optical rotations were measured in 1–2% chloroform solutions unless noted otherwise.

tion from ether–ethanol, the product melted at 158–163°: $[\alpha]^{23}D$ −68°; λ_{max} 267 mμ (ε 480); λ_{max}^{Nujol} 6.08 (C=N), 6.35 and 7.65 (NO_2), 8.57 μ (F); H nmr, 0.67 (18-H), 0.85 (26 and 27-H, doublet, J = 6 cps), 0.97 (19-H), 4.97 ppm (3α-H, $W_{1/2}$ = *ca.* 25 cps); F^{19} nmr, +9008 and +9056 cps (5α-F).

Anal. Calcd for $C_{29}H_{47}FN_2O$: C, 68.47; H, 9.31; F, 3.74; N, 5.51; mol wt, 508.48. Found: C, 68.74; H, 9.58; F, 3.87, 3.85; N, 5.41; mol wt, 510 ± 12 (ebullioscopic in ethylene dichloride).

The examples in Table I were prepared similarly.

3-Fluoro-3-methyl-2-nitrosobutane Dimer (2) and 3-Hydroxy-3-methylbutan-2-one Oxime (4).—Into a stirred solution of 2-methyl-2-butene (**1**, 15.0 g) and carbon tetrachloride (15 ml) cooled in an ice–salt bath was passed a slow stream of nitrosyl fluoride (4 g) over a 3-hr period. The green reaction mixture was poured into water and the phases were separated. The aqueous phase was thoroughly extracted with carbon tetrachloride. The carbon tetrachloride extracts were washed with water and saturated salt solution, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to leave a blue mixture of liquid and crystals. The crude reaction product was adsorbed from petroleum ether (bp 30–60°) onto neutral alumina (100 g, activity III). Elution with petroleum ether gave 3.1 g of white solid. A portion was recrystallized from petroleum ether to afford 3-fluoro-3-methyl-2-nitrosobutane dimer (**2**, 1.5 g) as flat white needles having a camphorlike odor: mp 58–60°; λ_{max} 300 mμ (ε 7100); $\lambda_{max}^{CCl_4}$ 8.3 (broad and strong), 9.05, 9.40, 9.85, 10.20, 10.50, 11.35, 11.50, 11.75 μ.

Anal. Calcd for $(C_5H_{10}FNO)_2$: C, 50.41; H, 8.46; F, 15.96; N, 11.76; mol wt, 238.26. Found: C, 50.77; H, 8.43; F, 15.51; N, 11.93; mol wt, 239 (freezing point depression in benzene).

Elution with ether returned 2.11 g of a polar white solid: mp 75° (sinters at 55°); $\lambda_{max}^{CCl_4}$ 2.95 (very strong), 6.05 μ. Recrystallization from methylene chloride–petroleum ether (bp 30–60°) afforded 3-hydroxy-3-methylbutan-2-one oxime (**4**) as colorless needles: mp 85–88° (lit.[11] mp 86–87); $\lambda_{max}^{CCl_4}$ 3.0, 6.0 μ; H nmr (*d*-acetone), 1.30 (6 H) and 1.86 ppm (3 H).

Anal. Calcd for $C_5H_{11}NO_2$: C, 51.26; H, 9.46; N, 11.96. Found: C, 51.72; H, 9.42; N, 12.25.

The NOF adduct **2** could also be converted into 3-hydroxy-3-methylbutan-2-one oxime (**4**) by heating a solution of the adduct (1.0 g) and 2-propanol (25 ml) which contained a few drops of water at reflux for 1 hr, evaporating the solution under reduced pressure, and recrystallizing the residue from methylene chloride–petroleum ether.

3-Fluoro-3-methylbutan-2-one (3).—A slow stream of nitrosyl fluoride (3.5 g over 4 hr) was passed into a stirred solution of 2-methyl-2-butene (1 2.5 g) and carbon tetrachloride (5.0 ml) cooled to −15°. The blue reaction mixture was allowed to remain overnight cooled in an ice bath. An infrared spectrum of the blue carbon tetrachloride solution displayed the following bands: λ_{max} 5.75, 5.79 μ (partially resolved doublet). The volatile portion of the reaction mixture was distilled under reduced pressure and the distillate was separated by vpc on 20% trifluorohexanoic acid diglycerate on 40–60 Chromosorb at 45°. The major peak with a retention time of 19 min was collected; mass spectral analysis showed a parent ion (highest m/e) of 104 and a fragmentation pattern which supported the assigned structure; infrared showed $\lambda_{max}^{CCl_4}$ 5.76 and 5.79 (sharp doublet), 8.70 μ (F).

5α-Fluoro-3β-hydroxycholestan-6-one Acetate (11a).—Chromatography of the 5α-fluoro-6-nitrimine **6a** (17.0 g) on neutral alumina (500 g, activity III) followed by crystallization of the crystalline fractions from ether–methanol furnished the fluoro ketone **11a** (13.64 g in two crops) as colorless, flat needles: mp 122–125°, not raised by further recrystallization; $[\alpha]^{23}D$ −7°; λ_{max} 5.78, 8.55 μ (lit.[27] mp 122–124°; $[\alpha]D$ −1°; $\nu_{max}^{CS_2}$ 1703 and 1735 cm^{-1}); H nmr, 0.67 (18-H), 0.93 (19-H), 5.02 ppm (3α-H, axial, $W_{1/2}$ = *ca.* 24 cps); F^{19} nmr, +8988 and +9037 cps (5α-F, two sharp peaks of equal intensity).

Anal. Calcd for $C_{29}H_{47}FO_3$: C, 75.28; H, 10.24; F, 4.11. Found: C, 75.59; H, 10.13; F, 4.13.

The examples in Table II were prepared similarly, except that the fluoronitrimines were not isolated, as the total crude reaction product was chromatographed directly.

3β-Hydroxycholestan-6-one Acetate (14b).—A mixture of fluoro ketone **11a** (1.22 g), zinc dust (7.5 g), and acetic acid (66 ml) was heated at reflux for 24 hr. The reaction mixture was filtered, poured into water, and extracted with ether. The

ether extracts were washed with 5% sodium bicarbonate solution and dried (MgSO). Evaporation of the solvent under reduced pressure afforded a solid residue which was recrystallized from aqueous methanol to give 0.45 g of 3β-hydroxycholestan-6-one acetate (**14b**), mp 125–128°. Recrystallization from methanol afforded material with mp 128.5–130°; $[\alpha]^{24}D$ −16° {lit.[28] mp 127–128°; $[\alpha]^{24}D$ −15.5° ± 1.0° ($CHCl_3$)}.

Anal. Calcd for $C_{29}H_{48}O_3$: C, 78.68; H, 10.47. Found: C, 78.27; H, 10.87.

5α-Fluoro-6-oximinocholestan-3β-ol Acetate (14a).—A solution of fluoro ketone **11a** (2.0 g), hydroxylamine hydrochloride (0.43 g), and sodium acetate (0.43 g) in absolute ethanol (80 ml) was heated briefly on a steam bath, filtered hot, and allowed to stand at room temperature for 6 hr. Dilution of the reaction mixture with water afforded a white precipitate which was washed well with water, dried, and recrystallized from a mixture of petroleum ether (bp 30–60°) and hexane to afford fluoro oxime **14a** (1.22 g): mp 167–169.5°; $[\alpha]D$ −60°; λ_{max} 2.88, 5.71, 6.03, 8.57 μ; H nmr (deuteriopyridine), 0.68 (18-H), 0.92 (19-H), 5.08 ppm (3α-H, axial $W_{1/2}$ = *ca.* 25 cps); F^{19} nmr (deuteriopyridine), +8873 and +8919 cps (5α-F, two sharp peaks of equal intensity).

Anal. Calcd for $C_{29}H_{47}FNO_3$: C, 73.07; H, 9.94; F, 4.00; N, 2.93. Found: C, 72.75; H, 10.15; F, 4.13; N, 2.61.

5α-Fluoro-6-nitriminocholestan-3β-ol Acetate (6a). From Reaction of Nitrosyl Fluoride and 5α-Fluoro-6-oximinocholestan-3β-ol Acetate (14a).—Treatment of the fluoro oxime **14a** (1.0 g) with nitrosyl fluoride as described in the general procedures furnished a blue-green syrup which solidified when triturated with hexane, yield 0.7 g. Recrystallization from hexane and then ether–ethanol furnished 398 mg of fluoronitrimine **6a**: mp 157–160° (not raised by further recrystallization and undepressed in admixture with material prepared by reaction of nitrosyl fluoride with cholesteryl acetate); indistinguishable by infrared spectroscopy from the reference material; λ_{max} 266 mμ (ε 486).

5α-Fluorocholestane-3β,6β-diol 3-Acetate (16a).—To a stirred solution of 5α-fluoro-3β-hydroxycholestane-6-one acetate (**11a**, 13.0 g) and tetrahydrofuran (500 ml) cooled in an ice bath was added portionwise 41 g of lithium hydrotri-*t*-butoxyaluminate. The ice bath was then removed, and the resultant mixture was stirred at ambient temperature for 48 hr. The reaction mixture was then poured with stirring into 2 l. of cold 5% acetic acid. The precipitated solid was filtered off, washed well with water, and dried to yield 12.2 g, mp 158–163. Recrystallization from methanol afforded 5α-fluoro-6β-ol **16a** (10.94 g) as colorless blades: mp 169–170.5°; $[\alpha]^{24}D$ −4°; λ_{max} 2.84, 5.82, 8.04, 8.59 μ; $\lambda_{max}^{CCl_4}$ 2.77 and 2.87 5.77 μ (lit.[27] mp 171–172°; $[\alpha]D$ −9°).

Anal. Calcd for $C_{29}H_{49}FO_3$: C, 74.96; H, 10.63; F, 4.09. Found: C, 75.19, 75.19; H, 10.25, 10.61; F, 4.28.

5α-Fluorocholestane-3β,6β-diol (17).—A solution of fluorohydrin **16a** (5.0 g), concentrated hydrochloric acid (8 ml), and methanol (110 ml) was heated at reflux for 1 hr, after which the solution was carefully diluted with hot water and allowed to cool slowly to room temperature. The precipitated reaction product was collected, washed well with water, and air dried to yield 4.34 g. This was recrystallized from ethyl acetate to give pure fluorodiol **17** (3.33 g). An additional crystallization from ethyl acetate furnished an analytical sample: mp 191–193°; $[\alpha]^{24}D$ +3° (dioxane) (lit.[27] mp 196–197°; $[\alpha]D$ +13°); λ_{max} 2.83 and 2.93, 8.60 μ.

Anal. Calcd for $C_{27}H_{47}FO_2$: C, 77.26; H, 10.57; F, 4.52. Found: C, 76.80; H, 11.09; F, 4.50.

5α-Fluorocholestane-3,6-dione (18).—To a stirred solution of 5α-fluorocholestane-3β,6β-diol (**17**, 1.86 g) in acetone (50 ml) cooled in an ice bath was added excess 8 *N* chromic acid[29] (permanent orange color). The ice bath was then removed, and the reaction mixture was stirred an additional 15 min; a few milliliters of methanol was then added to consume the excess oxidizing agent. The mixture was filtered to remove chromium salts, and the filtrate was diluted with water to precipitate the product: yield 1.5 g; mp 141–143.5°. Recrystallization from methanol afforded pure fluorodione **18** (1.34 g) as glistening leaflets: mp 143–145°; $[\alpha]^{24}D$ +10° (dioxane); λ_{max}^{KBr} 5.79; 8.59 μ; λ_{max} 298 mμ (ε 76) (lit.[27] mp 143–144°; $[\alpha]D$ +10°; ν_{max} 1720 cm^{-1}).

Anal. Calcd for $C_{27}H_{43}FO_2$: C, 77.46; H, 10.36; F, 4.54. Found: C, 77.37; H, 10.27; F, 4.44.

5β,6β-Oxidocholestan-3β-ol (15b).—A mixture of fluorohydrin **16a** (2.91 g), and potassium *t*-butoxide (5.9 g) in *t*-butyl alcohol was stirred at ambient temperature for 16 hr. The solution was diluted with 100 ml of 40% acetic acid and then concentrated under reduced pressure. The residue was dissolved in methylene chloride, and the methylene chloride solution was washed with water and saturated salt solution, dried ($MgSO_4$), and evaporated to dryness under reduced pressure. The partially solid residue was precipitated from methanol to give 1.29 g of white solid, mp 140–150° (softening at 120°). This was chromatographed on neutral alumina (50 g, activity III). Elution with benzene returned a colorless solid melting at 125–128°, yield 159 mg. Recrystallization from aqueous methanol furnished pure β-epoxide **15b** (120 mg) as fine colorless needles: mp 130–133°; $[\alpha]^{24}D$ +9° (lit.[30] mp 130.5–133°; $[\alpha]D$ +9.5° and mp 131–132°; $[\alpha]D$ +11.5°, +10.7°).

Anal. Calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.22; H, 11.47.

Continued elution with benzene returned a mixture of β-epoxide **15b** and fluorodiol **17** and finally pure fluorodiol **17**, mp 180–190°, raised to 193–195° (undepressed in admixture with starting material) after recrystallization from aqueous methanol.

Cholest-4-ene-3,6-dione (19a). A. By Dehydrofluorination of 5α-Fluorocholestane-3,6-dione (18).—A solution of fluorodione **18** (0.93 g) and sodium acetate (2.44 g) in methanol (75 ml) was heated at reflux under nitrogen for 3 hr; the solution turned pale yellow. Dilution with water followed by recrystallization of the precipitated product from methanol afforded the enedione **19a** (0.83 g) as pale yellow blades: mp 124°; $[\alpha]^{24}D$ −41°; λ_{max}^{Nujol} 5.92, 6.22 μ; λ_{max} 251 mμ (ε 10,600) and 327 mμ (ε 89) {lit.[32] mp 124–125°; $[\alpha]D$ −40°; λ_{max}^{EtOH} 253 mμ (ε 10,300)}.

Anal. Calcd for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62. Found: C, 81.59, 81.77; H, 10.61, 10.48.

B. By Reaction of Cholesterol (5g) and Nitrosyl Fluoride.—Cholesterol (10.0 g) was allowed to react with nitrosyl fluoride as described in the general procedure. The usual work-up afford a yellow syrup, $\lambda_{max}^{CCl_4}$ 2.99 (—OH), 5.78 (C=O, strong), 6.1 (C=N), 6.32 and 7.60 (NO_2), 8.55 μ (C–F), which was adsorbed from benzene onto neutral alumina (300 g, activity III). Elution with hexane–benzene (1:1) yielded pale yellow solids which upon recrystallization from methanol afforded enedione **19a** (2.26 g) as pale yellow blades: mp 123–124°; $[\alpha]^{24}D$ −42°; λ_{max} 252 mμ (ε 11,000) and 328 mμ (ε 86); λ_{max}^{Nujol} 5.92, 6.22 μ.

Anal. Calcd for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62. Found: C, 81.32; H, 10.59.

Elution with benzene–ether (1:1) returned a yellow oil which solidified when triturated with cold methanol, yield 0.54 g (1st crop) and 0.49 g (and crop). This was recrystallized from methanol to yield 425 mg of 5α-fluoro-3β-hydroxycholestan-6-one (**11g**): mp 88–90 and 114–117° (double melting point); $[\alpha]^{24}D$ −6°; λ_{max} 300 mμ (ε 76); λ_{max} 2.83, 2.96, 5.81, 8.65 μ.

Anal. Calcd for $C_{27}H_{45}FO_2$: C, 77.09; H, 10.78; F, 4.51. Found: C, 77.14, 77.23; H, 10.57, 10.66; F, 5.12.

5α-Fluoro-6β-nitraminocholestan-3β-ol Acetate (7a). A. Lithium Hydrotri-*t*-butoxyaluminate Reduction of Fluoronitrimine 6a.—To a stirred solution of lithium hydrotri-*t*-butoxyaluminate (5.0 g) in dry tetrahydrofuran (100 ml) cooled in an ice bath was added portionwise fluoronitrimine **6a** (10.0 g). The reaction mixture was then stirred for 20 hr at ambient temperature. The reaction mixture was poured into 1 l. of 5% acetic acid, and the mixture was extracted with methylene chloride. The extracts were washed with water and saturated salt solution, dried ($MgSO_4$), and evaporated to dryness under reduced pressure to yield a crystalline residue. Recrystallization from acetone–hexane furnished 5α-fluoro-6β-nitramine **7a** (6.09 g), mp 220–222°. The analytical sample was recrystallized again from the same solvent pair: mp 214–216.5°; $[\alpha]^{23}D$ −53°; λ_{max} 235 mμ (ε 7600); λ_{max} 3.13 and 3.20, 5.87 (hydrogen-bonded acetate C=O), 7.24 and 7.52 (NO_2), 7.90, 9.55 μ; $\lambda_{max}^{CHCl_3}$ 2.96 and 3.05 (NH), 5.79 (acetate C=O), 6.30 and 7.53 (NO_2), 8.0, 8.56 μ; H nmr, 0.70 (18-H), 1.12 (19-H), 4.48 (6α-H, $W_{1/2}$ = 14 cps), 5.11 ppm (3α-H axial, $W_{1/2}$ = 24 cps); F^{19} nmr +8965 and +9016 cps (5α-F, two sharp peaks of equal intensity).

Anal. Calcd for $C_{29}H_{49}FN_2O_4$: C, 68.47; H, 9.71; F, 3.74; N, 5.50. Found: C, 68.56; H, 9.74; F, 3.98, 4.05; N, 5.88.

5α-Fluoro-6β-nitraminopregnane-3β,20ξ-diol (7c).—To a stirred solution of crude 5α-fluoro-3β-hydroxy-6-nitraminopregnan-20-one acetate (**6e**), prepared by treating pregnenolone acetate (**5e**, 10.0 g) with nitrosyl fluoride (8 g) in tetrahydrofuran (125 ml) was added portionwise lithium aluminum hydride (3.0 g). The reaction mixture was worked up in the usual manner and the product was isolated with ether. The ether extracts were washed with water and saturated salt solution, dried over

magnesium sulfate, and evaporated to dryness under reduced pressure to leave a viscous, yellow syrup. This was crystallized from ethanol–hexane to afford the fluoronitramine **7c** (4.50 g), mp 155°. Recrystallization of a portion of this material afforded small colorless prisms: mp 158–160°; $[\alpha]^{22}D$ −71° (dioxane); λ_{max} 235 mμ (ε 7100); λ_{max} 3.0, 6.30, 7.65, 8.60 μ; F^{19} nmr (deuterioacetone), +4995 and +5020 cps (from external 1,1,2,2-tetrachloro-1,2-difluoroethane).

Anal. Calcd for $C_{21}H_{35}FN_2O_4$: C, 63.29; H, 8.85; N, 7.03. Found: C, 63.69; H, 9.19; N, 7.42.

5α-Fluoro-6β-nitraminoandrostane-3β,17β-diol Diacetate (7b). A. By Lithium Hydrotri-*t*-butoxyaluminate Reduction.—Lithium hydrotri-*t*-butoxyaluminate (5.0 g) was added portionwise with stirring to a solution of fluoronitrimine **6c** (10.0 g) in tetrahydrofuran (150 ml). The resultant mixture was stirred for 3 days at room temperature and was then added to cold dilute acetic acid (5%). Isolation of the product with methylene chloride gave a colorless partially solid syrup. Trituration with cold methanol and filtration of the solid gave 4.0 g of crystalline product. Recrystallization from methylene chloride–methanol yielded the fluoronitramine **7b** (1.45 g): mp 228–231° dec; $[\alpha]^{24}D$ −85°; λ_{max} 234 (ε 8120); λ_{max}^{KBr} 2.91, 3.06, 3.15, 5.74, 5.82, 6.26, 8.10, 8.60; $\lambda_{max}^{CHCl_3}$ 2.69, 2.76, 2.94, 5.77, 6.25, 8.0, 8.55 μ; λ_{max} 3.11, 3.18, 5.73, 5.86, 6.27, 8.10, 8.60 μ; H nmr, 0.82 (18-H), 1.13 (19-H), 4.55 (6α-H), 5.10 (3α-H, axial, $W_{1/2}$ = 20 cps); F^{19} nmr, +8819 and +8864 cps (5α-F).

Anal. Calcd for $C_{23}H_{35}FN_2O_6$: C, 60.77; H, 7.77; F, 4.18; N, 6.16. Found: C, 61.04; H, 7.95; F, 4.38; N, 5.92.

The mother liquors yielded an amorphous product whose infrared spectrum indicated it to be mainly starting fluoronitrimine **6c**.

B. By Sodium Borohydride Reduction.—To a stirred solution of fluoronitrimine **6c** (5.0 g,) in dioxane (50 ml) and ethanol (50 ml) cooled in an ice bath was added portionwise 2.5 g of sodium borohydride. The resultant solution was stirred for 1 hr, and then was poured into ice water. The resultant mixture was aged with stirring for an hour, the precipitated solid was filtered off, washed well with water, and air dried to give 4.92 g of colorless solid. Recrystallization from aqueous methanol afforded 5α-fluoro-6β-nitraminoandrostane-3β,17β-diol diacetate (**7b**, 4.85 g) which was identical in every respect with the material prepared above.

6β-(N-Methylnitramino)-5α-fluoroandrostane-3β,17β-diol Diacetate (8a).—A solution of fluoronitramine **7b** (5.50 g) in acetone (100 ml) containing methyl iodide (50 ml) and suspended potassium carbonate (10 g) was heated to reflux with stirring under nitrogen for 10 hr. The product was isolated with ethyl acetate and crystallized when triturated with a mixture of ether and hexane, yield 4.25 g. This was crystallized from aqueous methanol to give the N-methylnitramine **8a** (2.58 g) as colorless needles: mp 129–131°; $[\alpha]^{24}D$ −108°; λ_{max} 216 mμ (ε 8050); $\lambda_{max}^{CCl_4}$ 5.73, 6.42, 7.98, 8.54 μ; λ_{max}^{KBr} 5.75, 6.43, 8.0, 8.54 μ; H nmr, 0.78 (19-H), 1.21 (19-H), 3.98 (N-methyl), 4.53 (6α-H, multiplet), 5.08 ppm (3α-H, axial, $W_{1/2}$ = *ca.* 24 cps); F^{19} nmr, +8897, +8920, and +8941 cps (5α-F, ratio 2:1:2).

Anal. Calcd for $C_{24}H_{37}FN_2O_6$: C, 61.52; H, 7.96; F, 4.14; N, 6.11. Found: C, 61.92; H, 7.75; F, 4.08; N, 5.97.

The mother liquors afforded an additional 1.21 g of less pure product, mp 120–125°.

2α-Fluorocholestan-3-one (35) and 3-Nitrocholest-2-ene (34).—A solution of cholest-2-ene (**33**, 5.0 g) in methylene chloride (50 ml) was treated with a slow stream of nitrosyl fluoride (*ca.* 7 g over 7 hr) at 20–25° as described in the general procedure. The crude product was adsorbed from benzene (20 ml) onto neutral alumina (200 g, activity III). Elution with hexane and hexane–benzene (2:1, 1:1, 1:2) returned a mixture of oil and solids (fractions 3–32). Continued elution with hexane–benzene (1:2) and benzene brought off a colorless solid which was recrystallized from ethanol to give 2α-fluorocholestan-3-one (**35**, 40 mg) as colorless, glistening plates: mp 173–174°; $\lambda_{max}^{CCl_4}$ 5.78, 9.23 μ (lit.[18] mp 170–173; $[\alpha]^{25}D$* +60°; λ_{max}^{KBr} 5.79, 9.23 μ).

Anal. Calcd for $C_{27}H_{45}FO$: C, 80.15; H, 11.21; F, 4.70. Found: C, 79.65; H, 11.13; F, 4.98.

Fractions 3–32 (2.50 g) were combined and adsorbed from hexane (*ca.* 50 ml) onto Florisil[65] (75 g). Elution with hexane containing 2.5% acetone by volume and evaporation of the solvent afforded an amorphous solid. Recrystallization from ether–methanol furnished 3-nitrocholest-2-ene (**34**, 0.76 g): mp 95–115° (variable); $[\alpha]^{24}D$ +104°; λ_{max} 257 mμ (ε 5350) and 225 mμ (ε 4150); λ_{max} 5.97, 6.58, 7.49 μ; H nmr, 7.23 ppm (2-H, $W_{1/2}$ = *ca.* 10 cps).

Anal. Calcd for $C_{27}H_{45}NO_2$: C, 78.02; H, 10.91; N, 3.37. Found: C, 78.33, 78.19; H, 10.61, 10.44; N, 3.37, 3.34.

Cholestan-3-one (36).—A mixture of 3-nitrocholest-2-ene (**34**, 0.38 g), zinc dust (2.3 g), water (2.5 ml), and glacial acetic acid (22.5 ml) was heated at reflux for 4 hr, and then filtered, and the filtrate was poured into water. The precipitate was collected, washed well with water, and air dried: yield 257 mg; λ_{max} 5.83 μ. Several recrystallizations from methanol yielded cholestan-3-one (**36**, 76 mg): mp 126–128°, not depressed by admixture with authentic material; $[\alpha]D$ +41.4°; λ_{max} (lit.[48] mp 129–130°; $[\alpha]D$ +41.5°). Analysis by tlc showed the product to be homogeneous and to have an R_f identical with that of authentic material.

Anal. Calcd for $C_{27}H_{56}O$: C, 83.87; H, 11.99. Found: C, 83.11; H, 10.77.

5α-Fluoro-4-nitriminoandrostan-17β-ol Acetate (24a).—A solution of androst-4-en-17β-ol acetate (**23a**, 11.2 g) in methylene chloride (35 ml) was treated with nitrosyl fluoride (*ca.* 6 g over 6 hr) as described in the general procedure. The usual work-up yielded a crude solid which was crystallized from methanol to afford 5α-fluoro-4-nitriminoandrostan-17β-ol acetate (**24a**, 9.40 g). The analytical sample was recrystallized from methylene chloride–methanol: mp 178–180° dec; $[\alpha]^{24}D$ +123°; λ_{max} 267 mμ (ε 532); λ_{max}^{KBr} 5.75, 6.09, 6.34, 8.04, 8.90, 9.75 μ; F^{19} nmr, +9163, +9189, and +9213 cps (5α-F, triplet, s, w, s); H nmr, 0.78 (18-H), 0.95 ppm (19-H).

Anal. Calcd for $C_{21}H_{31}FN_2O_3$: C, 63.93; H, 7.92; F, 4.80; N, 7.10. Found: C, 63.63; H, 8.11; F, 4.97; N, 6.68.

5α-Fluoro-17β-hydroxyandrostan-4-one Acetate (26a) and 4-Nitriminoandrost-5-en-17β-ol Acetate (27).—5α-Fluoro-4-nitriminoandrostan-17β-ol acetate (**24a**, 15.5 g) was adsorbed from benzene (40 ml) onto neutral alumina (400 g, activity III). After 1 hr, the column was eluted with hexane–benzene (2:1). Evaporation of the solvents followed by recrystallization of the crystalline residue from aqueous methanol afforded 5α-fluoro-17β-hydroxyandrostan-4-one acetate (**26a**, 6.49 g): mp 119–123°, raised by repeated recrystallizations from aqueous methanol to 125–127°; $[\alpha]^{24}D$ −5°; λ_{max} 300 mμ (ε 70); λ_{max} 5.72, 5.76, 8.05, 8.90 μ; H nmr (*d*-benzene), 0.57 (18-H), 0.71 (19-H), 1.76 ppm (acetate CH_3); H nmr (*d*-$CHCl_3$), 0.796 (18-H and 19-H) and 2.02 ppm (acetate CH_3); F^{19} nmr, +9163, +9189, +9213 cps (5α-F, s, w, s).

Anal. Calcd for $C_{21}H_{31}FO_3$: C, 71.95; H, 8.92; F, 5.42. Found: C, 71.83, 72.00; H, 8.95, 9.12; F, 5.31.

A second crop amounted to 0.68 g. Continued elution with hexane–benzene (1:2 and 1:1) and benzene returned a mixture of solids. These were combined and rechromatographed on neutral alumina (400 g, activity III). Elution with hexane–benzene (1:1) returned colorless product which was recrystallized from aqueous methanol to give 1.56 g of fluoro ketone **26a**: mp 120–123°; indistinguishable by infrared spectroscopy from the material prepared above. Further elution with benzene, evaporation of the solvent, and crystallization of the solid residue from aqueous methanol furnished 17β-hydroxyandrost-5-ene-4-nitrimine acetate (**27**, 0.17 g) as glistening white plates: mp 185° dec; $[\alpha]^{23}D$ −276°; λ_{max} 297 mμ (ε 8300); λ_{max} 5.79, 5.92, 6.25, 8.05 μ; H nmr, 0.82 (18-H), 0.95 (19-H), 2.02 (acetate CH_3), 5.0 ppm (6-H, broad multiplet).

Anal. Calcd for $C_{21}H_{30}N_2O_4$: C, 67.35; H, 8.08; N, 7.48. Found: C, 67.52; H, 8.19; N, 7.40.

5α-Fluoro-4β-nitraminoandrostan-17β-ol Acetate (31a).—To a stirred solution of 5α-fluoro-4-nitriminoandrostan-17β-ol acetate (**24a**, 1.45 g) in dioxane (30 ml) and ethanol (50 ml) cooled in an ice bath was added portionwise sodium borohydride (1.20 g) (vigorous frothing). The reaction mixture was stirred for 1 hr at ambient temperature, and then diluted with cold 5% acetic acid. The precipitated product was collected, washed well with water, and dried. Recrystallization from methylene chloride–methanol gave the fluoronitramine **31a** (0.80 g): mp 252–253°; $[\alpha]^{23}D$ +61°; λ_{max} 236 mμ (ε 7800); λ_{max} 3.11 3.16, 5.77, 6.26, 7.90 μ; F^{19} nmr, +8933 and +8977 cps (5α-F, doublet); H nmr, 0.78 (18-H), 1.00 (19-H), 2.02 (acetate CH_3), *ca.* 4.50 ppm (4α-H, 17α-H, broad multiplet).

Anal. Calcd for $C_{21}H_{32}FN_3O_4$: C, 63.61; H, 8.39; F, 4.79; N, 7.07. Found: C, 63.89; H, 8.10; F, 4.83; N, 7.19.

(65) A synthetic magnesia–silica gel made by the Floridin Co., Warren, Pa.

5α-Fluoro-4β-(N-methylnitramino)androstan-17β-ol 17-Acetate (31b).—Fluoronitrimine **31a** was methylated to give N-methyl derivative **31b** as described above. Recrystallization of the crude product from methanol gave 1.62 g of N-methylnitramine **31b**: mp 126–128°; $[\alpha]^{23}D$ +78°; λ_{max} 216 mμ (ε 5860); λ_{max} 5.80, 6.46, 8.0 μ; F^{19} nmr, +8990 and +9032 cps (5α-F, doublet); H nmr, 0.775 (18-H), 1.15 (19-H), 2.00 (acetate CH_3), 3.93 (N-CH_3, 4.58 ppm (4α-H and 17α-H, broad multiplet).

Anal. Calcd for $C_{22}H_{35}FN_2O_4$: C, 64.36; H, 8.59; F, 4.63; N, 6.83. Found: C, 64.75, 64.37; H, 8.37, 8.23; F, 4.86, 4.40; N, 7.05.

Androst-5-ene-3β,6,17β-triol Triacetate (9). From 5α-Fluoro-6-nitriminoandrostane-3β,17β-diol Diacetate (6c).—A mixture of 5α-fluoro-6-nitriminoandrostane-3β,17β-diol diacetate (**6c**, 5.0 g) zinc dust (30 g), and glacial acetic acid (250 ml) was heated at reflux with stirring for 2 hr. The reaction mixture was cooled and the zinc filtered off. The filtrate was diluted with water and then isolated with methylene chloride. The residue was recrystallized from hexane to afford 0.7 g of colorless androst-5-ene-3β,6,17β-triol triacetate (**9**): mp 166–174°, raised by additional recrystallizations from acetone–hexane to 176–178°; $[\alpha]^{24}D$ −70°; λ_{max}^{Nujol} 5.74, 5.78, 8.15 μ; H nmr, 0.81 (18-H), 1.08 (19-H), 2.03 (3, 17-acetates), and 2.13 ppm (6-acetate).

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.39, 69.49; H, 8.39, 8.50.

3β,17β-Dihydroxy-5α-androstan-6-one (10).—A solution of triacetate **9** (1.0 g) in methanol (50 ml) which contained concentrated hydrochloric acid (5 ml) was heated at reflux for 1 hr and then allowed to stand at room temperature overnight. The product was precipitated with water, filtered off, washed well with water, and air dried to give 0.9 g. Recrystallization from acetone afforded 3β,17β-dihydroxyandrostan-6-one (**10**, 0.55 g) as massive colorless plates: mp 205° (sinters at 200°), not raised by additional recrystallizations; $[\alpha]D$ −25°; λ_{max} 287 mμ (ε 21); λ_{max} 2.84, 2.92, 5.86 μ; H nmr, 0.75 (18-H), 0.77 ppm (19-H) (lit.[16] mp 208–210°).

Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.27, 74.46; H, 9.65, 9.30.

5α-Fluoroandrostan-17β-ol (32).—A stirred solution of 5α-fluoro-4β-(N-methylnitramino)-17β-ol (**31b**) and tetrahydrofuran (50 ml) which contained suspended lithium aluminum hydride (0.50 g) was heated at reflux for 8 hr, then allowed to stand at room temperature for 3 days. The reaction mixture was cooled in an ice bath while saturated sodium sulfate solution was added dropwise with stirring. The mixture was filtered, and the filtrate was evaporated under reduced pressure to leave a white solid which was crystallized from hexane to afford 5α-fluoroandrostan-17β-ol (**32**, 0.275 g): mp 167–172°; $[\alpha]^{23}D$ +25°; λ_{max} 3.06 μ; F^{19} nmr, +9355 cps (broad multiplet).

Anal. Calcd for $C_{19}H_{31}FO$: C, 78.37; H, 10.19. Found: C, 78.67; H, 9.98.

17β-Hydroxyandrost-5-en-4-one Acetate (28a).—A mixture of 5α-fluoro-17β-hydroxyandrostan-4-one acetate (**26a**, 6.0 g), lithium bromide (6.0 g), lithium carbonate (6.0 g), and N,N-dimethylformamide (500 ml) was heated at reflux with stirring for 72 hr (N_2). The nearly colorless reaction mixture was filtered hot, and the filtrate was poured into 2 l. of ice water. The product, a viscous, yellow oil, was purified by chromatography on neutral alumina (180 g, activity III). Elution with hexane–benzene (1:1) gave a colorless, crystalline solid which was recrystallized from hexane to give 17β-hydroxyandrost-5-en-4-one acetate (**28a**, 3.12 g from first crop and 0.73 g from second crop): mp 112–113° (lit.[43] mp 118–119°) (first crop) raised by recrystallization to 118–119°; $[\alpha]D$ −67°; λ_{max} 240 mμ (ε 6100) and 316 mμ (ε 66); λ_{max}^{KBr} 5.77, 5.95, 6.16, 8.0 μ; H nmr, 0.82 (18-H), 0.97 (19-H), 2.17 (acetate), 6.43 ppm (5-H, a doublet with J = *ca.* 4.5 cps further split into a doublet with J = *ca.* 3 cps).

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.80, 76.60; H, 9.47, 9.13.

17β-Hydroxyandrost-5-en-4-one (28b).—A solution of 17β-hydroxyandrost-5-en-4-one acetate (**28a**, 2.70 g) in methanol (50 ml) which contained concentrated hydrochloric acid was heated at reflux for 1 hr; the dark reaction mixture was cooled and diluted with water. The precipitated product was adsorbed from benzene–hexane onto neutral alumina (100 g, activity III). Elution with benzene and benzene containing 10% ether (by volume) returned colorless solids which were recrystallized from acetone–hexane to afford 17β-hydroxyandrost-5-en-4-one (**28b**, 1.51 g) as fine white needles: mp 158–161°; $[\alpha]D$ −63°; λ_{max} 241 mμ (ε 6140) and mμ 317 (ε 63); λ_{max} 3.08, 5.92, 5.97 (double carbonyl peak), 6.14 μ; H nmr, 0.78 (18-H), 0.99 (19-H), 3.70 (17α-H, triplet, J = *ca.* 8 cps), 6.43 ppm (5-H, a doublet with J = 5 cps further split into a doublet with J = *ca.* 2.5 cps) {lit.[43] mp 158–159°; $[\alpha]^{20}D$ −42.3° (ethanol); $\lambda_{max}^{ethanol}$ 240 mμ (ε 5600)}.

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.03; H, 9.50.

5α-Fluoro-4-nitriminopregnane-3β,20β-diol Diacetate (30).—A solution of pregn-4-ene-3B,20β-diol diacetate[44] (**29**, 5.0 g) and carbon tetrachloride (75 ml) was treated with a slow stream of nitrosyl fluoride as described in the general procedure. The product was isolated as an oil which slowly solidified. Recrystallization from methylene chloride–hexane afforded 5α-fluoro-4-nitrimine **30** (0.90 g) as colorless needles: mp 185–188°; $[\alpha]^{22}D$ +114°; $[\alpha]^{22}_{5780}$ +126°, $[\alpha]^{22}_{5461}$ +138°; λ_{max} 265 mμ (ε 730); λ_{max}^{KBr} 5.65, 5.70, 6.05, 6.30, 7.60, 8.0, 8.25 μ.

Anal. Calcd for $C_{25}H_{37}FN_2O_6$: C, 62.49; H, 7.76; N, 5.81; F, 3.96. Found: C, 62.93; H, 7.00; N, 6.93; F, 3.78.

The mother liquors yielded additional solid, which was shown to be **30** by its infrared spectrum.

5α-Fluoro-17β-hydroxyestran-4-one Acetate (26b) and 5α-Fluoro-4β-nitrosoestran-17β-ol Acetate Dimer (25).—A solution of estr-4-en-17β-ol acetate (**23b**, 10.0 g) and methylene chloride (75 ml) was treated with a slow stream of nitrosyl fluoride (15 g over 6 hr) at ambient temperature as described in the general procedure. The usual work-up afforded a green syrup which solidified on trituration with methanol. The methanol was evaporated under a slow stream of nitrogen, and the solid residue was slurried with cold acetone–hexane and collected: yield 2.65 g; mp 150, 195–201°. Recrystallization from methanol–methylene chloride gave 5α-fluoro-4β-nitrosoestran-17β-ol acetate dimer (**25**, 1.19 g) as colorless microcrystals: mp 203–205°; $[\alpha]D$ +53°; λ_{max} 300 mμ (ε 5120); λ_{max}^{KBr} 5.73, 8.02, 8.62, 9.55 μ; H nmr, 0.80 (18-H), 2.01 ppm (acetate H); F^{19} nmr, +9312, +9344, and +9387 (5α-F, partially resolved triplet, w, s, w).

Anal. Calcd for $(C_{20}H_{30}FNO_3)_2$: C, 68.35; H, 8.60; F, 5.37; N, 3.97; mol wt, 702.88. Found: C, 68.44; H, 8.74, F, 5.20, 5.18; N, 3.90, 3.92; mol wt, 644 (vapor pressure osmometer, 37°).

The filtrate from the trituration and isolation of the fluoronitroso dimer was evaporated to dryness under reduced pressure to give a viscous, green syrup which was chromatographed on neutral alumina (activity III). Elution with hexane (fractions 7–21) gave colorless crystalline solids which were combined and recrystallized from hexane to give 5α-fluoro-17β-hydroxyestran-4-one acetate (**26b**, 1.40 g) as fine colorless needles: mp 147–149°; $[\alpha]D$ +11°, $[\alpha]_{546}$ +7°, $[\alpha]_{436}$ −35°, $[\alpha]_{405}$ −84°, $[\alpha]_{365}$ −200°; λ_{max} 297 mμ (ε 74); λ_{max}^{KBr} 5.75, 5.78, 8.00, 8.90, 9.50 μ; F^{19} nmr, +9590 cps (5α-F, broad multiplet).

Anal. Calcd for $C_{20}H_{29}FO_3$: C, 71.37; H, 8.68; F, 5.65. Found: C, 70.94; H, 8.62; F, 5.95.

5α-Fluoro-6-oximinoestrane-3β,17β-diol Triacetate (21b).—Fluoronitroso dimer **20a** (12.50 g) was dissolved in methylene chloride (75 ml) to give a deep blue solution. Methanol (50 ml) was added, and the solution was concentrated on a steam bath until a precipitate began to form. The mixture was cooled and allowed to stand at room temperature for 60 hr, during which time the precipitated solid redissolved to give a straw-colored solution. Addition of hexane containing a little acetone precipitated a white solid: yield 11.7 g; λ_{max} 2.82, 5.72, 5.78, 6.03, 8.05 μ; no absorption in the uv spectrum; H nmr, 0.80 (18-H), 2.05 ppm (acetate H). The precipitate in acetic anhydride (100 ml) was heated to reflux for 1 hr. The cooled reaction mixture was poured into 1 l. of ice–water, and the resultant mixture was stirred for 1 hr. The precipitated solid was collected, washed well with water, and dried. Recrystallization of the crude product from acetone–hexane afforded 5α-fluoro-6-oximinoestrane-3β,17β-diol tracetate (**21b**, 11.14 g in two crops) as fine colorless needles: mp 218–220°; $[\alpha]D$ −70°; λ_{max} 5.64, 5.75, 5.81, 6.07, 8.05, 8.42 μ; no absorption in the uv spectrum; H nmr, 0.80 (18-H), 2.02 (3,17-acetate H), 2.20 ppm (oxime acetate H); F^{19} nmr, +9236, +9270, and +9303 cps (5α-F, triplet w, s, w).

Anal. Calcd for $C_{24}H_{34}FNO_5$: C, 63.84; H, 7.59; F, 4.22. Found: C, 64.03, 64.15; H, 7.55, 7.45; F, 4.54, 4.60.

6-Oximinoestrane-3β,5α,17β-triol 3,17-Diacetate (22a).—In the preparation of 5α-fluoro-3β,17β-dihydroxyestran-6-one diacetate (**11n**) by chromatography of the reaction products of estr-5-ene-3β,17β-diol diacetate (**5n**) and nitrosyl fluoride, stripping the column with ether returned, in variable amounts, a yellow solid which on several recrystallizations from acetone–

hexane furnished 6-oximinoestrane-3β,5α,17β-triol 3,17-diacetate (**22a**): mp 238–245°; $[\alpha]D$ −119°; λ_{max} 2.90, 2.96, 5.77, 5.85, 6.01, 7.95, 8.05, μ; H nmr, 0.75 (18-H), 2.15 (3,17-acetate H), 4.63 (17α-H), 5.0 ppm (3α-H, $W_{1/2}$ = 25 cps).

Anal. Calcd for $C_{22}H_{33}NO_6$: C, 64.84; H, 8.16; N, 3.44. Found: C, 64.94, 64.90; H, 7.96, 7.58; N, 3.41; F, <0.3.

Androst-5-ene-3β,17β-diol Diacetate (5c) and 5α-Fluoroandrostane-3β,17β-diol Diactate (13).—5α-Fluoro-6β-nitraminoandrostane-3β,17β-diol diacetate (**7b**, 5.00 g), zinc dust (30 g), and glacial acetic acid (250 ml) were heated at 100° with vigorous stirring for 2 hr as described for **6c**. The crude product was chromatographed on neutral alumina (150 g, activity III). Elution with hexane–benzene (3:1) returned colorless solids (1.01 g) which were homogeneous by tlc and gave a bright yellow color with tetranitromethane. A portion was recrystallized from acetone–hexane to give material with mp 140–150°. A portion (0.75 g) of this material was rechromatographed on neutral alumina (25 g, activity III). Elution with hexane–benzene (3:1) returned colorless, crystalline material which upon recrystallization from hexane containing a little acetone afforded androst-5-ene-3β,17β-diol diacetate (**5c**, 156 mg): mp 157–159°, not depressed when admixed with a reference sample (lit.[18] mp 156–158°); H nmr, 0.81 (18-H), 1.04 (19-H), 2.03 (acetate H), 4.66 (17α-H, triplet, J = 7 cps), 5.42 ppm (6-H).

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.89; H, 9.11.

Continued elution with hexane–benzene (2:1 and 1:1) of the original chromatographic column gave 1.25 g of white solid which was homogeneous by tlc migrating slightly behind androst-5-ene-3β,17β-diol diacetate. Recrystallization from acetone–hexane afforded 5α-fluoroandrostane-3β,17β-diol diacetate (**13**, 1.11 g) as glistening leaflets: mp 131–137°, raised to 136–137° after drying under vacuum; $[\alpha]D$ −9°; H nmr, 0.68 (18-H), 0.97 (19-H), 2.04 (acetate H), 4.75 (17α H, triplet, J = 7 cps), 5.06 ppm (3α-H, $W_{1/2}$ = 13 cps); F^{19} nmr, +9187 cps (5α-F, broad peak).

Anal. Calcd for $C_{23}H_{35}FO_4$: C, 70.02; H, 8.94; F, 4.82. Found: C, 70.39; H, 8.56; F, 4.60.

4ξ-Fluoro-5ξ-nitrocholestan-3-one (43).—A mixture of cholestenone (**42**, 4.00 g), nitrosyl fluoride (2.3 g), and carbon tetrachloride (40 ml) was shaken at 25° under autogenous pressure in a "Hastelloy C" steel shaker tube for 10 hr. The tube was then vented and the product was worked up in the usual manner. The residual yellow oil was chromatographed on neutral alumina (120 g, activity III). Elution with petroleum ether–benzene (1:1) gave unreacted cholestenone (**42**, 0.68 g). Continued elution using benzene and benzene–ether (1:1) gave 196 mg of a pale yellow solid. Recrystallization from acetone–hexane (twice) yielded an analytical sample of ketone **43** as colorless rods: mp 170° (sinters at 161°); λ_{max} 282 mμ (ε 126); λ_{max} 5.68 (strong, sharp band), 6.30 (strong, sharp band), 7.65 μ (weak).

Anal. Calcd for $C_{27}H_{44}FNO_3 \cdot H_2O$: C, 69.35; H, 9.92; N, 3.00. Found: C, 69.09; H, 9.85; N, 3.50.

16-Nitropregna-4,16-diene-3,20-dione (41).—A solution of pregna-4,16-diene-3,20-dione (**39**, 10.00 g) in methylene chloride (100 ml) was treated with a slow stream of nitrosyl fluoride (*ca.* 4.5 g) (general directions). The crude reaction product was triturated with cold acetone–hexane and the solid was collected. Recrystallization from acetone gave starting material **39** (3.2 g, first crop, 2.4 g) as colorless leaflets, mp 192–193°. The filtrate was concentrated under reduced pressure to leave an oil which was chromatographed on neutral alumina (120 g, activity III). Elution with benzene (cuts 5–8) gave a crystalline solid. Recrystallization of this from acetone gave additional starting material **39** (1.19 g). Continued elution with the same solvent gave oily fractions (cuts 11–16), 0.89 g. Recrystallization from methanol gave 16-nitropregna-4,16-diene-3,20-dione (**41**, 585 mg) as pale yellow needles: mp 165° (sharp); $[\alpha]D$ +88°; λ_{max} 239 mμ (ε 20,700) and 280 mμ (ε 5050); λ_{max} 5.87, 5.99, 6.09, 6.16, 6.59, 7.40 μ.

Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; Found: C, 70.60; H, 7.61.

Sodium Salt of 5α-Fluoro-6β-nitraminocholestan-3β-ol 7a.—A solution of nitramine **7a** (2.50 g) in ethanol (50 ml) containing sodium hydroxide (0.398 g) was warmed briefly on a steam bath and then allowed to stir for 24 hr at room temperature. Careful dilution of the solution with water caused a precipitate to form which was filtered, washed with cold water and dried: yield 1.72 g; mp 264–268 (capillary); λ_{max} 2.95, 3.05, 6.10 (broad peak), 8.65 μ.

Anal. Calcd for $C_{27}H_{46}FN_2O_3Na2 \cdot H_2O$: C, 61.7; H, 9.55; Na, 4.38. Found: C, 61.66, 61.68; H, 9.53, 9.62; Na, 4.30.

A portion was recrystallized from N,N-dimethylformamide–water to give well-formed colorless needles, mp 285° dec (capillary). The salt is soluble in hot water and behaves as a surface-active agent.

5α-Fluoroandrostane-3β,6β,17β-triol 3,17-Diacetate (16b).—A solution of 5α-fluoro-3β,17β-dihydroxyandrostan-6-one diacetate (**11c**, 10.0 g), lithium hydrotri-*t*-butoxyaluminate (32 g), and tetrahydrofuran was stirred for 60 hr at ambient temperature. The homogeneous reaction mixture was poured into 3 l. of ice-cold 5% acetic acid and the precipitate was filtered, washed well with water, and air dried. Recrystallization from acetone–petroleum ether (bp 30–60°) afforded the triol diacetate **16b** (8.1 g), mp 155–160°. One additional recrystallization from acetone–hexane furnished the analytical sample: mp 168–169; $[\alpha]^{24}D$ −22°; λ_{max} 2.89, 5.76, 5.85, 8.05 μ; $\lambda_{max}^{CCl_4}$ 2.77, 2.87, 5.77, 8.08 μ; H nmr, 0.81 (18-H), 1.17 (19-H), 2.01 ppm (acetate); F nmr, +9060 and +9107 cps (5α-F).

Anal. Calcd for $C_{23}H_{35}FO_5$: C, 67.29; H, 8.59; F, 4.63. Found: C, 67.58; H, 8.53; F, 4.58.

Registry No.—Nitrosyl fluoride, 7789-25-5; **2**, 17328-21-1; **3**, 15344-28-2; **4**, 7431-25-6; **5c**, 2099-26-5; **6a**, 4661-09-0; **6b**, 13649-89-3; **6c**, 15426-21-8; **6d**, 5359-98-8; **6f**, 5360-00-9; **6q**, 17328-30-2; **6n**, 17328-31-3; **7a**, 4616-29-9; **7b**, 17328-33-5; **7c**, 17328-34-6; **8a**, 17328-35-7; **9**, 17328-36-8; **10**, 17328-37-9; **11a**, 2560-87-4; **11b**, 4558-55-8; **11c**, 5359-97-7; **11d**, 5359-99-9; **11e**, 17328-42-6; **11f**, 5359-96-6; **11g**, 4728-39-6; **11h**, 5529-62-4; **11i**, 5359-95-5; **11j**, 17328-45-9; **11k**, 17328-46-0; **11l**, 17328-47-1; **11m**, 17328-48-2; **11n**, 17328-49-3; **11o**, 17328-50-6; **11p**, 17328-51-7; **11q**, 17328-52-8; **11r**, 17328-53-9; **11s**, 17328-54-0; **11t**, 17328-55-1; **13**, 17328-56-2; **14a**, 17328-57-3; **14b**, 1256-83-3; **15b**, 4025-59-6; **16a**, 7600-95-5; **16b**, 17328-60-8; **17**, 4447-87-4; **18**, 4649-89-2; **19a**, 984-84-9; **21b**, 17342-69-7; **22a**, 17328-63-1; **24a**, 17328-64-2; **25**, 17326-93-1; **26a**, 17328-65-3; **26b**, 17329-03-2; **27**, 17342-70-0; **28a**, 17329-04-3; **28b**, 17329-05-4; **30**, 17329-06-5; **31a**, 17329-07-6; **31b**, 17329-08-7; **32**, 17329-09-8; **34**, 13643-70-4; **35**, 3872-09-1; **36**, 566-88-1; **41**, 17342-71-1; **43**, 17329-13-4; **49**, 17329-14-5; sodium salt of **7a**, 17342-65-3.

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