in 1.0 ml. of pyridine and 1.0 ml. of acetic anhydride was allowed to stand overnight at room temperature. The excess acetic anhydride was decomposed by the addition of ice and water, and the crystalline product (47 mg., m.p. 181–182.5°) was isolated by filtration and then washed with water. One crystallization of this material from acetone–hexane gave the desired 6β-acetoxy-1,4-androstadiene-3,17-dione, m.p. 184–185.5°; $[\alpha]_D$ +59°; λ_{max} 244 mμ (ε 15,300); $\lambda_{max}^{CHCl_3}$ 5.74, 5.98, 6.15, 6.22 (shoulder), and 8.02 μ.

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.65; H, 7.65. Found: C, 73.48; H, 7.48.

6β-Acetoxy-1,4-androstadiene-3,17-dione (XV) from 6β-Acetoxy-4-androstene-3,17-dione (XVI).—A solution of 0.500 g. (1.45 mmoles) of 6β-acetoxy-4-androstene-3,17-dione in 25 ml. of benzene was heated to boiling to free it from traces of water. To the dry solution was added 0.395 g. (1.74 mmoles, 1.20 equiv.) of 2,3-dichloro-5,6-dicyanobenzoquinone. The resulting solution was heated under reflux for 48 hr. It was then cooled, and the solution decanted from the precipitated hydroquinone. The hydroquinone was washed with benzene and then with ether. The combined organic solution was washed with saturated aqueous sodium sulfite, water, saturated aqueous sodium sulfite, then finally water in that order, dried over sodium sulfate, and then evaporated to dryness. The residue (388 mg.), after crystallization from dilute acetone then acetone–cyclohexane, yielded 308 mg. of 6β-acetoxy-1,4-androstadiene-3,17-dione (XV), m.p. 179.5–181°; $[\alpha]_D$ +58°, +60°; λ_{max} 243.4 mμ (ε 16,500). This material proved to be identical (m.m.p. and infrared spectrum) with that prepared from the fermentation product.

Hydrolysis of this 6β-acetoxy-1,4-androstadiene-3,17-dione (XV) with sodium hydroxide in aqueous methanol produced 6β-hydroxy-1,4-androstadiene-3,17-dione, m.p. 202–205°, identical (infrared spectrum) with that produced from the fermentation product.

The Reaction of Sulfur Tetrafluoride with Steroids[1]

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Sulfur tetrafluoride containing 20% hydrogen fluoride effected room temperature transformations of a variety of carbonyl-containing steroids into fluorinated derivatives in moderate to high yield. Included were the conversions of a carboxylic acid into its trifluoromethyl derivative and of a formyl group into a difluoromethyl group as well as of ketones at C-3, C-17, and C-20 into *gem*-difluoro groupings. This relatively mild procedure permitted the selective fluorination of the carbonyl groups mentioned above in steroids also containing acetate and α,β-unsaturated ketone functions.

The profound effects on the biological properties of certain steroids elicited by the introduction of fluorine[2] combined with the introduction of sulfur tetrafluoride as a reagent for the replacement of carbonyl oxygen with fluorine[3] prompted our investigations on steroid fluorination with this new reagent. Since the completion of our work, a report has appeared[4] on the conversion of cholestanone and several steroid diketones into *gem*-difluoro steroids with this reagent; however, low yields and restriction to comparatively simple steroids containing only ketone functions limit the utility of the reported procedure. The investigations reported herein led to procedures compatible with the preparation of relatively complex fluorinated steroids in moderate to good yields. An example of the degree of complexity feasible was the fluorination of a cortical steroid intermediate containing a dihydroxy acetone side chain protected as its bismethylenedioxy derivative.[5] A modified procedure was vigorous enough to convert lithocholic acid 3-acetate into its trifluoromethyl derivative Ib in moderate yield. To our knowledge this is the first report of the conversion of a steroid carboxylic acid into its trifluoromethyl derivative.

Although catalytic amounts of hydrogen fluoride have been found by other investigators[3,4] to favor the reaction of sulfur tetrafluoride with certain carbonyl groups, we found that the presence of *substantial amounts of hydrogen fluoride* was essential for the successful fluorination of a variety of steroids. Considerations of expediency and convenience in the exploration of steroid fluorination prompted our attempts at adapting the conditions of Hasek, Smith, and Engelhardt[3] to the fluorination of comparatively small samples. Investigations on the fluorination of relatively small amounts of stearic acid dramatically indicated that more than catalytic amounts of hydrogen fluoride were required for the successful conversion of a carboxyl group into its trifluoromethyl derivative. This transformation has been reported to proceed stepwise *via* an initial facile conversion into an acyl fluoride[3] with the liberation of an equivalent of hydrogen fluoride, *e.g.*,

$$-CO_2H + SF_4 \longrightarrow -COF + HF + SOF_2 \quad (1)$$

$$-COF + SF_4 \longrightarrow -CF_3 + SOF_2 \quad (2)$$

Significant results of three pertinent experiments on the fluorination of stearic acid are tabulated in Table I. These data made it readily apparent that a critical concentration of hydrogen fluoride was

(1) Presented at the Symposium on Fluorine Containing Compounds of Biological Interest, at the 140th Meeting of the American Chemical Society, September 6, 1961, Chicago, Illinois.

(2) *Cf.* L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Co., New York, 1959, pp. 593, 682–686.

(3) W. R. Hasek, W. C. Smith, and V. A. Engelhardt, *J. Am. Chem. Soc.*, **82**, 543 (1960).

(4) J. Tadanier and W. Cole, *J. Org. Chem.*, **26**, 2436 (1961).

(5) D. G. Martin and J. E. Pike, to be published.

TABLE I

EFFECT OF SF_4 ON STEARIC ACID[a]

Grams stearic acid	Equiv. stearic acid	Equiv. SF_4 for step 2	Equiv. HF for step 2	Ratio Equiv. HF / Equiv. SF_4	Product
20.0	1	5	1	0.20	$-CF_3$
1.0	1	120	1	.008	—COF
1.0	1	108	24	.22	$-CF_3$

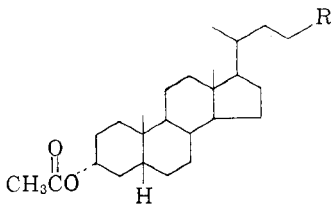
[a] All reactions were agitated at 130° for six hours.

The action of a large excess of a reagent comprised of one part of hydrogen fluoride to five parts of sulfur tetrafluoride on lithocholic acid acetate at 130°, the temperature previously reported for carboxyl transformations,[3] completely charred the sample. Avoidance of charring required operation at room temperature or slightly below and the use of an inert solvent such as methylene chloride. Although the reaction of sulfur tetrafluoride with halogenated hydrocarbons has been reported,[6] such displacement reactions did not interfere with the desired fluorinations at room temperature. Operation at temperatures above room temperature apparently degraded the acetate function at C-3 in a nonspecific manner; discrete reaction products were not readily isolated. Since conversion of an acyl fluoride function into a trifluoromethyl group required a critical concentration of hydrogen fluoride, it was not surprising that Lewis bases such as diethyl ether, tetrahydrofuran, and 1,2-dimethoxyethane inhibited this transformation. The facile conversion of the carboxyl function into an acyl fluoride did occur in the presence of such inhibiting solvents; for example, fluorination of lithocholic acid acetate in tetramethylene sulfone afforded the acid fluoride Ia in high yield.

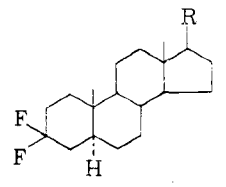
In the reaction of sulfur tetrafluoride with aliphatic aldehydes and ketones, Hasek, Smith, and Engelhardt noted that carbonyl compounds containing an α-hydrogen atom were easily charred by the reagent.[3] These workers found it necessary to carry out the fluorination of cyclohexanone below 50°; treating the ketone with one equivalent of sulfur tetrafluoride at 39° for thirteen hours, they obtained 1,1-difluorocyclohexane in 31% yield.[3]

The procedure described above for the preparation of 24,24,24-trifluoro-5β-cholan-3α-ol, acetate was found to be well suited for the preparation of *gem*-difluorosteroids from steroid ketones and aldehydes.[5] This procedure afforded fluoro steroids II–VIII—from the corresponding carbonyl precursors in moderate to high yields (*cf.* Table II). required for the conversion of an acyl fluoride function into its trifluoromethyl derivative.

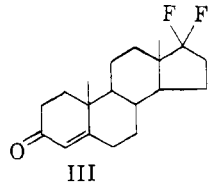
A rough order of reactivity of various steroidal carbonyl groups toward the hydrogen fluoride–sulfur tetrafluoride reagent was established from the yields of fluorinated products and from the amount



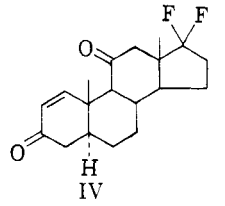
Ia. R = COF
Ib. R = CF_3



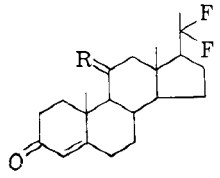
IIa. R = C_8H_{17}
IIb. R = $OCOCH_3$



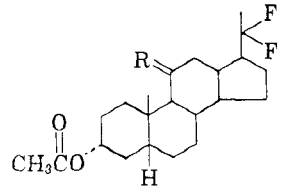
III



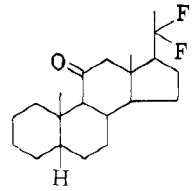
IV



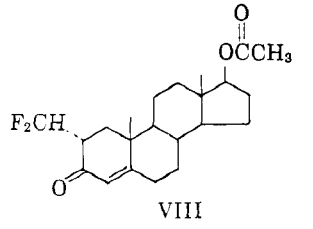
Va. R = H, H
Vb. R = O



VIa. R = H, H
VIb. R = O



VII



VIII

of hydrogen fluoride required for the reaction. For example it was found that highly reactive carbonyl groups such as the saturated 3-ketone function of 3-cholestanone and the 6-formyl function of a corticoid intermediate[5] were converted into their difluoro derivatives in good yields with sulfur tetrafluoride containing approximately 1 mole % of hydrogen fluoride whereas less reactive groups such as the 17-ketone function of androst-4-ene-3,17-dione were largely recovered under the same conditions. However, sulfur tetrafluoride containing approximately 20 mole % of hydrogen fluoride afforded difluoro derivatives of such less reactive groups in moderate yields. If no hydrogen fluoride was present even the unconjugated 3-ketone and 6-formyl functions were unaffected by sulfur tetrafluoride. Listed in order of decreasing reactivity towards the hydrogen fluoride–sulfur tetrafluoride reagent, the functions were 3-ketone $\cong$ 6-formyl > 17-ketone > 20-ketone of an 11-keto steroid > 20-ketone of an 11-desoxy steroid $\cong$ primary acyl fluoride > conjugated 3-ketone[7] > 11-ketone.

The utility of this comparatively mild fluorination procedure for the preparation of complex fluorinated steroids or other polyfunctional mole-

(6) C. W. Tullock, R. A. Carboni, R. J. Harder, W. C. Smith, and D. D. Coffman, *J. Am. Chem. Soc.*, **82**, 5107 (1960).

(7) See footnote *f* of Table II.

TABLE II

Product	Yield, %	$[\alpha]_D$	M.p.	ν_{max} ($cm.^{-1}$)	λ_{max} ($m\mu$)	Formula	Calcd. C	Calcd. H	Calcd. F	Found C	Found H	Found F
Ia	95[a]	+44	156–158	1838 1733		$C_{26}H_{41}FO_3$	74.24	9.83	4.52	74.72	9.89	4.40
Ib	25	+44	148–150	1727[b]		$C_{26}H_{41}F_3O_2$	70.55	9.34	12.88	70.77	9.49	12.53
IIa[c]	78[a]	+22	109.5–111	[b]		$C_{27}H_{46}F_2$	79.35	11.35	9.30	79.55	11.39	9.79
IIb	82	+2	136.5–138	1725[b] (1732 sh)		$C_{21}H_{32}F_2O_2$	71.15	9.10	10.72	71.08	9.39	10.37
III[d]	63[e]	+97	185–187	1660[b] 1615	240 ϵ 16,750	$C_{19}H_{26}F_2O$	73.99	8.50	12.32	74.19	8.78	12.20
IV	66[f]	+86	126–127	1705[b] 1677 (1685 sh) 1607	226 ϵ 11,300	$C_{19}H_{24}F_2O_2$	70.78	7.50	11.79	71.33 70.84	7.63 7.95	12.30
Va[g]	36[h]	+98	116–116.5	1663[b] 1615	241 ϵ 16,700	$C_{21}H_{30}F_2O$	74.96	9.20	11.29	75.30	9.32	10.95
Vb[i]	37		160.5–162	(1700 sh)[b] 1693 1675 1620	237 ϵ 15,450	$C_{21}H_{28}F_2O_2$	71.97	8.05	10.84	72.51	8.13	11.35
VIa	23		90–91.5	1725[b]		$C_{23}H_{36}F_2O_2$	72.21	9.49	9.93	72.32	9.65	10.23
VIb[j]	58		140–141	1730[b] 1700		$C_{23}H_{34}F_2O_3$	69.66	8.64	9.58	69.57	8.56	10.15
VII[i]	50		157–158.5	1693[b]		$C_{21}H_{32}F_2O$	74.74	9.53	11.26	74.32	9.48	11.38
VIII[j]	26[k]	+93	179–180	1725[b] 1666 1620	241 ϵ 16,000	$C_{22}H_{30}F_2O_3$	69.45	7.95	9.99	70.36 69.32	8.14 8.51	9.97

[a] Chromatography was not required. The crude product was recrystallized to afford the stated yield. [b] The fingerprint region contained a series of absorptions between 1200 and 1000 $cm.^{-1}$. [c] Reported[4] m.p. 109–111°, $[\alpha]_D$ +24°. These workers obtained a 32% yield using lower ratios of reagents to steroid and hydrogen fluoride to sulfur tetrafluoride, higher temperatures, and chloroform instead of methylene chloride. [d] Reported[4] m.p. 181–183°, $[\alpha]_D$ +82°, ν_{max} 1668, 1622. These workers obtained a 3% yield with hydrogen fluoride catalysis or a 10% yield with boron trifluoride catalysis. [e] About 4% androst-4-ene-3,17-dione was recovered by chromatography. [f] No recovered androst-1-ene-3,11,17-trione was detected by chromatography. A by-product was isolated in low yield (7% crude), m.p. 144–145°, having analysis and infrared consistent with 3,3,17,17-tetrafluoro-androst-1-ene-11-one but was not completely characterized. [g] Reported[4] m.p. 108–110°, $[\alpha]_D$ +94°, ν_{max} 1672, 1620. These workers obtained a 2% yield with boron trifluoride catalysis. [h] About half of the progesterone was recovered. Chromatographic separation on Florisil was incomplete, affording 40% of the product as mixed fractions with progesterone. The composition of these mixed fractions was estimated by paper chromatography and the yield stated in this case represents the total Va formed in the reaction. [i] These steroids were prepared by Dr. W. J. Wechter of these laboratories using the procedure described. Use of his unpublished results is gratefully acknowledged. [j] The 2α-configuration was tentatively assigned to the difluoromethyl group since the optical rotatory dispersion curve was practically identical with that of testosterone acetate [R. L. Houtman, unpublished results. The equipment and procedure followed were the same as those described in a recent publication by W. A. Struck and R. L. Houtman, *J. Org. Chem.*, **26**, 3883 (1961)]. The required starting material, 2-hydroxymethylenetestosterone 17-acetate, m.p. 164.5–165.5°, $[\alpha]^{CHCl_3}_D$ +16° (Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.72; H, 8.47) was kindly supplied by Dr. N. A. Nelson of these laboratories. The action of acetic anhydride in pyridine on 2-hydroxymethylenetestosterone [F. L. Weisenborn, D. C. Remy, and T. L. Jacobs, *J. Am. Chem. Soc.*, **76**, 552 (1954)] afforded a diacetate but the enol acetate of the 2-hydroxymethylene group was selectively saponified with potassium bicarbonate in aqueous methanol. [k] Isolation and purification were complicated by the presence of a chlorine containing contaminant which was not characterized.

cules was greatly enhanced by the relative stability of the ester, conjugated ketone, and bismethylenedioxy functions towards these conditions.

Although others have reported that boron trifluoride was a more potent catalyst than hydrogen fluoride,[3,4] in our hands, hydrogen fluoride was preferred because it catalyzed the desired fluorination with a minimum of side reactions whereas boron trifluoride was less selective, promoting side reactions even at low concentrations. Thus, the action of sulfur tetrafluoride containing 1% boron trifluoride etherate on androst-4-ene-3,17-dione afforded a black tarry product comprised of 8% difluoro derivative III, 45% starting material, and 25% of a mixture of at least six more polar materials.

Although the n.m.r. spectra of 3,3,20,20-tetrafluoro-5α-pregnane and 3,3,20,20-tetrafluoro-5β-pregnane have been discussed,[4] the positions of the absorption bands of the C-21 protons were not mentioned. Accordingly the n.m.r. spectra of 3α-hydroxy-5β-pregnan-20-one acetate and 20,20-difluoro-5β-pregnan-3α-ol acetate (VIa) are compared in Table III.

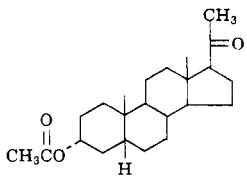
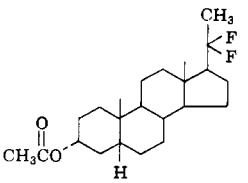
Replacement of the C-20 carbonyl with the *gem*-difluoro grouping shifted the C-21 proton absorption from 128 c.p.s. to 96 c.p.s. Spin-spin coupling with the fluorine atoms splits this absorption into a triplet (J = 19 c.p.s.). The appearance of the C-18 proton absorption as a triplet (J = 2 c.p.s.) was apparently the result of long-range spin-spin coupling[8] with the fluorine atoms at C-20.

Although our investigations were confined to synthetic applications of sulfur tetrafluoride, the

(8) D. R. Davis, R. P. Lutz, and J. D. Roberts, *J. Am. Chem. Soc.*, **83**, 246 (1961).

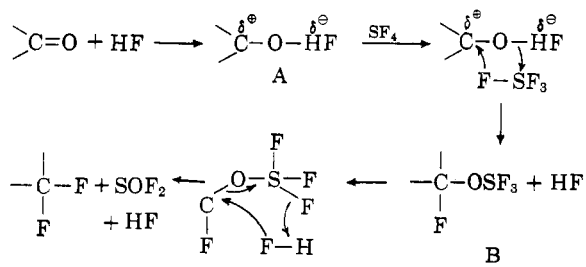
TABLE III

N.M.R. SPECTRA[a]

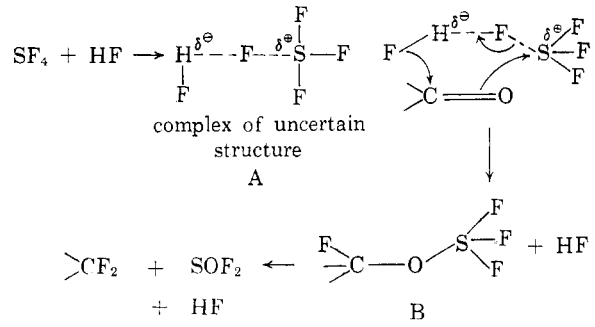
Methyl protons	$CH_3C(=O)O$	C-19	C-18	C-21
		123	58	38	128
		123	58	50[b]	96[c]

[a] Spectra were determined in deuterochloroform on a Varian DP-60 spectrometer at 60 Mc. and calibrated against internal tetramethylsilane by audiofrequency-side band interpolations. The spectra were calibrated in c.p.s. downfield from tetramethylsilane. The authors are grateful to Dr. G. Slomp and Mr. F. A. MacKellar for the determination and interpretation of these spectra. [b] This absorption band appeared as a triplet (J = 2 c.p.s.). In a discussion of the n.m.r. spectrum of 3,3,20,20-tetrafluoro-5β-pregnane,[4] other workers described the C-18 proton absorption as a singlet at 49 c.p.s. [c] The absorption band appeared as a triplet (J = 19 c.p.s.).

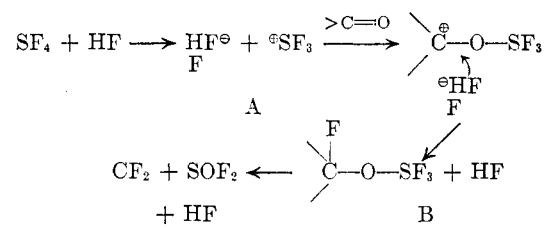
discovery that a significant rather than catalytic proportion of hydrogen fluoride permitted fluorination under milder conditions prompts us to speculate on the reaction pathway involved. Perhaps under conditions employing catalytic amounts of Lewis acid the pathway suggested by earlier workers[3] would be in effect. The hydrogen fluoride would simply polarize the carbonyl. A molecule of sulfur tetrafluoride then would add across the activated carbonyl and the adduct B would collapse to form the products. As indicated earlier[3] hydrogen fluoride could participate in the collapse of adduct B. However since definite interaction or compound



formation between covalent fluorides and sulfur tetrafluoride is known,[9] a significant proportion of hydrogen fluoride would generate an appreciable concentration of such a complex. The structure of such a complex or adduct is uncertain[9]; nevertheless, complex formation assures the presence of both hydrogen fluoride and sulfur tetrafluoride at the site of reaction and thereby would allow hydrogen fluoride to participate directly in the fluorination. One of the possible ways in which hydrogen fluoride might participate is depicted below. This affords the same adduct B as the previous suggestion. In



another possible pathway, the hydrogen fluoride–sulfur tetrafluoride interaction might consist of an ionic process[10] generating $SF_3^{\oplus}$ and $HF_2^{\ominus}$; in such an event the reaction would be expected to proceed by initial attack of the cation on the carbonyl oxygen as illustrated below. Donation of a fluoride ion by $HF_2^{\ominus}$ would then lead to the same intermediate B.[11]



This study has afforded a practical and convenient procedure for the selective replacement of carbonyl oxygen of steroids and other polyfunctional molecules with fluorine by treatment with sulfur tetrafluoride. The proportions of hydrogen fluoride and sulfur tetrafluoride determine the vigor of the reaction; one part of hydrogen fluoride to five parts of sulfur tetrafluoride was a particularly effective combination. Applications of this procedure to new systems and further transformations on fluorinated products will be reported in later publications.

(9) *Cf.* A. T. Oppegard, W. C. Smith, E. T. Muetterties, and V. A. Englehardt, *J. Am. Chem. Soc.*, **82**, 3835 (1960).

(10) N. Bartlett and P. L. Robinson, *J. Chem. Soc.*, 3417 (1961), cite indications that the related sulfur tetrafluoride, boron trifluoride adduct consists of an ionic formulation $SF_3^{\oplus}BF_4^{\ominus}$.

(11) Besides the pathways discussed above, the referee suggested an additional pathway by which hydrogen fluoride might participate in the reaction. If hydrogen fluoride added across the carbonyl, the resulting F—C—OH intermediate might be transformed into the *gem*-difluoride by sulfur tetrafluoride.

Experimental[12]

The fluorinations were carried out in a 316 stainless steel autoclave employing a copper gasket. A rupture disk of 316 stainless steel was employed and changed after every fifth run. Hydrogen fluoride was generated *in situ* by the hydrolysis of sulfur tetrafluoride[3] ($SF_4 + H_2O \rightarrow SOF_2 + 2\ HF$). Sulfur tetrafluoride was measured by the pressure drop across a stainless steel reservoir of known volume on opening the reservoir to a frozen autoclave containing all other reactants. The fluorination procedure is illustrated by the preparation of 24,24,24-trifluoro-5β-cholan-3α-ol acetate. Other fluorinations were carried out under the same conditions.

24,24,24-Trifluoro-5β-cholan-3α-ol Acetate (Ib).—A mixture of 1.0 g. of lithocholic acid acetate, 20 ml. of methylene chloride, and 0.75 ml. of water was placed in a 100-ml. autoclave. The autoclave was sealed and frozen in a bath of Dry Ice and acetone before approximately 46 g. of sulfur tetrafluoride[13] was condensed into the autoclave. The autoclave was then agitated for 16 hr. at room temperature. The temperature of the cubicle used for high pressure reactions was 20°; several hours were required for the frozen autoclave to attain cubicle temperature. The autoclave was vented through caustic solution, evacuated to remove volatile materials, and finally opened. Its contents were taken up in 200 ml. of methylene chloride and washed with 10% potassium bicarbonate solution. The methylene chloride solution was dried over sodium sulfate and concentrated to dryness under reduced pressure leaving 1.20 g. of brown gum which was chromatographed on 60 g. of Florisil.[14] The column was developed with Skellysolve B[15] and methylene chloride–Skellysolve B mixtures containing an increasing concentration of methylene chloride. The Skellysolve B and 1% methylene chloride–Skellysolve B eluates contained a small amount of sulfur and trace amounts of a yellow gum lacking carbonyl absorption in the infrared. The eluates comprising 2 to 20% methylene chloride–Skellysolve B afforded crystalline fractions totaling 273 mg. Recrystallization from acetone–water afforded 2 crops totaling 268 mg. (25% yield) of crystalline solid, m.p. 147–149°. Recrystallization from acetone–water gave a sample $[\alpha]_D$ +44° (chloroform); ν_{mull} 1727 cm.$^{-1}$; m.p. 148–150°.

Anal. Calcd. for $C_{26}H_{41}O_2F_3$: C, 70.55; H, 9.34; F, 12.88. Found: C, 70.77; H, 9.49; F, 12.53.

3α-Hydroxy-5β-cholanyl Fluoride Acetate (Ia). Procedure A.—A mixture of 5.00 g. of lithocholic acid acetate, 20 ml. of methylene chloride, and 46 g. of sulfur tetrafluoride was agitated for 16 hr. at room temperature. The autoclave was vented and its contents taken up in methylene chloride, washed with 10% potassium bicarbonate, dried over sodium sulfate, and concentrated to dryness under reduced pressure leaving 5.00 g. of crystalline residue. Recrystallization from methylene chloride–Skellysolve B afforded 4.75 g. (95% yield), m.p. 157–158°. Three recrystallizations from the same solvents afforded a sample, m.p. 158–159°; ν 1838, 1733 cm.$^{-1}$; $[\alpha]_D$ +44°.

Anal. Calcd. for $C_{26}H_{41}FO_3$: C, 74.24; H, 9.83; F, 4.52. Found: C, 74.72; H, 9.89; F, 4.40.

Procedure B.—The fluorination procedure employed for 24,24,24-trifluoro-5β-cholan-3α-ol acetate, was followed except that 20 ml. of tetramethylene sulfone[16] replaced the methylene chloride. The crude product was diluted with methylene chloride, washed with 10% potassium bicarbonate and two portions of water, dried over sodium sulfate, and concentrated under reduced pressure leaving the product in approximately 8 ml. of tetramethylene sulfone. Dilution with water precipitated 0.82 g. crude Ia, m.p. 152–155°.

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(12) Melting points are uncorrected. Rotations were observed at 26° on chloroform solutions. Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer from Nujol mulls. Ultraviolet spectra were taken on 95% ethanol solutions using a Cary Model 14.

(13) Obtained from the E. I. DuPont de Nemours Co., Wilmington, Del., and the Matheson Co., East Rutherford, N. J.

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

(15) A saturated hydrocarbon fraction, b.p. 60–71°.

(16) Obtained from the Columbia Organic Chemicals Co., Columbia, South Carolina, and redistilled.

The Synthesis of Certain α-Cyano Keto Steroids

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The 2α-cyano derivatives of testosterone, progesterone, deoxycorticosterone, hydrocortisone, and cortisone were prepared by reaction of the corresponding 2-hydroxymethylene derivatives, having properly blocked side chains, with O,N-bis(trifluoroacetyl)hydroxylamine (II). The 16ξ-cyano derivatives of testosterone, estrone 3-methyl ether, and estradiol 3-methyl ether were prepared in the same manner from the corresponding 16-hydroxymethylene-17-keto precursors.

The introduction of halogen atoms or additional methyl or hydroxyl groups into the nucleus of steroid hormones in certain instances has had important effects on the biological activities of these hormones. It appears to us that with the present state of knowledge in this field, the discovery of other groups which would also favorably modify the biological activity of the parent hormones must largely stem from an empirical approach. As part of a continuing effort in our laboratory based on such an approach, we have prepared certain steroid hormones substituted at C-2 or C-16 with the cyano group.[1] These compounds are of interest *per se* and also as precursors for a variety of other steroid analogs.[2] Hitherto, cyano steroids have received little attention, but among those which have been

(1) For a preliminary communication see H. M. Kissman, A. S. Hoffman, and M. J. Weiss, *J. Org. Chem.*, **26**, 2610 (1961).

(2) Further transformations of these cyano steroids will be described in a forthcoming publication.