hydrofuran. Upon the addition of 175 ml. of liquid ammonia, a clear solution resulted. To the stirred solution was then added over a period of 5 min. 2.3 g. (0.332 g.-atom) of lithium wire. After 3 hr. the bronze and deep blue colors of the reaction mixture discharged spontaneously. Twenty milliliters of methanol was then carefully added, and the ammonia was evaporated under a stream of nitrogen. The residue was diluted with 100 ml. of water and then distilled under reduced pressure until 125 ml. of distillate was collected. The residual gel was diluted with an additional 500 ml. of water and acidified with 40 ml. of glacial acetic acid. The finely divided, colorless precipitate was collected by filtration, washed well with water, and dried.

The crude enol ether was hydrolyzed by dissolving in 200 ml. of methanol containing 18 ml. of 12*N* hydrochloric acid. The reaction mixture was allowed to stand at room temperature for 4 hr. and then poured into 1 l. of water. The product was extracted with chloroform. The chloroform solution was evaporated to dryness to afford 3.5 g. of a pale yellow oil, which crystallized when treated with ether. The crystalline product was collected and recrystallized twice from ethyl acetate after treatment with charcoal to yield 0.700 g. (19%) of XXII as colorless dense crystals, m.p. 155°; infrared (potassium bromide) 5.63, 6.01, and 6.20 μ; $\lambda_{max}^{CH_3OH}$ 238 mμ (ϵ 17,000).

Anal. Calcd. for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.49; H, 7.80.

An additional 0.405 g. (11%) of XXII, m.p. 152–153°, was recovered from the mother liquors.

CHICAGO 80, ILL.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

The Synthesis of Certain 7α-Alkylthio and 7α-Acylthio Steroid Hormone Derivatives

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Received April 6, 1961

7α-Alkylthio and/or 7α-acylthio derivatives of cortisone, 9α-fluorohydrocortisone, progesterone, deoxycorticosterone and testosterone have been prepared by condensation of the corresponding 6-dehydro derivatives with sulfur nucleophiles. 7α-Methylthiotestosterone acetate (XVI) and 7α-mercaptotesterone acetate (XIX) showed anabolic activity (levator ani assay). Various additional derivatives of testosterone containing the 7α-methylthio and/or the 7α-acetylthio group have been synthesized.

As part of our steroid analog program[1] it was of interest to prepare various structures containing a substituent at C-7. At the start of this investigation we were aware of no fully elaborated steroid hormone substituted at this position. However, since then several such analogs have been reported. These analogs include the 7α-hydroxy derivatives[2a] of cortisone and prednisone, the 7α- and 7β-hydroxy derivatives[2b] of progesterone and deoxycorticosterone, the 7α-acylthio derivatives[3a] of testosterone, progesterone, deoxycorticosterone, cortisone, and hydrocortisone,[3b] and the 7α- and 7β-methyl derivatives of hydrocortisone,[4] testosterone,[4a,c] and progesterone.[4c,5,6] For our program, convenient entry into the C-7 position appeared possible *via* the 1,6-addition of various nucleophiles with the known and readily available 6-dehydro derivatives of appropriate Δ^4-3-keto steroids. Although at the start of this study, such a condensation had not been reported in the literature, similar reactions with the analogous $\Delta^{3,5}$-7-keto system were on record.[7] However, during the course of our investigation Dodson and Tweit[3a] reported the reaction of thio acids with several $\Delta^{4,6}$-3-ketones to give a series of 7α-acylthio derivatives, certain of which were closely related to or identical with some of the compounds already prepared in our laboratory.

Our initial studies were carried out with 6-dehydrocortisone acetate (I).[8] Treatment of this compound with various sulfur nucleophiles (methyl mercaptan, ethyl mercaptan, thioacetic acid and

(1) For the previous report from this laboratory concerning this program see H. M. Kissman, A. S. Hoffman, and M. J. Weiss, *J. Org. Chem.*, **26**, 2610 (1961).

(2)(a) A. L. Nussbaum, G. Brabazon, T. L. Popper, and E. P. Oliveto, *J. Am. Chem. Soc.*, **80**, 2722 (1958). (b) W. J. McAleer, M. A. Kozlowski, T. H. Stoudt, and J. M. Chemerda, *J. Org. Chem.*, **23**, 958 (1958); see also J. Fried, U. S. Pat. **2,836,608**.

(3)(a) R. M. Dodson and R. C. Tweit, *J. Am. Chem. Soc.*, **81**, 1224 (1959).

(3)(b) Several 7α-acylthio derivatives of the 17-spirolactones having important aldosterone blocking properties on oral administration have been reported [J. A. Cella and R. C. Tweit, *J. Org. Chem.*, **24**, 1109 (1959)].

(4)(a) J. A. Zderic, H. Carpio, and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 432 (1959). (b) R. E. Beyler, A. E. Oberster, F. Hoffman, and L. H. Sarett, *J. Am. Chem. Soc.*, **82**, 170 (1960). (c) J. A. Campbell and J. C. Babcock, *J. Am. Chem. Soc.*, **81**, 4069 (1959). (d) C. H. Robinson, O. Gnoj, and E. P. Oliveto, *J. Org. Chem.*, **24**, 121 (1959).

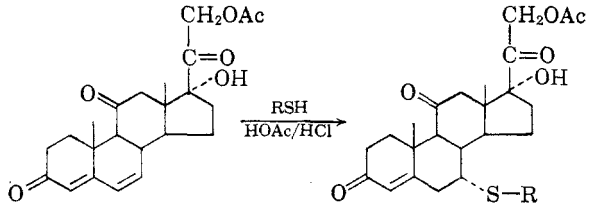
(5) C. H. Robinson, O. Gnoj, W. Charney, M. L. Gilmore, and E. P. Oliveto, *J. Am. Chem. Soc.*, **81**, 408 (1959).

(6) The synthesis of the 7-keto derivatives of testosterone progesterone, deoxycorticosterone, 17α-acetoxyprogesterone, progesterone and substance S had been reported by B. Riegel and co-workers, *J. Am. Chem. Soc.*, **79**, 6303 (1957).

(7)(a) J. W. Ralls, R. M. Dodson and B. Riegel, *J. Am. Chem. Soc.*, **71**, 3320 (1949). (b) J. W. Ralls, *J. Am. Chem. Soc.*, **75**, 2123 (1953). (c) J. Romo, G. Rosenkranz and C. Djerassi, *J. Org. Chem.*, **17**, 1413 (1952).

(8) V. R. Mattox, E. L. Woroch, G. A. Fleisher, and E. C. Kendall, *J. Biol. Chem.*, **197**, 261 (1952).

thiocyanic acid) in glacial acetic acid in the presence of hydrochloric acid[7a,9] for three days at 5–8° gave good yields of the corresponding 7-substituted analogs II–V.[10a]



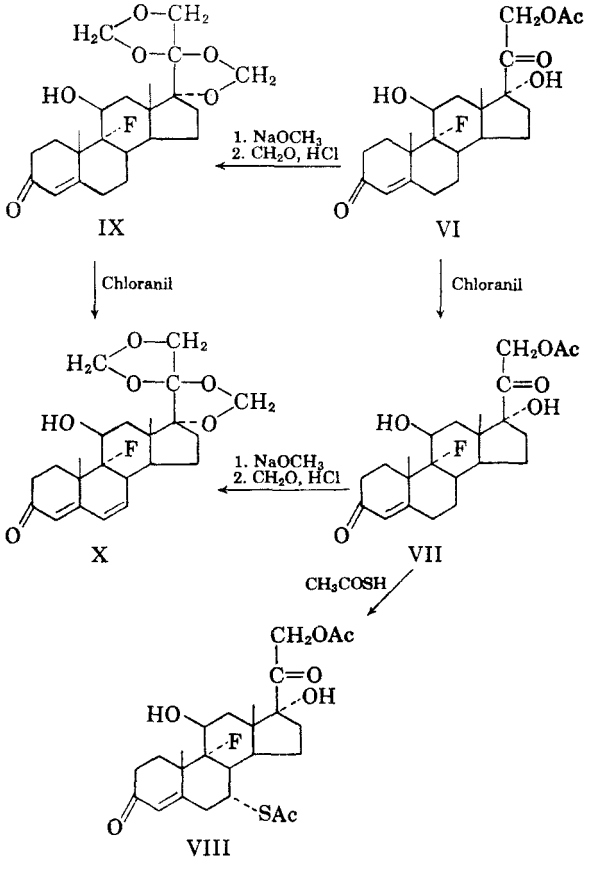
II. R = CH_3
III. R = C_2H_5
IV. R = CH_3CO
V. R = CN

Formation of the expected 7-substituted derivative was indicated by the loss of the characteristic $\Delta^{4,6}$-3-one chromophore ($\lambda_{max}^{CH_3OH}$ 280–282mμ) and the appearance of the characteristic Δ^4-3-one chromophore ($\lambda_{max}^{CH_3OH}$ 235–240 mμ). The C-7 substituents are considered to be in the α-configuration on the basis of a comparison of molar rotation differences (see Table I). Similar considerations led Dodson and Tweit[3a] to assign the α-configuration to the 7-acylthio substituent in their products.

At best, the several cortisone derivatives (II–V) had only a low order of adrenocorticoid activity-less than 0.2 × hydrocortisone as measured by the liver glycogen assay. Therefore, it was of some interest to prepare the correspondingly substituted derivatives of 9α-fluorohydrocrotisone,[10b] a structure having considerably greater biological activity than cortisone.

It was presumed that the 9α-fluorohydrocortisone derivatives could be prepared, analogously to the cortisone derivative, from 6-dehydro-9α-fluorohydrocortisone acetate (VII). The preparation of this latter compound by chloranil treatment of 9α-fluorohydrocortisone acetate (VI) has been reported by Agnello and Laubach.[11] Since in our hands the material prepared by this procedure had ν_{max}^{KBr} 1010 cm.$^{-1}$, a band often associated with D-homo compounds,[12] it was necessary to prove the structure of this product. Thus, the presumed VII was de-*O*-acetylated with methanolic methoxide (71% yield) and then converted on treatment[13] with formaldehyde and hydrochloric acid to the 17α,20; 20, 21-bismethylenedioxy (BMD) derivative X in 53% yield. This latter compound (X) was then unequivocally synthesized by a sequence which excluded the possibility of D-homo rearrangement. 9α-Fluoro-hydrocortisone was converted to the 17α,20;20,21-bismethylenedioxy derivative IX[13] in 43% yield. Hydrolysis of IX with aqueous formic acid[13] gave the parent 9α-fluorohydrocortisone in 54% yield, and dehydrogenation of IX with chloranil afforded the 17α,20;20,21-bismethylenedioxy derivative (X) of 6-dehydro-9α-fluorohydrocortisone, identical in all respects with the material prepared from VII.

When VII was treated with ethyl mercaptan under the conditions described above for the preparation of 7α-ethylthiocortisone acetate, the desired reaction apparently did not occur to any significant extent. Instead, 52% of VII was recovered and there was obtained, in addition, a sulfur-containing glass which still possessed strong absorption at 282 mμ. Prolonged reaction times afforded amorphous products containing three to four times the expected sulfur content. Similar negative results were obtained with methyl mercaptan. However, when VII was heated with excess thiolacetic acid (procedure of Dodson and Tweit[3a]), 7α - acetylthio - 9α - fluorohydrocortisone acetate (VIII) was obtained in 56% yield. When assayed, compound VIII had an activity 0.2 × hydrocorti-



(9) Catalysis by strong acid is apparently a requirement for this reaction; thus treatment of 6-dehydrotestosterone acetate (XV) with methyl mercaptan in acetic acid resulted in at least a 75% recovery of XV. The same conditions plus hydrochloric acid afford about 60% of 7α-methylthio derivative.

(10)(a) Dodson and Tweit[3a] have reported the synthesis of 7α-acetylthiocortisone acetate (IV). (b) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **76**, 1455 (1954).

(11) E. J. Agnello and G. D. Laubach, *J. Am. Chem. Soc.*, **79**, 1257 (1957); **82**, 4293 (1960).

(12) W. Fulmor, private communication.

(13) R. E. Beyler, R. M. Moriarty, F. Hoffman , and L. H. Sarett, *J. Am. Chem. Soc.*, **80**, 1517 (1958).

TABLE I

MOLECULAR ROTATION DIFFERENCES (Δ[M]D) RESULTING FROM C-7 SUBSTITUTION

Parent Compound	Substituent	$[M]_D$[a]	$\Delta[M]_D$[b]
Cortisone acetate	—	+745[c]	
	—S—CH_3 (II)	+594	−151
	—S—C_2H_5 (III)	+610	−135
	—S—$COCH_3$ (IV)	+438	−307
	—S—CN (V)	+610	−135
9α-Fluorohydrocortisone acetate	—	+518[d]	
	—S—$COCH_3$ (VIII)	−104	−622
Progesterone	—	+603[e]	
	—S—CH_3 (XI)	+262	−341
	—S—$COCH_3$ (XII)	+ 37	−566
Deoxycorticosterone acetate	—	+692	
	—S—$COCH_3$ (XIV)	+147	−545
Testosterone acetate	—	+307[f]	
	—S—CH_3 (XVI)	+ 16	−291
	—S—$COCH_3$ (XVII)	−133	−430
	—S—CN (XVIII)	+164	−143
	—SH (XIX)	+241	− 66
	—S—C_2H_5 (XX)	+ 43	−264
	—S—$CH(CH_3)_2$ (XXII)	− 49	−356
	—S—$CH_2CH{=}CH_2$ (XXIII)	− 89	−396
17α-Methyltestosterone	—	+242[f]	
	—S—CH_3 (XXVII)	− 29	−271
19-Nortestosterone acetate	—	+138[g]	
	—S—CH_3 (XXV)	−163	−301
	—S—$COCH_3$ (XXIV)	−230	−368
4-Chlorotestosterone propionate	—	+432[h]	
	—S—CH_3 (XXVIII)	+181	−251
9α-Fluoro-11β-hydroxy-17α-methyltestosterone	—	+367[i]	
	—S—$COCH_3$ (XXVI)	−168	−535
17β-Acetoxyandrostan-3-one	—	+ 86[f]	
	—S—CH_3 (XXIX)	−168	−254

[a] All rotations in chloroform, except where noted. [b] The molecular rotation difference resulting from the introduction of what is apparently a 7β-acetylthio group into cholesteryl benzoate is +1057 [H. Hauptmann and P. A. Bobbio, *Ber.*, **93**, 280 (1960)]. [c] J. Fried *et al.*, *J. Am. Chem. Soc.*, **74**, 3962 (1952). [d] J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **76**, 1455 (1954). [e] W. Dirscherl and F. Hanusch, *Z. physiol. Chem.*, **252**, 49 (1938). [f] C. Djerassi, *J. Org. Chem.*, 12, 823 (1947). [g] J. A. Hartman, A. J. Tomasewsky, and A S. Dreiding, *J. Am. Chem. Soc.*, **78**, 5662 (1956). [h] Ref. 27. [i] In ethanol, Ref. 21.

TABLE II[a]

ANDROGEN-ANABOLIC EVALUATION[b]

Compound	Route of Administration[d]	Relative Potency[c]	
		Levator Ani	Ventral Prostate
7α-Methylthiotestosterone acetate, XVI	sc	0.9 (0.5–1.6)	1.4 (1.2–1.7)
7α-Methylthiotestosterone acetate, XVI	o	0.1 (0.05–0.3)	0.4 (0.2–1.0)
7α-Acetylthiotestosterone acetate, XVII	sc	0.5 (0.2–1.3)	0.4 (0.2–1.0)
7α-Mercaptotestosterone acetate, XIX	sc	0.8 (0.4–1.9)	1.1 (0.7–1.8)

[a] We are grateful to Drs. C. Boshart and I. Ringler for these results. [b] Compounds were evaluated by a modification of the levator-ani assay reported by Hershberger, Shipley, and Meyer.[19] [c] Statistical values, 95% confidence limits in parenthesis; 17α-ethyl-19-nortestosterone[20] = 1. [d] Sc = subcutaneous, o = oral.

sone by the liver glycogen test and 0.4 × hydrocortisone by the thymus involution test.

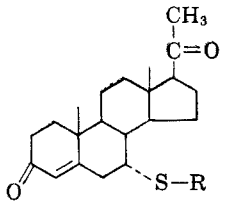
We can offer no completely satisfactory explanation for the relative inertness of the $\Delta^{4,6}$-3-keto system in the presence of a ring C fluorohydrin. However, if, as appears to be the case, the addition of a nucleophile under acid-catalyzed conditions to a $\Delta^{4,6}$-3-keto system takes place *via* an axial approach to the 7α-position, it is conceivable that the neighboring axial 9α-fluorine atom might exert at least an electrostatic repulsion to the incoming group.

For the preparation of progesterone and deoxycorticosterone analogs, the respective 6-dehydro derivatives[15] were condensed with methyl mercaptan and with thiolacetic acid (acetic acid–hydrochloric acid procedure) to give compounds XI–XIV.[14] The 6-dehydro derivatives, both of which have been reported previously,[15] were prepared by dehydrobromination (collidine) of the intermediate 6-bromo derivatives obtained by *N*-bromsuccini-

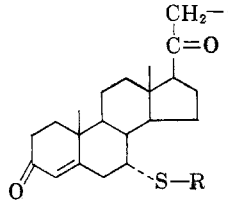
(14) Dodson and Tweit[3a] have reported the 7α-propionylthio derivatives of progesterone and deoxycorticosterone.

(15) F. Sondheimer, C. Amendolla and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 5932 (1953). These workers prepared the 6-dehydro derivatives by treatment of the corresponding Δ^5-3β-ol with manganese dioxide.

mide (NBS) bromination of the Δ^4-3-ketones. The progesterone analogs XI and XII gave no progestational response at a total dose of 1.0 mg. in the Clauberg-McPhail assay.[16]

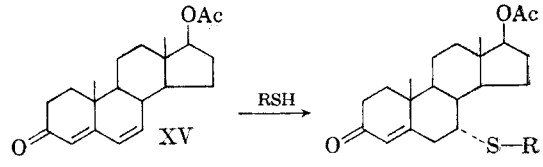


XI. R = CH_3
XII. R = CH_3CO



XIII. R = CH_3
XIV. R = CH_3CO

The reaction of 6-dehydrotestosterone acetate (XV)[17] with the various sulfur nucleophiles was also investigated. Condensation of XV with the appropriate reagents afforded in good yields the 7α-methylthio (XVI), 7α-acetylthio (XVII),[18] and 7α-thiocyano (XVIII) derivatives of testosterone acetate. Brief (twenty minutes) treatment of the 7α-acetylthio derivative (XVII) with methanolic sodium methoxide allowed preferential de-*S*-acetylation and furnished 7α-mercaptotestosterone acetate (XIX) in excellent yield. An attempt to effect 17-de-*O*-acetylation by treatment with methanolic methoxide for a longer reaction period (twenty-two hours) resulted in hydrogen sulfide stripping and isolation of 6-dehydrotestosterone.

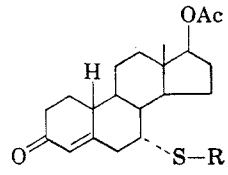


XV

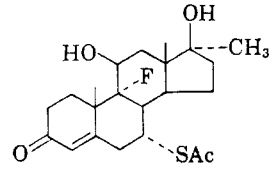
XVI. R = CH_3
XVII. R = CH_3CO
XVIII. R = CN
XIX. R = H

XX. R = C_2H_5
XXI. R = C_3H_7
XXII. R = iso-C_3H_7
XXIII. R = CH_2—HC=CH_2

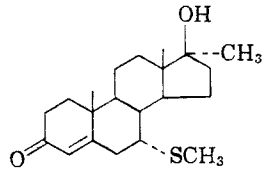
These testosterone derivatives, save the 7α-thiocyano compound, possessed significantly enhanced anabolic-androgenic ratios, being approximately equivalent in potency (levator ani assay,[19] subcutaneous route of administration) to 17α-ethyl-19-nortestosterone[20] (see Table II). Therefore it was of considerable interest to extend this series and also to prepare the 7α-methylthio- and/or 7α-acetylthio derivatives of those C-19 steroids already reported to have interesting biological properties in this area. Hence, reaction of XV with the appropriate mercaptan furnished the 7α-ethylthio, 7α-propylthio, 7α-isopropylthio, and 7α-allylthio derivatives (XX-XXIII). Additionally, the 7α-acetylthio derivatives of 19-nortestosterone acetate[19] (XXIV) and 9α-fluoro-11β-hydroxy-17α-methyltestosterone[21] (XXVI) as well as the 7α-methylthio derivatives of 19-nortestosterone acetate[19] (XXV), 17α-methyltestosterone[22] (XXVII), 4-chlorotestosterone propionate[23] (XXVIII), 17β-hydroxy-2-hydroxymethylenandrostan - 3 - one[24] (XXXI), and 17β-hydroxyandrostano[3,2-c]pyrazole[25] (XXX) were prepared. With the exception of the last two compounds, these derivatives were obtained by addition of the appropriate sulfur reagent to the required 6-dehydro steroid.



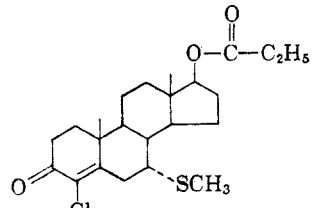
XXIV. R = CH_3CO
XXV. R = CH_3



XXVI



XXVII



XXVIII

For the synthesis of 17β-hydroxy-2-hydroxymethylene-7α-methylthioandrostan-3-one (XXXI), 7α-methylthiotestosterone acetate (XVI) was converted in fair yield to the 4,5-dihydro derivative (XXIX) by reaction with lithium in liquid ammonia. Condensation of XXIX with methyl formate in the presence of sodium hydride then afforded XXXI[26] and treatment of XXXI with hydrazine smoothly gave the pyrazole derivative XXX.

Evaluation of compounds XX–XXXI by the levator-ani procedure indicated that they were less interesting as potential anabolic agents than the lead compounds XVI, XVII, and XIX.

A considerable effort was made to determine the scope of the 1,6-addition reaction with the $\Delta^{4,6}$-3-keto system. In addition to the sulfur reagents re-

(16) Testing by The Endocrine Laboratories, Madison, Wis.

(17) In our hands the preparation of XV from testosterone acetate by the bromination-dehydrobromination sequence [C. Djerassi, G. Rosenkranz, J. Romo, St. Kaufmann, and J. Pataki, *J. Am. Chem. Soc.*, **72**, 4534 (1950)] was significantly superior to the chloranil dehydrogenation procedure (see Experimental section).

(18) Dodson and Tweit[3a] have prepared several related 7α-acylthio derivatives of testosterone.

(19) L. G. Hershberger, E. G. Shipley, and R. K. Meyer, *Proc. Soc. Exp. Biol. and Med.*, **83**, 175 (1953).

(20) F. B. Colton, L. N. Nysted, B. Riegel, and A. L. Raymond, *J. Am. Chem. Soc.*, **79**, 1123 (1957).

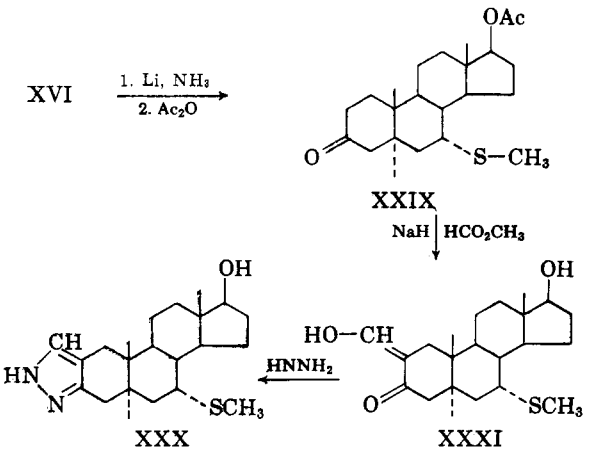
(21) M. E. Herr, J. A. Hogg, and R. H. Levin, *J. Am. Chem. Soc.*, **78**, 500 (1956).

(22) R. I. Dorfman and R. A. Shipley, *Androgens*, Wiley, New York, 1956, p. 384.

(23) B. Camerino, B. Patelli, and A. Vercellone, *J. Am. Chem. Soc.*, **78**, 3540 (1956).

(24) H. J. Ringold, E. Batres, O. Halpern, and E. Necoechea, *J. Am. Chem. Soc.*, **81**, 427 (1959).

(25(a) R. O. Clinton, A. J. Manson, F. W. Stonner, A. L. Beyler, G. O. Potts, and A. Arnold, *J. Am. Chem. Soc.*, **81**, 1513 (1959). (b) G. O. Potts, A. L. Beyler, and D. F. Burnham, *Proc. Soc. Exp. Biol. and Med.*, **103**, 383 (1960).



ported here and also by Dodson and Tweit,[3a] the successful reaction of methylmagnesium iodide with $\Delta^{4,6}$-3-keto systems to give 7α- and 7β-methyl derivatives[4c] has been reported.[28,29] We have investigated the reactivity of this system towards methanol, hydroiodic acid, ammonia, dimethylamine, hydrogen cyanide, and nitromethane under conditions of acid and/or base catalysis. For this study, 6-dehydrocortisone acetate (I) and 6-dehydrotestosterone acetate (XV) were used as prototypes of the $\Delta^{4,6}$-3-keto system. In general the above-mentioned reagents failed to react with I and/or XV under the conditions tried. In a few instances some indication of reaction was noted, but identifiable products could not be isolated and essentially these experiments must be considered to have been unsuccessful. The relative inactivity of the $\Delta^{4,6}$-3-keto system towards the various nucleophiles mentioned above is in direct contrast to the facile reactivity of the Δ^{16}-20-keto system with the same or similar reagents.[30]

(26) Compound XXXI was prepared by a procedure previously reported[27] for the preparation of 17β-hydroxy-2-hydroxymethyleneandrostane-3-one. It should be noted that the assigned structure XXIX (and consequently XXX and XXXI) for the product obtained on lithium-liquid ammonia reduction is not entirely unequivocal. This reduction procedure affords the thermodynamically more stable structure which is generally the A/B *trans* fused product. In the present instance, we have assumed that the A/B *trans* fused product XXIX is also more stable despite any possible destabilizing effects resulting from 1:3 interaction between the axial 7α-methylthio group and the 5α-hydrogen atom.

(27) F. L. Weisenborn and H. E. Applegate, *J. Am. Chem. Soc.*, **81**, 1960 (1959).

(28) The formation of a 3,7-bispyrrolidyl derivative on treatment of a $\Delta^{4,6}$-3-keto system with pyrrolidine in the presence of *p*-toluenesulfonic acid has been reported.[4c] It is reasonable to assume that the formation of this derivative proceeds *via* 1,6-addition of pyrrolidine followed by enamine formation.

(29) The failure of a $\Delta^{4,6}$-3-keto system to react with diazomethane has been noted.[3a]

(30)(a) ROH: D. K. Fukushima and T. F. Gallagher, *J. Am. Chem. Soc.*, **73**, 196 (1951); D. Gould, F. Gruen and E. B. Hershberg, *J. Am. Chem. Soc.*, **75**, 2510 (1953) *inter alia*. (b) Amines: D. Gould, E. L. Shapiro, L. E. Finckenor, F. Gruen, and E. B. Hershberg, *J. Am. Chem. Soc.*, **78**, 3158 (1956). (c) HCN: J. Romo, *Tetrahedron*, **3**, 37 (1958). (d) CH_3NO_2: R. N. Dodson, U. S. Pat. **2,697,109** (Dec. 14, 1954).

EXPERIMENTAL

General. All melting points were determined in a capillary tube and are uncorrected. The ultraviolet spectra were determined in methanol solution on a Cary recording spectrophotometer, unless otherwise specified. The infrared spectra (pressed potassium bromide disk) were determined with a Perkin-Elmer spectrophotometer (model 21). Optical rotations were determined in a 1-cm. semimicro tube at wave length 5893 A° (D). All evaporations were carried out under reduced pressure unless otherwise specified. Except where otherwise noted, the petroleum ether used was that fraction boiling at 60–70°.

7α-Methylthiocortisone acetate (21-acetoxy-17α-hydroxy-7α-methylthio-4-pregnene-3,11,20-trione, II). To a cold solution containing 3 g. of 6-dehydrocortisone acetate (21 - acetoxy-17α-hydroxy-4,6-pregnadiene-3,11,20-trione, I)[8] in 300 ml. of glacial acetic acid was added 6 ml. of concd. hydrochloric acid and then 15 cc. of methyl mercaptan.[7a] The solution was kept at 8° for 3 days. Evaporation to dryness gave a syrupy material which was dissolved in methylene chloride. After neutralization with sodium bicarbonate, the solution was washed with water, dried with anhydrous magnesium sulfate and evaporated to dryness. Crystallization of the residual syrup from acetone–petroleum ether gave 1.43 g. (43%) of product (II), m.p. 244–245° dec.

From another experiment starting with 1 g. of I and carried out according to the procedure described above, except that the reaction time was 22 hr. instead of 3 days, there was obtained 235 mg. (21%) of product (II), m.p. 243–245°. Several recrystallizations from acetone-petroleum ether afforded white crystals, m.p. 246–248° dec.; $[\alpha]_D^{25}$ +132° (2.0% in chloroform); λ_{max} 239 mμ (ε 15,500); ν_{max} 3380, 1760, 1730, 1710, 1650, 1630, 1380, 1230 cm.$^{-1}$

Anal. Calcd. for $C_{24}H_{32}O_6S$: C, 64.26; H, 7.19; S, 7.15. Found: C, 64.12; H, 7.28; S, 7.19.

7α-Ethylthiocortisone acetate (21-acetoxy-7α-ethylthio-17α-hydroxy-4-pregnene-3,11,20-trione, III). To a cold solution of 500 mg. of 6-dehydrocortisone acetate (I) in 25 ml. of glacial acetic acid was added 1 ml. of concd. hydrochloric acid and then 3 ml. of ethyl mercaptan. The red solution was kept at 5–7° for 24 hr. Work-up according to the procedure described above for compound II gave 201 mg. (35%) of product (III), m.p. 229–231° dec. Recrystallization from acetone–petroleum ether afforded white crystals, m.p. 235–237° (dec.); $[\alpha]_D^{25}$ +132° (2.1% in chloroform); λ_{max} 239 mμ (ε 13,000); ν_{max} 1760, 1735, 1710, 1650, 1630, 1235 cm.$^{-1}$

Anal. Calcd. for $C_{25}H_{34}O_6S$: C, 65.0; H, 7.40; S, 6.93; OAc, 9.30. Found: C, 65.1; H, 7.67; S, 6.90; OAc, 9.80.

7α-Acetylthiocortisone acetate (21-acetoxy-7α-acetylthio-17α-hydroxy-4-pregnene-3,11,20-trione, IV). Treatment of 1 g. of 6-dehydrocortisone acetate (I) with 2 ml. of concd. hydrochloric acid and 3 g. of potassium thiol acetate in 100 ml. of glacial acetic acid according to the procedure described above for the preparation of 7α-methylthiocortisone acetate (II) gave 700 mg. (59%) of product melting at 243–244°. Recrystallization from acetone-petroleum ether afforded white crystals, m.p. 250–251°; $[\alpha]_D^{25}$ +92° (0.96% in chloroform); λ_{max} 235 mμ (ε 17,900); ν_{max} 3500, 1750, 1730, 1700, 1630, 1235 cm.$^{-1}$

Dodson and Tweit[3a] report a m.p. of 238–239° and $[\alpha]_D$ + 102.5° for compound IV.

Anal. Calcd. for $C_{25}H_{32}O_7S.1^1/_2\ H_2O$: C, 59.78; H, 7.01; S, 6.38; H_2O, 5.35. Found: C, 59.24; H, 7.14; S, 6.43; H_2O (Karl Fischer), 5.09.

7α-Thiocyanocortisone acetate (21-acetoxy-17α-hydroxy-7α-thiocyano-4-pregnene-3,11,20-trione, V). Treatment of 1 g. of 6-dehydrocortisone acetate (I) with 4.8 ml. of concd. hydrochloric acid and 3 g. of potassium thiocyanate in

75 ml. of glacial acetic acid for 24 hr. at 5–7°, according to the procedure described above for the preparation of 7α-methylthiocortisone acetate (II), gave 650 mg. of crystalline material, m.p. 200–203° dec. Recrystallization from acetone–petroleum ether afforded 189 mg. (19%) of starting material, m.p. and mixed m.p. 231–234°. Evaporation of the filtrate and recrystallization of the residue from the above solvents gave 420 mg. (37%) of product (V), m.p. 178–181° dec. Two additional recrystallizations furnished white crystals, m.p. 190–191° dec.; $[\alpha]_D^{25}$ +133° (1.2% in chloroform); λ_{max} 238 mμ (ε 13,100); ν_{max} 3450, 2060, 1750, 1710, 1650, 1630, 1240 cm.$^{-1}$

Anal. Calcd. for $C_{24}H_{29}NO_6S$: C, 62.72; H, 6.36; N, 3.05; S, 6.98. Found: C, 62.81; H, 6.55; N, 3.14; S, 6.57.

6-Dehydro-9α-fluorohydrocortisone acetate (21-acetoxy-11β-17α-dihydroxy-9α-fluoro-4,6-pregnadiene-3,20-dione, VII).[11] A mixture containing 3 g. of 9α-fluorohydrocortisone acetate (21-acetoxy-11β,17α-dihydroxy-9α-fluoro-4-pregnene-3,20-dione, VI),[10a] 2.9 g. of chloranil (2,3,5,6-tetrachlorobenzoquinone) and 225 ml. of freshly distilled *t*-butyl alcohol was flushed with nitrogen and then refluxed for 18 hr., solution being complete in approximately 30 min. The cooled solution was diluted with 500 cc. of chloroform, washed with several small portions of ice cold 5% sodium hydroxide, then with water, dried with anhydrous magnesium sulfate, and evaporated to dryness leaving a semisolid. Recrystallization from acetone–petroleum ether furnished 1 g. (33%) of product (VII), m.p. 215–216°. Several recrystallizations from the same solvents raised the m.p. to 219–221°; $[\alpha]_D^{30}$ +138° (1.0% in chloroform); λ_{max} 280 mμ (ε 26,700); ν_{max} 3380, 1730, 1650, 1620, 1590, 1235, 1010 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{29}FO_6$: C, 65.69; H, 6.95; F, 4.52. Found: C, 65.67; H, 7.04; F, 4.79.

An attempt to obtain the 6-dehydro compound (VII) by reaction of 9α-fluorohydrocortisone acetate (VI) with bromine followed by dehydrohalogenation with *sym*-collidine gave an amorphous material with an ultraviolet absorption maximum at 240 mμ and negligible absorption at 280 mμ.

6-Dehydro-9α-fluorohydrocortisone (9α-fluoro-11β,17α,21-trihydroxy-4,6-pregnadiene-3,20-dione). To a solution of 2.0 g. of 6-dehydro-9α-fluorohydrocortisone acetate (VII) in 100 ml. of absolute methanol, through which nitrogen was bubbled, was added 5.25 ml. of 1*N* methanolic sodium methoxide. After 10 min. the solution was acidified with glacial acetic acid and concentrated to a small volume. The crystalline product which separated was filtered and washed several times with water; yield 1.28 g. (71%), m.p. 232–238° dec. Recrystallization from acetone–petroleum ether gave white crystals, m.p. 240–241° dec.; $[\alpha]_D^{26}$ +96.8° (1.1% in methanol); λ_{max} 280 mμ (ε 25,300); ν_{max} 3420, 1720, 1660, 1600, 1590 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{27}FO_6$: C, 66.65; H, 7.19; F, 5.02. Found: C, 66.32; H, 7.31; F, 5.20.

9α-Fluoro-11β-hydroxy-17α,20;20,21-bismethylenedioxy-4,6-pregnadien-3-one (X). A. *From 6-Dehydro-9α-fluorohydrocortisone.* A mixture containing 3.19 g. of 6-dehydro-9α-fluorohydrocortisone, 120 ml. of chloroform, 30 ml. of formalin (37% aqueous formaldehyde), and 30 ml. of concd. hydrochloric acid was vigorously stirred at room temperature for 48 hr.[13] The separated organic phase was washed with water, saturated sodium bicarbonate, and finally with water, dried with anhydrous magnesium sulfate, and evaporated to dryness. After several extractions with hot water, the residue was crystallized from acetone-petroleum ether to give 1.86 g. (53%) of product in two crops, m.p. 281–289°.

In a pilot run, the yield was 520 mg. (46%), m.p. 289° dec. Recrystallization from acetone-petoleum ether furnished white crystals, m.p. 290° dec.; $[\alpha]_D^{26}$ −27° (0.47% in chloroform); λ_{max} 280 mμ (ε 26,500); ν_{max} 3410, 1660, 1620, 1010 cm.$^{-1}$

B. *By Chloranil treatment of* IX. A solution of 3 g. of 9α-fluoro-11β-hydroxy-17α,20;20,21-bismethylenedioxy-4-pregnen-3-one (IX)[13] (see below) in 250 ml. of freshly distilled *t*-butyl alcohol through which nitrogen was bubbled, was treated with 2.9 g. of chloranil at reflux temperature for 40 hr.; passage of nitrogen was discontinued after approximately 30 min. After dilution with 600 ml. of chloroform, the solution was washed with several ice cold portions of 5% sodium hydroxide, water (three times), dried with anhydrous magnesium sulfate, and evaporated to dryness. Trituration of the residue with benzene furnished 290 mg. of product (X), m.p. 288–289° dec.; λ_{max} 280 mμ. The residue obtained upon evaporation of the triturates was chromatographed over 100 g. of silica gel.

A noncrystallizable material (1 g.) was eluted with 10–20% ether in benzene. This product showed absorption at 240 mμ in the ultraviolet and was not further investigated. The product was then eluted with 40% ether in benzene. Recrystallization from acetone–petroleum ether of the solids obtained from the combined 40% eluates gave an additional 275 mg. (17% total yield) of product X, m.p. 288° (dec.). This material was identical with the product obtained according to procedure A (above) as shown by mixed melting point, ultraviolet and infrared comparisons.

9α-Fluoro-11β-hydroxy-17α,20:20,21-bismethylenedioxy-4-pregnen-3-one (IX).[13] Treatment of 10 g. of 9α-fluoro-11β,17α,21-trihydroxy-4-pregnene-3,20-dione (9α-fluorohydrocortisone) in 400 ml. of reagent chloroform with 100 ml. of formalin (37% aqueous formaldehyde) as described above for the preparation of 9α-fluoro-11β-hydroxy-17α,20;20,21-bismethylenedioxy-4,6-pregnadien-3-one (X) gave 4.76 g. (43%) of product (IX), m.p. 258–260° dec. Recrystallization from acetone–petroleum ether afforded white crystals, m.p. 275–276° dec.; $[\alpha]_D^{29}$ +17° (1.0% in chloroform); λ_{max} 239 mμ (ε 15,600); ν_{max} 3450, 1670, 1630, 1005 cm.$^{-1}$ The literature[13] reports m.p. 250–260° or 285–290°; $[\alpha]_D$ +30° (chloroform).

Anal. Calcd. for $C_{23}H_{31}FO_6$: C, 65.38; H, 7.39. Found: C, 65.43; H, 7.66.

Hydrolysis of 17α,20;20,21-bismethylenedioxy derivative IX to give 9α-fluorohydrocortisone. A mixture of 500 mg. of the above-prepared 9α-fluoro-11β-hydroxy-17α,20;20,21-bismethylenedioxy-4-pregnen-3-one (IX) and 10 ml. of 60% formic acid was heated in the steam bath for 30 min.[13] during which period solution was completed. After evaporation to dryness the residue was evaporated with absolute alcohol two times, triturated with chloroform, and filtered to give 242 mg. (54%) of 9α-fluorohydrocortisone, m.p. 230° dec. Recrystallization from acetone–petroleum ether gave white crystals, m.p. 235–237° dec., which had an infrared spectrum identical with that of authentic 9α-fluorohydrocortisone.[10b])

7α-Acetylthio-9α-fluorohydrocortisone acetate (21-acetoxy-7α-acetylthio-11β,17α-dihydroxy-9α-fluoro-4-pregnene-3,20-dione VIII). A suspension of 1 g. of 6-dehydro-9α-fluorohydrocortisone acetate (VII) in 2 ml. of freshly distilled thiolacetic acid was heated under reflux on the steam bath for 22 hr.,[3a] solution being complete at the boiling point. The solution was evaporated to dryness. The residual glass was crystallized from ether-acetone and the white crystalline material was collected by filtration to give 665 mg. (56%) of product (VIII), m.p. 253–255° dec. Two recrystallizations from acetone–petroleum ether raised the m.p. to 256–258° dec.; $[\alpha]_D^{25}$ −21° (1.1% in chloroform); λ_{max} 236 mμ (ε 19,850); λ_{max} 2.90, 5.71, 5.78, 5.95, 6.01, 6.04 (shoulder), 8.13 μ.

Anal. Calcd. for $C_{25}H_{33}FO_7S$: C, 60.46; H, 6.70; F, 3.83; S, 6.45. Found: C, 60.68; H, 6.87; F, 3.73; S, 6.35.

6-Dehydroprogesterone (4,6-pregnadiene-3,20-dione). A stirred mixture containing 3 g. of 6β-bromoprogesterone [this compound was reported[31] without assignment of configuration; on the basis[17] of a bathochromic shift for the ultraviolet maximum (λ_{max} 246 mμ) and an analysis of the molecular rotation data, $[\alpha]_D$ + 66° (1% in chloroform), it

(31) F. Sondheimer, St. Kaufmann, J. Romo, H. Martinez, and G. Rosenkranz, *J. Am. Chem. Soc.*, 75, 4712 (1953).

is now assigned the β-configuration] and 45 ml. of *sym*-collidine was heated under reflux, under an atmosphere of carbon dioxide, for 1 hr.; solution was complete at the boiling point. After filtration from collidine hydrobromide, the mother liquor was diluted with 250 ml. of benzene and washed successively with water, 8% sulfuric acid, water, saturated sodium bicarbonate solution, and water, dried with anhydrous magnesium sulfate, and evaporated to dryness to give 2.2 g. of a semisolid. This material was recrystallized from acetone-petroleum ether to furnish 1.49 g. (63%) of 6-dehydroprogesterone, m.p. 133–136°. Three additional recrystallizations from the same solvent pair afforded white crystals, m.p. 139–141°; $[\alpha]_D^{25}$ +180° (1.1% in chloroform); λ_{max} 283 mμ (ε 24,800); λ_{max} 5.86, 6.00, 6.16, 6.29 μ.

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.43; H, 9.19.

Constants reported[15] for 6-dehydroprogesterone: m.p. 145–146°; λ_{max} 284 mμ; $[\alpha]_D$ + 185°.

An attempt to prepare this product by dehydrogenation of progesterone with chloranil proved unsuccessful.

7α-Methylthioprogesterone (7α-methylthio-4-pregnene-3,20-dione, XI). As described above for the preparation of II, treatment of a solution of 688 mg. of 6-dehydroprogesterone in 55 ml. of glacial acetic acid with 2 ml. of concd. hydrochloric acid and 7 ml. of methyl mercaptan for 4 days gave 246 mg. (31%) of product (XI), m.p. 154–156°. Recrystallization from acetone-petroleum ether gave white crystals, m.p. 159–160°; $[\alpha]_D^{25}$ +72.5° (1.1% in chloroform); λ_{max} 240 mμ (ε 15,500); ν_{max} 1700, 1675, 1620 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{32}O_2S$: C, 73.29; H, 8.95; S, 8.89. Found: C, 72.68; H, 8.79; S, 8.54.

7α-Acetylthioprogesterone (7α-acetylthio-4-pregnene-3,20-dione, XII). Treatment of 688 mg. of 6-dehydroprogesterone in 55 ml. of glacial acetic acid with 3 ml. of concd. hydrochloric acid and 2.2 g. of potassium thiolacetate for 72 hr. in the manner described above for the preparation of II afforded 336 mg. (39%) of product XII, m.p. 168–171°. Several recrystallizations from acetone–petroleum ether gave white crystals, m.p. 184–186°; $[\alpha]_D^{25}$ +9.5° (0.85% in chloroform); λ_{max} 238 mμ (ε 18,800); ν_{max} 1700, 1670, 1630 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{32}O_3S$: C, 71.09; H, 8.30; S, 8.25. Found: C, 70.68; H, 8.37; S, 8.01.

6β-Bromodeoxycorticosterone acetate (21-acetoxy-6β-bromo-4-pregnene-3,20-dione). A solution of 8.5 g. of deoxycorticosterone acetate in 500 ml. of carbon tetrachloride was concentrated by distillation to about 450 ml. to remove moisture. To the cooled solution was added 17 ml. of a 10% solution of reagent pyridine in carbon tetrachloride. After flushing with carbon dioxide 4.5 g. of *N*-bromosuccinimide was added and the solution was heated at reflux for 35 min. while under illumination with a 60-watt frosted bulb. The cooled solution was filtered, washed with water, dried with anhydrous magnesium sulfate, and evaporated to dryness. Crystallization of the residue from acetone–petroleum ether furnished 8.4 g. (82%) of product, m.p. 128–131° dec.

In a pilot run, there was obtained 4.31 g. (71%), m.p. 128–130° dec. Recrystallization from acetone–petroleum ether afforded white crystals, m.p. 136–138° dec.; $[\alpha]_D^{25}$ +70.5° (0.63% in chloroform); λ_{max} 246 mμ (ε 13,800); ν_{max} 1750, 1730, 1690, 1610, 1235 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{31}BrO_4$: C, 61.19; H, 6.92; Br, 17.70. Found: C, 60.82; H, 7.10; Br, 18.21.

The bathochromic shift for the ultraviolet maximum and an analysis of the molecular rotation data indicated the β-configuration for this compound.[17]

6-Dehydrodeoxycorticosterone acetate (21-acetoxy-4,6-pregnadiene-3,20-dione). 6β-Bromodeoxycorticosterone acetate (8 g.) was suspended in 80 ml. of *sym*-collidine. The suspension was brought to the boiling point, whereupon solution was complete; refluxing was then continued under an atmosphere of carbon dioxide for 45 min. The cooled solution was filtered from collidine hydrobromide and the mother liquor, after being diluted with 100 ml. of benzene was washed successively with 8% sulfuric acid, saturated aqueous sodium bicarbonate, and water, dried with anhydrous magnesium sulfate, and evaporated to dryness. The resulting amorphous material (6 g.) was dissolved in 100 ml. of benzene and chromatographed on 300 g. of silica gel. The column was washed with 1 l. of benzene, 1 l. of 15% chloroform in benzene solution, 1 l. of 30% chloroform in benzene, and 1 l. of 40% chloroform in benzene solution; these washings were discarded. Then the desired product was eluted with 60–80% chloroform in benzene (1,500 ml.). The combined eluates were evaporated to dryness and the solid which formed was crystallized from acetone–petroleum ether to yield 3 g. (46%) of 6-dehydrodeoxycorticosterone acetate, m.p. 112–114°. Recrystallization from the same solvents afforded white crystals, m.p. 113–114°; $[\alpha]_D^{25}$ +174° (1.1% in chloroform); λ_{max} 282 mμ (ε 21,600); λ_{max} 5.72, 5.79, 6.00, 6.17, 6.30, 8.13 μ. Constants reported[15] for 6-dehydrodeoxycorticosterone acetate: m.p. 114–115°; λ_{max} 284 mμ, $[\alpha]_D$ + 164°.

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.33; H, 8.41.

7α-Methylthiodeoxycorticosterone acetate (21-acetoxy-7α-methylthio-4-pregnen-3-one, XIII).[32] Treatment of 1 g. of 6-dehydrodeoxycorticosterone acetate with 2 ml. of concd. hydrochloric acid and 6 ml. of methyl mercaptan in 75 ml. of glacial acetic acid according to the procedure described above for the preparation of compound II gave 18 mg. (2%) of product, m.p. 220–223°. Recrystallization from acetone-petroleum ether gave white cyrstals, m.p. 222–225°; λ_{max} 5.73, 5.80, 6.00, 6.17, 8.17 μ. Insufficient material was available for complete characterization and the 7α-configuration is assumed.

Anal. Calcd. for $C_{24}H_{34}O_4S$: C, 68.87; H, 8.19; S, 7.66. Found: C, 67.91; H, 8.20; S, 7.86.

7α-Acetylthiodeoxycorticosterone acetate (21-acetoxy-7α-acetylthio-4-pregnene-3,20-dione, XIV). A solution of 527 mg. of 6-dehydrodeoxycorticosterone acetate was treated with 2 ml. of freshly distilled thiolacetic acid according to the procedure described above for the preparation of 21-acetoxy-7α-acetylthio-11β,17α-dihydroxy-9α-fluoro-4-pregnene-3,20-dione (VIII), except that the reflux period was 2 hr. There was obtained 543 mg. (85%) of product (XIV), m.p. 100–102° (gas). Two recrystallizations from acetone–petroleum ether afforded white crystals, m.p. 103–106° (gas); $[\alpha]_D^{25}$ +33.1° (1.8% in chloroform); λ_{max} 238 mμ (ε 18,300); λ_{max} 5.71, 5.81, 5.95, 6.16, 8.12 μ.

Anal. Calcd. for $C_{25}H_{34}O_5S$: C, 67.23; H, 7.67; S, 7.18. Found: C, 67.15; H, 8.01; S, 6.51.

6-Dehydrotestosterone acetate (17β-acetoxy-4,6-androstadien-3-one, XV). A. *By bromination-dehydrobromination.*[17] To a solution of 3.9 g. of testosterone acetate in 100 ml. of reagent carbon tetrachloride, freed from moisture by distillation of 15 ml. of solvent, was added 2.3 g. (1.1 moles) of *N*-bromosuccinimide. The solution was refluxed, under an atmosphere of carbon dioxide for 1 hr. and then for an additional 10 min. while under illumination from a 60-watt frosted bulb (contrary to other reports,[17] in our hands the reaction fails in the absence of light) whereupon the *N*-bromosuccinimide was consumed. Filtration and evaporation of the solvent to dryness gave 5.5 g. of syrupy 6-bromotestosterone acetate.

The material was dissolved in 20 ml. of *sym*-collidine and refluxed for 40 min. Collidine hydrobromide was filtered off and the mother liquor, after dilution with 250 ml. of benzene, was washed successively with water, 8% (v./v.) sulfuric acid, saturated sodium bicarbonate solution, and water, dried with anhydrous magnesium sulfate, and evaporated to dryness to give 4.8 g. of a semisolid. Recrystallization from petroleum ether–acetone gave 2.69 g. (68%) of 6-dehydrotestosterone acetate (XV), m.p. 136–139°.

(32) Experiment carried out by Mr. J. F. Poletto.

In a pilot experiment with 1 g. of testosterone acetate, there was obtained 620 mg. (63%) of product XV, m.p. 136–140°. Several recrystallizations from ether afforded white crystals, m.p. 140–143°; $[\alpha]_D^{25}$ + 37°(2.1% in chloroform); λ_{max} 282 mμ (ε 23,700); ν_{max} 1740, 1665, 1620, 1580 1240 cm.$^{-1}$ Reported[17] constants: m.p. 143–144°; $[\alpha]_D^{20}$ +36° (chloroform); $\lambda_{max}^{C_2H_5OH}$ 284 mμ.

B. By dehydrogenation with chloranil. A solution containing 4.0 g. of testosterone acetate and 4.95 g. of chloranil[11] in 390 ml. of freshly distilled *t*-butyl alcohol, flushed with nitrogen, was refluxed for 20 hr. during which period nitrogen flushing was discontinued. Upon dilution with 600 ml. of chloroform, the solution was washed with several small portions of 5% aqueous sodium hydroxide and then with water, dried with anhydrous magnesium sulfate and evaporated to dryness to give 3.8 g. of a semisolid material. Recrystallization from petroleum ether-acetone afforded 1.45 g. (36%) of 6-dehydrotestosterone acetate (XV), melting point and mixture melting point with the material prepared by Method A was 140–144°. Recrystallization from petroleum ether afforded white crystals, m.p. 143–144°. This material had an infrared spectrum identical with that of the material prepared by Method A.

7α-Methylthiotestosterone acetate (17β-acetoxy-7α-methylthio-4-androsten-3-one, XVI). A solution of 0.6 g. of 6-dehydrotestosterone acetate (XV), 1 ml. of concd. hydrochloric acid, and 5 ml. of methyl mercaptan in 25 ml. of glacial acetic acid was allowed to stand at 5–8° for 48 hr. The reaction mixture was worked up by the procedure described above for the preparation of II. Crystallization of the crude product from acetone–petroleum ether afforded 290 mg. (44%) of XVI, m.p. 200–203°.

The petroleum ether mother liquor was evaporated to dryness giving 302 mg. of a hard glass. This material was subjected to partition chromatography on Celite diatomaceous earth[33] according to a procedure developed by C. Pidacks of this laboratory and described previously.[34] The system heptane-methanol was used; the column was packed with 200 g. of Celite diatomaceous earth and the recording spectrophotometer was set at 240 mμ. The first 380 ml. of effluent contained a negligible amount of material; the next 320 ml. of effluent contained the major peak which on evaporation afforded 176 mg. of recovered 6-dehydrotestosterone acetate (XV) (m.p. 148–150°, identified by mixture melting point and infrared comparison); the final 320 ml. of effluent on evaporation gave 10 mg. of solid; λ_{max} 240 mμ (ε 13,200) and 280 mμ (ε 1,970).

From another experiment with a reaction time of 22 hr. at room temperature there was obtained 30% of XVI, m.p. 207–208°. Several recrystallizations from acetone-petroleum ether afforded white crystals, m.p. 208–209°; $[\alpha]_D^{25}$ +4.4° (2.0% in chloroform); λ_{max} 240 mμ (ε 16,900); ν_{max} 1730, 1675, 1620, 1240 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{32}O_2S$: C, 70.18; H, 8.57; S, 8.52. Found: C, 69.92; H, 8.82; S, 8.81.

Treatment of 6-dehydrotestosterone acetate (XV) *with methyl mercaptan in the absence of hydrochloric acid. Recovery of starting material* XV. Treatment of 1 g. of 6-dehydrotestosterone acetate (XV) with 10 ml. of methyl mercaptan in 75 ml. of glacial acetic acid, to which 1.2 ml. of water had been added, at 5–7° for 3 days gave, after the usual work-up, 750 mg. of starting material (XV) identical with an authentic sample by infrared comparison and mixture melting point comparison. The mother liquors contained additional crystalline material plus gum, the combination of which did not show significant adsorption at 240 mμ but showed strong absorption at 280 mμ.

7α-Acetylthiotestosterone acetate (17β-acetoxy-7α-acetylthio-4-androsten-3-one, XVII).[18] A solution containing 1.0 g. of 6-dehydrotestosterone acetate (XV), 4 ml. of concd. hydrochloric acid, and 3 g. of potassium thiolacetate in 75 ml. of glacial acetic acid was kept at 5–8° for 72 hr. The reaction mixture was worked up as described above for II to give 821 mg. of a glass, crystallization of which from acetone–petroleum ether afforded 748 mg. (61%) of XVII, m.p. 180–183°. Several recrystallizations from acetone–petroleum ether afforded white crystals, m.p. 191–193°; $[\alpha]_D^{25}$ −33.2° (0.99% in chloroform); λ_{max} 238 mμ; (ε 18,800); ν_{max} 1730, 1690, 1662, 1620, 1250 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{32}O_4S$: C, 68.27; H, 7.97; S, 7.93. Found: C, 68.57; H, 8.41; S, 8.15.

7α-Thiocyanotestosterone acetate (17β-acetoxy-7α-thiocyano-4-androsten-3-one, XVIII). A solution containing 0.600 g. of 6-dehydrotestosterone acetate, 2.9 ml. of concd. hydrochloric acid, and 1.8 g. of potassium thiocyanate in 25 ml. of glacial acetic acid was kept at 5–8° for 72 hr. The reaction mixture was worked up as described above for the preparation of II to give, after crystallization from acetone–petroleum ether, 290 mg. (41%) of XIX, m.p. 148–150°.

In a pilot run, the yield was 144 mg. (25%), m.p. 145–147°. Recrystallization from acetone–petroleum ether gave white crystals, m.p. 150–151°; $[\alpha]_D^{25}$ +42.3° (1.7% in chloroform); λ_{max} 238 mμ; (ε 13,300); ν_{max} 2060, 1730, 1675, 1620, 1250 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{29}NO_3S$: C, 68.19; H, 7.54; N, 3.61; S, 9.27. Found: C, 67.84; H, 7.64; N, 3.84; S, 9.34.

7α-Mercaptotestosterone acetate (17β-acetoxy-7α-mercapto-4-androsten-3-one, XIX). A. *Hydrolysis with methanolic methoxide.* To a stirred mixture of 234 mg. of 7α-acetylthiotestosterone acetate (XVII) and 10 ml. of reagent methanol, through which nitrogen was bubbled, was added 1.28 ml. (2.2 moles) of 1*N* methanolic sodium methoxide. Stirring was continued, under an atmosphere of nitrogen, for 20 min., during which period solution was completed. Acidification with glacial acetic acid, concentration to a small volume and filtration afforded 147 mg. (70%) of XIX, m.p. 175–178°. Several recrystallizations from acetone–petroleum ether afforded white crystals, m.p. 182–183°; $[\alpha]_D^{25}$ +66.7° (1.1% in chloroform); λ_{max} 238 mμ; (ε 13,750); ν_{max} 2520, 1730, 1670, 1620, 1240 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{30}O_3S$: C, 69.55; H, 8.32; S, 8.84. Found: C, 69.15; H, 8.39; S, 9.37.

B. Hydrolysis with potassium carbonate. To a stirred mixture of 300 mg. of 7α-acetylthiotestosterone acetate (XVII) and 5 ml. of reagent methanol, through which nitrogen was bubbled, was added 1.3 ml. of 10% aqueous potassium carbonate (oxygen-free). Stirring was continued for 60 min., during which period solution was completed. Acidification and flooding with water (30 ml.) caused an amorphous material to separate which was extracted with methylene chloride (3 × 10 ml.). The combined extracts were dried with anhydrous magnesium sulfate and evaporated to dryness. The residue was chromatographed over 15 g. of silica gel. The product was eluted with 5–15% ether in benzene and was crystallized from acetone-petroleum ether to give 155 mg. (58%) of XIX, m.p. 179–181°. This material was identical to that prepared by method A according to infrared, ultraviolet, optical rotation, and mixture melting point comparisons.

Treatment of 7α-acetylthiotestosterone acetate (XVII) *with methanolic methoxide to give 6-dehydrotestosterone.* To a stirred suspension of 7α-acetylthiotestosterone acetate (XVII) (756 mg.) in 20 ml. of reagent methanol, through which nitrogen was bubbled, was added 4.12 ml. (2.2 moles) of 1*N* methanolic sodium methoxide, solution being completed in 10 min. The resulting solution was allowed to stand at room temperature, under an atmosphere of nitrogen, for 22 hr. After acidification with acetic acid, the solution was taken to near dryness and diluted with water. The separated crystalline material was collected by filtration to afford 465 mg. (87%) of 6-dehydrotestosterone,

(33) Celite is the trademark for Johns-Manville's diatomaceous silica products.

(34) G. R. Allen, Jr., and M. J. Weiss, *J. Am. Chem. Soc.*, **81**, 4968 (1959); see the preparation of compound XXVII, p. 4978 in this reference.

m.p. 198–200° dec. Three recrystallizations from acetone–petroleum ether raised the m.p. to 202–204°; $[\alpha]_D^{25}$ +80° (1.1% in chloroform); λ_{max} 283 mμ (ε 26,300); λ_{max} 2.96, 6.01, 6.18, 6.32 μ.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.42; H, 9.22.

7α-Ethylthiotestosterone acetate (17β-acetoxy-7α-ethylthio-4-androsten-3-one, XX). A solution of 0.865 g. of 6-dehydrotestosterone acetate (XV), 2 ml. of concd. hydrochloric acid, and 10 ml. of ethyl mercaptan in 75 ml. of glacial acetic acid was allowed to stand at 5–8° for 72 hr. Work-up by the procedure given above for compound II afforded, after crystallization from acetone–petroleum ether, 565 mg. (55%) of product (XX), m.p. 189–191° dec. Recrystallization from acetone–petroleum ether gave white crystals, m.p. 197–199° dec.; $[\alpha]_D^{25}$ −10.9° (1.10% in choroform); λ_{max} 240 mμ (ε 15,800); ν_{max} 1730, 1675, 1620, 1240 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{34}O_3S$: C, 70.72; H, 8.78; S, 8.21. Found: C, 70.40; H, 8.83; S, 8.04.

7α-n-Propylthiotestosterone acetate (17β-acetoxy-7α-n-propylthio-4-androsten-3-one, XXI).[35] Treatment of 1.5 g. of 6-dehydrotestosterone acetate (XV) with 2.5 ml. of concd. hydrochloric acid and 12.5 ml. of *n*-propyl mercaptan in 63 ml. of acetic acid according to the procedure described above for the preparation of compound II furnished 450 mg. (25%) of XXI, m.p. 192–197°. Several recrystallizations from methanol afforded white crystals, m.p. 202–203°; $[\alpha]_D^{25}$ − 20.9° (1% in chloroform); λ_{max} 241 mμ (ε 16,000); λ_{max} 5.74, 5.98, 6.15, 8.07 μ.

Anal. Calcd. for $C_{24}H_{36}O_3S$: C, 71.26; H, 8.97; S, 7.94. Found: C, 70.86; H, 9.12; S, 8.19.

7α-Isopropylthiotestosterone acetate (17β-acetoxy-7α-isopropylthio-4-androsten-3-one, XXII). Treatment of 1 g. of 6-dehydrotestosterone acetate (XV) with 2 ml. of concd. hydrochloric acid and 8 ml. of isopropyl mercaptan in 75 ml. of acetic acid according to the procedure described above for the preparation of compound II, except that the reaction time was 7 days, furnished 1 g. of an amorphous material. This material was dissolved in 25 ml. of benzene and chromatographed on 90 g. of silica gel. The column was washed with 500 ml. of ether in benzene, and these washings were discarded. The column was then washed with 1 l. of 5% ether in benzene. This eluate was taken to dryness, and the residue was recrystallized from acetone–petroleum ether to give 216 mg. (18%) of product (XXII), m.p. 163–166°. Recrystallization from the same solvents followed by recrystallization from methanol afforded white needles, m.p. 170–172°; $[\alpha]_D^{25}$ −12° (1.2% in chloroform); λ_{max} 241 mμ (ε 16,600); λ_{max} 5.74, 5.96, 6.15, 8.08 μ.

Anal. Calcd. for $C_{24}H_{36}O_3S$: C, 71.26; H, 8.97; S, 7.94. Found: C, 71.22; H, 9.17; S, 8.27.

7α-Allylthiotestosterone acetate (17β-acetoxy-7α-allylmercapto-4-androsten-3-one, XXIII).[32] Treatment of 1.45 g. of 6-dehydrotestosterone acetate (XV) with 2.5 ml. of concd. hydrochloric acid and 0.54 ml. of allyl mercaptan in 63 ml. of acetic acid according to the procedure described above for the preparation of compound II furnished 170 mg. (10%) of XXIII, m.p. 168–172°. Recrystallization from acetone-petroleum ether gave white crystals, mp. 178–180°; $[\alpha]_D^{25}$ −22.1° (1.1% in chloroform); λ_{max} 242 mμ (ε 18,300); λ_{max} 5.76, 6.00, 6.16, 8.05 μ.

Anal. Calcd. for $C_{24}H_{34}O_3S$: C, 71.59; H, 8.51; S, 7.96. Found: C, 71.43; H, 8.72; S, 8.14.

6β-Bromo-17α-methyltestosterone (6β-bromo-17β-hydroxy-17α-methyl-4-androsten-3-one).[32] A solution of 3 g. of 17α-methyltestosterone in 100 ml. of reagent carbon tetrachloride was concentrated by distillation to a volume of about 85 ml. to remove moisture. After flushing with carbon dioxide, 1.77 g. of *N*-bromosuccinimide was added and the solution was refluxed, while under illumination with a 60-watt frosted bulb and under an atmosphere of carbon dioxide for 40 min. At this stage solution showed a negative test with moist potassium iodide-starch test paper. The hot solution was filtered and the filtrate was concentrated to dryness. The residue was taken up in methylene chloride and washed with water, dried with anhydrous magnesium sulfate and evaporated to dryness leaving a glass. Crystallization from acetone–petroleum ether furnished 2 g. (53%) of 6β-bromo-17α-methyltestosterone, m.p. 130–132° dec. Three recrystallizations from the same solvent pair gave white crystals, m.p. 139–140° dec.; $[\alpha]_D^{25}$ − 26° (0.8% in chloroform); λ_{max} 246 mμ (ε 12,000); λ_{max} 2.88, 5.93, 6.20 μ. .

Anal. Calcd. for $C_{20}H_{29}BrO_2$: C, 62.99; H, 7.66; Br, 20.96. Found: C, 62.94; H, 8.19; Br, 21.25.

6-Dehydro-17α-methyltestosterone (17β-hydroxy-17α-methyl-4,6-androstadien-3-one).[32] A solution of 1.5 g. of 6β-bromo-17α-methyltestosterone in 20 ml. of *sym*-collidine was refluxed under an atmosphere of carbon dioxide for 45 min. The cooled solution was filtered from collidine hydrobromide and the filtrate, after dilution with 100 ml. of benzene, was washed successively with 8% (V/V) sulfuric acid, saturated aqueous sodium bicarbonate and water, dried with anhydrous magnesium sulfate, and evaporated to dryness leaving a semisolid. Crystallization from acetone–petroleum ether furnished 700 mg. (59%) of 6-dehydro-17α-methyltestosterone, m.p. 180° (gas). Two recrystallizations from the same solvent pair gave white crystals, m.p. 194–195°; $[\alpha]_D^{25}$ +33° (0.5% in choroform); λ_{max} 283 mμ (ε 27,200); λ_{max} 2.91, 6.06, 6.21, 6.34 μ.

Reported[40] constants for 6-dehydro-17α-methyltestosterone, prepared by the chloranil procedure, are as follows: m.p. 193–196°; $[\alpha]_D$ +35°; $\lambda_{max}^{C_2H_5OH}$ 285 mμ (ε 26,850).

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.10; H, 9.96.

17α-Methyl-7α-methylthiotestosterone (17β-hydroxy-17α-methyl-7α-methylthio-4-androsten-3-one, XXVII).[32] To a cold solution of 932 mg. of 6-dehydro-17α-methyltestosterone in 39 ml. of glacial acetic acid was added 1.5 ml. of concd. hydrochloric acid and then 7.8 ml. of methyl mercaptan. The solution was kept at 8° for 6 days. The reaction mixture was worked up by the procedure described above for compound II giving, after crystallization from acetone–petroleum ether, 100 mg. of product (XXIV), m.p. 192–193°; λ_{max} 241 mμ (ε 14,600); λ_{max} 2.83, 6.03, 6.19 μ.

Anal. Calcd. for $C_{21}H_{32}O_2S$: C, 72.39; H, 9.18; S, 9.20. Found: C, 71.78; H, 9.42; S, 9.28.

6-Dehydro-19-nortestosterone acetate (17β-acetoxy-19-nor-4,6-androstadien-3-one). This compound was prepared from 3,17β-diacetoxy-19-nor-3,5-androstadiene (3 g.) by the procedure reported by Velluz and co-workers.[36] However, the product (1.2 g.) obtained after dehydrobromination could not be directly crystallized as reported by the French workers. Purification was effected by chromatography, as follows.

The glass-like product was dissolved in 15 ml. of benzene and adsorbed on a silica gel column (75 g.). The column was washed successively with 250 ml. of 10% chloroform in benzene, 250 ml. of 20% chloroform in benzene, 250 ml. of 35% chloroform in benzene, and 250 ml. of 50% chloroform in benzene; these washings were discarded. Elution with 1500 ml. of 60% chloroform in benzene and evaporation of the eluate gave 990 mg. of a glass. Crystallization from petroleum ether (b.p. 20–40°) then afforded 780 mg. (30%) of product, m.p. 95–97° (gas). Recrystallization from petroleum ether and then from 60% aqueous methanol gave white crystals, m.p. 103–105°; $[\alpha]_D^{25}$ −33.2° (1.4% in chloroform); λ_{max} 283 mμ (ε 26,000); λ_{max} 5.73, 5.96, 6.14, 6.27, 7.95 μ. J. A. Zderic and co-workers[37] reported m.p. 113–114°; $[\alpha]_D$ − 38° (chloroform); $\lambda_{max}^{C_2H_5OH}$ 282–284 mμ (log ε 4.29). L. Velluz and co-workers[36] recorded

(35) Experiment carried out by Mr. S. Peluso.

(36) L. Velluz, B. Goffinet, and G. Amiard, *Tetrahedron*, **4**, 241 (1958).

(37) J. A. Zderic, A. Bowers, H. Carpio, and C. Djerassi, *J. Am. Chem. Soc.*, **80**, 2596 (1958).

m.p. 68° dec.; $[\alpha]_D^{20}$ −36° ± 2 (1% in chloroform); $\lambda_{max}^{C_2H_5OH}$ 284 mμ (ε 27,500).

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.30; H, 8.48.

7α-Methylthio-19-nortestosterone acetate (17β-acetoxy-7α-methylthio-19-nor-4-androsten-3-one, XXV). A solution containing 500 mg. of 6-dehydro-19-nortestosterone acetate, 1 ml. of concd. hydrochloric acid, and 5 ml. of methylmercaptan in 35 ml. of glacial acetic acid was allowed to stand at 5–8° for 4 days. The reaction mixture was worked up as described above for the preparation of compound II to give 400 mg. of a glass. This glass was subjected to partition chromatography on Celite diatomaceous earth according to a procedure developed by Mr. C. Pidacks of this laboratory and described previously.[34] The system petroleum ether (b.p. 90–100°)–methanol-2-methoxyethanol (8:1:1) was used. The column was packed with 300 g. of Celite diatomaceous earth and the recording spectrophotometer was set at 240 mμ. The first 950 ml. of effluent contained only small amounts of ultraviolet-absorbing material which were discarded. The next 400 ml. fraction contained the desired product. This fraction was evaporated to dryness to give a glass, crystallization of which from acetone–petroleum ether (b.p. 20–40°) afforded 90 mg. (16%) of XXV as white crystals, m.p. 123–125°. Two recrystallizations from the same solvents raised the m.p. to 131–132°; $[\alpha]_D^{25}$ −45° (0.65% in chloroform); λ_{max} 240 mμ (ε 16,100); λ_{max} 5.78, 5.97, 6.15, 7.97 μ.

Anal. Calcd. for $C_{21}H_{30}O_3S$: C, 69.58; H, 8.34; S, 8.85 Found: C, 69.16; H, 8.45; S, 8.81.

7α-Acetylthio-19-nortestosterone acetate (17β-acetoxy-7α-acetylthio-19-nor-4-androsten-3-one, XXIV). A solution of 6-dehydro-19-nortestosterone acetate (500 mg.) in freshly distilled thiolacetic acid (2 ml.) was heated under reflux for 2 hr. The reaction mixture was evaporated to dryness, and the residual glass was dissolved in 15 ml. of benzene and chromatographed on 50 g. of silica gel. The column was washed successively with 300 ml. of 2% ether in benzene, 300 ml. of 4% ether in benzene, 300 ml. of 6% ether in benzene, and 350 ml. of 8% ether in benzene; these washings were discarded. The column was then eluted with 500 ml. of 10% ether in benzene and the eluate was evaporated to dryness to give 200 mg. of a glass.

This glass was subjected to partition chromatography according to a procedure developed by Mr. C. Pidacks of this laboratory and described previously.[34] The system heptane-2-methoxyethanol was used. The column was packed with 100 g. of Celite and the recording spectrophotometer was set at 238 mμ. The first 950 ml. of effluent contained only trace amounts of ultraviolet-absorbing material, which were discarded. The next 330 ml. contained the desired product. This fraction was taken to dryness to give 136 mg. (22%) of XXVI as an amorphous solid which could not be crystallized; $[\alpha]_D^{25}$ −59° (1.0% in chloroform); λ_{max} 238 mμ (ε 18,300); λ_{max} 5.71, 5.87, 6.12, 8.00 μ.

Anal. Calcd. for $C_{22}H_{30}O_4S$: C, 67.67; H, 7.74; S, 8.21. Found: C, 67.40; H, 8.22; S, 8.03.

6β-Bromo-4-chlorotestosterone propionate (6β-bromo-4-chloro-17β-propionoxy-4-androsten-3-one). A solution of 4-chlorotestosterone propionate[38] (2.0 g.) in 120 ml. of reagent carbon tetrachloride was concentrated by distillation to about 100 ml. to remove moisture. To the cooled solution was added 2 ml. of a 10% solution of reagent pyridine in carbon tetrachloride. After flushing with carbon dioxide (bone dry), *N*-bromsuccinimide (1.0g.) was added and the solution was heated at reflux for 80 min. while under illumination with a 60-watt frosted bulb. The cooled solution was filtered, washed with water, dried with anhydrous magnesium sulfate, and evaporated to dryness. Crystallization of the residue from hexane by the addition of a few drops of acetone furnished 2.1 g. (87%) of 6-bromo-4-chlorotestosterone propionate, m.p. 155–157° dec. Recrystallization from acetone–petroleum ether afforded white crystals, m.p. 158–160° dec.; $[\alpha]_D^{25}$ −185° (1.1% in chloroform); λ_{max} 266 mμ (ε 11,200); λ_{max} 2.95, 3.41, 5.80, 5.93, 7.9 μ.

The β-configuration for the 6-bromine atom is assigned on the basis[17] of a bathochromic shift for the ultraviolet maximum and an analysis of the molecular rotation data.

Anal. Calcd. for $C_{22}H_{30}BrClO_3$: C, 57.72; H, 6.60; Br, 17.45; Cl, 7.74. Found: C, 57.38; H, 6.77; Br, 17.53; Cl, 8.30.

6-Dehydro-4-chlorotestosterone propionate (4-chloro-17β-propionoxy-4,6-androstadien-3-one). 6β-Bromo-4-chlorotestosterone propionate (1.5 g.) was suspended in 15 ml. of *sym*-collidine and refluxed under an atmosphere of carbon dioxide for 30 min., solution being complete at the boiling point. The cooled solution was filtered from collidine hydrobromide, and the mother liquor, after being diluted with 100 ml. of benzene, was washed successively with 8% sulfuric acid, saturated aqueous sodium bicarbonate and water, dried with anhydrous magnesium sulfate, and evaporated to dryness. The resulting amorphous material (1.1 g.) was dissolved in 25 ml. of benzene and chromatographed on 60 g. of silica gel. The column was washed with 500 ml. of benzene and then with 1 l. of 1% ether in benzene solution; these washings were discarded. The product was eluted by further washing the column with 1–2% ether in benzene solution (1800 ml.). The eluants were evaporated to dryness and the crude residual solid was crystallized from petroleum ether to yield 546 mg. (44%) of 6-dehydro-4-chloro-testosterone propionate, m.p. 100–102°. Recrystallization from the same solvent afforded white crystals, m.p. 103–104°; $[\alpha]_D^{25}$ +79° (0.41% in chloroform); λ_{max} 295 mμ (ε 24,600); λ_{max} 5.73, 5.96, 6.20, 6.42, 8.4 μ.

Anal. Calcd. for $C_{22}H_{29}ClO_3$: C, 70.10; H, 7.75; Cl, 9.41. Found: C, 69.78; H, 8.08; Cl, 10.08.

4-Chloro-7α-methylthiotestosterone propionate (4-chloro-7α-methylthio-17β-propionoxy-4-androsten-3-one, XXVIII). To a cold solution of 6-dehydro-4-chlorotestosterone propionate (800 mg.) in 50 ml. of glacial acetic acid was added 2 ml. of concd. hydrochloric acid and then 8 ml. of methyl mercaptan. The solution was kept at 8° for 8 days. Work-up of the reaction mixture was carried out as described above for the preparation of compound II. Crystallization of the residual syrup from acetone–petroleum ether afforded 85 mg. of XXVII, m.p. 235–240°. Recrystallization from the same solvents gave white crystals, m.p. 252–254° dec.; $[\alpha]_D^{25}$ +43° (0.5% in chloroform); λ_{max} 255 mμ (ε 13,800); λ_{max} 5.72, 5.90, 6.28, 8.40 μ.

Anal. Calcd. for $C_{23}H_{33}ClO_3S$: C, 65.00; H, 7.83; Cl, 8.34; S, 7.54. Found: C, 64.97; H, 8.08; Cl, 8.49; S, 7.80.

6-Dehydro-9α-fluoro-11β-hydroxy-17α-methyltestosterone (9α-fluoro-11β,17β-dihydroxy-17α-methyl-4,6-androstadien-3-one). To a solution of 9α-fluoro-11β,17β-dihydroxy-17α-methyl-4-androsten-3-one[21] (1.0 g.) in 100 ml. of dry *t*-butyl alcohol, freed from moisture by distillation of 30 ml. of solvent, was added 1 g. of chloranil and 10 mg. of *p*-toluenesulfonic acid. The mixture was refluxed, under an atmosphere of nitrogen, for 20 hr., solution being complete in approximately 45 min. The solution was evaporated to dryness. The residual syrup was dissolved in methylene chloride and the solution was washed with three portions of ice cold 5% sodium hydroxide solution and then with water (to neutrality), dried with anhydrous magnesium sulfate, and evaporated to dryness leaving an amorphous solid. Crystallization from acetone–petroleum ether afforded 200 mg. (20%) of product, m.p. 239° dec. Recrystallization from the same solvents gave white crystals, m.p. 242° dec.; $[\alpha]_D^{25}$ + 53.6° (0.6% in methanol); λ_{max} 282 mμ (ε 28,000); λ_{max} 2.79, 2.88, 6.03, 6.18, 6.31 μ.

Anal. Calcd. for $C_{20}H_{27}FO_3$: C, 71.83; H, 8.14; F, 5.68. Found: C, 71.68; H, 8.34; F, 5.78.

7α-Acetylthio-9α-fluoro-11β-hydroxy-17α-methyltestosterone (7α-acetylthio-9α-fluoro-11β,17β-dihydroxy-17α-methyl-4-

(38) W. J. Adams, D. N. Kirk, and V. Petrow, Brit. Pat. 92,727 (April 2, 1958).

androsten-3-one, XXVI). A suspension of 6-dehydro-9α-fluoro-11β-hydroxy-17α-methyltestosterone (100 mg.) in 1 ml. of thiolacetic acid was refluxed for 18 hr., solution being complete after approximately 25 min. The solution was evaporated to dryness. Trituration of the residual solid with ether afforded 88 mg. (72%) of XXVI, m.p. 241° dec. Several recrystallizations from acetone–petroleum ether gave white crystals, m.p. 243–246° dec.; $[\alpha]_D^{25}$ −41° (0.24% in chloroform); λ_{max} 236 mμ (ϵ 19,600); λ_{max} 2.91, 5.94, 6.04, 6.15, 8.0 μ.

Anal. Calcd. for $C_{22}H_{31}FO_4S$: C, 64.37; H, 7.61; F, 4.62; S, 7.81. Found: C, 63.68; H, 7.93; F, 4.42; S, 7.85.

17β-Acetoxy-7α-methylthioandrostan-3-one (XXIX). A solution containing 2.0 g. of 17β-acetoxy-7α-methylthio-4-androsten-3-one (XVI) in 25 ml. of dioxane and 25 ml. of ether was added dropwise to a solution of lithium (300 mg.) in 250 ml. of liquid ammonia over a period of 15 min. After stirring for an additional 35 min. the blue color of the solution was discharged by the addition of 6.0 g. of ammonium chloride and the ammonia was allowed to evaporate. The residue was distributed between ether and water, and the water extract was washed several times with methylene chloride. The combined organic extracts were washed with water, dried with anhydrous magnesium sulfate and evaporated to dryness leaving 1.6 g. of amorphous material. As at least partial deacetylation apparently had occurred (hydroxyl absorption at 2.89 μ), the material was acetylated with acetic anhydride in pyridine solution at room temperature overnight. After dilution with water, the mixture was extracted with methylene chloride, washed with water, dried over anhydrous magnesium sulfate, and evaporated to dryness leaving a syrup. Trituration with ether and filtration afforded 720 mg. (36%) of 17β-acetoxy-7α-methylthioandrostan-3-one (XXIX) as a white powder, m.p. 175–179°. The material had no ultraviolet absorption; $[\alpha]_D^{25}$ − 44.4° (0.61% in chloroform); λ_{max} 5.75, 5.80, 8.00 μ.

Anal. Calcd. for $C_{22}H_{34}O_3S$: C, 69.79; H, 9.05; S, 8.47. Found: C, 69.80; H, 9.15; S, 8.55.

17β-Hydroxy-2-hydroxymethylene-7α-methylthioandrostan-3-one (XXXI).[26] Sodium hydride (2.24 g. of a 50% dispersion in oil) was added to a solution of 2.8 g. of 17β-acetoxy-7α-methylthioandrostan-3-one (XXIX) in 100 ml. of reagent benzene (freed from moisture by azeotropic distillation of 20 ml.) containing 5.6 ml. of ethyl formate. The reaction mixture was allowed to stand under nitrogen for 5 days. Methanol (5.6 ml.) was then added to decompose the excess hydride, and the solution was diluted with 280 ml. of benzene and 280 ml. of water. The layers were separated and the aqueous phase was extracted with benzene. The aqueous layer was then acidified with dilute hydrochloric acid and the precipitated enol was extracted with ether. The extracts were washed with water, dried with anhydrous magnesium sulfate, and evaporated to dryness to give a glass. Crystallization from acetone–petroleum ether gave 1.6 g. (60%) of XXXI, m.p. 130–140° (gas). The compound gave a deep red color with 1% alcoholic ferric chloride solution. Recrystallization from ethyl acetate afforded white crystals, m.p. 163–165° (previous softening); $[\alpha]_D^{25}$ −29.2° (1.4% in chloroform); λ_{max} 282 mμ (ϵ 7,300); λ_{max} 2.88, 6.10, 6.25 μ.

Anal. Calcd. for $C_{21}H_{32}O_3S$: C, 69.20; H, 8.85; S, 8.80. Found: C, 69.54; H, 9.01; S, 8.43.

17β-Hydroxy-7α-methylthioandrostano[3,2-c]pyrazole (XXX). To a solution of 200 mg. of 17β-hydroxy-2-hydroxymethylene-7α-methylthioandrostan-3-one (XXXI) in 7 ml. of absolute alcohol was added 3.0 ml. of absolute alcohol containing 0.03 ml. of 98–100% hydrazine hydrate. The solution became turbid and a crystalline material separated after 10 min. The mixture remained colorless when tested with 1% alcoholic ferric chloride solution. The mixture was cooled and filtered to give 181 mg. of product (XXX) in two crops, m.p. 170–173° (gas). Several recrystallizations from acetone-water gave white crystals, m.p. 174° (gas); $[\alpha]_D^{25}$ −22.2° (0.4% in chloroform); λ_{max} 223 mμ (ϵ 4,750); λ_{max} 3.05, 6.90, 10.46 μ.

Anal. Calcd for $C_{21}H_{32}N_2OS \cdot {}^1/_2H_2O$: C, 68.24; H, 9.00; N, 7.58; S, 8.68. Found: C, 68.14; H, 9.09; N, 8.09; S, 8.64

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[CONTRIBUTION FROM THE NATURAL PRODUCTS RESEARCH DEPARTMENT, SCHERING CORP.]

Enol Ethers of Steroidal Δ^4-3-Ketones

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A method is described for the preparation of a number of unsaturated steroidal enol ethers, involving alkoxyl interchange between Δ^4-3-ketones, 2,2-dimethoxypropane, and alcohols.

Recently, Tanabe and Bigley[1] described a new method to protect the hydroxyl groups of the dihydroxyacetone side chain typical of the cortical steroids. This procedure involves acid-catalyzed ketal interchange between 2,2-dimethoxypropane and the corticoid to be protected to produce 17α,21-isopropylidenedioxy steroids. In connection with another problem, we had occasion to apply this reaction to 17α,21-dihydroxy-Δ^4-pregnen-3,20-dione, Reichstein's S (I). When the reaction was allowed to proceed until a small aliquot was negative to the TPTZ color reagent (disappearance of the dihydroxyacetone side chain)—this occurred after two and one-half hours—the desired 17α,21-isopropylidenedioxy derivative II was isolated. However, a second product, considerably

(1) Masato Tanabe and Barbara Bigley, *J. Am. Chem. Soc.*, **83**, 756 (1961).