Reaction of the Seco Compound 21 with Cyanogen Bromide.—To a solution of **21** (1.0 g.) in benzene (50 ml.) was added 0.4 g. of cyanogen bromide, and the mixture was warmed at 60° for 1 hr. After cooling, the benzene solution was washed with 5% hydrogen chloride and water, and dried over sodium sulfate. An oily residue obtained by evaporation of the benzene was crystallized by trituration with ether; yield, 0.79 g.; m.p. 80–94°.

An analytical sample, recrystallized from an acetone–*n*-hexane mixture and ether, melted at 94° with presoftening at 82–83°.

Anal. Calcd. for $C_{18}H_{20}O_3N_2$: C, 69.21; H, 6.45; N, 8.97. Found: C, 68.91; H, 6.64; N, 8.84.

Decyanation of 22 and Ring Closure.—To a solution of 0.78 g. of **22** in ethanol (15 ml.) was added 20% potassium hydroxide (5 ml.), and the mixture was heated in a bath kept at 110° for 10 hr. After cooling, the reaction mixture was diluted with water and extracted with benzene. The extract was washed with water and dried over sodium sulfate Evaporation of the benzene afforded 0.43 g. of an oily product, which was chromatographed on alumina (Woelm, grade III). Elution with benzene afforded 0.23 g. of crystalline product. Elution with chloroform gave another 0.18 g. of an oily substance, which was not characterized.

An analytical sample, recrystallized from an acetone–*n*-hexane mixture, melted at 148–149°.

Anal. Calcd. for $C_{17}H_{21}O_3N$: C, 71.05; H, 7.37; N, 4.87. Found: C, 70.97; H, 7.32; N, 4.96.

Wolff–Kishner Reduction of the Keto Compound 23.—To a solution of the ketone **23** (1.0 g.) in diethylene glycol (50 ml.), 80% hydrazine hydrate (10 ml.) and potassium hydroxide (3.0 g.) were added, and the mixture was heated at 100° for 1 hr. and at 140–160° for 3 hr. During this time, 1 mole of nitrogen was evolved. After cooling, water (50 ml.) was added to the reaction mixture, and the mixture was extracted with benzene. The extract was washed with water and dried over sodium sulfate. Evaporation of the benzene afforded a semisolid product amounting to 0.79 g.

An analytical sample was purified by chromatography on alumina (Woelm, grade III), by elution with benzene and by sublimation, m.p. 85–86°.

Anal. Calcd. for $C_{17}H_{23}O_2N$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.55; H, 8.35; N, 4.99.

Acknowledgment.—We wish to thank Dr. M. Matsui and Professor K. Tsuda for their encouragement and discussions throughout this work.

A Novel Reduction with Alkylmercaptans and a New Route to 2-Keto Steroids

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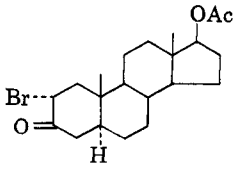
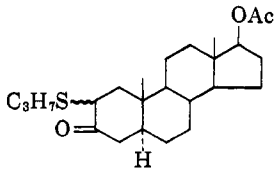
n-Propyl mercaptan reacts with 17β-acetoxy-2α-bromo-5α-androstan-3-one (I) to produce 17β-acetoxy-5α-androstan-2-one (IIIa). The intermediates have been shown to be 17β-acetoxy-2ξ-*n*-propylmercapto-5α-androstan-3-one (II), 2,3-bis(*n*-propylmercapto)-5α-androst-2-en-17β-ol acetate (VI), and 2-*n*-propylmercapto-5α-androst-2-en-17β-ol acetate (VIII), in that order; hydrolysis of VIII produces the 2-ketone. Reduction of the intermediate 2,3-bis(*n*-propylmercapto)-5α-androst-2-en-17β-ol acetate (VI) by *n*-propyl mercaptan occurs only under strongly acidic conditions and in a symmetrical manner to produce 2- and 3-*n*-propylmercapto-5α-androst-2-en-17β-ol acetate (VIII and IX, respectively) in essentially equal quantities. 17β-Acetoxy-5α-androstan-2-one and -3-one can be separated quantitatively through preferential formation of a bisulfite adduct of the 3-ketone. Complete hydrolysis of the products from the above rearrangement with separation *via* the bisulfite reaction affords the 2-ketone (IIIa) in 41% yield and the 3-ketone in 49% yield.

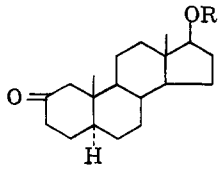
An attempt was made to prepare 17β-acetoxy-2ξ-*n*-propylmercapto-5α-androstan-3-one (II) from the corresponding 2α-bromo steroid (I) by heating the latter compound with *n*-propyl mercaptan in chloroform. Among the products of the reaction was 17β-acetoxy-5α-androstan-2-one (IIIa). This paper describes the investigation of this unusual reaction. The conditions which afford an optimum yield of the 2-ketone are given after the course of the reaction has been established.



I



II

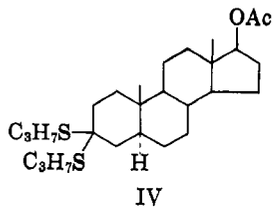


IIIa, R = $COCH_3$
b, R = H
c, R = COC_2H_5

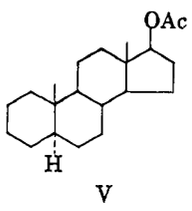
Replacement reactions at the C-2 of steroids have been plagued by rearrangements. For example, 2α-bromo-5α-cholestan-3-one reacts with potassium acetate in boiling acetic acid to give a 1:1 complex of 2α- and 4α-acetoxy-3-ketones.[1] At 200°, these same reactants give a Δ^5-4-keto steroid.[2] A different source of acetate ion, tetramethylammonium acetate, causes 2α-bromo-5α-cholestan-3-one to form 3β-acetoxy-5α-cholestan-2-one.[3] In the acid-catalyzed methanolysis of 2-acetoxytestosterone, the 2β-epimer yields 17β-hydroxy-5α-androstane-3,6-dione,[4] whereas the 2α-epimer yields 2-methoxy-4-methyl-1,3,5(10)-estratrien-17β-ol.[5]

In the presently reported work a solution of 17β-acetoxy-2α-bromo-5α-androstan-3-one (I) and four molar equivalents of *n*-propyl mercaptan in chloroform was refluxed for six hours. Chromatography of the reaction products afforded 17β-acetoxy-5α-androstan-2-one (IIIa) in 23% yield, 17β-acetoxy-5α-androstan-3-one di-*n*-propylmercaptole (IV) in 9% yield, di-*n*-propyl disulfide in 75% yield, and a mixture of sulfur-containing oils. One portion of this oily mixture could be desulfurized with Raney nickel to give 5α-androstan-17β-ol acetate (V) in about 65% yield. When methanol was used as the solvent for recrystallization of the 2-ketone IIIa, the yield of 2-ketone dropped, and some dimethyl-

(1) L. F. Fieser and M. A. Romero, *J. Am. Chem. Soc.*, **75**, 4716 (1953).
(2) A. Butenandt and A. Wolff, *Chem. Ber.*, **68**, 2091 (1935); A. Butenandt and G. Ruhenstroth-Bauer, *ibid.*, **77**, 397 (1944).
(3) K. L. Williamson and W. S. Johnson, *J. Org. Chem.*, **26**, 4563 (1961).
(4) R. L. Clarke, *J. Am. Chem. Soc.*, **82**, 4629 (1960).
(5) Ref. 4, **84**, 467 (1962).



IV

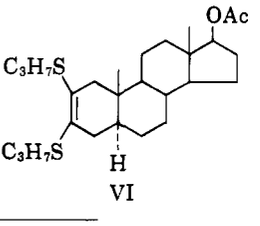


V

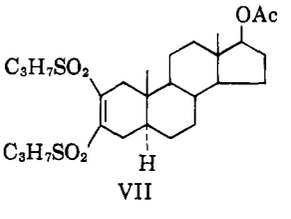
ketal of IIIa was isolated.[6] A trace of pyridine in the methanol prevented ketal formation. The formation of di-*n*-propyl disulfide in this rearrangement is the result of a reduction process.

The 2-ketone, IIIa was identified by its conversion through the corresponding 17-hydroxy compound IIIb into 5α-androstane-2,17-dione,[7] and by direct comparison of the 17-propionate IIIc with an authentic sample kindly furnished by Dr. Carl Djerassi. Saponification of the dimethylketal of 17β-acetoxy-5α-androstan-2-one with alkali afforded the dimethylketal of 17β-hydroxy-5α-androstan-2-one. The 3-mercaptole IV was compared directly with an authentic sample prepared from 17β-acetoxy-5α-androstan-3-one.

In the present rearrangement reaction, hydrogen bromide evolution develops about five minutes after the original reaction mixture is brought to boiling. Hydrogen bromide acceptors were added to the mixture in an effort to improve the yield of 2-ketone IIIa. The presence of phenoxypropylene oxide resulted in 68% recovery of starting material. In the presence of collidine, small and erratic yields of 17β-acetoxy-2ξ-*n*-propylmercapto-5α-androstan-3-one (II) were obtained. The use of *t*-butyl alcohol as both solvent and hydrogen bromide acceptor, but with only one molar equivalent of *n*-propyl mercaptan, afforded the 2ξ-*n*-propylmercapto compound II in 34% yield as the only product isolated. Use of four molar equivalents of *n*-propyl mercaptan under the same conditions produced 2,3-bis(*n*-propylmercapto)-5α-androst-2-en-17β-ol acetate (VI) in 48% yield.[8] Only a 6% yield of di-*n*-propyl disulfide was noted here. Consequently, negligible reduction appears to have occurred. Compounds II and VI ultimately proved to be intermediates in the rearrangement under discussion.



VI



VII

Identification of the 17β-acetoxy-2ξ-*n*-propylmercapto-5α-androstan-3-one (II) was established by elemental composition, desulfurization to produce 17β-acetoxy-5α-androstan-3-one, and by conversion into 17β-acetoxy-5α-androstan-2-one (IIIa) as described subsequently. An attempt to establish the configuration at C-2 by equilibration with sodium methoxide gave an intractable mixture. N.m.r. spectra have been used to establish the configurations of 2-substituted 3-keto steroids[9] but the spectral curve for II did not yield sufficient information to permit assignment of configuration.

Identification of the 2,3-bis(*n*-propylmercapto)-5α-androst-2-en-17β-ol acetate (VI) was based upon its elemental composition, desulfurization with deactivated Raney nickel to form 5α-androst-2-en-17β-ol acetate, oxidation to 2,3-bis(*n*-propanesulfonyl)-5α-androst-2-en-17β-ol acetate (VII), and correspondence of the ultraviolet spectrum of VI with that of a similar sturcture. Thus, *cis*-1,2-bis(methylmercapto)ethylene shows λ_{max} 228 mμ (ε 4917) and 253 (9051).[9] Compound VI shows λ_{max} 221 mμ (ε 5710) and 253 (5660).

A clue to the mode of formation of the 2-ketone appeared when the rearrangement was performed with 2α-bromo-5α-cholestan-3-one. Chromatography of the crude reaction product on silica gel afforded a 26% yield of crystalline 5α-cholestan-2-one in addition to some less polar oils. The oils were combined and hydrolyzed with aqueous, methanolic hydrogen chloride at 35° for two and one-half hours. Chromatography of this reaction product gave an additional 28% yield of ketonic material which was shown by gas chromatography to be a 52:48 mixture of 5α-cholestan-2-one and -3-one. The nonpolar oils which constituted the remainder of the reaction mixture contained only carbon, hydrogen, and sulfur and *no oxygen*. Further hydrolysis of the nonpolar oils gave an additional 30% yield of ketonic material (95% 3-ketone and 5% 2-ketone). The ketonic material accounts for 84% of the total reaction products, but the most interesting fact is that there was no evidence of oxygenated intermediates or by-products in the reaction mixture.

At this stage of the investigation, the reaction sequence (p. 2628) was postulated.

As one test of the validity of this sequence, 17β-acetoxy-2ξ-*n*-propylmercapto-5α-androstan-3-one (II) was treated with *n*-propyl mercaptan and hydrogen bromide in refluxing chloroform. The 2-ketone III was produced in 28% yield. This reaction failed to occur in the absence of hydrogen bromide.

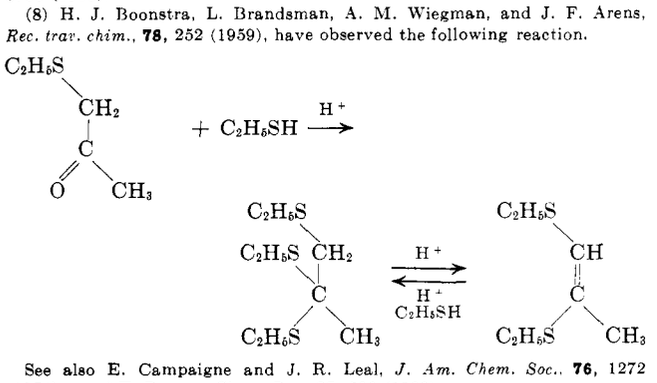
One molar equivalent of water should be formed in step 3 of the sequence. Indeed, the reaction mixture becomes cloudy shortly, and water separates after hydrogen bromide evolution begins. Some water droplets remain at the end of the normal reflux period.

The next test involved treatment of 2,3-bis(*n*-propylmercapto)-5α-androst-2-en-17β-ol acetate (VI) with *n*-propyl mercaptan, hydrogen bromide, and water. In this experiment, two molar equivalents of water were

(6) This ketal formation may have been catalyzed by traces of acidity on the glassware used. Such ready ketal formation is in marked contrast to an essentially negligible tendency to form a 2-di-*n*-propylmercaptole as reported later in this paper.

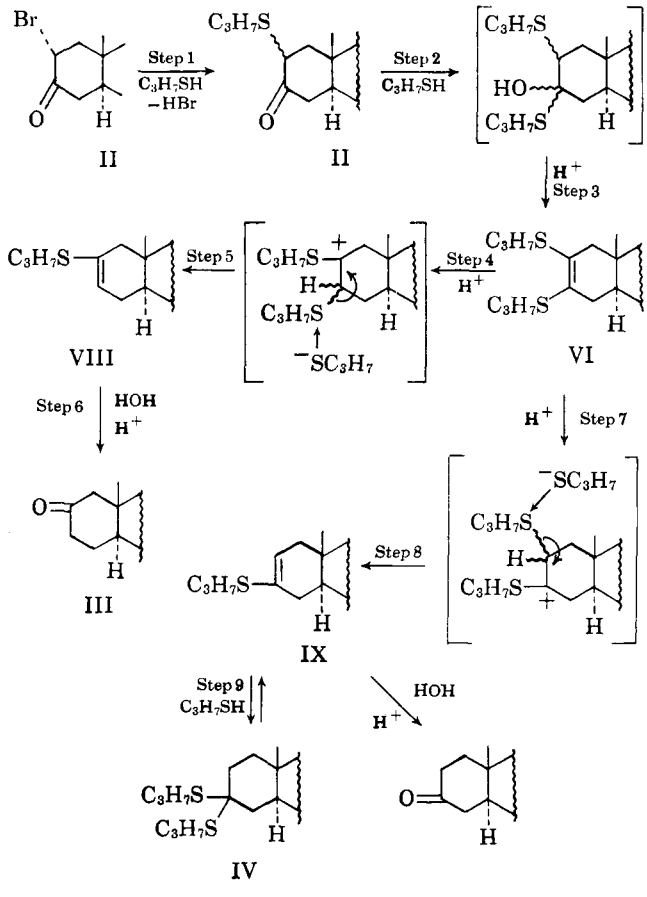
(7) C. Djerassi, R. Yashin, and G. Rosenkranz, *J. Am. Chem. Soc.*, **72**, 5750 (1950).

(8) H. J. Boonstra, L. Brandsman, A. M. Wiegman, and J. F. Arens, *Rec. trav. chim.*, **78**, 252 (1959), have observed the following reaction.



See also E. Campaigne and J. R. Leal, *J. Am. Chem. Soc.*, **76**, 1272 (1954); and T. Pozner, *Chem. Ber.*, **35**, 506 (1902).

(9) W. E. Parham, R. F. Motter, and G. L. O. Mayo, *J. Am. Chem. Soc.*, **81**, 3386 (1959).



used, and a 61% yield of ketonic material was isolated by chromatography (48% yield of 2-ketone and 13% yield of 3-ketone) together with an 84% yield of di-*n*-propyl disulfide. A blank run without the steroid afforded only a 3% yield of di-*n*-propyl disulfide. Consequently, the formation of disulfide here is related to removal of a propylmercapto group from the steroid and not to simple oxidation of the mercaptan.

The question then remained as to whether the reduction step occurred before or after the hydrolytic step in forming ketonic material. In an experiment designed to allow reduction of VI without hydrolysis, compound VI was treated with dry *n*-propyl mercaptan and dry hydrogen bromide in dry, alcohol-free chloroform. Concentration of the reaction mixture and gas chromatography of a sample of the residual oil gave two major steroidal peaks (ratio 62:32) with 6% of minor impurities. The lesser peak corresponded to the 3-mercaptole IV. The greater peak corresponded to 2- and 3-*n*-propylmercapto-5α-androst-2-en-17β-ol acetate (VIII and IX), both of which have the same retention time. A highly resolved infrared spectrum of this same residual oil revealed no ketonic material. On the other hand, attempted hydrolysis of compound VI with boiling aqueous, methanolic hydrochloric acid gave only a complex, oily mixture containing no ketonic material (infrared spectral evidence). Therefore, it can be concluded that the reduction step precedes hydrolysis.

In the reduction step there appears to be little selectivity to removal of the 2- *vs.* the 3-mercapto group (from VI). Thus, in the rearrangement of 2α-bromocholestan-3-one previously described, the yields of 2-ketone and 3-ketone were both 42% (based on gas chromatographic evidence). This reduction step is acid catalyzed. Disulfide VI was recovered unchanged after treatment with *n*-propylmercaptan in boiling benzene for five hours.[10] The result with added hydrogen bromide was previously described. Mechanistically, the course of the reduction is probably related to that shown in steps 4, 5, 7, and 8 of the reaction sequence. Sufficient acidity for appreciable reduction could not develop when *t*-butyl alcohol was used as the reaction solvent. Consequently, it was possible to isolate the disulfide VI as mentioned before.

Considering further the reduction of disulfide VI under anhydrous conditions, it already has been noted that gas chromatography of the crude reaction product indicated a 32% yield of the 3-mercaptole IV. Under the reaction conditions, IV could not have formed through mercaptolization of 3-ketone. It must have formed by acid-catalyzed addition of *n*-propyl mercaptan to 3-*n*-propylmercapto-5α-androst-2-en-17β-ol acetate (IX) (step 9 of the sequence). Indeed, when the thioenol ether IX was treated with *n*-propyl mercaptan and hydrogen bromide, mercaptole IV could be isolated in 37% yield.[11]

3-*n*-Propylmercapto-5α-androst-2-en-17β-ol acetate (IX) was prepared in 21% yield from 17β-acetoxy-5α-androstan-3-one di-*n*-propylmercaptole (IV) by acid-catalyzed decomposition in boiling benzene.[8] This thioenol ether IX shows λ_{max} 223 mμ (ϵ 4900) and 238–243 sh (3500). Other thioenol ethers have been reported to absorb similarly. For example, 2-methylthiacyclohex-2-ene shows 227 mμ (ϵ 5160) and 245 sh (2400)[12]; methyl vinyl sulfide shows 225 mμ (ϵ 16,000) and 240 (10,000).[13] Compound IX has the same retention time (21.5 min.) on a gas chromatograph as does the major peak from the product of anhydrous reduction of the 2,3-bis-*n*-propylmercapto steroid VI. Incidentally, this thioenol ether IX can be oxidized with monoperphthalic acid to give 3-*n*-propanesulfonyl-5α-androst-2-en-17β-ol acetate.

Addition of *n*-propyl mercaptan to the 2-thioenol ether VIII probably is hindered by development of a 1,3-diaxial repulsion between the entering group and the C-19 methyl group. Attempts to make a di-*n*-propylmercaptole derivative of the 2-ketone IIIa resulted in recovery of 43% of starting material and isolation of the 2-thioenol ether, 2-*n*-propylmercapto-5α-androst-2-en-17β-ol acetate (VIII), in 25% yield. This 2-thioenol ether shows λ_{max} 223 mμ (ϵ 4200) and 238–243 sh (3100) and has the same retention time (21.5 min.) on a gas chromatogram as do the 3-thioenol ether IX and the major product of anhydrous reduction of the 2,3-bis-*n*-propylmercapto steroid VI. As was the case with IX, this thioenol ether VIII can be oxidized with monoperphthalic acid to give 2-*n*-propanesulfonyl-5α-androst-2-en-17β-ol acetate.

To summarize the data to this point, all indications are that the reaction sequence as postulated describes the actual course of the reaction. Reduction of the 2,3-disulfide VI gives a mixture of nearly equal quanti-

(10) Benzene was used as a solvent in preference to chloroform in this experiment in an effort to avoid possible development of acidity by chloroform.

(11) M. F. Shostakovskii, E. P. Gracheva, and N. K. Kul'bovskaya, *Zh. Obshch. Khim.*, **30**, 383 (1960), found that ethyl mercaptan adds to ethyl isopropenyl sulfide in the presence of hydrogen chloride to form acetone diethylmercaptole.

(12) L. Bateman and R. W. Glazebrook, *J. Chem. Soc.*, 2834 (1958).

(13) C. C. Price and H. Morita, *J. Am. Chem. Soc.*, **75**, 4747 (1953).

ties of thioenol ethers VIII and IX, and the greater portion of the 3-thioenol ether IX adds *n*-propyl mercaptan to form the 3-mercaptole IV as the third major component of the reaction mixture. Only two peaks are apparent in a gas chromatogram of the product because the two thioenol ethers come off together. Two factors are operative to lower the yield of pure 2-ketone IIIa. The amount of water produced in the reaction does not, in actuality, hydrolyze all of the 2-thioenol ether present to give a maximum amount of 2-ketone IIIa. Secondly, small quantities of 3-ketone are generated simultaneously and make purification of the 2-ketone dificult. If more water is added to effect complete formation of 2-ketone, more 3-ketone is simultaneously generated. These ketones are very difficult to separate by crystallization or column chromatography.

Fortunately, it was found that 17β-acetoxy-5α-androstan-3-one forms a bisulfite addition product in high yield under conditions where the corresponding 2-ketone does not form an addition product at all.[14] Essentially quantitative separation can be effected. The difference in reactivity of the two ketones apparently lies in the steric influence of the axial C-19 methyl group.

With this useful separation technique available, 17β-acetoxy-2α-bromo-5α-androstan-3-one was refluxed with *n*-propyl mercaptan in chloroform, the solvent and excess mercaptan were removed, and the crude, oily residue was hydrolyzed with aqueous, methanolic hydrogen chloride. All of the *n*-propyl mercaptan and di-*n*-propyl disulfide present were removed by codistillation with water. The mixture was re-acetylated at C-17, and all 3-ketone present was removed as its bisulfite addition product. In this manner, there was obtained a 41.5% yield of pure 17β-acetoxy-5α-androstan-2-one (IIIa). Hydrolysis of the bisulfite adduct of the 3-ketone afforded a 49% yield of the 3-ketone which was then available to be used again.

17β-Acetoxy-2α-chloro-5α-androstan-3-one did not react satisfactorily in this rearrangement. Only a trace of 2-ketone could be isolated.

The use of dimethylformamide instead of chloroform as a solvent for the rearrangement under discussion gave the 2,3-bis-*n*-propylmercapto compound VI in 23% yield as the only pure product isolated. Acetic acid, acetonitrile, and dimethyl sulfoxide were also unsatisfactory. Dioxane was acceptable, but offered no advantage over chloroform. A reaction temperature of 70–75° was used with all of these solvents.

When the reaction was run at reflux in chloroform for one hour or at room temperature for twenty hours, no pure product was isolated.

Of the mercaptans substituted for *n*-propyl mercaptan in the production of 2-ketone IIIa, isopropyl and isobutyl mercaptans served about as well as did *n*-propyl mercaptan. Methyl mercaptan gave a lower yield and *t*-butyl mercaptan gave none. Also unsatisfactory were thioacetic acid, mercaptoacetic acid, thiophenol, hydrogen sulfide, and tetramethylenedithiol.

Further applications of this reaction are being studied.

(14) R. E. Counsell, P. D. Klimstra, and F. B. Colton, *J. Org. Chem.*, **27**, 248 (1962), report the separation of a saturated 3-keto steroid from α,β-unsaturated 3-keto steroids through preferential formation of a bisulfite adduct.

Experimental[15]

Reaction of 2α-Bromo-17β-acetoxy-5α-androstan-3-one with *n*-Propyl Mercaptan.[16]—A mixture of 20 g. (0.049 mole) of 2α-bromo-17β-acetoxy-5α-androstan-3-one (I), 15.2 g. (0.2 mole) of *n*-propyl mercaptan, and 250 ml. of chloroform was refluxed under nitrogen for 6 hr. The solvent was removed at <60° under 15-mm. pressure. The pressure was then lowered to 0.08 mm., whereupon 5.6 g. (75% yield) of slightly impure **dipropyl disulfide** distilled, b.p. 37–40° (0.08 mm.) or 195–196° (1 atm.); $n^{25}D$ 1.4952 (lit.[17] b.p. 193.5°; $n^{25}D$ 1.4981). When this compound was isolated in a later experiment described subsequently, its infrared spectrum was found to be identical with that of an authentic sample.

Anal. Calcd. for $C_6H_{14}S_2$: S, 42.66. Found: S, 44.0.

The residual reaction mixture was then heated at 100° for 1 hr. with 50 ml. of pyridine and 25 ml. of acetic anhydride. Excess reagents were removed by warming *in vacuo*, and the residual oil was dissolved in ether. The solution was washed with 2 *N* sodium hydroxide, 2 *N* hydrochloric acid, and saturated salt solution, and was concentrated to an oily residue. The residue in 1:9 ether–pentane was poured onto a column of 500 g. of silica gel. The column was eluted with 4 l. of this same 1:9 mixture to give 13 g. of an oil which will be referred to below as mixture A. Further elution with 9 l. of the 1:9 solvent mixture followed by 13 l. of a 1:4 ether–pentane mixture afforded 5.5 g. of crystalline solid.

The 5.5-g. sample was dissolved in 50 ml. of hot methanol and the solution was concentrated to a 20-ml. volume. The solution was cooled to 6° and the precipitate of white plates was collected (3.2 g.). This product was recrystallized from methanol to give 2.85 g. (17% yield) of **17β-acetoxy-5α-androstan-2-one (IIIa)**, m.p. 148–150°. One further recrystallization raised the melting point to 149–150°; $[\alpha]^{25}D$ +26.8°.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 76.1; H, 9.4.

Immediately following the separation of the 3.2 g. of IIIa, a heavy precipitation of needles occurred in the filtrate. This solid was collected (1.0 g.) and recrystallized twice from methanol to give 0.8 g. (4% yield) of **17β-acetoxy-5α-androstan-2-one dimethylketal**, m.p. 142.5–144.5; $[\alpha]^{25}D$ +5.2°.

Anal. Calcd. for $C_{23}H_{38}O_4$: C, 72.97; H, 10.12; OCH_3, 16.40. Found: C, 72.8; H, 9.9; OCH_3, 16.2.

In similar runs, the use of acetone instead of methanol as the recrystallization solvent avoided formation of 2-ketal and resulted in 20–23% yields of the 2-ketone.

Mixture A, described previously, was rechromatographed on 280 g. of neutral alumina. Elution of the column with 5% ether–95% pentane caused immediate removal of 2.65 g. of oily **17β-acetoxy-5α-androstan-3-one di-*n*-propylmercaptole (IV)** which solidified. One recrystallization from methanol gave 2.0 g. (9% yield) of fine needles, m.p. 96.5–98°. This melting point was undepressed upon admixture of the material with an authentic sample of m.p. 96.5–98° prepared from 17β-acetoxy-5α-androstan-3-one, and the infrared spectra of the two samples were identical.

An oil (3.35 g.) was eluted immediately following the di-*n*-propylmercaptole IV.

Desulfurization of this oily product by refluxing it in 50 ml. of absolute ethanol with 35 g. of Raney nickel for 12 hr. followed by separation of the catalyst and concentration of the filtrate, gave 2.4 g. of white crystals. Two recrystallizations of the solid from the methanol and reworking of the mother liquors afforded 1.71 g. (64% yield based on a mol. wt. of 400 for the sulfur-containing oils) of **5α-androstan-17β-ol acetate (V)**, m.p. 81–82.5°; $[\alpha]^{25}D$ +4.9° (lit.[18] m.p. 72–75°; $[\alpha]^{20}D$ +5°.)

(15) All optical rotations were measured in chloroform, and all ultraviolet spectra were measured in 95% ethanol. Except where noted otherwise, gas chromatograms were run using an F & M flame ionization gas chromatograph Model 609 fitted with a 0.25-in. o.d., stainless steel column 6 ft. long and packed with 1% silicone oil DC-FS1265 (formerly QF-1-0065) on acid-washed Chromosorb W, 80–100 mesh. The carrier gas was nitrogen under 60-p.s.i.g. pressure with the outlet flow adjusted to 20 ml. per min. The column temperature was held at 225°, the injection port at 325°, and the detector at 275°. The retention times are uncorrected.

(16) For details on the reaction conditions which afford an optimum yield of 2-ketone, see the last experiment in this paper.

(17) A. I. Vogel and D. M. Cowan, *J. Chem. Soc.*, 16 (1943).

(18) G. Rosenkranz, S. Kaufmann, and J. Romo, *J. Am. Chem. Soc.*, **71**, 3689 (1949).

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.3; H, 10.2.

When the melting point on this 5α-androstan-17β-ol acetate was higher than that reported, and the hydrogen analysis was not within desired limits, this product (0.50 g.) was hydrolyzed with 0.40 g. of potassium hydroxide in 25 ml. of 95% ethanol by refluxing the solution for 1.5 hr. The solvent was removed, the product was dissolved in ether, and the solution was washed with saturated salt solution, then dried over sodium sulfate. The solution was concentrated and the residue was recrystallized from methanol to give 0.41 g. (95% yield) of **5α-androstan-17β-ol**, m.p. 166.5–168°. A second recrystallization raised the melting point to 167.5–168.5°; $[\alpha]^{25}D$ +11.7° (lit.[18] m.p. 163°; $[\alpha]^{20}D$ +12°).

Anal. Calcd. for $C_{19}H_{32}O$: C, 82.54; H, 11.66. Found: C, 82.8; H, 11.6.

17β-Hydroxy-5α-androstan-2-one (IIIb).[19]—17β-Acetoxy-5α-androstan-2-one was hydrolyzed by the method described in ref. 19, and the product was recrystallized from ethyl acetate to give a 94% yield of blades, m.p. 181–183.5°, unchanged by two further recrystallizations; $[\alpha]^{25}D$ +47.6° (lit.[19] m.p. 180–181°; $[\alpha]^{20}D$ +49°).

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.6; H, 10.2.

5α-Androstane-2,17-dione.—A solution of 215 mg. of 17β-hydroxy-5α-androstan-2-one in 5 ml. of acetic acid was treated with 55 mg. of chromic oxide in 11 ml. of acetic acid at room temperature, and the solution was allowed to stand for 1 hr. The excess of chromic oxide was destroyed by addition of methanol and the solution was concentrated to a residue *in vacuo*. The residue was partitioned between water and ether, and the ether layer was separated, washed with saturated salt solution, dried over sodium sulfate, and concentrated to a residue *in vacuo*. The residue was recrystallized from a small quantity of methanol to give 141 mg. (66% yield) of the 2,17-dione, m.p. 155–156.5°. A second recrystallization of these plates raised the melting point to 155.5–157°; $[\alpha]^{25}D$ +114.6°; λ_{max}^{KBr} 5.74 and 5.87 μ (lit.[7] m.p. 152.5–154.5°; $[\alpha]^{20}D$ +119.9°).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.0; H, 9.7.

17β-Propionoxy-5α-androstan-2-one (IIIc).—17β-Hydroxy-5α-androstan-2-one (0.20 g.) was heated on the steam bath with 1 ml. of propionic anhydride and 2 ml. of pyridine for 45 min., and the mixture was poured into ice–water. The precipitated solid was collected and recrystallized twice from acetone to give white needles, m.p. 113–114°; $[\alpha]^{25}D$ +25.2°. This melting point was undepressed upon admixture with a sample of the title compound furnished by Dr. Carl Djerassi, and the infrared spectra of the samples were identical.

17β-Hydroxy-5α-androstan-2-one Dimethylketal.—The acetate of the title compound (0.40 g.) was refluxed for 2 hr. in aqueous alcoholic sodium hydroxide solution and the solution was concentrated *in vacuo* until all alcohol was removed. Water was added to the residual suspension, and the solid present was collected. It was recrystallized twice from methanol to give 0.18 g. of tablets, m.p. 185–187.5° with intumescence; λ_{max}^{KBr} 2.92, 6.85, and 6.94 μ; $[\alpha]^{25}D$ +11.1°.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78; OCH_3, 18.44. Found: C, 74.7; H, 10.4; OCH_3, 18.4.

17β-Acetoxy-5α-androstan-3-one Bis-*n*-propylmercaptole (IV).—A solution of 1.0 g. of 17β-acetoxy-5α-androstan-3-one in 20 ml. of benzene was treated with 1.5 g. of *n*-propyl mercaptan followed by 6 drops of boron trifluoride etherate. The mixture was allowed to stand for 17 hr. and was concentrated to a residue *in vacuo*. The residual oil was dissolved in ether, and the solution was washed with 2 *N* sodium hydroxide and with saturated salt solution, then dried over sodium sulfate. Concentration of the solution and recrystallization of the residue twice from methanol gave 0.65 g. (46% yield) of fine needles, m.p. 95–96.5°. Further recrystallization gave material of m.p. 97–98°; $[\alpha]^{25}D$ +22.4°.

Anal. Calcd. for $C_{27}H_{46}S_2O_2$: C, 69.47; H, 9.93; S, 13.74. Found: C, 69.3; H, 9.9; S, 13.5.

If care is exercised to restrict heating this reaction product to a minimum in the concentration operations, the yield can be raised to 78%.

Admixture of this material with the 3-mercaptole isolated from the bromo ketone–propylmercaptan reaction caused no depression in melting point, and the infrared spectra of the two samples were identical.

Gas chromatography showed a retention time of 23 min. for this mercaptole compared with 21.5 min. for 3-*n*-propylmercapto-5α-androst-2-en-17β-ol acetate.

17β-Acetoxy-2ξ-*n*-propylmercapto-5α-androstan-3-one (II).—A mixture of 16.4 g. (0.040 mole) of 2α-bromo-17β-acetoxy-5α-androstan-3-one (I) and 3.34 g. (0.044 mole) of *n*-propyl mercaptan in 250 ml. of dry *t*-butyl alcohol was refluxed for 5.5 hr., then concentrated to a residue by warming *in vacuo*. The residual oil was diluted with 25 ml. of ether and 475 ml. of pentane and poured onto 300 g. of silica gel. Only a faint odor of di-*n*-propyl disulfide was detected, and in the first fractions none of this oil was observed. The first 25 l. of eluate contained negligible material, and the first solid subsequently eluted was mushy and was discarded (less than 1 g.). The title compound was then collected and recrystallized three times to give 4.55 g. of white, massive prisms, m.p. 116–118.5°, and a second crop of 1.04 g., m.p. 113–117° (34% yield). This product had an infrared spectrum identical with that of the corresponding compound described immediately.

2,3-Bis(*n*-propylmercapto)-5α-androst-2-en-17β-ol Acetate (VI).—A mixture of 16.0 g. (0.039 mole) of 2α-bromo-17β-acetoxy-5α-androstan-3-one and 12.2 g. (0.16 mole) of *n*-propyl mercaptan in 350 ml. of dry *t*-butyl alcohol was refluxed for 5.5 hr., then concentrated to a residue by warming *in vacuo*. The residual oil was diluted with 25 ml. of ether and 475 ml. of pentane, and poured onto a silica gel column (500 g.). Elution of the column with 2 l. of 1:19 ether–pentane removed di-*n*-propyl disulfide (0.36 g., 6% yield), and the same solvent mixture removed the title compound shortly thereafter. The 10.7 g. of desired product was recrystallized from 11 ml. of absolute ethanol to give 8.7 g. (48% yield) of long, white prisms, m.p. 48–54°. Two further recrystallizations afforded 7.35 g. of material melting at 50–53.5°; $[\alpha]^{25}D$ +58.8°; λ_{max} 221 mμ (ε 5710) and 253 (5660).

Anal. Calcd. for $C_{27}H_{44}O_2S_2$: C, 69.78; H, 9.54; S, 13.80. Found: C, 69.5; H, 9.8; S, 13.8.

Further elution of the column with the same solvent afforded **17β-acetoxy-2ξ-*n*-propylmercapto-5α-androstan-3-one (II)** which was recrystallized four times from methanol to give 1.35 g. (8.5% yield) of massive prisms, m.p. 116.5–119.5°; $[\alpha]^{25}D$ +66.0°; λ_{max} mμ 248 (ε 320) and 302 (250).

Anal. Calcd. for $C_{24}H_{38}O_3S$: C, 70.89; H, 9.42; S, 7.88. Found: C, 70.8; H, 9.2; S, 8.0.

Desulfurization of 17β-Acetoxy-2ξ-*n*-propylmercapto-5α-androstan-3-one (II).—A mixture of the title compound (0.40 g.), 25 ml. of acetone, and 1 teaspoonful of Raney nickel was refluxed for 21 hr., cooled, and filtered. The filtrate was concentrated to a residue which was treated with 2 ml. of acetic anhydride and 4 ml. of pyridine at 100° for 1 hr. This solution was cooled, poured into 125 ml. of water, and the precipitated solid was collected. This crude product contained no sulfur. It was chromatographed on 20 g. of silica gel.

Elution of the column with 1:9 ether–pentane afforded 0.10 g. of one product which could not be purified by recrystallization and was not investigated further. A 1:4 ether–pentane mixture eluted a second product which was recrystallized once from methanol to furnish 0.078 g. (24% yield) of 17β-acetoxy-5α-androstan-3-one, m.p. 158.5–160° and undepressed upon admixture with an authentic sample, m.p. 159–160°. The infrared spectrum of the desulfurized product was quite similar to that of the authentic sample, the difference being due to the presence of a few extra bands in the spectrum of the reaction product.

Desulfurization of 2,3-Bis-(*n*-propylmercapto)-5α-androst-2-en-17β-ol Acetate (VI).—A teaspoonful of Raney nickel was refluxed with acetone for 2 hr., the acetone was replaced by 100 ml. of 95% undenatured alcohol, and 1.5 g. of the title compound was added. This mixture was refluxed for 12 hr., cooled, and filtered. The filtrate was concentrated to a residue which was heated on a steam bath with 3 ml. of acetic anhydride and 6 ml. of pyridine for 1 hr. This solution was poured into water and the precipitated solid was collected and recrystallized from methanol to give prisms (or needles which reverted to prisms on standing), 0.55 g., m.p. 91–94°. A second recrystallization afforded 0.47 g. of **5α-androst-2-en-17-ol acetate**, m.p. 92.5–95°; $\lambda_{max}^{CS_2}$ 5.78 and 8.00 (acetate), 6.06 μ (Δ^2). This melting point was undepressed upon admixture with an authentic sample, and the infrared spectra were quite similar except for indications of a small

(19) J. A. Edwards, P. G. Holton, J. C. Orr, L. C. Ibáñez, E. Necoechea, A. de la Roz, E. Segovia, R. Urguiza, and A. Bowers, *J. Med. Pharm. Chem.*, **6**, 174 (1963).

amount of impurity in the present sample. Gas chromatography[20] showed that the impurity was 5α-androstan-17β-ol acetate, constituting 11.5% of the sample.

2,3-Bis(*n*-propanesulfonyl)-5α-androst-2-en-17β-ol Acetate (VII).—A solution of 3.0 g. (0.0065 mole) of 2,3-bis(*n*-propylmercapto)-5α-androst-2-en-17β-ol acetate (VI) in 15 ml. of acetic acid was treated with 6 g. (0.5 mole) of 30% hydrogen peroxide in 1-g. increments. The temperature rose spontaneously to 46°, then dropped. This solution was heated at 60° for 19 hr., cooled, and poured into water. The solid which precipitated was collected, air-dried, and recrystallized from methanol to give 2.85 g. of white needles, m.p. 140.5–144.5°. Chromatography of this solid on 100 g. of silica gel using ether–pentane mixtures (finally 3:7) for elution afforded the title compound which was recrystallized from methanol to give 1.97 g. (58% yield) of needles, m.p. 147.5–149°; $[\alpha]^{25}D$ +82.8°; λ_{max} 215 mμ (ε 9300).

Anal. Calcd. for $C_{27}H_{44}O_6S_2$: C, 61.34; H, 8.39; S, 12.11. Found: C, 61.0; H, 8.4; S, 12.1.

Reaction of 2α-Bromo-5α-cholestan-3-one with *n*-Propyl Mercaptan.—A solution of 6.96 g. (0.0145 mole) of 2α-bromo-5α-cholestan-3-one and 4.40 g. (0.058 mole) of *n*-propylmercaptan in 150 ml. of chloroform was refluxed for 7 hr. and then concentrated to a residual oil by warming *in vacuo*. This oil was dissolved in 250 ml. of 1:9 ether–pentane and poured onto a column of 250 g. of silica gel. Elution of the column with 1 l. of this same solvent mixture afforded 5.64 g. of an oily mixture which is discussed subsequently. Directly following the oil from the column was 1.66 g. of 5α-cholestan-2-one which was recrystallized from acetone to give 1.45 g. (26% yield) of white blades, m.p. 127.5–130°. It melted at 128–130° after an additional recrystallization from acetone; $[\alpha]^{25}D$ +49.4° (lit.[21] m.p. 130.5–131.5°; $[\alpha]^{25}D$ +49°). Gas chromatography indicated the presence of only a trace of impurity.

Anal. Calcd. for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.8; H, 11.8.

The oily fraction above was mixed with 90 ml. of methanol, 20 ml. of methylene dichloride, 2 ml. of water, and 3 ml. of concentrated hydrochloric acid and warmed to 55° with stirring. The temperature was allowed to fall to 35° and stirring was continued for 2.5 hr. This mixture was concentrated to a residue by warming *in vacuo*, and the residual oil was dissolved in ether. The solution was washed with water and saturated sodium bicarbonate solution and concentrated to an oil.

Chromatography of this oil in 1:19 ether–pentane using 200 g. of silica gel gave a nonpolar oily mixture (3.4 g.) followed by 1.55 g. of ketonic material shown by gas chromatography to be 52% 5α-cholestan-2-one and 48% 5α-cholestan-3-one, (retention times of 14.4 and 16.4 min., respectively, at column temperature of 220°). A sample of the nonpolar oil was heated at 78° (6 mm.) for 8 hr. to remove all di-*n*-propyl disulfide. It contained 77.5% carbon, 11.4% hydrogen, and 10.8% sulfur which accounts for 99.7% of the sample; *i.e.*, no significant amount of oxygenated material was present.

The nonpolar oil was then dissolved in 60 ml. of *t*-butyl alcohol, treated with gaseous hydrogen bromide for 5 min., and heated under reflux for 1 hr. Two layers developed. The mixture was concentrated to a residue which was chromatographed on 200 g. of silica gel in 1:19 ether–pentane. The nonpolar oil obtained here amounted to 0.7 g. after all di-*n*-propyl disulfide had been evaporated from it. The ketonic fraction (1.71 g.) was shown by gas chromatography to contain 5% 5α-cholestan-2-one and 95% 5α-cholestan-3-one.

The two hydrolytic steps just described furnished 0.89 g. (16% yield) of 2-ketone and 2.37 g. (42% yield, a total yield) of 3-ketone. The total yield of 5α-cholestan-2-one was 42%.

Reaction of 17β-Acetoxy-2ξ-(*n*-propylmercapto)-5α-androstan-3-one (II) with *n*-Propyl Mercaptan and Hydrogen Bromide.—A solution of 1.50 g. (0.0037 mole) of 17β-acetoxy-2ξ-(*n*-propylmercapto)-5α-androstan-3-one, m.p. 116.5–118.5°, and 1.5 g. (0.02 mole) of *n*-propyl mercaptan in 25 ml. of chloroform was saturated with dry hydrogen bromide and then refluxed under nitrogen for 6 hr. Concentration of the reaction mixture by warming *in vacuo* gave an oil which was chromatographed on 40 g. of silica gel. Elution with 1:19 ether–pentane afforded an early oil fraction which weighed 0.52 g. following evaporation of all dipropyl disulfide present. This oil is discussed after the next paragraph.

Following the oil from the column was 0.40 g. (33% yield) of 17β-acetoxy-5α-androstan-2-one (IIIa) which came off in 1:4 ether–pentane. This product was shown by gas chromatography to contain no 3-ketone. No other peaks were noted. One recrystallization from acetone afforded 0.29 g. (24% yield) of 2-ketone (IIIa), m.p. 148.5–150°, identified by mixture melting point and infrared spectral comparison with authentic material.

The 0.52 g. of nonpolar oil was refluxed with 25 ml. of 95% ethanol, 3 ml. of water, and 1 ml. of concentrated hydrochloric acid for 2.5 hr. The mixture was concentrated to a residue by warming *in vacuo*, and the residue was dissolved in ether. This solution was washed with water, dried over sodium sulfate, and concentrated to a residue which was chromatographed on 40 g. of silica gel using 1:19 ether–pentane gradually changed to 2:3 ether–pentane for elution. The major fractions which showed similar infrared spectra were combined (largely 17β-hydroxy-5α-androstan-2-one at this point) and treated with 1.5 ml. of acetic anhydride and 3.0 ml. of pyridine at 100° for 1 hr. The solution was poured into water, the solid precipitate was collected and dissolved in ether, and the ether solution was washed with dilute hydrochloric acid and saturated sodium bicarbonate solution, then dried over sodium sulfate. Concentration of the solution and recrystallization of the residue once from acetone, gave 53 mg. (4%) more of 17β-acetoxy-5α-androstan-2-one (IIIa), m.p. 146–148°, identified by mixture melting point and infrared spectral comparison. The total yield of 2-ketone was 28%.

Reaction of 2,3-Bis(*n*-propylmercapto)-5α-androst-2-en-17β-ol Acetate (VI) with *n*-Propyl Mercaptan in the Presence of Hydrogen Bromide and Water.—A solution of 2.8 g. (0.006 mole) of 2,3-bis(*n*-propylmercapto)-5α-androst-2-en-17β-ol acetate (VI) and 1.0 g. (0.013 mole) of *n*-propyl mercaptan in 50 ml. of chloroform was treated with 0.22 g. (0.012 mole) of water and with gaseous hydrogen bromide for 5 min. This mixture was refluxed for 5 hr. and then concentrated by warming *in vacuo*. The residual oil was heated at 100° for 1 hr. with 7 ml. of acetic anhydride and 14 ml. of pyridine, cooled, and poured into 400 ml. of water. Extraction of this mixture with ether, washing of the extracts with dilute hydrochloric acid and with saturated sodium bicarbonate solution, and drying (sodium sulfate) followed by concentration of the solution, gave an oil which was chromatographed on 75 g. of silica gel. Elution of the column with 1:9 ether–pentane removed nonpolar products including di-*n*-propyl disulfide and elution with 1:4 ether–pentane gave 1.22 g. of ketonic material which was shown by gas chromatography to contain 80% **17β-acetoxy-5α-androstan-2-one (IIIa)** (retention time, 23 min.) and 20% **17β-acetoxy-5α-androstan-3-one** (retention time, 27 min.) with 0.2% impurities. These amounts represent a 48% yield of 2-ketone and 13% of 3-ketone.

Reaction of 2,3-Bis(*n*-propylmercapto)-5α-androst-2-en-17β-ol Acetate (VI) with *n*-Propyl Mercaptan in the Presence of Hydrogen Bromide without Water.—The chloroform used in this experiment was washed with sulfuric acid and water, dried over calcium chloride, and distilled. A solution of 4.40 g. (0.0095 mole) of 2,3-bis(*n*-propylmercapto)-5α-androst-2-en-17β-ol acetate (VI) in 50 ml. of chloroform was treated with gaseous hydrogen bromide for 2 min. *n*-Propyl mercaptan (1.82 g., 0.025 mole) was added, the system was flushed with nitrogen, and the solution was refluxed for 5 hr. Removal of volatile material by warming to 35° under 6-mm. pressure gave an oily residue.

Gas chromatography of the oil showed two peaks, one with a retention time of 21.5 min. (62% of the total) which corresponds to **2- and 3-*n*-propylmercapto-5α-androst-2-en-17β-ol acetate (VIII and IX)**, and the other with a retention time of 23.0 min. (32% of the total) which corresponds to 17β-acetoxy-5α-androstan-3-one bis-*n*-propylmercaptole (IV) or 17β-acetoxy-5α-androstan-2-one (IIIa). No carbonyl band other than that for acetate (5.76) could be demonstrated in this oil with the Beckman IR-7 infrared spectrophotometer. The di-*n*-propyl disulfide present came off the gas chromatograph with the solvent. The 6% of material not represented by the aforementioned two peaks was accounted for by several minor peaks.

Chromatography of the oil on 250 g. of silica gel (without neutralization of residual hydrogen bromide) using pentane as an eluent gave 1.20 g. of di-*n*-propyl disulfide which was 93% pure by sulfur analysis. Its infrared spectrum was identical with that

(20) The column used here was 4 ft. long, 1/8-in. o.d., and was packed with 3% neopentyl glycol adipate (terminated) on 80–90-mesh Anakrom ABS (Analabs, Hamden, Conn.). Helium was used as the carrier gas under 40-p.s.i.g. pressure with a flow-rate of 46 ml. per min. The column was operated at 180° with the injection port at 275° and the detector at 215°.

(21) L. Ruzicka, Pl. A. Plattner, and M. Furrer, *Helv. Chim. Acta*, **27**, 524 (1944).

of an authentic sample. The corrected yield was 80%. A mixture of 2% ether–98% pentane eluted 0.66 g. of oil which solidified. It was recrystallized twice from methanol to give 0.30 g. (7% yield) of 17β-hydroxy-5α-androstan-3-one acetate bis-*n*-propylmercaptole (IV), m.p. 97.5–98.5°, and undepressed upon admixture with an authentic sample.

The mercaptole IV was followed from the column by oily mixtures of IV with another compound or compounds which showed as a second strong spot on a thin layer chromatogram.[22] Hydrolysis of some of the later fractions of this oil (0.59 g.) using 2 ml. of 1:1 hydrochloric acid–water, 25 ml. of methanol, and 10 ml. of methylene dichloride at 50° for 2 hr. gave 0.45 g. of solid which was shown by gas chromatography to consist of 75% 17β-acetoxy-5α-androstan-2-one (IIIa) and 21% 17β-hydroxy-5α-androstan-3-one.

Elution of the column with 100% ether then afforded 1.14 g. of ketonic material (36% yield) which was shown by gas chromatography to consist of 87% 2-ketone (IIIa) and 13% 3-ketone.

Stability of 2,3-Bis(*n*-propylmercapto)-5α-androst-2-en-17β-ol Acetate (VI) to *n*-Propyl Mercaptan in Neutral Medium.—A solution of 1.0 g. of 2,3-bis(*n*-propylmercapto)-5α-androst-2-en-17β-ol acetate, m.p. 50–53°, and 1.0 g. of *n*-propyl mercaptan in 25 ml. of benzene was refluxed under nitrogen for 5 hr. and then concentrated to a residual oil by warming *in vacuo*. The characteristic odor of di-*n*-propyl disulfide was not detected. The oil solidified and was recrystallized from 2 ml. of absolute ethanol to give 0.90 g. (90% recovery) of massive prisms, m.p. 50–52°, and undepressed upon admixture with starting material. The infrared spectra of the two samples were identical.

17β-Acetoxy-5α-androstan-3-one Di-*n*-propylmercaptole (IV) from 3-*n*-Propylmercapto-5α-androst-2-en-17β-ol Acetate (IX).—A solution of 0.30 g. of 3-*n*-propylmercapto-5α-androst-2-en-17β-ol acetate (IX) in 15 ml. of chloroform at room temperature was treated with gaseous hydrogen bromide for 15 sec. and then with 0.3 g. of *n*-propyl mercaptan. This solution was allowed to stand for 24 hr., concentrated to a residue *in vacuo*, and diluted with ether. The ether solution was washed with 10% sodium carbonate solution, dried over sodium sulfate, and concentrated to a residue which solidified. Recrystallization of the solid three times from methanol containing a trace of pyridine afforded 0.13 g. (37% yield) of 17β-acetoxy-5α-androstan-3-one di-*n*-propylmercaptole (IV), m.p. 94.5–96°, and undepressed upon admixture with an authentic sample. The infrared spectra of the two samples were identical.

3-*n*-Propylmercapto-5α-androst-2-en-17β-ol Acetate (IX).—A solution of 9.58 g. of 17β-acetoxy-5α-androstan-3-one di-*n*-propylmercaptole (IV) and 0.3 g. of *p*-toluenesulfonic acid monohydrate in 100 ml. of benzene was boiled slowly for 4 hr. with the vapors escaping through a 10-in. Vigreux column. Fresh benzene was added occasionally to maintain the volume. The solvent was then removed by warming *in vacuo*, the residual oil was dissolved in ether, and this solution was washed with dilute sodium hydroxide solution and dried over sodium sulfate. Removal of solvent gave a pasty solid which was triturated with one 5-ml. portion and three 2-ml. portions of methanol containing a trace of pyridine. The resulting powdery solid was recrystallized from 45 ml. of methanol to give 1.7 g. (21% yield) of the title compound, m.p. 76–77.5°. A single further recrystallization gave the analytical sample, m.p. 77–78.5°; $[\alpha]^{25}D$ +60.6°; λ_{max} 223 mμ (ε 4900) and 238–243 sh (3500).

Anal. Calcd. for $C_{24}H_{38}O_2S$: C, 73.80; H, 9.81; S, 8.20. Found: C, 73.6; H, 9.7; S, 8.3.

3-*n*-Propanesulfonyl-5α-androst-2-en-17β-ol Acetate.—A stirred solution of 4.2 g. (0.011 mole) of 3-*n*-propylmercapto-5α-androst-2-en-17β-ol acetate in 50 ml. of ether at −30° was treated with 93 ml. (0.051 mole) of an ethereal solution of monoperphthalic acid which contained 100 mg. of peracid per ml. of solution. The resulting solution was allowed to warm to room temperature and stand for 6 days, was filtered, and the filtrate was washed with 10% sodium carbonate, dried over sodium sulfate, and concentrated to a residual oil which solidified. Two recrystallizations from methanol afforded 2.68 g. (59% yield) of colorless needles, m.p. 120–129°. The product was recrystallized twice more from methanol with drying at 78° (1 mm.) for 8 hr. to give material which melted at 121–129°; $[\alpha]^{25}D$ +45.4°; ultraviolet showed end absorption only. This melting point was 124–129° in an evacuated capillary tube.

Anal. Calcd. for $C_{24}H_{38}O_4S$: C, 68.21; H, 9.06; S, 7.59. Found: C, 67.9; H, 9.3; S, 7.8.

Reaction of 17β-Acetoxy-5α-androstan-2-one (IIIa) with *n*-Propyl Mercaptan.—A solution of 2.0 g. of 17β-acetoxy-5α-androstan-2-one (IIIa) and 2.0 g. of *n*-propyl mercaptan in 30 ml. of benzene was treated with 4 drops of boron trifluoride etherate and allowed to stand for 48 hr. Water droplets separated from solution. The mixture was concentrated to a residue by warming at <35° *in vacuo*, the residue was dissolved in ether, and this solution was washed with 2 *N* sodium hydroxide solution, then dried over sodium sulfate. Concentration of the ether solution gave an oil which was dissolved in 10 ml. of pentane. A solid precipitated which was collected and washed with two 5-ml. portions of cold pentane. This solid, 0.87 g., melted at 148.5–150° and represents a 43% recovery of starting material. It was identified by infrared spectral comparison with starting material.

The filtrate was concentrated to a residual oil which solidified when chilled. This solid was slurried with 5 ml. of cold methanol containing a trace of pyridine and the solid was collected. It was then crystallized from 10 ml. of methanol containing a drop of pyridine to give 0.58 g. (25% yield) of colorless needles of **2-*n*-propylmercapto-5α-androst-2-en-17β-ol acetate (VIII)**, m.p. 59–60.5°. A second recrystallization from the same solvent gave material which melted at 60.5–62°, resolidified, and then melted at 70.0–70.5°; $[\alpha]^{25}D$ +52.2°, λ_{max} 223 mμ (ε 4200), 238–243 sh (3100).

Anal. Calcd. for $C_{24}H_{38}O_2S$: C, 73.80; H, 9.81; S, 8.20. Found: C, 74.1; H, 9.5; S, 8.4.

2-*n*-Propanesulfonyl-5α-androst-2-en-17β-ol acetate was prepared from 2-*n*-propylmercapto-5α-androst-2-en-17β-ol acetate (2.7 g., 0.0069 mole) and 0.035 mole of ethereal perphthalic acid according to the procedure used for the the preparation of 3-*n*-propanesulfonyl-5α-androst-2-en-17β-ol acetate. The product was recrystallized twice from methanol to give 1.15 g. (39% yield) of analytically pure material, m.p. 185–187°; $[\alpha]^{25}D$ +45.4°; ultraviolet end absorption only.

Anal. Calcd. for $C_{24}H_{38}O_4S$: C, 68.21; H, 9.06; S, 7.59. Found: C, 68.1; H, 9.1; S, 7.6.

Preparation of 17β-Acetoxy-5α-androstan-2-one under Optimum Conditions.—A mixture of 157.5 g. (0.384 mole) of 17β-acetoxy-2α-bromo-5α-androstan-3-one, 118.5 g. (1.55 moles) of *n*-propyl mercaptan and 1750 ml. of chloroform was refluxed in a nitrogen atmosphere for 14 hr. and then concentrated *in vacuo* to a residual oil. This oil was dissolved in a mixture of 1 l. of methanol, 50 ml. of concentrated hydrochloride acid, and 50 ml. of water. The resultant cloudy solution was refluxed with stirring for 4 hr. During this reflux period, 10-ml. portions of water were added every 15 min. Finally, 1.5 l. of water was added, and the mixture was distilled at the water pump. As the volume of the still pot contents diminished, 5% aqueous hydrochloric acid was added to maintain approximately the original volume. After 8 l. of distillate had been collected, no further oily droplets could be observed codistilling with the water. The pot contents were cooled, and the solid material was collected and dried.

The solid material was heated for 1 hr. with 250 ml. of acetic anhydride and 500 ml. of pyridine, and the cooled mixture was poured into 10 l. of cold water. The precipitated solid was collected and air-dried.

A solution of the solid reaction product in 3 l. of boiling methanol was treated with a solution of 450 g. of sodium metabisulfite in 2.2 l. of water at 25°. This mixture was stirred for 15 min. and then diluted with 2.5 l. of methylene dichloride and 2.5 l. of water. Stirring was continued for 15 min. The mixture was filtered, the layers of the filtrate were separated, and the water layer and the solid were set aside. The organic layer was dried over sodium sulfate and concentrated to a solid residue. This residue was dissolved in 250 ml. of acetone and 250 ml. of hexane, the solution was treated with "Darco G-60," and filtered, and the filtrate was concentrated to a 100-ml. volume. Cooling afforded 50 g. (39% yield) of **17β-acetoxy-5α-androstan-2-one**, m.p. 147–150°. Further recrystallization of the product and reworking of the mother liquors gave a 41.5% yield of material melting at 150–151°.

The water layer and the solid which were set aside in the bisulfite separation just described were combined, treated with 4 l. of methylene dichloride and 500 g. of sodium bicarbonate, and heated for 5 hr. under reflux. The mixture was cooled, filtered,

(22) Development of this silica gel-coated plate was done with 1:19 ether–pentane.

and the methylene dichloride layer of the filtrate was dried over sodium sulfate. This solution was concentrated to a residual solid which was heated for 1 hr. with 50 ml. of acetic anhydride and 100 ml. of pyridine. Cooling of the reaction mixture and dilution with 3 l. of cold water gave a solid which was recrystallized once from ethyl acetate. The **17β-acetoxy-5α-androstan-3-one** so obtained (62 g., 49% yield) melted at 156–159°. Its identity was confirmed by infrared spectral comparison with an authentic sample.

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9α-Fluoro-11-deoxy Steroids[1]

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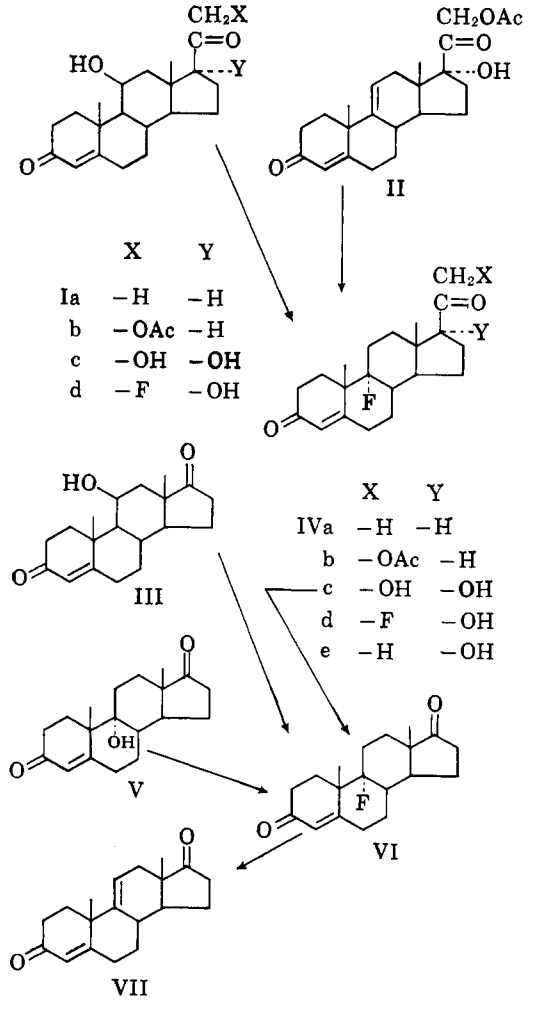
The treatment of a 9α- or 11β-hydroxy or a 9(11)-dehydro steroid with a 70% solution of hydrogen fluoride in pyridine resulted in the introduction of fluorine at 9α. Preliminary biological evaluation of representative compounds indicated activity similar to or greater than that of the 9α-hydrogen analog. 9α-Fluorodeoxycorticosterone acetate was twelve times as potent as deoxycorticosterone acetate as a salt retainer.

The great increase in the biological activity of the antiinflammatory corticoids resulting from the introduction of a 9α-fluoro group into these molecules has prompted the introduction of this group into many of the other steroid hormones. In all previous examples the 9α-fluoro group was accompanied by the introduction of an additional group (−OH,[2] halogen[3,4]) into ring C. In fact, it has been postulated[3,4] that the influence of the 9α-fluoro group on biological activity is mediated through its inductive effect on the adjacent oxygen function. Here, we report the synthesis of 9α-fluoro steroidal hormones devoid of other substituents in ring C. The increased biological activity of many of these compounds over that of the parent compounds clearly indicates that the influence of the 9α-fluoro group is not necessarily mediated through an adjacent oxygen function.

These new compounds resulted from a study of the reactions of a solution of pyridine in anhydrous hydrogen fluoride. When anhydrous hydrogen fluoride was bubbled into pyridine a clear straw-colored solution resulted which at least to outward appearances was stable at room temperature for months. The reagent began to fume strongly when the concentration of hydrogen fluoride was about 70% by weight, and it was this material which was used in the work to be described. Originally the interest in the hydrogen fluoride–pyridine solution resided in its possible use in the preparation of 9α-fluoro-11β-hydroxy steroids from 9β,11β-epoxides.[5] The results of these experiments were very discouraging. The reagent also was used in a study of the dehydration of 11β-hydroxy steroids and while the yields of 9(11)-dehydro steroids were poor, new fluorine-containing products were discovered.

When hydrocortisone acetate (Ic-acetate) was treated with hydrogen flouride-pyridine reagent, only the dehydration product II could be isolated by crystallization or chromatography. If, however, the mixture was treated with hypobromous acid followed by potassium acetate, thus converting the 9(11)-double bond to the 9β,11β-epoxide, it was possible by chromatography to separate from this mixture the least polar component, 9α-fluoro-17α,21-dihydroxy-4-pregnene-3,20-dione 21-acetate (IVc-acetate). This same fluoro compound was produced by the addition of hydrogen fluoride to 17α,21-dihydroxy-4,9(11)-pregnadiene-3,20-dione 21-acetate (II) but in even poorer yield. The protection



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