[CONTRIBUTION FROM THE MEDICAL RESEARCH LABORATORY, DEPARTMENT OF MEDICINE, VETERANS ADMINISTRATION HOSPITAL, AND THE DEPARTMENT OF BIOCHEMISTRY, INDIANA UNIVERSITY SCHOOL OF MEDICINE]

Seroflocculants in the Androstane Series

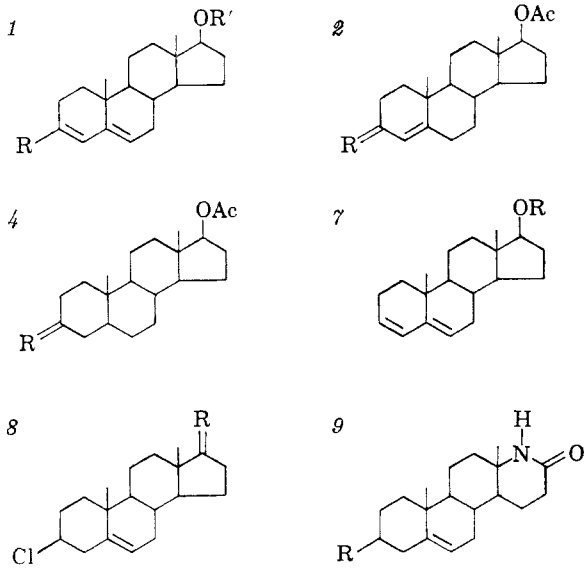
ROBERT T. BLICKENSTAFF AND EMERSON L. FOSTER

Received June 14, 1961

Testosterone esters were converted to dienethiol ethers and dithioketals with mono- and dithiols, respectively. Dithioketals were obtained also from the reaction of both mono- and dithiols with steroidal ketones lacking α,β-unsaturation. Some *N*-containing derivatives of 3β-chloro-5-androsten-17-one were prepared, including the ring D lactam. 3,3-Bisethylthio-5α-androstan-17β-yl acetate (*4b*), 3,3-bisallylthio-5α-androstan-17β-yl acetate (*4c*), and 3,5-androstadien-17β-yl phenylacetate (*7e*) are highly active seroflocculating agents.

In connection with our general interest in reactions of thiols with keto steroids, we repeated the preparation of 3-benzylthio-3,5-androstandien-17β-yl acetate (*1a*).[1] When this thio ether was found to have modest activity in a seroflocculation reaction with cancer sera,[2] analogous thio ethers and dithioketals were prepared and similarly tested. In addition, because of the reported increase in androstenolone excretion associated with adrenal tumor,[3] and because androstenolone is easily converted in one step to 3β-chloro-5-androsten-17-one (which is structurally related to ethyl 3β-chloro-5-bisnorcholenate,[4] a known seroflocculant), several derivatives of the chloro ketone were prepared. This paper described the synthesis and screening of these and related compounds.

Oxidation of 3-benzylthio-3,5-androstadien-17β-yl acetate (*1a*) with hydrogen peroxide gave the sulfoxide *1b*. Thiophenol condensed with testosterone acetate in the presence of boron trifluoride ether complex to give 3-phenylthio-3,5-androstadien-17β-yl acetate (*1c*). Testosterone reacted with ethanethiol in the presence of *p*-toluenesulfonic acid and formic acid to produce 3-ethylthio-3,5-androstadien-17β-yl formate (*1e*), which was readily hydrolyzed under alkaline conditions to 3-ethylthio-3,5-androstadien-17β-ol (*1d*).[5] Cholestenone is known to react with ethanethiol in acetic acid and hydrochloric acid to give 3-ethylthio-3,5-cholestadiene[6]; under the same conditions, testosterone benzoate gave 3-ethylthio-3,5-androstadien-17β-yl benzoate (*1f*).[7]



1a. R = $PhCH_2S$; R′ = Ac
b. R = $PhCH_2SO$; R′ = Ac
c. R = PhS; R′ = Ac
d. R = C_2H_5S; R′ = H
e. R = C_2H_5S; R′ = OCH
f. R = C_2H_5S; R′ = Bz

4a. R = O
b. R = $(C_2H_5S)_2$
c. R = $(CH_2{=}CHCH_2S)_2$
d. R = SCH_2CH_2S
e. R = SCH_2CH_2O
f. R = SCH_2CHNH (|) $CO_2C_2H_5$

8a. R = O
b. R = $NNHC_6H_3(NO_2)_2$
c. R = SCH_2CH_2S
d. R = NOH
e. R = $NOCH_2CO_2H$
f. R = $NOCH_2CO_2C_2H_5$

2a. R = O
b. R = SCH_2CH_2S
c. R = $SCH_2CH_2CH_2S$
d. R = H_2

7a. R = H
b. R = Ac
c. R = $OCCH_2CH_3$
d. R = Bz
e. R = $OCCH_2Ph$

9a. R = Cl
b. R = OH
c. R = OAc

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

(2) F. C. Chang, *et al.*, *J. Am. Chem. Soc.*, **79**, 2161 (1957).

(3) J. K. Wolfe, L. F. Fieser, and H. B. Friedgood, *J. Am. Chem. Soc.*, **63**, 582 (1941); A. C. Crooke and R. K. Callow, *Quart. J. Med.*, **8**, 233 (1939).

(4) F. C. Chang, *et al.*, *J. Am. Chem. Soc.*, **79**, 2164 (1957).

(5) This compound is reported in a patent [Kereszty, Wolf, and Foldi Zoltan, Hung. Patent No. **135,687**, Sept. 24 (1949)] to have a melting point and optical rotation similar to our formate *1e*. That *1e* is, indeed, the formate is clearly shown by its elemental analysis and its infrared spectrum (ester carbonyl at 5.75 μ). Interestingly, in our hands thio ether formation failed to occur when the reaction was attempted in ethyl formate, as described in the patent, but proceeded satisfactorily in formic acid, as perceived by the abstracter [*Chem. Abs.*, **44**, 4047 (1950)].

(6) J. W. Ralls, R. M. Dodson, and Byron Riegel, *J. Am. Chem. Soc.*, **71**, 3320 (1949).

(7) A parallel experiment with testosterone acetate produced a low yield of 3,3-bisethylthio-5-androsten-17β-yl acetate, m.p. 127° (identified by analysis and its desulfurization to 5-androsten-17β-yl acetate), and similarly small proportions of two other unidentified, *S*-containing products. The contrasting, high-yield formation of 3-ethylthio-3,5-cholestadiene and 3-ethylthio-3,5-androstadien-17β-yl benzoate may be a result of their sufficiently low solubility that they crystallize out of the reaction medium, driving the reaction to completion.

Boron trifluoride ether complex was employed[8] in the preparation of the cyclic dithioketals (*2b* and *2c*) of testosterone acetate and (*3b*) of 9(11)-dehydrotestosterone acetate (*3a*). The trimethylenedithioketal (*2c*) was desulfurized with Raney nickel to 4-androsten-17β-yl acetate (*2d*), which appears to be dimorphous.

A series with the allo configuration was prepared similarly from 3-keto-5α-androstan-17β-yl acetate (*4a*). In acetic acid, ethanethiol and hydrochloric acid gave the dithioketal *4b*, while allyl mercaptan and boron trifluoride ether complex gave the dithioketal *4c*.[9] With the latter catalyst, 3-keto-5α-androstan-17β-yl acetate was converted to the ethylenedithioketal *4d* and the ethylenemonothioketal *4e*. Ethyl L-cysteinate hydrochloride, and *4a* in pyridine gave the thiazolidine *4f*, apparently in only one of the two possible diasterieomeric forms, as is the case with other steroid thiazolidines.[10] In the light of the broad melting range of the ethylenemonothioketal *4e*, however, both diasteriomers may have been obtained in this case.

Reduction of 3,5-androstadien-17-one (*6*)[11] with lithium aluminum hydride gave 3,5-androstadien-17β-ol (*7a*), which was converted to the known acetate *7b*, the propionate *7c*, the benzoate *7d*, and the phenylacetate *7e*. The benzoate was prepared also by dehydrotosylation of 3β-tosyloxy-5-androsten-17β-yl benzoate (*5*).

3β-Chloro-5-androsten-17-one (*8a*), from the chlorination of androstenolone with thionyl chloride, was converted to the *O*-carboxymethyl oxime *8e* by the method of Erlanger,[12] and the acid was easily esterified with ethanol and concentrated hydrochloric acid at room temperature. Beckmann rearrangement of 3β-chloro-5-androsten-17-one oxime (*8d*) gave the chloro lactam *9a*, which was synthesized alternatively by chlorination of 3β-hydroxy-5-androsten-17α-lactam (*9b*), obtained from the acetate *9c*.[13] The rearrangement reaction is accompanied by the appearance of a lactam C=O band in the infrared spectrum (5.90 μ),[14] and the simultaneous loss of a band for the oxime hydroxyl group (3.91 μ).

When screened in a seroflocculation reaction[2] against cancer and normal sera, compounds *4b*, *4c*, and *7e* were found to be very active. Compounds *1a* and *8f* are moderately active, *1e*, *2a*, *2d*, *3a*, *6a*, *7b*, *7c*, *7d*, testosterone, and 9(11)-dehydrotestosterone are inactive, and nearly all the rest are too insoluble to be tested. The active compounds represent the first examples of seroflocculating activity among steroids with the allo configuration, among simple derivatives of C_{19} steroids, among dienethiol ethers and dithioketals, and among *N*-containing steroids.

EXPERIMENTAL[15]

3-Benzylsulfinyl-3,5-androstadien-17β-yl acetate (1b). A saturated aqueous solution of sodium carbonate (0.5 ml.), then 1.5 ml. of 30% hydrogen peroxide were added to a solution of 250 mg. of 3-benzylthio-3,5-androstadien-17β-yl acetate (*1a*)[1] in 15 ml. of warm ethanol. After heating on the steam bath for 15 min., the hot solution was filtered. Dilution of the filtrate with 50 ml. of water precipitated 236 mg. of crude product. One recrystallization in methanol gave small prisms, m.p. 192.8–196.8°, $[\alpha]_D$ −197° (1%), $\lambda_{max}^{CH_3OH}$ 260 mμ, λ_{max}^{Nujol} 5.74, 6.04, 8.01, 9.42, 9.68, 12.86, 14.2 μ.

Anal. Calcd. for $C_{28}H_{36}O_3S$: C, 74.29; H, 8.02; S, 7.09. Found: C, 74.28; H, 7.88; S, 7.04.

3-Phenylthio-3,5-androstadien-17β-yl acetate (1c). A clear solution of 1.00 g. of testosterone acetate, 1 ml. of thiophenol, and 1 ml. of 47% boron trifluoride-ether complex in 20 ml. of glacial acetic acid was kept at room temperature overnight, then poured onto crushed ice. The precipitate was filtered, washed with water and cold methanol, dried, and recrystallized in benzene-methanol (1:5) to give 520 mg. of product, m.p. 148–157°. The analytical sample crystallized from benzene-methanol (2:3) as a mixture of plates and laths, m.p. 154.8–158.2°, $[\alpha]_D$ −259°, $\lambda_{max}^{CH_3OH}$ 259 mμ, λ_{max}^{Nujol} 5.72, 6.26, 7.95, 9.49, 9.61, 11.21, 13.45, 14.4 μ.

Anal. Calcd. for $C_{27}H_{34}O_2S$: C, 76.73; H, 8.11; S, 7.59. Found: C, 77.02; H, 8.14; S, 7.55.

3-Ethylthio-3,5-androstadien-17β-ol (1d). Alkaline hydrolysis of the formate *1e* gave a product which crystallized from acetone-water (5:3), containing a drop of pyridine, in the form of fine needles, m.p. 128.6–130.4°, $[\alpha]_D$ −156° (lit.,[5] m.p. 112°, $[\alpha]_D$ −200°), $\lambda_{max}^{CH_3OH}$ 270 mμ, λ_{max}^{Nujol} 2.93, 9.41, 11.09, 13.80 μ.

(8) L. F. Fieser, *J. Am. Chem. Soc.*, 76, 1945 (1954).

(9) A second, high *S*-containing product also formed and was separated chromatographically (see Experimental).

(10) Seymour Lieberman, Paul Brazeau, and L. B. Hariton, *J. Am. Chem. Soc.*, 70, 3094 (1948).

(11) Prepared by dehydration of androstenolone with P_2O_5 [W. C. J. Ross, *J. Chem. Soc.*, 25 (1945)]. Reaction of this ketone with ethanedithiol and boron trifluoride gave a product crystallizing from ethyl acetate as platelets, m.p. 185–189°, $[\alpha]_D$ +145° (1.7% in benzene). It is not the anticipated ethylenedithioketal for it lacks the 3,5-diene system. A corresponding reaction between ethanedithiol and 3,5-cholestadiene gave a noncrystalline product, $[\alpha]_D$ +77° (1.2% in benzene), which gives an analysis corresponding to $(C_{28}H_{47}S)_x$, and which is desulfurized by Raney nickel to 4-cholestene. These products may be 1,2-bisthioethers of ethanedithiol formed by 1,4-addition of —SH across the 3,5-diene system.

(12) B. F. Erlanger, F. Borek, S. M. Beiser, and S. Lieberman, *J. Biol. Chem.*, 234, 1090 (1959).

(13) B. M. Regan and F. N. Hayes, *J. Am. Chem. Soc.*, 78, 639 (1956).

(14) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Wiley, New York, 1958, p. 213.

(15) Microanalyses are by Galbraith Laboratories, Knoxville, Tenn. Melting points were taken on an electrical hot-stage and are uncorrected. The ligroin used in chromatography was petroleum ether (b.p. 60–68°), purified by sulfuric acid treatment and distillation. Optical rotations were determined in 2% benzene solutions (unless otherwise indicated) at about 25°, using a Keston polarimeter attachment to a Beckman DU spectrophotometer. Ultraviolet spectra were determined with a Beckman DK spectrophotometer on solutions having a concentration of 10 mg. per L. Infrared spectra were determined on an Infracord; medium and strong bands are reported (except for common C—H stretching and bending bands). In the seroflocculation testing, dimethylformamide was used throughout as the organic solvent, rather than alcohol as described previously (ref. 2).

Anal. Calcd. for $C_{21}H_{32}OS$: C, 75.85; H, 9.70; S, 9.64. Found: C, 76.13; H, 9.98; S, 9.40.

The formate 1e was prepared by swirling a mixture of 0.17 ml. of ethanethiol, 376 mg. of testosterone, 120 mg. of *p*-toluenesulfonic acid, and 0.2 ml. of 88% formic acid for several minutes, until a clear solution resulted. The mixture stood at room temperature for 3 hr., during which time crystals formed. It was diluted with 2 ml. of methanol, 4 drops of pyridine, and 0.6 ml. of water and filtered. The crude product was recrystallized in methanol to give 260 mg. of product, m.p. 107–113°. The analytical sample crystallized from methanol and a trace of pyridine in the form of laths, m.p. 108.6–113.6°, $[\alpha]_D$ −210°, λ_{max}^{ether} 271 mμ, λ_{max}^{Nujol} 5.75, 6.21, 8.4, 9.59, 10.02, 10.30, 10.41, 11.48, 13.11 μ.

Anal. Calcd. for $C_{22}H_{32}O_2S$: C, 73.28; H, 8.95; S, 8.89. Found: C, 73.30; H, 9.05; S, 8.90.

The benzoate 1f. Crystals of the crude product began forming immediately after 10 drops of concd. hydrochloric acid were added to a solution of 500 mg. of testosterone benzoate and 1 ml. of ethanethiol in 10 ml. of glacial acetic acid. The mixture was kept at room temperature for 2 hr., refrigerated overnight, and filtered. The crude product, 485 mg., m.p. 175–180°, was recrystallized in benzene-methanol (7:10) to give plates, m.p. 184.0–190.6°. The analytical sample crystallized from dimethylformamide as platelets, m.p. 186.4–190.2°, $[\alpha]_D$ −84°, λ_{max}^{ether} 227, 271 mμ, λ_{max}^{Nujol} 5.81, 7.82, 8.95, 11.44, 14.04 μ.

Anal. Calcd. for $C_{28}H_{36}O_2S$: C, 77.02; H, 8.31; S, 7.34. Found: C, 77.03; H, 8.27; S, 7.25.

Testosterone acetate ethylenedithioketal (2b). Under the conditions described by Fieser,[8] 1.00 g. of testosterone acetate, 0.3 ml. of ethanedithiol and 1 ml. of 47% boron-trifluoride–ether complex in 20 ml. of glacial acetic acid gave 1.10 g. of product m.p. 196–212°. Recrystallization in benzene-methanol (2:3) and in acetone containing pyridine gave large rods, m.p. 214.0–218.5°, $[\alpha]_D$ +137°, λ_{max}^{Nujol} 5.72, 7.92, 9.55, 9.75, 9.90, 11.56, 11.66, 11.84, 12.00 μ.

Anal. Calcd. for $C_{23}H_{34}O_2S_2$: C, 67.93; H, 8.42; S, 15.77. Found: C, 68.09; H, 8.34; S, 15.55.

Testosterone acetate trimethylenedithioketal (2c). A similar preparation employing 1,3-propanedithiol gave 908 mg. of product m.p. 180–186°. The analytical sample crystallized from dimethylformamide-water (10:1) in the form of small prisms, m.p. 188.2–190.6°, $[\alpha]_D$ +113°, λ_{max}^{Nujol} 5.70, 7.90, 11.51 μ.

Anal. Calcd. for $C_{24}H_{36}O_2S_2$: C, 68.52; H, 8.65; S, 15.25. Found: C, 68.27; H, 8.58; S, 15.39.

4-Androsten-17β-yl acetate (2d). Desulfurization of the dithioketal (*2c*) according to the method of Rosenkranz *et al.*,[1] gave an oil which was chromatographed on alumina and eluted with ligroin. Recrystallization in methanol gave laths which in part melted and resolidified from 100 to 111°, then melted completely at 111–113.0°, (lit.[16] m.p. 97–100°), $[\alpha]_D$ +71° (1.3%), λ_{max}^{Nujol} 5.70, 8.01, 9.53, 9.74 μ.

3-Keto-4,9(11)-androstadien-17β-yl acetate[17] *(3a).* Esterification of 9-dehydrotestosterone with glacial acetic acid and concentrated hydrochloric acid gave platelets which crystallized out of methanol-water (10:1) or acetone-water (10:1) m.p. 138.2–140.2° $[\alpha]_D$ +50° (chloroform), λ_{max}^{KBr} 5.72, 5.91, 8.11, 9.46, 9.56, 9.71 μ.

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 76.80; H, 8.59. Found: C, 77.14; H, 8.37.

3-Keto-4,9(11)-androstadien-17β-yl acetate trimethylenedithioketal (3b). Under conditions similar to the preparation of *2c*, 0.50 g. of 17β-acetoxy-4,9(11)-androstadien-3-one (*3a*), and 1,3-propanedithiol gave 0.41 g. of crude product, m.p. 165–177°. The analytical sample crystallized from dimethylformamide-water (25:4) in the form of rods, m.p. 180.0–180.6°, $[\alpha]_D$ +108°, λ_{max}^{Nujol} 5.71, 8.02, 9.50, 9.71, 11.50, 12.81 μ.

Anal. Calcd. for $C_{24}H_{34}O_2S_2$: C, 68.85; H, 8.19; S, 15.32. Found: C, 68.79; H, 8.45; S, 15.07.

3,3-Bisethylthio-5α-androstan-17β-yl acetate (4b). Concentrated hydrochloric acid (10 drops) was added to a solution of 250 mg. of 17β-acetoxy-5α-androstan-3-one and 0.5 ml. of ethanethiol in 5 ml. of glacial acetic acid. Within 15 min. the product crystallized. After overnight refrigeration the mixture was filtered and the crystals were washed with methanol: 300 mg. of product, m.p. 129–135°. The analytical sample crystallized from benzene–methanol (1:6) in the form of large plates, m.p. 132.0–134.8°, $[\alpha]_D$ +12°, λ_{max}^{Nujol} 5.72, 8, 9.65, 10.20, 10.81, 11.12, 12.89 μ.

Anal. Calcd. for $C_{25}H_{42}O_2S_2$: C, 68.44; H, 9.65; S, 14.62. Found: C, 68.28; H, 9.91; S, 14.33.

3,3-Bisallylthio-5α-androstan-17β-yl acetate (4c). A similar reaction with allyl mercaptan gave an oil which was chromatographed on alumina. Elution with ligroin-benzene (9:1 and 5:1) furnished the product which crystallized from methanol-benzene (10:1) or acetone-water (5:2) in the form of large, transparent plates, m.p. 71.3–74.8°, $[\alpha]_D$ +3° (1%), λ_{max}^{Nujol} 5.70, 8.00, 9.50, 9.64, 10.86 μ.

Anal. Calcd. for $C_{27}H_{42}O_2S_2$: C, 70.07; H, 9.15; S, 13.86. Found: C, 70.30; H, 9.30; S, 13.93.

Further elution of the column gave a second fraction which crystallized from acetone-water or from methanol as clusters of small needles, m.p. 212.0–216.5°, $[\alpha]_D$ +23° (1.5%), λ_{max}^{Nujol} 5.74, 8, 9.68, 10.41, 10.85, 11.17, 12.79 μ.

Anal. Found: C, 68.66; H, 8.55; S, 17.41.

3-Keto-5α-androstan-17β-yl acetate ethylenedithioketal (4d) was prepared similarly to *2b*. Recrystallization of the crude product in benzene-methanol (1:4) and in dimethylformamide-water (10:1) gave plates, m.p. 186.2–188.2°, $[\alpha]_D$ +19°, λ_{max}^{Nujol} 5.74, 8.00, 9.66, 10.17, 10.40, 11.12, 12.75, 13.8, 14.5, 14.86 μ.

Anal. Calcd. for $C_{23}H_{36}O_2S_2$: C, 67.59; H, 8.88; S, 15.70. Found: C, 67.63; H, 8.67; S, 16.03.

3-Keto-5α-androstan-17β-yl acetate ethylenemonothioketal (4e). The reaction of *4a* with β-mercaptoethanol under conditions similar to the preparation of *2b* gave a crude product, m.p. 102–156°. Fractional crystallization gave portions all having about 18° melting ranges. These were combined and recrystallized in methanol-water (10:1) containing a drop of pyridine, to give platelets, m.p. 145.6–163.0°, $[\alpha]_D$ +8°, λ_{max}^{Nujol} 5.71, 7.98, 9.14, 9.25, 9.34, 9.52, 9.64 μ.

Anal. Calcd. for $C_{23}H_{36}O_2S$: C, 70.36; H, 9.24; S, 8.17. Found: C, 70.30; H, 9.03; S, 8.19.

Ethyl spiro[17β-acetyl-5α-androstane-3,2′-thiazolidine-4′-carboxylate] (4f). Following the method of Lieberman *et al.*,[10] a solution of 240 mg. of *4a* and 120 mg. of ethyl L-cysteinate hydrochloride in 10 ml. of dry pyridine stood at room temperature for 24 hr. Dilution with water gave 255 mg. of crude product, which was recrystallized in ethanol and in acetone to give needles, m.p. 168.0–172.2°, $[\alpha]_D$ −50°, λ_{max}^{Nujol} 5.71, 8.00, 9.68, 12.08 μ.

Anal. Calcd. for $C_{26}H_{41}O_4NS$: C, 67.34; H, 8.91; N, 3.02; S, 8.71. Found: C, 67.24; H, 9.04; N, 3.23; S, 8.88.

3β-Tosyloxy-5-androsten-17β-yl benzoate (5) was prepared by room temperature tosylation of 5-androsten-3β,17-diol 17-benzoate with *p*-toluenesulfonyl chloride in pyridine. The product crystallized from acetone-water as needles, and from isopropyl ether in the form of laths, m.p. 150.2–153.6°, $[\alpha]_D$ −15° (chloroform), λ_{max}^{Nujol} 5.70, 7.79, 8.49, 8.95, 10.68, 11.54, 14, 14.8 μ.

Anal. Calcd. for $C_{33}H_{40}O_5S$: C, 72.23; H, 7.35; S, 5.84. Found: C, 72.31; H, 7.35; S, 6.01.

3,5-Androstadien-17β-ol (7a) was prepared by reduction of the ketone *6*[11] with lithium aluminum hydride. The product crystallized from methanol in the form of large needles, m.p. 148–164°; successive recrystallizations did not produce a sharply melting product. The highest melting sample, m.p.

(16) R. E. Marker, E. L. Wittle, and B. R. Tullar, *J. Am. Chem. Soc.*, **62**, 223 (1940).

(17) This compound is mentioned, but not described in two patents: Upjohn Co., Brit. Patent **752,033**, July 4, 1956, and M. E. Herr and F. W. Heyl, U. S. Patent **2,769,-019**, Oct. 30, 1956.

157–169°, $[\alpha]_D$ −120° (ethanol) [lit. m.p. 155°,[18] 158°,[1] $[\alpha]_D$ −139° (chloroform)[1]], $\lambda_{max}^{CH_3OH}$ 234 mμ, λ_{max}^{Nujol} 2.96, 9.30, 9.42, 9.65, 11.75, 13.8 μ.

The acetate 7b crystallized from acetone-water (5:1) as plates, m.p. 125.8–130.2°, $[\alpha]_D$ −132° (ethanol) [lit. m.p. 122–123°,[18] 128°,[1] $[\alpha]_D$ −147.4° (ethanol)[1]], $\lambda_{max}^{CH_3OH}$ 234 mμ, λ_{max}^{Nujol} 5.71, 8.01, 9.64, 11.69, 11.92, 12.39 μ.

The propionate 7c, from *7a* and propionic anhydride, crystallized from acetone-water in the form of needles, m.p. 133.8–140.6°, $[\alpha]_D$ −151° (chloroform), $\lambda_{max}^{CH_3OH}$ 234 mμ, λ_{max}^{Nujol} 5.72, 8.38, 9.69, 11.69, 12.41 μ.

Anal. Calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.33; H, 9.94.

The benzoate 7d was chromatographed on alumina (ligroin-benzene, 19:1 and 9:1) and crystallized from methanol-benzene (3:1). Two recrystallizations from ethyl acetate gave prisms, m.p. 183.2–188.8°, $[\alpha]_D$ −68° (chloroform), λ_{max}^{ether} 228, 234 (inflection) mμ, λ_{max}^{Nujol} 5.78, 7.56, 7.81, 8.44, 8.93, 9.29, 9.69, 10.16, 11.74, 12.37, 14.03 μ.

Anal. Calcd. for $C_{26}H_{32}O_2$: C, 82.93; H, 8.57. Found: C, 83.20; H, 8.69.

The same product (melting point and infrared) was obtained by dehydrotosylation of 3β-tosyloxy-5-androsten-17β-yl benzoate (*5*) in refluxing collidine for 3 hr.

The phenylacetate 7e was prepared from *7a* and phenylacetyl chloride in pyridine. The crude product was chromatographed on alumina, eluted with ligroin-benzene (1:1) and crystallized from methanol-benzene (10:1). Recrystallization in acetone-water (4:1) gave laths, m.p. 113.4–115.6°, $[\alpha]_D$ −114° (chloroform), λ_{max}^{ether} 234 mμ, λ_{max}^{Nujol} 5.69, 7.70, 7.90, 8.76, 9.70, 9.83, 11.65, 13.55, 13.95, 14.40 μ.

Anal. Calcd. for $C_{27}H_{34}O_2$: C, 83.03; H, 8.78. Found: C, 83.01; H, 9.08.

3β-Chloro-5-androsten-17-one (8a) was prepared by chlorination of androstenolone with thionyl chloride at room temperature. The crude product was chromatographed on alumina (ligroin-ether) and recrystallized from acetone: m.p. 155–158°, $[\alpha]_D$ +18° (0.6%, alcohol) [lit.[19] m.p. 156–157°, $[\alpha]_D$ +19° [alcohol]].

The 2,4-dinitrophenylhydrazone 8b crystallized from ethyl acetate–ethanol as a yellow powder, m.p. 263.5–266.5°, $[\alpha]_D$ −44° (0.6%, chloroform), λ_{max}^{Nujol} 2.91, 6.12, 6.25, 6.60, 7.43, 7.59, 7.74, 7.90 μ.

Anal. Calcd. for $C_{25}H_{31}ClN_4O_4$: C, 61.65; H, 6.42, Cl, 7.28; N, 11.51. Found: C, 61.84; H, 6.47; Cl, 7.38; N, 11.35.

The ethylenedithioketal 8c crystallized from benzene–methanol (1:3) in the form of needles, m.p. 153.0–158.0°, $[\alpha]_D$ −116°, λ_{max}^{Nujol} 12.10, 13.12, 13.83 μ.

Anal. Calcd. for $C_{21}H_{31}ClS_2$: C, 65.84; H, 8.16; Cl, 9.26; S, 16.74. Found: C, 65.95; H, 8.11; Cl, 9.14; S, 16.91.

The oxime 8d crystallized from ethanol in the form of miniature, diamond-shaped prisms, m.p. 185–194° (lit.,[20] m.p. 168–169°), $[\alpha]_D$ −67° (chloroform), λ_{max}^{Nujol} 3.91, 10.58, 10.89, 11.25, 13.10, 13.28, 13.90 μ.

Anal. Calcd. for $C_{19}H_{28}ClNO$: C, 70.89; H, 8.77; Cl, 11.02; N, 4.35. Found: C, 70.59; H, 8.89; Cl, 10.74; N, 4.42.

The O-carboxymethyl oxime 8e was prepared from the ketone *8a* and the hydrochloride of *O*-aminoglycolic acid (carboxy methoxyl amine hemihydrochloride, K&K Laboratories, Jamaica, N.Y.) following conditions used previously with estrone.[12] The crude product was recrystallized in acetone, tiny laths, m.p. 180.0–188.5°, $[\alpha]_D$ −33° (1%, chloroform), λ_{max}^{Nujol} 5.76, 7.10, 7.40, 7.54, 8.99, 9.10, 9.29, 11.44, 12.04 μ.

Anal. Calcd. for $C_{21}H_{30}ClNO_3$: C, 66.39; H, 7.96; Cl, 9.34; N, 3.69. Found: C, 66.15; H, 7.87; Cl, 9.52; N, 3.50.

The O-carbethoxymethyl oxime 8f was prepared from *8e*, ethanol, and concentrated hydrochloric acid at room temperature. Recrystallization of the crude ester in acetone gave dense rods, m.p. 94.2–97.0°, $[\alpha]_D$ −28° (1%, chloroform), λ_{max}^{Nujol} 5.71, 7.01, 8.3, 8.99, 9.12, 9.28, 9.7, 11.4, 11.75, 11.99, 13.17, 13.90 μ.

Anal. Calcd. for $C_{23}H_{34}ClNO_3$: C, 67.70; H, 8.40; Cl, 8.69; N, 3.43. Found: C, 67.79; H, 8.24; Cl, 8.60; N, 3.50.

13α-Amino-3β-chloro-13,17-seco-5 androsten-17-oic 13,17-lactam (9a) was prepared from the oxime *8d* in a manner identical to that described for the corresponding 3β-acetoxy lactam.[13] Recrystallization of the crude product in methanol gave platelets, m.p. 255–259°, $[\alpha]_D$ −66° (1%, chloroform), λ_{max}^{Nujol} 5.90, 6.17, 7.09, 8.58, 10.31, 12.09, 14.8 μ.

Anal. Calcd. for $C_{19}H_{28}ClNO$: C, 70.89; H, 8.77; Cl, 11.02; N, 4.35. Found: C, 70.63; H, 8.68; Cl, 11.38; N, 4.34.

The product prepared by chlorination of 13α-amino-3β-hydroxy-13,17-seco-5-androsten-17-oic 13,17-lactam (*9b*) from the hydrolysis of the acetate (*9c*)[13] with thionyl chloride had a melting point and mixed melting point identical with with that just described.

Acknowledgment. We are grateful to Mr. George Hayes for technical assistance in some of the chemical work, and for conducting the serological tests. Also, we wish to thank Dr. E. P. Oliveto for a gift of 9(11)-dehydrotestosterone and Dr. R. B. Forney for the use of an ultraviolet spectrophotometer.

INDIANAPOLIS, IND.

(18) A. Butenandt and A. Heusner, *Ber.*, **71**, 198 (1938).

(19) H. L. Mason and E. J. Kepler, *J. Biol. Chem.*, **161**, 235 (1945).

(20) A. Butenandt and H. Dannenbaum, *Z. physiol. Chem.*, **229**, 192 (1934).