(−)-**N-Benzoylneothujylamine** (IIc) had mp 95–97°, $[\alpha]^{25}D$ −13° (*c* 2.1, methanol); lit.[3] mp 94.5°, $[\alpha]^{25}D$ −12.16° (methanol).

(+)-**Isothujylamine** (IIIa) had bp 113° (62 mm), $n^{25}D$ 1.4559, $[\alpha]^{25}D$ +114° (*c* 2.4, 95% ethanol); lit.[3] bp 76.8° (11 mm), $n^{25}D$ 1.4564, $[\alpha]^{25}D$ +107.9, +108.4° (*c* 1.6, ethanol).

(+)-**N-Benzoylisothujylamine** (IIIc) had mp 132–135°, $[\alpha]^{25}D$ +89° (*c* 1.1, methanol); lit.[3] mp 131.5°, $[\alpha]^{25}D$ +87.74° (methanol).

(+)-**Neoisothujylamine** (IVa) had bp 110° (52 mm), $n^{25}D$ 1.4658, $[\alpha]^{25}D$ +52.2° (*c* 2.2, 95% ethanol); lit.[3] bp 77.0° (12 mm), $n^{25}D$ 1.4654, $[\alpha]^{25}D$ +51.27° (*c* 3, ethanol).

(+)-**N-Benzoylneoisothujylamine** (IVc) had mp 74–75°, $[\alpha]^{25}D$ +95° (*c* 1.0, methanol); lit.[3] mp 73–75°, $[\alpha]^{25}D$ +91.44° (methanol).

Nmr Measurements.—The nmr spectra at 60 and 100 Mc/sec were recorded on Varian A-60 and HR-100 spectrometers, using samples dissolved in deuteriochloroform containing tetramethylsilane (TMS) as an internal standard. All chemical shifts are reported in parts per million downfield from TMS.

Acknowledgment.—We wish to thank the National Science Foundation for a grant (G-14524) supporting the earlier stages of this work, Professor Arthur W. Ingersoll, Vanderbilt University, for a generous gift of thujylamine salts and thujylamides, and Professor Carl Djerassi for his hospitality to H. E. S. during the summer of 1964 at Stanford University.

Steroids. CCLXVI.[1] A Series of C-19 Modified Analogs of Testosterone and Related Compounds[2]

O. HALPERN, I. DELFIN, L. MAGAÑA, AND A. BOWERS

Institute of Steroid Chemistry, Syntex Research, Stanford Industrial Park, Palo Alto, California

Received September 22, 1965

The preparation of the 10β-angular hydroxymethyl, formyl, carboxyl, chloromethyl, vinyl, ethyl, N,N-dimethylcarboxamido, and N,N-diethylaminomethyl analogs of various 3,17-bisoxygenated Δ^4- and Δ^5-androstenes as well as a series of 6β,19-oxides is described. A new synthesis of 17α-ethinyl-19-nortestosterone acetate is presented.

The marked difference in biological properties between testosterone or several structural modifications of testosterone and their corresponding 19-nor analogs[3] clearly indicates that the nature of the 10β-angular substituent plays an important role in structure–activity relationships. However, variations of the angular substituent have been extremely limited owing to the chemical inaccessibility of the C-19 angular methyl group.[4] Functionalization of the nonactivated 19-carbon became possible through the pioneering work of Barton and his collaborators.[5] Recent work in our laboratories[6–9] and independent studies by the CIBA group[10–12] have led to ready syntheses of 19-oxygenated steroids from the reaction of readily available 6β-hydroxy precursors with lead tetraacetate, and hence made the way clear to the preparation on industrial scale of a variety of 19-substituted compounds. Other independent investigators have pursued different routes to 19-substituted steroids.[13] This paper describes the preparation of the 10β-angular hydroxymethyl, formyl, carboxyl, chloromethyl, vinyl, ethyl, N,N-dimethylcarboxamido, and N,N-diethylaminomethyl analogs of various 3,17-bisoxygenated Δ^4- and Δ^5-androstenes (Chart I).

Cleavage of 3β-hydroxy-5α-bromo-6β,19-oxidoandrostan-17-one acetate (Ia)[8] with zinc dust in ethanol under reflux afforded the Δ^5-19-alcohol (IIa) in high yield. When this reaction was carried out in acetic acid, the product was the corresponding diacetate IIb. Acetylation of IIa with acetic anhydride in pyridine solution gave the diacetate IIb. Tosylation of IIa proceeded normally to yield the C-19 tosylate IIc which underwent displacement with lithium chloride in isopropyl alcohol solution under reflux for 5 hr to afford 3β-hydroxy-19-chloroandrost-5-en-17-one acetate (IId).[14] Similarly, treatment of IIc with lithium bromide led to 19-bromoandrost-5-en-17-one acetate (IIe). Alkaline hydrolysis of IId furnished the alcohol IIf, which upon Oppenauer oxidation gave 19-chloroandrost-4-ene-3,17-dione (IIIa). Reduction of IIIa with lithium aluminum hydride gave a product which did not exhibit any selective absorption in the ultraviolet above 210 mμ but which was readily oxidized with dichlorodicyanobenzoquinone (DDQ) in dioxane solution[15] at room temperature to 19-chlorotestosterone (IIIb).

(1) Part CCLXV: J. C. Orr, A. de la Roz, and A. Bowers, *J. Org. Chem.*, **29**, 3300 (1964).

(2) A part of this work was presented by A. B. at the Gordon Research Conference for Steroids and Natural Products, New Hampton, N. H., on July 16, 1962, and as a preliminary communication, O. Halpern, R. Villotti, and A. Bowers, *Chem. Ind.* (London), 116 (1963).

(3) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., 1959, pp 588–599.

(4) For a summary of the biochemical methods (adrenal incubation and microbiological hydroxylations) used for the oxygenation of the C-19 methyl group, *cf.* ref 5 and T. Takahashi, *Agr. Biol. Chem.* (Tokyo), **27**, 639 (1963).

(5) A. Bowers, E. Denot, L. C. Ibanez, M. E. Cabezas, and H. J. Ringold, *J. Org. Chem.*, **27**, 1862 (1962).

(6) For a recent review and relevant references, see A. L. Nussbaum and C. H. Robinson, *Tetrahedron*, **17**, 35 (1962).

(7) A. Bowers, L. C. Ibañez, M. E. Cabezas, and H. J. Ringold, *Chem. Ind.* (London), 1299 (1960).

(8) A. Bowers, R. Villotti, J. A. Edwards, E. Denot, and O. Halpern, *J. Am. Chem. Soc.*, **84**, 3204 (1962).

(9) B. Berkoz, E. Denot, and A. Bowers, *Steroids*, **1**, 251 (1963).

(10) C. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein, *Experientia*, **17**, 475 (1961).

(11) K. Heusler, J. Kalvoda, C. Meystre, H. Ueberwasser, P. Wieland, G. Anner, and A. Wettstein, *ibid.*, **18**, 464 (1962).

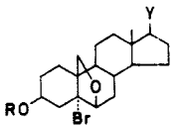
(12) J. Kalvoda, K. Heusler, H. Ueberwasser, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **46**, 1361 (1963).

(13) 10β-Cyano hormone analogs have been reported recently: *cf.* (a) E. P. Oliveto, L. Weber, M. M. Pechet, and E. B. Hershberg, *J. Am. Chem. Soc.*, **81**, 2833 (1959); (b) R. Gardi and C. Pedrali, *Gazz. Chim. Ital.*, **91**, 1420 (1961); (c) R. Gardi and C. Pedrali, *ibid.*, **93**, 514 (1963); (d) R. Gardi, C. Pedrali, and A. Ercoli, *ibid.*, **93**, 525 (1963); (e) T. Jen and M. E. Wolff, *J. Med. Pharm. Chem.*, **5**, 876 (1962); (f) M. E. Wolff and T. Jen, *ibid.*, **6**, 726 (1963); M. E. Wolff and W. Ho, *ibid.*, **7**, 681 (1964).

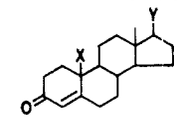
(14) Reactions of the Δ^5-19-tosylate system with anions usually afford 5,19-cyclo steroids as the major reaction products: *cf.* O. Halpern, P. Crabbe, A. D. Cross, I. Delfin, L. Cervantes, and A. Bowers, *Steroids*, **4**, 1 (1964).

(15) D. Burn, V. Petrow, and G. O. Weston, *Tetrahedron Letters*, **No. 9**, 14 (1960).

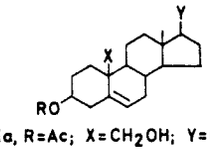
CHART I



Ia, R=Ac; Y=O
b, R=Ac; Y=
c, R=H; Y=
d, R=H; Y=O
e, R=H; Y=
f, R=Ac; Y=
g, R=Ac; Y=
h, R=H; Y=



IIIa, X=CH_2Cl; Y=O
b, X=CH_2Cl; Y= 
c, X=CH=CH_2; Y=O
d, X=CH=CH_2; Y= 
e, X=Et; Y=O
f, X=Et; Y= 
g, X=$CONEt_2$; Y=O
h, X=$CONEt_2$; Y=
i, X=CH_2OH; Y= 
j, X=COOH; Y= 
k, X=H; Y= 



IIa, R=Ac; X=CH_2OH; Y=O
b, R=Ac; X=CH_2OAc; Y=O
c, R=Ac; X=CH_2OTs; Y=O
d, R=Ac; X=CH_2Cl; Y=O
e, R=Ac; X=CH_2Br; Y=O
f, R=H; X=CH_2Cl; Y=O
g, R=Ac; X=CH_2OH; Y= 
h, R=H; X=CH_2OH; Y= 
i, R=Ac; X=CHO; Y= 
j, R=Ac; X=CH=CH_2; Y=O
k, R=H; X=CH=CH_2; Y=O
l, R=Ac; X=Et; Y=O
m, R=H; X=CHO; Y= 
n, R=H; X=Et, Y=O
o, R=H; X=CH=$N(CH_2)_2$-NEt_2; Y= 
p, R=Ac; X=COOH; Y=O
q, R=Ac; X=CHO; Y=O
r, R=H; X=CHO; Y=O
s, R=Ac; X=COCl; Y=O
t, R=Ac; X=$CONEt_2$; Y=O
u, R=H; X=$CONEt_2$; Y=O
v, R=H; X=CH_2OH; Y= 

A suitable route to the 19-methylene and 19-methyl compounds IIk and III appeared to be *via* a Wittig reaction on a 10β-formyl compound in which the carbonyl group at C-17 had been suitably protected. Accordingly, attempts were made to convert IIa to the corresponding 17-ethylene ketal IIg *via* an acid-catalyzed condensation with ethylene glycol in benzene solution. The yield of IIg from IIa, however, was not very satisfactory, partly owing to concomitant hydrolysis at C-3 and formation of the corresponding diol (IIh), and partly owing to the instability of the Δ^5-19-hydroxy system (β,γ-unsaturated neopentyl alcohol) to the acid conditions necessary for ketal formation of C-17. The preferred approach to IIg involved conversion of the bromo oxide Ia into the corresponding C-17 ketal Ib which then smoothly underwent cleavage with zinc dust in ethanol solution to afford the desired 19-hydroxy 17-ketal IIg. Alkaline hydrolysis of both Ib and IIg led to the corresponding 3β-alcohols Ic and IIh. Oxidation of IIg with chromium trioxide in pyridine solution led to the 10β-formyl compound IIi, which was hydrolyzed with potassium carbonate in methanol solution to 10β-formyl-17-ethylenedioxy-19-norandrost-5-en-3β-ol (IIm). Treatment of this aldehyde with methylenetriphenylphosphorane[16] and acid hydrolysis of the Wittig product to remove the protective ketal group, followed by reacetylation, furnished 3β-hydroxy-19-methyleneandrost-5-en-17-one acetate (IIj). Mild alkaline hydrolysis of IIj gave the alcohol IIk, the nmr spectrum of which showed a complex pattern of peaks between 4.7 and 5.9 ppm. This was analyzed as an ABC pattern for the three protons of a vinyl substituent resonating, respectively, at 4.90 (H_A), 5.23 (H_B), and 5.66 ppm (H_C), with J_{AB} = 3 cps, J_{AC} = 16 cps, and J_{BC} = 10 cps. A fourth olefinic proton (C-6) resonance appeared as a multiplet at 5.5 ppm.

Oppenauer oxidation of IIk gave 19-methyleneandrost-4-ene-3,17-dione (IIIc). The corresponding testosterone derivative IIId was prepared from IIIc by the same general procedure used in the 19-chloro series, namely, reduction of the dione IIIc with lithium aluminum hydride followed by selective oxidation of the allylic alcohol with DDQ[15] to afford 19-methylenetestosterone (IIId).

A route to the 19-methyl compounds became clear when it was found that it was possible to hydrogenate selectively the 19-methylene double bond in both IIk and IIj with a 5% palladium-on-carbon catalyst in ethanol solution, leaving the Δ^5 double bond intact to afford, respectively, 19-methyldehydroisoandrosterone (IIn) and its corresponding acetate III.

Oppenauer oxidation of IIn led to 19-methylandrost-4-ene-3,17-dione (IIIe), which was converted into 19-methyltestosterone IIIf *via* reduction with lithium aluminum hydride and subsequent oxidation of the intermediate allylic alcohol with DDQ.

It was of interest to prepare C-19 amino steroids, and various approaches were investigated. Initially, attempts were made to condense the suitably protected aldehyde IIi with various amines, but the resulting Schiff bases presumably were extremely labile since, with one exception, it was only possible to isolate starting material. The only successful condensation was with N,N-diethylethylenediamine. In this case it was possible to isolate the condensation product IIo, but all attempts to remove the protecting ketal group at C-17 led to a reverse of the condensation and regeneration of the aldehyde group. Attempts to carry out an Oppenauer oxidation on IIo and retain the substitution at C-19 were unsuccessful.

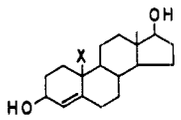
A more successful approach to C-19 amino compounds was *via* the 19-carboxylic acid. Oxidation of 19-hydroxydehydroisoandrosterone acetate (IIa) with 8 *N* chromic acid in acetone solution[17] led to a mixture of products. The major product isolated in 30% yield was the corresponding C-19 carboxylic acid IIp. Chromatography of the neutral fraction led to the isolation of the 3β-acetoxy C-19 aldehyde IIq, which afforded the corresponding 3β-alcohol IIr upon mild alkaline hydrolysis identical in all respects with the product obtained from the acid hydrolysis of the ketal IIm.

The C-19 carboxylic acid IIp was readily converted into its acid chloride IIs by treatment with oxalyl chloride. Reaction of IIs with diethylamine afforded the corresponding N,N-diethylcarboxamide IIt together with the acid anhydride of the acid IIp. Prolonged heating of the acid anhydride with water gave the acid IIp. Mild alkaline hydrolysis of IIt gave the corresponding alcohol IIu, which was oxidized under Oppenauer conditions to afford the corresponding Δ^4-3-ketone IIIg. Sodium borohydride reduction of IIIg gave the Δ^4-3,17-diol (IVa), which was selectively

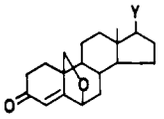
(16) G. Wittig and V. Schollkopf, *Ber.*, **87**, 1318 (1954).

(17) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *ibid.*, 2548 (1953).

oxidized with DDQ to N,N-diethyl-19-carboxamido-17β-hydroxyandrost-4-en-3-one (IIIh). Lithium aluminum hydride treatment of IIIg reduced the amide group to the corresponding C-19-amine as well as reducing the keto groups at C-3 and C-17, thereby affording 3β,17β-dihydroxy-N,N-diethyl-19-aminoandrost-4-ene (IVb).



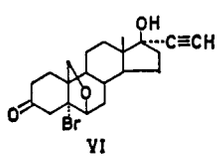
IVa, X=CONEt$_2$
b, X=CH$_2$NEt$_2$



Va, Y=O
b, Y= 

To complete the biological studies on C-19-substituted derivatives of testosterone, it was necessary to prepare 6,19-oxidotestosterone (Vb). This was readily obtained from 6,19-oxidoandrost-4-ene-3,17-dione (Va)[9,11,12] by reduction with lithium aluminum hydride followed by selective oxidation of the Δ^4-3,17-diol with DDQ.

In view of the importance of 17α-ethinyl-19-nortestosterone and its acetate as fertility control agents, it was clearly of interest to prepare their corresponding 10β-hydroxymethyl and carboxylic acid analogs. A convenient approach began with 3β-hydroxy-5α-bromo-6,19-oxidoandrostan-17-one[8] (Id), which was treated with acetylene in *t*-butyl alcohol in the presence of potassium *t*-butoxide to afford the 17α-ethinyl bromo oxide Ie. Acetylation of Ie with acetic anhydride in pyridine at room temperature led to the 3β-monoacetate If, whereas, under the more vigorous conditions of acetic anhydride in benzene solution in the presence of *p*-toluenesulfonic acid, the 3,17-diacetate Ig was obtained in high yield. It was originally planned to oxidize the diol Ie to the bromo ketone VI and proceed to the corresponding 19-hydroxy and 19-carboxy Δ^4-3-ketones by the established procedures.[8] However, oxidation of Ie under a variety of conditions led to the ketone VI in only very low yield. A competing



VI

reaction was always the reversal of the addition of the ethinyl group and generation of the C-17 ketone group. This problem was resolved by preferential ester hydrolysis at C-3 of the diacetate Ig with sodium hydroxide in anhydrous methanol to afford the C-17 monoacetate Ih. Cleavage of Ih with zinc dust in ethanol[8,18] smoothly gave the Δ^5-3,19-diol (IIv) which underwent a preferential Oppenauer oxidation[8] to give 19-hydroxy-17α-ethinyltestosterone acetate (IIIi). Oxidation of the C-19 primary alcohol with 8 *N* chromic acid in acetone solution[17] gave the carboxylic acid IIIj which was readily converted by acid[19] into 19-nor-17α-ethinyltestosterone acetate (IIIk).

(18) A. Bowers, U. S. Patent 3,065,228 (Nov 20, 1962).

(19) H. Hagiware, S. Noguchi, and M. Nishikawa, *Chem. Pharm. Bull.* (Tokyo) **8**, 84 (1960).

Experimental Section[20]

3β,19-Dihydroxyandrost-5-en-17-one 3-Acetate (IIa).—Zinc powder (20 g) was added to a solution of 3β-hydroxy-5α-bromo-6β,19-oxidoandrostan-17-one acetate (Ia, 10 g) in ethyl alcohol (100 ml) and the mixture was heated under reflux with stirring for 3 hr. The warm suspension was filtered and the residue was washed with hot ethanol. Removal of the solvent from the combined filtrates afforded a residue which was dissolved in ethyl acetate and washed three times with water (100 ml). The organic layer was then dried and evaporated to afford a product which was crystallized from acetone–hexane to give 7.95 g of IIa, mp 157–162°. The analytical sample, from the same solvent pair, exhibited mp 167–168°, $[\alpha]_D$ +7°.[21]

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73; O, 18.47. Found: C, 73.08; H, 8.60; O, 18.59.

3β,19-Dihydroxyandrost-5-en-17-one Diacetate (IIb). A.—A mixture of 3β-hydroxy-5α-bromo-6β,19-oxidoandrostan-17-one acetate (Ia, 10 g), zinc powder (30 g), and acetic acid (200 ml) was heated under reflux with stirring for 20 hr. The mixture was filtered; the filtrate was poured into ice–water (1000 ml). Filtration and chromatography of the dry precipitate over washed alumina (300 g) with benzene–hexane (1:9) afforded 5.6 g of the crude diacetate IIb, mp 95–102°. Recrystallization from methylene chloride–hexane gave the analytical sample of 3β,19-dihydroxyandrost-5-en-17-one diacetate, mp 105–106°, $[\alpha]_D$ −32°.[22]

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30; O, 20.60. Found: C, 71.43; H, 8.13; O, 20.56.

B.—A solution of 3β,19-dihydroxyandrost-5-en-17-one 3-acetate (IIa, 1 g) in pyridine (1 ml) and acetic anhydride (1 ml) was heated on the steam bath for 8 hr. Addition of water, filtration, and crystallization of the product from methylene chloride–hexane afforded IIb (950 mg, mp 103–104°), identical in all respects with the product obtained above.

3β,19-Dihydroxyandrost-5-en-17-one 3-Acetate 19-Tosylate (IIc).—A mixture of the 19-alcohol IIa (23.6 g), tosyl chloride (23.6 g), and pyridine (236 ml) was stirred at 20° for 20 hr and then poured into water (750 ml). The product was extracted with ethyl acetate; the extracts were washed with water, dilute hydrochloric acid (2 *N*), sodium bicarbonate solution, and water. Removal of the solvent gave a product which was crystallized from acetone–hexane to afford IIc (29.0 g) with mp 155–157°, $[\alpha]_D$ −81°, λ_{max} 226 mμ (log ε 4.09).

Anal. Calcd for $C_{28}H_{36}O_6S$: C, 67.17; H, 7.25; S, 6.04. Found: C, 67.20; H, 7.17; S, 6.18.

3β-Hydroxy-19-chloroandrost-5-en-17-one Acetate (IId).—A mixture of the 19-tosylate IIc (10 g), isopropyl alcohol (600 ml), and lithium chloride (10 g) was heated under reflux for 5 hr, concentrated to small bulk, and poured into water. The product was isolated by filtration, mp 149–152°, 7.15 g. A sample was filtered in benzene solution over a short column of washed alumina and then crystallized several times from acetone–hexane to give the pure sample of IId, mp 151–152°, $[\alpha]_D$ −10°.

Anal. Calcd for $C_{21}H_{29}ClO_3$: C, 69.12; H, 8.01; Cl, 9.71. Found: C, 69.53; H, 8.42; Cl, 10.20.

3β-Hydroxy-19-bromoandrost-5-en-17-one Acetate (IIe).—A mixture of the 19-tosylate IIc (6.4 g), lithium bromide (6.4 g), and isopropyl alcohol (360 ml) was heated under reflux for 5 hr, concentrated to small bulk, and poured into water. The product was collected, dried, and crystallized from acetone–hexane to give IIe, 3.7 g, mp 157–163°. The pure sample had mp 162–164°, $[\alpha]_D$ −19°.

Anal. Calcd for $C_{21}H_{29}BrO_3$: C, 61.61; H, 7.14; Br, 19.52; O, 11.73. Found: C, 61.65; H, 7.16; Br, 19.93; O, 12.03.

3β-Hydroxy-19-chloroandrost-5-en-17-one (IIf).—A solution of the acetate IId (4.79 g) in methanol (192 ml) was mixed with

(20) All rotations are for chloroform solutions, ultraviolet spectra for ethanol solutions, and infrared spectra for KBr disks, except where stated otherwise. Nmr spectra were recorded on a Varian A-60 spectrometer kindly made available by the Universidad Nacional Autonoma de Mexico, using 10% solutions in deuteriochloroform containing a little tetramethylsilane as an internal reference. Microanalyses were by Midwest Micro Labs, Indianapolis 20, Ind., or by Dr. A. Bernhardt, Mülheim (Ruhr), Germany.

(21) K. Tanabe, *et al.* [*Chem. Pharm. Bull.* (Tokyo), **10**, 1126 (1962)] recorded mp 160–161°, $[\alpha]_D$ +4°.

(22) Tanabe,[21] recorded mp 107–108°, $[\alpha]_D$ −41°, while J. Tadanier [*J. Org. Chem.*, **28**, 1744 (1963)] found mp 108–109°, $[\alpha]_D$ −35.4°, and K. Heusler, *et al.* [*Experientia*, **18**, 464 (1962)] gave mp 103–105°, $[\alpha]_D$ −40°.

1 *M* sodium methoxide in methanol (3.3 ml) and stirred 1.5 hr at 20°. After neutralization with acetic acid, the solution was concentrated and poured into water (100 ml). The precipitate of IIf was collected and dried. It showed mp 190–195°, raised by recrystallizations from acetone–hexane to mp 194–196°, $[\alpha]_D$ −19°.

Anal. Calcd for $C_{19}H_{27}ClO_2$: C, 70.68; H, 8.43; Cl, 11.48. Found: C, 70.63; H, 8.44; Cl, 11.48.

19-Chloroandrost-4-ene-3,17-dione (IIIa).—A mixture of the alcohol IIf (5.35 g), aluminum isopropylate (10.7 g), cyclohexanone (107 ml), and dry toluene (535 ml) was slowly distilled to half the original volume in 1 hr. Removal of the solvent by steam distillation and filtration of the solid residue afforded the crude dione IIIa (4.1 g): mp 167–177°, raised by crystallization from acetone–hexane to mp 182–184°; $[\alpha]_D$ +159°; λ_{max} 238–240 mμ (log ε 4.23).

Anal. Calcd for $C_{19}H_{25}ClO_2$: C, 71.12; H, 7.85; Cl, 11.05; O, 9.97. Found: C, 70.98; H, 7.33; Cl, 10.73; O, 10.91.

19-Chlorotestosterone (IIIb).—An excess of lithium aluminum hydride was added to a solution of 19-chloroandrost-4-ene-3,17-dione (IIIa, 1.45 g) in tetrahydrofuran (50 ml) and the mixture was stirred at 20° for 1 hr. The excess of reagent was then destroyed with ethyl acetate and aqueous saturated sodium sulfate solution. Dilution with ethyl acetate, filtration, and removal of the solvent afforded a product which was dissolved in dioxane (70 ml) containing dichlorodicyanobenzoquinone (DDQ) (1.45 g). After standing at 20° for 60 hr, the mixture was diluted with methylene chloride and filtered over alumina (15 g), and the filtrates were evaporated to dryness. The residue (1.2 g) was recrystallized from acetone–hexane to give 19-chlorotestosterone (820 mg): mp 163–167°, raised by several recrystallizations from acetone–hexane to mp 170–172°; $[\alpha]_D$ +93°; λ_{max} 240 mμ (log ε 4.19).

Anal. Calcd for $C_{19}H_{27}ClO_2$: C, 70.68; H, 8.43; Cl, 10.98. Found: C, 70.45; H, 8.37; Cl, 11.51.

Ketalization of 3β,19-Dihydroxyandrost-5-en-17-one 3-Acetate (IIa).—A mixture of the 17-ketone IIa (3.25 g), ethylene glycol (24 ml), benzene (32.5 ml), and *p*-toluenesulfonic acid (162 mg) was heated under reflux with a water separator for 24 hr and then poured into 5% aqueous sodium carbonate solution (200 ml). The products were extracted with methylene chloride; the extracts were washed twice with water, dried, and evaporated. The residue was crystallized with acetone–hexane containing 1 drop of pyridine, whereby the 17-ethylenedioxyandrost-5-ene-3β,19-diol (IIh, 800 mg, mp 173–175°) could be separated. Recrystallization from acetone–hexane gave the analytical sample, mp 175–176°, $[\alpha]_D$ −94° (dioxane).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26; O, 18.37. Found: C, 72.82; H, 9.26; O, 18.37.

The mother liquors were chromatographed in benzene solution on alumina (60 g). Benzene elution gave the 3-acetate of 17-ethylenedioxyandrost-5-ene-3β,19-diol (IIg): 750 mg; mp 140–142°, raised by crystallization from acetone–hexane to mp 143.5–144.5°; $[\alpha]_D$ −84°.

Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78; O, 20.49. Found: C, 70.98; H, 8.71; O, 20.61.

5α-Bromo-6β,19-oxido-17-ethylenedioxyandrostan-3β-ol Acetate (Ib). A.—A solution of the 17-keto compound Ia (20 g) in ethylene glycol (130 ml) and benzene (200 ml) containing *p*-toluenesulfonic acid (1 g) was heated under reflux for 18 hr, using a water separator. After cooling, the solution was poured into sodium bicarbonate solution (1 l., 5%). The organic layer was separated, the aqueous layer was extracted with ethyl acetate (two 100-ml portions), and the combined organic extracts were washed with water (two 100-ml portions), dried, and evaporated under reduced pressure. The oily residue (25 g) was dissolved in pyridine (40 ml) and acetic anhydride (20 ml) and the mixture was then heated on the steam bath for 1 hr. Addition of ice–water, filtration, and crystallization of the product from acetone–hexane furnished the ketal Ib (18.88 g): mp 162–165°, raised by several crystallizations from acetone–hexane to mp 164–165°; $[\alpha]_D$ −10°.

Anal. Calcd for $C_{23}H_{33}BrO_5$: C, 58.85; H, 7.09; Br, 17.03; O, 17.04. Found: C, 59.42; H, 7.31; Br, 17.22; O, 16.73.

B.—A solution of the 17-keto compound Ia (2 g) in ethylene glycol (40 ml) and ethyl orthoformate (40 ml) containing *p*-toluenesulfonic acid (150 mg) was heated under reflux for 1 hr. The cooled solution was then poured into sodium bicarbonate solution (500 ml, 5%) and extracted several times with ethyl acetate. The washed and dried extracts gave a crude residue (2 g) which upon crystallization from methanol–water gave the ketal Ib (1.4 g, mp 155–161°) identical with the product obtained above.

Action of Zinc on 5α-Bromo-6β,19-oxido-17-ethylenedioxyandrostan-3β-ol Acetate (Ib).—A mixture of the ketal Ib (7.53 g), zinc powder (15 g), and ethanol (15 ml) was heated under reflux for 3 hr, filtered, and evaporated to dryness. The residue was dissolved in chloroform (100 ml), washed with water (three 25-ml portions), dried, and evaporated. The oily residue was crystallized from acetone–hexane to give 17-ethylenedioxyandrost-5-ene-3,19-diol 3-acetate (IIg): 4.45 g; mp 138–140°, raised by recrystallizations from acetone–hexane to mp 143.5–144.5°; $[\alpha]_D$ −84°; identical in all respects with the material obtained above.

Saponification of IIg (790 mg) in methanol solution (6 ml) containing sodium methoxide (7 mg) at 20° for 1.5 hr, followed by neutralization with 1 drop of acetic acid and concentration to small volume and addition of water, gave a precipitate. Filtration, washing, and drying of this precipitate gave the free diol IIh, 650 mg, mp 171–174°, identical in all respects with the material obtained above.

5α-Bromo-6β,19-oxido-17-ethylenedioxyandrostan-3β-ol (Ic).—Sodium (12 mg) in absolute methanol (10 ml) was added to a solution of the ketal Ib (1.2 g) in dry methanol (38 ml), and the mixture was kept at 20° for 1.5 hr. It was then neutralized with acetic acid (2 drops) and concentrated to *ca.* 10 ml, and water was added to precipitate the ketal Ic. After filtering and drying, 890 mg of Ic (mp 216–217°) was obtained. The analytical sample (from methanol–water) had mp 216–218°, $[\alpha]_D$ −22°.

Anal. Calcd for $C_{21}H_{31}BrO_4$: C, 59.01; H, 7.31; Br, 18.70; O, 14.97. Found: C, 59.09; H, 7.64; Br, 18.83; O, 15.08.

10β-Formyl-17-ethylenedioxy-19-norandrost-5-en-3β-ol Acetate (IIi).—A solution of 17-ethylenedioxyandrost-5-ene-3β,19-diol 3-acetate (IIg, 10 g) in pyridine (100 ml) was added to a mixture of chromic anhydride (10 g) in pyridine (100 ml) and the mixture was left at 20° for 16 hr. It was then diluted with ethyl acetate and filtered over Celite. The filtrate was washed several times with water and the organic layer was dried and evaporated. The crude oily residue was crystallized from acetone–water to give 10β-formyl-17-ethylenedioxy-19-norandrost-5-en-3β-ol acetate (IIi, 6.5 g), mp 148° dec. A second crop (250 mg, mp 144° dec) was obtained by concentration of the mother liquors. A pure sample was prepared by several recrystallizations from acetone–water: mp 159–169° dec. $[\alpha]_D$ −261°.

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30; O, 20.59. Found: C, 71.42; H, 8.14; O, 20.64.

10β-Formyl-17-ethylenedioxy-19-norandrost-5-en-3β-ol (IIm).—10β-Formyl-17-ethylenedioxy-19-norandrost-5-en-3β-ol acetate (IIi, 5.715 g) in methanol (200 ml) containing potassium carbonate (10 g) was heated under reflux for 1 hr. After neutralization with acetic acid, the solution was concentrated to a small volume and diluted with water. Extraction with ethyl acetate afforded an oil which crystallized from methylene chloride–hexane to give the alcohol IIm in two crops: 3.6 g with mp 165–178° dec and 840 mg with mp 171–185° dec. The pure sample had mp 165–182° dec, $[\alpha]_D$ −250°.

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73; O, 18.47. Found: C, 72.77; H, 8.66; O, 18.50.

3β-Hydroxy-19-methyleneandrost-5-en-17-one Acetate (IIj).—A suspension of butyllithium (22.8 g of 32.3% butyllithium in paraffin wax) was added in a nitrogen atmosphere to a suspension of freshly prepared methyltriphenylphosphonium bromide (45.8 g) in dry ether (500 ml). The mixture was stirred at 20° for 1.5 hr in a nitrogen atmosphere; then a solution of 10β-formyl-17-ethylenedioxy-19-norandrost-5-en-3β-ol (IIm, 9.2 g) in tetrahydrofuran (180 ml) was added dropwise. The mixture was stirred for a further 20 hr under reflux, maintaining a constant volume by the addition of dry tetrahydrofuran. The mixture was then evaporated to dryness and the residue was dissolved in ethyl acetate. This solution was washed with water, dried, and evaporated. The residue was dissolved in acetone (675 ml) and hexane (500 ml), and concentrated hydrochloric acid (4.7 ml) was added. After stirring 16 hr at 20°, aqueous sodium bicarbonate solution was added to neutralize the mixture and the organic solvents were removed under reduced pressure. The aqueous residue was extracted several times with a mixture of ethyl acetate–hexane (3:1); the extracts were washed with water, dried, and evaporated. The residue was chromatographed on silica gel (100 g) in hexane–benzene (3:5) solution. The first

eluates were soluble in hexane and were discarded; the hexane-insoluble material which followed was acetylated under standard conditions to give a crude gum (22.5 g), which was chromatographed on silica gel (700 g). Elution with benzene and crystallization from acetone–hexane afforded IIj, 9.02 g, mp 168–175°. The analytical sample of 3β-hydroxy-19-methyleneandrost-5-en-17-one acetate (IIj) was obtained by several recrystallizations from acetone–hexane and showed mp 174.5–175.5° subl, $[\alpha]_D$ −74°.

Anal. Calcd for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83; O, 14.02. Found: C, 77.47; H, 8.65; O, 13.92.

3β-Hydroxy-19-methyleneandrost-5-en-17-one (IIk).—A solution of the acetate IIj (8.5 g) in methanol (250 ml) containing potassium carbonate (12.5 g) was heated under reflux for 1 hr. After neutralizing with acetic acid, the solution was concentrated to a small volume, poured into water, and extracted with ethyl acetate. The extract was washed with water, dried, and evaporated. The residue (7.65 g) was crystallized from acetone–hexane to give 3β-hydroxy-19-methyleneandrost-5-en-17-one (IIk, 7.48 g, mp 141–147°) The pure sample showed mp 143–145° subl, $[\alpha]_D$ −67°.

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39; O, 10.65. Found: C, 79.98; H, 9.42; O, 10.52.

19-Methyleneandrost-4-ene-3,17-dione (IIIc).—Cyclohexanone (15 ml) and aluminum isopropylate (3 g) were added to a solution of IIk (1.5 g) in dry toluene (90 ml), and the mixture was slowly distilled over a period of 1 hr to one-half of the original volume. Addition of water and extraction with ethyl acetate (three 75-ml portions) gave an oily residue (3.7 g) which crystallized from acetone–hexane to afford 1.19 g of IIIc, mp 153–162°. The analytical sample, from acetone–hexane, had mp 160–161° subl, $[\alpha]_D$ +220°, λ_{max} 238 mμ (log ε 4.20).

Anal. Calcd for $C_{20}H_{26}O_2 \cdot {}^1/_3C_3H_6O$: C, 79.37; H, 8.88; O, 11.75. Found: C, 79.63; H, .46; O, 11.62.

19-Methylenetestosterone (IIId).—Lithium aluminum hydride (1.5 g) was added to a solution of IIIc (1.187 g) in tetrahydrofuran (10 ml) and the mixture was stirred at 20° for 1 hr. The excess of reagent was destroyed by the addition of ethyl acetate and saturated aqueous sodium sulfate solution, followed by anhydrous sodium sulfate. The inorganic salts were removed by filtration and washed well with ethyl acetate. Removal of the solvent gave a residue (2 g) which was dissolved in dioxane (50 ml). Dichlorodicyanobenzoquinone (1.187 g) was added, and the mixture was left at 20° for 72 hr. After dilution with benzene (200 ml), the mixture was filtered over a column of washed alumina (90 g) and the filtrate was evaporated to dryness. One crystallization of the residue from methylene chloride–acetone gave 0.875 g of crude IIId: mp 187–190°, raised by crystallizations from the same solvent pair to mp 191–193°; $[\alpha]_D$ +134°; λ_{max} 238–240 mμ (log ε 4.18).

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39; O, 10.65. Found: C, 79.96; H, 9.41; O, 10.82.

3β-Hydroxy-19-methylandrost-5-en-17-one (IIn).—A solution of IIj (1 g) in absolute ethanol (20 ml) was hydrogenated at 20° and 1 atm over a 5% palladium-on-charcoal catalyst. Filtration over Celite and removal of the solvent gave a product, which was filtered over a short column of washed alumina (2 g) in benzene–hexane (1:1) solution to afford 3β-hydroxy-19-methylandrost-5-en-17-one (IIn, 855 mg): mp 130–143, raised by crystallization from acetone–hexane to mp 142–145°; $[\alpha]_D$ +28°.

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00; O, 10.58. Found: C, 79.96; H. 9.96; O, 10.39.

3β-Hydroxy-19-methylandrost-5-en-17-one Acetate (III).—The methylene compound IIj (250 mg) was hydrogenated in ethanol solution (10 ml) over palladium-on-charcoal catalyst (5%, 54 mg) at 20° and 1 atm. After the uptake of 1 mole of hydrogen, the catalyst was removed by filtration. Removal of the solvent and crystallization of the residue from acetone–hexane gave III (170 mg): mp 134–136°, raised by recrystallizations from acetone–hexane to mp 134.5–136°; $[\alpha]_D$ +21°.

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36; O, 13.93. Found: C, 77.02; H, 9.48; O, 13.85.

19-Methylandrost-4-ene-3,17-dione (IIIe).—A solution of 3β-hydroxy-19-methylandrost-5-en-17-one (IIn, 630 mg) in dry toluene (31.5 ml) containing cyclohexanone (6.3 ml) and aluminum isopropoxide (1.26 g) was slowly distilled for a period of 1 hr to one-half the original volume. The reaction mixture was then diluted with water and the product was isolated by extraction with ethyl acetate. Adsorption onto alumina (18 g) and elution with hexane–benzene mixtures afforded IIIe (265 mg): mp 108–109°, raised by crystallizations from acetone–hexane to mp 109–111°; $[\alpha]_D$ +131°; λ_{max} 242 mμ (log ε 4.21).

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39; O, 10.65. Found: C, 80.11; H, 9.47; O, 10.56.

19-Methyltestosterone (IIIf).—A solution of 19-methylandrost-4-ene-3,17-dione (IIIe, 290 mg) in tetrahydrofuran (10 ml) was stirred at 20° with an excess of lithium aluminum hydride (500 mg) for a period of 1 hr. The excess of reagent was destroyed by the addition of ethyl acetate, and the product was isolated and oxidized with DDQ as described above (IIIc → IIId) to afford IIIf: 240 mg, mp 131–139°, raised by recrystallizations from acetone–hexane to mp 136–139°; $[\alpha]_D$ +53°; λ_{max} 242–244 mμ (log ε 4.21).

Anal. Calcd for $C_{20}H_{30}O_2 \cdot 0.5C_3H_6O$: C, 77.90; H, 10.03; O, 12.07. Found: C, 77.95; H, 9.79; O, 12.12.

10β-N,N-Diethylaminoethylimino-17-ethylenedioxy-3β-hydroxyandrost-5-ene (IIo).—A solution of the 10β-formyl derivative IIi (1 g) in N,N-diethylethylenediamine (10 ml) was heated under reflux for 18 hr and then evaporated to dryness under reduced pressure. The residue was dissolved in methanol (40 ml) containing potassium carbonate (2 g) and heated under reflux for 1 hr. The solution was then concentrated with ethyl acetate; the extract was washed with water, dried, and evaporated. The gummy residue was chromatographed over alumina (4 g) in hexane solution. Elution with hexane gave IIo: 690 mg; mp 85–92°, raised by crystallizations from hexane to mp 97–99°; $[\alpha]_D$ −176°.

Anal. Calcd for $C_{27}H_{44}N_2O_3$: C, 72.93; H, 9.97; N, 6.30; O, 10.80. Found: C, 73.32; H, 10.05; N, 6.25; O, 10.51.

Chromic Acid Oxidation of 3β,19-Dihydroxyandrost-5-en-17-one Acetate (IIa).—A solution of the 19-alcohol IIa (10 g) in acetone (300 ml) was treated with excess 8 *N* chromium trioxide (25 ml) at 0° for 10 min and then at 20° for 1 hr. The excess reagent was destroyed with aqueous sodium metabisulfite; the mixture was diluted with salt water and extracted with ethyl acetate. The organic extracts were extracted several times with 2% sodium hydroxide solution and with water, dried, and evaporated. Chromatography of the residue (5.78 g) on alumina (200 g) and elution with benzene–hexane (1:2) gave 3β-hydroxy-10β-formylandrost-5-en-17-one acetate (IIq), 560 mg, mp 151–152°, $[\alpha]_D$ −207°.

Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19; O, 18.58. Found: C, 73.25; H, 8.31; O, 18.53.

The original sodium hydroxide extracts were acidified with hydrochloric acid and extracted with ethyl acetate. The extracts were washed with water, dried, and evaporated, and the crude residue was dissolved in pyridine (10 ml) and acetic anhydride (5 ml). After standing at 20° for 16 hr, the excess of anhydride was destroyed with water and the mixture was poured into water. Filtration afforded 3β-hydroxyandrost-5-en-17-on-19-oic acid acetate (IIp, 3.02 g): mp 265–266°, raised by crystallizations from acetone–hexane to mp 265–267°; $[\alpha]_D$ −59° (lit[11,12,21] mp 252–253°, 253°; $[\alpha]_D$ −71°, −79°).

Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83; O, 22.20. Found: C, 69.57; H, 7.88; O, 22.63.

3β-Hydroxy-10β-formyl-19-norandrost-5-en-17-one (IIr). A.—A solution of 3β-hydroxy-10β-formyl-17-ethylenedioxyandrost-5-ene (IIm, 310 mg) in acetone (25 ml) containing concentrated hydrochloric acid (0.1 ml) was left at room temperature for 16 hr. After dilution with aqueous sodium bicarbonate solution (25 ml, 2%), the acetone was removed under reduced pressure and the mixture was extracted with ethyl acetate. The washed and dried extracts gave a dark oil which was filtered over alumina (4 g) in benzene solution. Removal of the solvent and crystallization from acetone–hexane gave IIr (220 mg): mp 133–146° dec, raised by further crystallizations to mp 141–146° dec; $[\alpha]_D$ −165°.

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67; O, 15.87. Found: C, 75.34; H, 8.51; O, 16.30.

B.—A solution of 3β-hydroxy-10β-formyl-19-norandrost-5-en-17-one acetate (IIq) in methanol (140 ml) containing potassium carbonate (1.4 g) was heated under reflux for 1 hr. Neutralization with acetic acid, concentration to a small volume, addition of water, and filtration followed by crystallization from acetone–hexane afforded IIr (1.06 g), mp 143–145° identical in all respects with the material prepared above.

3β-Hydroxyandrost-5-en-17-on-19-oic Acid Chloride 3-Acetate (IIs).—A solution of the 19-acid IIp (1 g) in anhydrous benzene (100 ml) was mixed with thionyl chloride (2 ml) and heated under

reflux for 2 hr. Evaporation of the solvents afforded the crude acid chloride IIs, mp 145–146°.

Anal. Calcd for $C_{21}H_{27}ClO_4$: Cl, 9.35. Found: C, 9.65. This product was not characterized further.

Reaction of the Acid Chloride IIs with Diethylamine.—Crude 3β-hydroxyandrost-5-en-17-on-19-oic acid chloride acetate (IIs, 5 g) was mixed with diethylamine (50 ml) and heated on the steam bath in a sealed tube for 8 hr. The reaction mixture was then poured into water. Isolation with ethyl acetate afforded a product which was adsorbed from benzene–hexane (1:4) onto alumina (200 g). Elution with the same solvent mixture first gave 3β-hydroxy-10β-N,N-diethylcarboxamido-19-norandrost-5-en-17-one acetate (IIt, 3.2 g): mp 158–161°, raised by crystallizations from acetone–hexane to mp 163–165°; $[\alpha]_D$ −69°.

Anal. Calcd for $C_{25}H_{37}NO_4$: C, 72.25; H, 8.98; N, 3.37; O, 15.40. Found: C, 71.57; H, 8.86; N, 3.50; O, 15.63.

Further elution with the same solvent pair gave mixed fractions followed by 3β-hydroxyandrost-5-en-17-on-19-oic acid anhydride 3-acetate (850 mg): mp 259–261°, raised by crystallizations from acetone–hexane to mp 261–262°; $[\alpha]_D$ −147°.

Anal. Calcd for $C_{42}H_{54}O_9$: C, 71.71; H, 7.74. Found: C, 71.175; H, 7.86.

The compound exhibited a strong band at 1800 cm^{-1} in the infrared while prolonged heating with water gave the acid IIp.

3β-Hydroxy-10β-N,N-diethylcarboxamido-19-norandrost-5-en-17-one (IIu).—A solution of 3β-hydroxy-10β-N,N-diethylcarboxamido-19-norandrost-5-en-17-one acetate (IIt, 5.6 g) in methanol (116 ml) containing potassium carbonate (5.6 g) was heated under reflux for 1 hr and then poured into water (500 ml). Filtration afforded IIu: 4.24 g; mp 194–196°, raised by crystallizations from acetone–hexane to mp 198–199°; $[\alpha]_D$ −50°.

Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.45; N, 3.75. Found: C, 73.96; H, 9.49; N, 3.93.

10β-N,N-Diethylcarboxamido-19-norandrost-4-en-3,17-dione (IIIg).—A mixture of 3β-hydroxy-10β-N,N-diethylcarboxamido-19-norandrost-5-en-17-one (IIu, 2 g), aluminum isopropoxide (4 g), cyclohexanone (40 ml), and dry toluene (200 ml) was slowly distilled to half the original volume in 1 hr. The solvents were then removed by steam distillation and the resulting aqueous suspension was cooled and filtered. The dried product was chromatographed over alumina (80 g) in hexane solution. Elution with hexane–benzene (2:1) gave the dione IIg: 1.25 g; mp 156–160°, raised by crystallizations from methanol–water to mp 164–165°; $[\alpha]_D$ +15°; λ_{max} 252 mμ (log ε 4.09).

Anal. Calcd for $C_{23}H_{33}NO_3$: C, 74.36; H, 8.95; N, 3.77; O, 12.92. Found: C, 74.56; H, 9.00; N, 3.81; O, 13.28.

10β-N,N-Diethylcarboxamido-19-norandrost-4-ene-3β,17β-diol (IVa).—Lithium aluminum hydride (1 g) was added to a solution of the dione IIIg (200 mg) in anhydrous tetrahydrofuran (20 ml), and the mixture was heated under reflux for 1 hr. The excess reagent was destroyed with ethyl acetate and aqueous sodium sulfate solution; the mixture was diluted with ethyl acetate, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The crystalline residue (120 mg, mp 240–244°) was purified by crystallization from acetone–hexane. The analytical sample of IVa showed mp 245–248°, $[\alpha]_D$ +44°.

Anal. Calcd for $C_{23}H_{37}NO_3$: C, 73.56; H, 9.93; N, 3.73; O, 12.78. Found: C, 73.59; H, 9.92; N, 3.40; O, 12.97.

17β-Hydroxy-10β-N,N-diethylcarboxamido-19-norandrost-4-en-3-one Acetate (IIIh).—A mixture of 10β-N,N-diethylcarboxamido-19-norandrost-4-ene-3β,17β-diol (IVa, 440 mg), dichlorodicyanobenzoquinone (DDQ, 440 mg), and dioxane (11 ml) was left at room temperature for 16 hr, diluted with methylene chloride (50 ml), and filtered over alumina (5 g). The filtrate was evaporated to dryness and the residue was acetylated in a mixture of pyridine (1 ml) and acetic anhydride (1 ml). The usual work-up afforded a gum which was filtered over alumina (2.0 g) in benzene solution and then crystallized from acetone–hexane to afford IIIh (244 mg): mp 136–138°, raised by recrystallizations from acetone–hexane to mp 141–142°; $[\alpha]_D$ −55°; λ_{max} 252–254 mμ (log ε 4.12).

Anal. Calcd for $C_{25}H_{37}NO_4$: C, 72.25; H, 8.98; N, 3.37. Found: C, 72.22; H, 8.99; N, 3.25.

19-Diethylaminoandrost-4-ene-3β,17β-diol (IVb).—Lithium aluminum hydride (6.25 g) was added to a solution of 10β-N,N-diethylcarboxamido-19-norandrost-4-ene-3,17-dione (IIIg, 1.25 g) in dioxane (125 ml) and the mixture was heated under reflux for 24 hr. The excess reagent was then destroyed with ethyl acetate and aqueous sodium sulfate solution; the mixture was diluted with ethyl acetate (500 ml), dried over anhydrous sodium sulfate, and filtered. Evaporation of the solvents gave the diol IVb: 970 mg; mp 195–202°, raised by recrystallizations from methanol–water to mp 207–209°; $[\alpha]_D$ +126°.

Anal. Calcd for $C_{23}H_{39}NO_2$: C, 76.40; H, 10.87; N, 3.87. Found: C, 76.34; H, 11.12; N, 3.70.

6β,19-Oxidotestosterone (Vb).—Sodium borohydride (3.6 g) in water (3.6 ml) was added to a solution of 6β,19-oxidoandrost-4-ene-3,17-dione (Va, 3.6 g) in methanol (360 ml), and the mixture was stirred for 1 hr at 20°. The mixture was then neutralized with acetic acid and diluted with water (2 l.), and the organic material was extracted with ethyl acetate. The washed and dried extracts were evaporated to dryness and the crude residue was dissolved in dioxane (180 ml). Dichlorodicyanobenzoquinone (3.6 g) was added to the dioxane solution and the mixture was allowed to react for 20 hr at 20°. Methylene chloride (200 ml) was added and the mixture was percolated through a column of washed alumina (200 g), washing with a further 200 ml of methylene chloride. The combined filtrates were evaporated to dryness and the semisolid residue was crystallized from acetone–hexane, giving 2.5 g of Vb: mp 63–65°, raised by crystallizations to mp 72–75°; $[\alpha]_D$ −96°; λ_{max} 238–242 mμ (log ε 4.02) (lit.[11] mp 78–80°, 127–130°; $[\alpha]_D$ −99°).

Anal. Calcd for $C_{19}H_{26}O_3 \cdot 0.5CH_3COCH_3$: C, 74.28; H, 8.82; O, 16.90. Found: C, 74.38; H, 8.68; O, 17.17.

5α-Bromo-6β,19-oxido-17α-ethinylandrostane-3β,17β-diol (Ie).—A solution of 3β-hydroxy-5α-bromo-6β,19-oxidoandrostan-17-one (Id, 5 g) in dry *t*-butyl alcohol (30 ml) was added to a solution of potassium (5 g) in *t*-butyl alcohol (100 ml). A stream of dry and pure acetylene was bubbled through the mixture for 12 hr, and then a solution of ammonium chloride (5 g) in water (100 ml) was added. The mixture was then acidified with concentrated hydrochloric acid (10 ml) and evaporated under vacuum to remove the organic solvent. The resulting precipitate was filtered, dried, and dissolved in chloroform, and the solution was filtered over washed alumina (10 g). The resulting product was crystallized from methylene chloride–benzene to afford Ie (2.1 g): mp 249° dec, raised by crystallizations to mp 252° dec (crystal change at 215°); $[\alpha]_D$ −27°.

Anal. Calcd for $C_{21}H_{29}BrO_3$: C, 61.61; H, 7.13; Br, 19.52; H, 11.73. Found: C, 61.63; H, 7.15; Br, 19.39; O, 11.93.

17β-Hydroxy-5α-bromo-6β,19-oxido-17α-ethinylandrostan-3-one (VI).—A solution of the diol Ie (365 mg) in 80% aqueous acetic acid (8.5 ml) was cooled to 8° and mixed with a solution of chromium trioxide (220 mg) in 90% aqueous acetic acid (2.5 ml). The mixture was stirred for 3 hr, maintaining the temperature at 8°, and then poured into a saturated sodium chloride solution (50 ml) containing sodium bisulfite (500 mg). The formed precipitate was filtered off, washed with water, and dried. Crystallization of this material from a small amount of acetone afforded VI (50 mg.): mp 170–175° dec, raised by further crystallizations from tetrahydrofuran–water and tetrahydrofuran–hexane to mp 180° dec.

Anal. Calcd for $C_{21}H_{27}BrO_3$: C, 61.91; H, 6.68; Br, 19.62; O, 11.78. Found: C, 61.81; H, 6.90; Br, 19.74; O, 11.88.

The mother liquors of VI afforded starting material Ie as the sole identifiable compound. Other oxidation conditions (chromium trioxide in aqueous acetic acid at lower and higher temperatures, 8 *N* chromic acid in sulfuric acid–acetone mixture,[17] and sodium bichromate in aqueous sulfuric acid and ether in a two-phase system[23]) furnished either starting material Ie or complex mixtures from which only minute amounts of the desired compound VI could be isolated, accompanied by the dione Va and Id. The latter compounds were identified by melting point, analyses, and infrared spectra comparison with authentic samples.

5α-Bromo-6β,19-oxido-17α-ethinylandrostane-3β,17β-diol 3-Acetate (If).—A solution of 5α-bromo-6β,19-oxido-17α-ethinylandrostane-3β,17β-diol (Ie, 200 mg) in pyridine (0.5 ml) and acetic anhydride (0.5 ml) was left at 20° for 16 hr and then evaporated to dryness. Crystallization from methanol–water afforded 185 mg of If, mp 200–204°. The analytical sample, from the same solvent pair, had mp 206–207°, $[\alpha]_D$ −31°.

Anal. Calcd for $C_{23}H_{31}BrO_4$: C, 61.19; H, 6.92; Br, 17.71. Found: C, 61.51; H, 7.00; Br, 19.19.

5α-Bromo-6β,19-oxido-17α-ethinylandrostane-3β,17β-diol Diacetate (Ig).—A mixture of 5α-bromo-6β,19-oxido-17α-ethinyl-

(23) H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2952 (1961).

androstane-3β,17β-diol (Ie, 1.43 g), acetic acid (28.3 ml), acetic anhydride (5.66 ml), and *p*-toluenesulfonic acid (283 mg) was stirred under a nitrogen atmosphere for 3 hr at 20°. Water was slowly added until the steroid had precipitated completely. Filtration afforded the crude diacetate Ig (mp *ca.* 200° subl), which was recrystallized from methylene chloride–hexane to give the analytical sample of Ig, mp 199–204° subl, $[\alpha]D$ −42°.

Anal. Calcd for $C_{25}H_{33}BrO_5$: C, 60.85; H, 6.74; Br, 16.20; O, 16.21. Found: C, 61.39; H, 6.67; Br, 15.71; O, 16.05.

5α-Bromo-6β,19-oxido-17α-ethinylandrostane-3β,17β-diol 17-Acetate (Ih).—To a suspension of 5α-bromo-6β,19-oxido-17α-ethinylandrostane-3β,17β-diol diacetate (Ig, 4 g) in absolute methanol (100 ml) was added a solution of pure sodium hydroxide (62.5 mg of 97% purity) in dry methanol (4 ml). After stirring at 20° under a nitrogen atmosphere for 80 min, the solution became homogeneous. Stirring was continued for a further 40 min, then the solution was neutralized with a few drops of concentrated hydrochloric acid and concentrated to low volume. This was poured into water and the formed precipitate was filtered off, washed, and dried. The crude Ih (3.6 g, mp 190–192°) was crystallized from acetone–hexane to furnish the analytical sample, mp 193–195°, $[\alpha]D$ −38°.

Anal. Calcd for $C_{23}H_{31}BrO_4$: C, 61.19; H, 6.92; Br, 17.71; O, 14.18. Found: C, 61.93; H, 7.46; Br, 17.65; O, 14.12.

17α-Ethinylandrost-5-ene-3β,17β,19-triol 17-Acetate (IIv).—A mixture of 5α-bromo-6β,19-oxido-17α-ethinylandrostane-3β,17β-diol 17-acetate (Ih, 1 g), zinc powder (2 g), and ethanol (20 ml) was heated under reflux for 4 hr, filtered, and evaporated. The residue was crystallized from methanol–water to afford IIv (0.72 g, mp 225–229°). The analytical sample showed mp 230–232°, $[\alpha]D$ −116°.

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66; O, 17.18. Found: C, 74.28; H, 8.68; O, 17.29.

17β,19-Dihydroxy-17α-ethinylandrost-4-en-3-one 17-Acetate (IIIi).—A solution of 17α-ethinylandrost-5-ene-3β,17β,19-triol 17-acetate (IIv, 1.5 g) in toluene (90 ml) was heated until a few milliliters of solvent had distilled off. To the hot solution were added cyclohexanone (6 ml) and aluminum isopropoxide (300 mg), and the mixture was then heated under reflux for 10 min. The cooled suspension was neutralized with acetic acid (0.3 ml) and steam distilled. The aqueous residue was extracted with chloroform, and the extracts were dried and then percolated over a column of washed alumina (20 g), washing with chloroform. The combined eluates were evaporated, giving the desired IIIi (mp 140–146°, 600 mg). Crystallizations from acetone–hexane afforded the pure compound, mp 158–162° $[\alpha]D$ +28°, λ_{max} 242–244 mμ (log ϵ 4.20).

Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16; O, 17.28. Found: C, 74.67; H, 8.28; O, 17.35.

17β-Hydroxy-17α-ethinylandrost-4-en-3-on-19-oic Acid 17-Acetate (IIIj).—A solution of 17β,19-dihydroxy-17α-ethinylandrost-4-en-3-one 17-acetate (IIIi, 100 mg) in acetone (10 ml) was cooled to 0–5° and oxidized with 8 *N* chromic acid in aqueous sulfuric acid during 1 hr. The excess of reagent was destroyed by the addition of sodium bisulfite solution; the mixture was poured into water and extracted with methylene chloride. The extracts were washed three times with 10 ml of 2% aqueous sodium hydroxide solution, and the combined basic extracts were then carefully acidified with concentrated hydrochloric acid and reextracted with methylene chloride. After being dried and concentrated to a small volume in a stream of air, the extracts were diluted with hexane and concentration was continued in an air stream until abundant precipitation occurred. The crude material was filtered off (635 mg, mp 143–149°) and crystallized several times as above to furnish the analytical sample of IIIj, mp 150–153°, $[\alpha]D$ +76°, λ_{max} 242 mμ (log ϵ 4.07).

Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34; O, 20.81. Found: C, 71.37; H, 7.67; O, 20.73.

17β-Hydroxy-17α-ethinyl-19-norandrost-4-en-3-one 17-Acetate (IIIk).—A solution of 17β-hydroxy-17α-ethinylandrost-4-en-3-on-19-oic acid 17-acetate (IIIj, 100 mg) in methanol (15 ml) containing concentrated hydrochloric acid (4 drops) was heated under reflux for 1 hr, neutralized with aqueous sodium hydroxide solution, concentrated to small bulk, and poured into water. The formed precipitate was filtered off, washed with water, and dried. The crude material (65 mg, mp 148–154°) was crystallized from acetone–hexane to give pure IIIk, mp 160–162°, identical in all respects with an authentic sample.

Stereochemical Studies. II.[1] Conformational Analysis of Δ^5-3-Keto Steroids[2]

MALKA GORODETSKY, AMNON YOGEV, AND YEHUDA MAZUR

Department of Organic Chemistry, Weizmann Institute of Science, Rehovoth, Israel

Received August 9, 1965

The conformation of ring A in Δ^5-3-keto steroids was determined through ultraviolet absorption, circular dichroism, and optical rotatory dispersion data. In most of the Δ^5-3-keto steroids investigated, a coupling of the two chromophores was observed as indicated by increased n → π^* transitions and the appearance of $\pi \rightarrow \pi^*$ transitions of the β,γ-unsaturated carbonyl group. Introduction of a C-7 keto function to a "coupled" Δ^5-3-keto system caused additional enhancement of the n → π^* transitions of the isolated C-3 carbonyl group and changed markedly the normal ultraviolet pattern of the α,β-unsaturated carbonyl chromophore. An absence of the interaction characteristics in 4,4-dialkyl Δ^5-3-ketones indicates a quasi-boat conformation for its ring A. Supporting evidence for the latter was found in the nmr data.

Recent literature contains ample and detailed information on the conformational studies of cyclic saturated ketones.[3] The method most widely used for conformational analysis involves studies of the rotatory properties of the carbonyl chromophor of unsymmetrical molecules. This method allows determination of the position of the carbonyl group in relation to other bonds in the molecule, and thereby enables elucidation of the conformation of the ring containing the carbonyl group.[4] This rather simple situation becomes more involved when the cyclic ketone contains a double bond in the neighborhood of the carbonyl group. In some of the latter instances an interaction occurs between the two chromophores causing, among others, changes in the rotatory properties of the carbonyl group, thereby invalidating deductive analogies with the saturated compounds.[4] On the other hand, this very interaction of the carbonyl and double-bond chromophores can be used to establish their relative

(1) Part I: M. Gorodetsky, D. Amar, and Y. Mazur, *J. Am. Chem. Soc.*, **86**, 5218 (1964).

(2) Part of this material was published in a preliminary form: M. Gorodetsky and Y. Mazur, *Tetrahedron Letters*, 227 (1964).

(3) M. Balasubramanian, *Chem. Rev.*, **62**, 591 (1962); G. R. Chaudhry, T. G. Halsall, and E. R. H. Jones, *J. Chem. Soc.*, 2725 (1961); A. Lablache-Combier, J. Levisalles, J. P. Pete, and H. Rudler, *Bull. Soc. Chim. France*, 1689 (1963).

(4) (a) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960; (b) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 4013 (1961); (c) for recent examples, see K. M. Wellamn, P. H. A. Laur, W. S. Briggs, A. Moscowitz, and C. Djerassi, *ibid.*, **87**, 66 (1965), and previous publications.