1,1-dichloro-2,2-dimethoxyhexane, b.p. 56–57° (1 mm.), $n^{20}D$ 1.4552. The infrared and proton n.m.r. spectra of this product were identical with those obtained on the product from the 1-hexyne-N-chlorosuccinimide reaction.

Anal. Calcd. for $C_8H_{16}Cl_2O_2$: C, 44.60; H, 7.50; Cl, 32.96. Found: C, 44.46; H, 7.66; Cl, 32.81.

Acknowledgment.—The author would like to show his appreciation to Dr. Frederic A. Johnson and Mrs. Carolyn Haney for the interpretation of the proton n.m.r. spectra and to Mr. J. O. Woods for technical assistance.

Steroids. CCLXXVIII.[1] Reductions of 19-Substituted Androst-4-en-3-ones and Related Compounds

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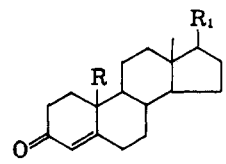
Catalytic hydrogenation of 19-hydroxy-Δ^4-3-keto steroids affords predominantly A,B-*cis* dihydro derivatives. Unexpectedly, reduction in a lithium–ammonia system also gave substantial yields of the A,B-*cis* isomer. Hydrogenation of the esters and ethers of the 19-hydroxy compounds led in general to significant increases in the yields of A,B-*trans* isomers. The reduction of some 19-chloro-Δ^5- and -Δ^4-androstenes is also discussed.

The reduction of steroidal Δ^4-3-ketones by catalytic and chemical means has been well documented. In general, the catalytic hydrogenation of these compounds (Δ^4-3-ketones unsubstituted at C-11 and C-19) leads to mixtures of the 5α- and 5β-dihydro compounds with the latter isomer predominating.[3] Birch reduction, on the other hand, affords the A,B-*trans* dihydro compounds exclusively.[4] However, few examples have been reported of the catalytic[5] and chemical reductions of 19-substituted Δ^4-3-ketones.

In a number of interrelated investigations carried out in these laboratories as a part of our general interest in 19-substituted steroids,[6] we had occasion to study qualitatively the hydrogenation of some 19-substituted Δ^4- and Δ^5-androstenes. In view of the limited experimental data available on this topic we wish to report a summary of our collected results.[7]

We first examined the hydrogenation of 17β,19-dihydroxyandrost-4-en-3-one (19-hydroxytestosterone)[9] (Ia) which was readily available by sodium borohydride reduction of 19-hydroxyandrost-4-ene-3,17-dione (Ib)[9] under Norymberski conditions.[10] Thus, hydrogenation of Ia in ethanol over 5% palladized charcoal at 3 atm. afforded a mixture from which two isomeric



Ia, R = CH_2OH; R_1 = OH (--H)

b, R = CH_2OH; R_1 = O

c, R = CH_2OH; R_1 = ketal

d, R = CH_2OCOCH_3; R_1 = $OCOCH_3$ (---H)

e, R = CH_2OCOCH_3; R_1 = O

f, R = CH_2OCOCH_3; R_1 = ketal

g, R = CH_2O-ketal; R_1 = ketal

h, R = CH_2O-tosylate; R_1 = O

i, R = CO_2H; R_1 = O

j, R = CH_2Cl; R_1 = O

dihydro compounds, m.p. 183–185° and 150–151°, could be isolated in yields of 90 and 3%, respectively. The structure of the higher melting isomer was firmly established as 17β,19-dihydroxy-5β-androstan-3-one (IIa) by rotatory dispersion since it exhibited a negative Cotton-effect curve characteristic for an A,B-*cis*-3-keto steroid.[11] Acetylation of this product afforded the diacetate IIg while reduction with lithium aluminum hydride gave 5β-androstane-3α,17β,19-triol (IIIc)[12] in high yield.

The lower melting isomer exhibited a positive Cotton effect curve in agreement with its formulation as 17β,19-dihydroxy-5α-androstan-3-one (IIb).[11] Lithium aluminum hydride reduction of this substance produced 5α-androstane-3β,17β,19-triol (IIId).

(1) Paper CCLXXVII: A. D. Cross, P. W. Landis, and J. W. Murphy, submitted for publication.

(2) To whom inquiries should be addressed: Syntex Research Center, Stanford Industrial Park, Palo Alto, Calif.

(3) For examples see (a) L. F. Fieser and M. Fieser in "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 272; (b) H. I. Hadler, *Experientia*, **11**, 175 (1955); (c) M. Harnik, *Steroids*, **3**, 359 (1964).

(4) A. J. Birch and H. Smith, *Quart. Rev.* (London), **12**, 17 (1958); A. Bowers, H. J. Ringold, and E. Denot, *J. Am. Chem. Soc.*, **80**, 6115 (1958).

(5) Catalytic hydrogenations of 19-substituted Δ^4-3-ketones in the cardiac aglycone series have been described. See G. Volpp, G. Baumgartner, and Ch. Tamm, *Helv. Chim. Acta*, **42**, 1418 (1959); J. S. Baran, *J. Org. Chem.*, **29**, 527 (1964). A predominance of the 5β isomer was obtained in the examples cited.

(6) (a) O. Halpern, P. Crabbé, A. D. Cross, I. Delfin, L. Cervantes, and A. Bowers, *Steroids*, **4**, 1 (1964); (b) B. Berkoz, E. Denot, and A. Bowers, *ibid.*, **1**, 251 (1963); (c) O. Halpern, R. Villotti, and A. Bowers, *Chem. Ind.* (London), 116 (1963); (d) A. Bowers, R. Villotti, J. A. Edwards, E. Denot, and O. Halpern, *J. Am. Chem. Soc.*, **84**, 3204 (1962).

(7) It is a pleasure to acknowledge a mutual exchange of results with Dr. K. Schaffner of the Eidg. Technische Hochschule, Zurich, prior to publication.[8]

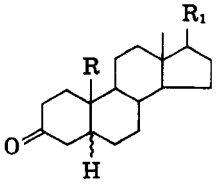
(8) D. Hauser, K. Heusler, J. Kalvoda, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **47**, 1961 (1964).

(9) (a) M. Ehrenstein and K. Otto, *J. Org. Chem.*, **24**, 2006 (1959); (b) K. Heusler, J. Kalvoda, Ch. Meystre, H. Uberwasser, P. Wieland, G. Anner, and A. Wettstein, *Experientia*, **18**, 464 (1962).

(10) J. K. Norymberski and G. F. Woods, *J. Chem. Soc.*, 3426 (1955).

(11) See C. Djerassi in "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, pp. 49, 50.

(12) Assignment of the 3α configuration to the product IIIc follows from the observation that lithium aluminum hydride reduction of 3-keto 5β-steroids yields the 3α-alcohol. *Inter alia*, see C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 687 (1950).



IIa, R = CH_2OH; R_1 =  ; with 5β-hydrogen

b, R = CH_2OH; R_1 =  ; with 5α-hydrogen

c, R = CO_2H; R_1 = O; with 5α-hydrogen

d, R = CH_2OH; R_1 = O; with 5β-hydrogen

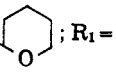
e, R = CH_2OH; R_1 =  ; with 5β-hydrogen

f, R = CH_2OCOCH_3; R_1 =  ; with 5α-hydrogen

g, R = CH_2OCOCH_3; R_1 =  ; with 5β-hydrogen

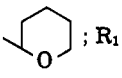
h, R = CH_2OCOCH_3; R_1 = O; with 5β-hydrogen

i, R = CH_2OCOCH_3; R_1 =  ; with 5β-hydrogen

j, R = CH_2O  ; R_1 = ; with 5β-hydrogen

k, R = CH_2O tosylate; R_1 = O; with 5α-hydrogen

l, R = CO_2H; R_1 = O; with 5β-hydrogen

m, R = CH_2O  ; R_1 = ; with 5α-hydrogen

n, R = CH_2Cl; R_1 = O; with 5α-hydrogen

o, R = CH_2OH; R_1 = O; with 5α-hydrogen.

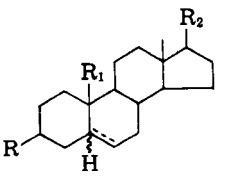
Chemical evidence to support the foregoing conclusions was forthcoming from the following sequence of reactions. Hydrogenation of 3β,19-dihydroxyandrost-5-en-17-one (IIIa)[13] over 10% palladized charcoal gave in good yield the 5α-dihydro compound IIIb. When this substance was oxidized with an excess of 8 *N* chromium trioxide–sulfuric acid reagent in acetone solution[14] two products were obtained, namely 3,17-dioxo-5α-androstan-19-oic acid (IIc) and 3β-hydroxy-17-oxo-5α-androstan-19-oic acid 3,19-lactone (IV). Since the 3β,19-lactone bridge is only possible in A,B-*trans* fused androstanes, it follows that the lactone IV, its companion acid IIc, and its precursor all possess the 5α stereochemical arrangement.

Reduction of the lactone IV and 3β,19-dihydroxy-5α-androstan-17-one (IIIb) with lithium aluminum hydride afforded 5α-androstane-3β,17β,19-triol (IIIc) which was identical in all respects with the triol obtained from the analogous reduction of 17β,19-dihydroxy-5α-androstan-3-one (IIb).

Under identical conditions the catalytic hydrogenation of 19-hydroxyandrost-4-ene-3,17-dione[6d] (Ib) afforded a mixture which was separated by fractional crystallization into two pure isomers, m.p. 137–138°

(13) O. Halpern, unpublished results from these laboratories.

(14) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).



IIIa, R =  ; R_1 = CH_2OH; R_2 = O; with Δ⁵ double bond

b, R =  ; R_1 = CH_2OH; R_2 = O; with 5α-hydrogen

c, R =  ; R_1 = CH_2OH; R_2 =  ; with 5β-hydrogen

d, R = R_2 =  ; R_1 = CH_2OH; with 5α-hydrogen

e, R =  ; R_1 = CH_2Cl; R_2 = O; with Δ⁵ double bond

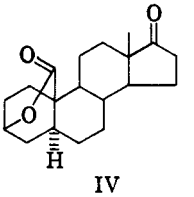
f, R =  ; R_1 = CH_2Cl; R_2 = O; with 5α-hydrogen

g, R =  ; R_1 = CH_2Cl; R_2 = O; with 5α-hydrogen

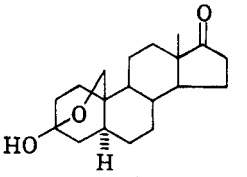
h, R =  ; R_1 = CH_2Cl; with 5α-hydrogen; R_2 = O

i, R =  ; R_1 = CH_2Cl; with 5α-hydrogen; R_2 = O

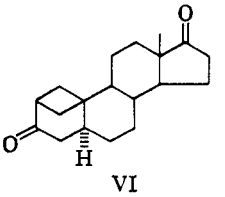
and 208–209°, in yields of 12 and 67%, respectively. While the more abundant isomer exhibited the expected carbonyl bands in the infrared at 1705 and 1735 cm.$^{-1}$, the second product displayed a single well-resolved band at 1735 cm.$^{-1}$. Clearly the 3-carbonyl group in the latter substance is masked by internal hemiketal formation (see structure V), an arrangement which requires the 5α stereochemistry for this product. Thus, hydrogenation of 19-hydroxyandrost-4-ene-3,17-dione (Ib) also proceeds essentially by β-face addition giving 19-hydroxy-5β-androstane-3,17-dione (IId) as the principal product. In accordance with these assignments it was found that lithium aluminum hydride reduction of the hemiketal V gave the known *trans*-triol IIId while the *cis* isomer IId was reduced in the same manner to the previously described 5β-androstane-3α,17β,19-triol (IIIc).



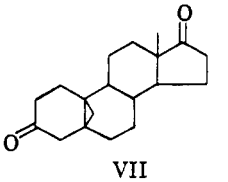
IV



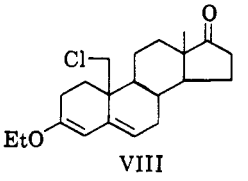
V



VI



VII



VIII

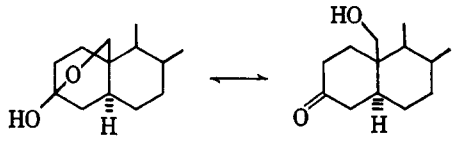


Figure 1

It was later observed that the hemiketal V existed in equilibrium with the 19-hydroxy 3-ketone (see Figure 1). Mixtures of the two forms varied in melting point from 137–181° with the pure dione, m.p. 178–181°, exhibiting absorption bands in the infrared at 1700 and 1735 cm.$^{-1}$ for the C-3 and C-17 carbonyl functions, respectively (see Experimental).

Catalytic hydrogenation of 17-cycloethylenedioxy-19-hydroxyandrost-4-en-3-one (Ic)[15] again led to a predominance of the 5β isomer and the 17-cycloethylenedioxy-19-hydroxy-5β-androstan-3-one (IIe) was isolated in 42% yield. This substance exhibited the negative Cotton-effect curve of an A,B-*cis*-3-keto steroid[11] and it furnished 19-hydroxy-5β-androstane-3,17-dione (IId) in excellent yield after hydrolysis with hydrochloric acid in boiling methanol.

When the C-19 hydroxyl group was replaced by acetate, then reduction of the corresponding Δ^4-3-ketones resulted in lower yields of the 5β isomers. Thus, hydrogenation of 19-hydroxytestosterone 17,19-diacetate[9a] (Id) with 5% palladium on charcoal gave a mixed product which could be separated by careful chromatography on Florisil into the corresponding 5α- and 5β-dihydro derivatives IIf and IIg in yields of 38 and 32%, respectively. Structural assignments for these products were again firmly established by their optical rotatory dispersion curves (see Experimental). Furthermore, alkaline hydrolysis of the two dihydro diacetates IIf and IIg afforded the 5α- and 5β-dihydroxy ketones IIb and IIa, respectively.

Similarly, catalytic hydrogenation of crystalline 19-acetoxyandrost-4-ene-3,17-dione[16] (Ie) yielded a mixed product from which the 5β-dihydro derivative IIh could be isolated in 35% yield by direct crystallization. The stereochemistry of this product was established by alkaline hydrolysis which provided 19-hydroxy-5β-androstane-3,17-dione (IId) in good yield. Attempts to obtain the 5α isomer by column chromatography were fruitless since oily material was obtained and its composition could not be reliably assessed by thin layer chromatography. Therefore, the mother liquors were saponified and, after purification, the hemiketal V was obtained in 14% yield.

When 19-acetoxy-17-cycloethylenedioxyandrost-4-en-3-one[15] (If) was hydrogenated with 10% palladized charcoal in ethanol, the corresponding 5β-dihydro compound IIi was obtained in 63% yield. This substance exhibited a negative rotatory dispersion curve, and it gave the previously described 17-cycloethylenedioxy-19-hydroxy-5β-androstan-3-one (IIe) on hydrolysis with dilute methanolic sodium hydroxide.

Substitution of the 19-acetate for a pyranyl ether grouping did not appreciably increase the amount of 5α isomer in the reduction of the corresponding Δ^4-3-keto derivative. In one experiment a 72% yield of the 5β-dihydro compound IIj was obtained when 17-cycloethylenedioxy-19-hydroxyandrost-4-en-3-one 19-tetrahydropyranyl ether[15] (Ig) was reduced with 10% palladized charcoal in ethanol at atmospheric pressure. On treatment with methanolic hydrogen chloride this product gave a diketo alcohol, m.p. 207–208°, which was identical in all respects with 19-hydroxy-5β-androstane-3,17-dione (IId)

In a second experiment, the same pyranyl ether derivative was reduced with 5% palladized charcoal at 2–3 atm. and this led to an increased amount of α-face hydrogenation, although the 5β isomer was still the major component. Prior to isolation, the crude hydrogenation mixture was exposed to dilute methanolic hydrogen chloride to remove the pyranyl ether and ketal functions. After purification there were obtained 19-hydroxy-5β-androstane-3,17-dione (IId) and 3β,19-dihydroxy-5α-androstan-17-one (IIIb) in 50 and 36% yield, respectively.

A significant change in the proportion of 5α- and 5β-dihydro compounds was found when the 19-tosyloxy Δ^4-3-ketone Ih[6a] was reduced with 10% palladium catalyst in ethyl acetate solution. On the basis of thin layer chromatography the crude hydrogenation product appeared to be a 7:3 mixture of 5α and 5β isomers from which the former was isolated in low yield. The stereochemistry of the 5α isomer IIk followed from the observation that its reduction with lithium aluminum hydride gave a triol, m.p. 233–234°, which was shown to be identical with 5α-androstane-3β,17β,19-triol (IIIc) by mixture melting point and infrared comparison. Attempts to establish the presence of the 5β isomer in the crude dihydro tosylate mixture by hydrolysis to the corresponding 19-alcohols with sodium hydroxide in methanol led to recovered starting material. If the hydrolysis was carried out under more vigorous conditions (10% potassium hydroxide in boiling ethylene glycol), then a cyclization reaction occurred and a product, tentatively assigned the structure of 2β,19-cyclo-5α-androstane-3,17-dione (VI), was isolated in 55% yield.

Finally lithium aluminum hydride reduction of the crude hydrogenation mixture afforded 5β-androstane-3α,17β,19-triol (IIIc) in low yield, in addition to the expected 5α-androstane-3β,17β,19-triol (IIId).

A second example in which a predominance of α-face hydrogenation occurred was noted in the reduction of 3,17-dioxoandrost-4-en-19-oic acid[6c] (Ii). Thus the palladium-catalyzed hydrogenation of this substance gave in 63% yield the corresponding 3,17-dioxo-5α-androstan-19-oic acid (IIc) identical in all respects with a sample prepared by an unambiguous synthesis (*vide supra*).

The authentic A,B-*cis*-diketo acid III was obtained by oxidation of 19-hydroxy-5β-androstane-3,17-dione (IIa) and showed the required rotatory dispersion curve for this stereoisomer.

While catalytic hydrogenation of the various 19-hydroxy Δ^4-3-ketones provided an efficient route to 19-oxygenated 5β-steroids, the 5α isomers could be obtained in moderate yields only by hydrogenation of the 19-acetoxyenones. It was anticipated that Birch reduction[4] would provide a superior route to the 19-oxygenated 5α-steroids and accordingly 19-hydroxytestosterone (Ia) was treated with lithium in liquid ammonia and ammonium chloride. Unexpectedly

(15) E. Blossey, unpublished results from these laboratories.

(16) This substance was previously reported as an uncrystallizable oil by A. S. Meyer [*Experientia*, 11, 99 (1955)].

TABLE I

CATALYTIC HYDROGENATION OF 19-SUBSTITUTED Δ^4-3-KETONES

Substrate	Method[a]	Yield of dihydro compounds or related products isolated—— % 5α	% 5β
19-Hydroxytestosterone (Ia)	A	3	90
19-Hydroxyandrost-4-ene-3,17-dione (Ib)	A	12	67
17-Cycloethylenedioxy-19-hydroxyandrost-4-en-3-one (Ic)	B	Not isolated	72
19-Hydroxytestosterone 17,19-diacetate (Id)	A	38	32
19-Hydroxyandrost-4-ene-3,17-dione 19-acetate (Ie)	A	14	35
17-Cycloethylenedioxy-19-hydroxyandrost-4-en-3-one 19-acetate (If)	B	Not isolated	63
17-Cycloethylenedioxy-19-hydroxyandrost-4-en-3-one 19-tetrahydropyranyl ether (Ig)	A	36	50
	B	Not isolated	72
19-Hydroxyandrost-4-en-3,17-dione 19-tosylate (Ih)	B	55[b]	Not isolated
3,17-Dioxoandrost-4-en-19-oic acid (Ii)	B	63	Not isolated
19-Chloroandrost-4-en-3,17-dione (Ij)	With platinum catalyst	Not isolated[c]	Not isolated

[a] With method A the substance was hydrogenated over 5% Pd–C catalyst at 2–3 atm. With method B the substance was hydrogenated over 10% Pd–C catalyst at atmospheric pressure. [b] The crude hydrogenation product appeared to be a 7:3 mixture of the 5α- and 5β-dihydro compounds by thin layer chromatography. [c] The crude hydrogenation product appeared to be a 1:1 mixture of 5α- and 5β-dihydro compounds by thin layer chromatography.

the major product from this reaction was 17β,19-dihydroxy-5β-androstan-3-one (IIa) accompanied by a smaller quantity of 5α-androstane-3β,17β,19-triol (IIId). The yields of IIa and IIId were 53 and 19%, respectively.

The triol IIId is formed by the normal Birch reduction process involving protonation of the more stable α-oriented carbanion at C-5,[17] followed by reduction of the carbonyl function of the intermediate A,B-*trans*-keto diol IIb. The formation of the 5β-dihydro derivative IIa is attributed to a fast internal delivery of a proton from the 19-hydroxyl group to the kinetic (5β) carbanion.

As expected, the metal–ammonia reduction proceeded normally when the 19-hydroxyl group was protected as the pyranyl ether. Thus Birch reduction of 17-cycloethylenedioxy-19-hydroxyandrost-4-en-3-one 19-tetrahydropyranyl ether (Ig) afforded the A,B-*trans* ketone IIm after oxidation of the crude product with either 8 *N* chromium trioxide–sulfuric acid reagent[12] or manganese dioxide.[18] Removal of the protecting groups at C-17 and C-19 by mild acid hydrolysis furnished the hemiketal V in good yield.

Finally, we examined the reduction of some 19-chloroandrostene derivatives. Hydrogenation of 19-chloro-3β-hydroxyandrost-5-en-17-one acetate (IIIe)[6c] in ethyl acetate over a 10% palladium-on-charcoal catalyst at atmospheric pressure afforded the 5α-dihydro derivative IIIf (65% yield) which was hydrolyzed with methanolic potassium carbonate to the corresponding 3β-ol IIIg. Oxidation of the latter gave 19-chloro-5α-androstane-3,17-dione (IIn) which exhibited the expected rotatory dispersion curve of an A,B-*trans* 3,17-diketone.[11]

Unfortunately, the above hydrogenation lacked reproducibility, and a more satisfactory route was sought. Hydrogenation of the 19-chloro Δ^4-3-ketone Ij[6c] in ethyl acetate over a platinum catalyst gave a 1:1 mixture of the corresponding dihydro derivatives from which the pure 5α isomer IIn could be isolated only in low yield. Attempts to prepare the *trans* isomer by Birch reduction proved equally unsatisfactory. Exposure of 19-chloroandrost-4-ene-3,17-dione (Ij) to lithium in liquid ammonia followed by oxidation provided in 50% yield the known 5β,19-cycloandrostane-3,17-dione[19] (VII) and only traces of the *trans*-chloro compound IIn. The cyclopropane VII was not an unexpected product since related cyclizations have been reported in the bicyclic[17b] and steroid[19] series with tosylate rather than chlorine serving as the departing group.

Reproducible yields of 19-chloro-5α-androstane-3,17-dione (IIn) were obtained by hydrogenation of 19-chloro-3-ethoxyandrosta-3,5-dien-17-one (VIII) with platinum in ethyl acetate. Chromatography on silica gel gave in 42% yield the desired 19-chloro-5α-androstane-3,17-dione (IIn). There was also isolated in low yield 19-chloro-5α-androstan-17-one (IIIh) and its 3β-ethoxy derivative IIIi. The structures of these two products were assigned on the basis of their elemental analyses and n.m.r. data.

In Table I the hydrogenations of the various 19-substituted steroids are summarized. Since these experiments are in most cases qualitative in nature, conclusions relating the effect of the substituent on product stereochemistry are questionable. However, it appears from the data that α-face hydrogenation is facilitated by the larger C-19 substituents in agreement with the steric-hindrance principle of catalytic hydrogenation.[20]

Experimental[21]

17β-19-Dihydroxyandrost-4-en-3-one (19-Hydroxytestosterone, Ia).—A solution of 20 g. of 19-hydroxyandrost-4-ene-3,17-dione (Ib)[9] in 3 l. of methanol was treated with 2.8 g. of sodium borohydride for 1 hr. at 0°. The mixture was then neutralized

(17) (a) D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954); (b) G. Stork and J. Tsuji, *J. Am. Chem. Soc.*, **83**, 2793 (1961).

(18) I. T. Harrison, *Proc. Chem. Soc.*, 110 (1964).

(19) L. H. Knox, E. Velarde, and A. D. Cross, *J. Am. Chem. Soc.*, **85**, 2533 (1963); J. J. Bonet, H. Wehrli, and K. Schaffner, *Helv. Chim. Acta*, **45**, 2615 (1962).

(20) R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine, and R. Whetstone, *J. Am. Chem. Soc.*, **64**, 1985 (1942).

(21) Melting points are uncorrected. Optical rotations were determined in chloroform solution at 16–22° and ultraviolet absorption spectra were measured in 95% ethanol. Infrared spectra determined in potassium bromide disks on a Perkin-Elmer Model 21 spectrometer equipped with sodium chloride optics are by Sr. Erlin Avila and his staff. N.m.r. spectra were taken in deuteriochloroform solution (*ca.* 10% w./v.) with a tetramethylsilane internal reference using a Varian A-60 spectrometer. Chemical shifts are quoted as cycles per second from the reference. The optical rotatory dispersion curves were obtained with a Rudolph spectropolarimeter.

with acetic acid, diluted with saturated sodium chloride solution, and extracted with ethyl acetate. The organic extract was washed with water, dried (Na_2SO_4), and concentrated to afford 16 g. of 19-hydroxytestosterone (Ia): m.p. 202–203°, (lit.[9] m.p. 201–203°), $[\alpha]_D$ +92°, λ_{max} 244 mμ (log ε 4.14).

Catalytic Hydrogenation of 19-Hydroxytestosterone (Ia).—A solution of 5.9 g. of Ia in 100 ml. of ethanol was hydrogenated with 1.5 g. of 5% palladium on charcoal at an initial pressure of 46 p.s.i. for 30 min. The catalyst was removed by filtration and the resulting solution was evaporated to dryness. Crystallization of the residue from ethyl acetate afforded 3.6 g. of 17β,19-dihydroxy-5β-androstan-3-one (IIa), m.p. 178–180°. A pure sample of the 5β isomer IIa exhibited m.p. 183–185°; $[\alpha]_D$ +26°; ν_{max} 3350 and 1715 cm.$^{-1}$; R.D. $[\Phi]_{700}$ +31°, $[\Phi]_{589}$ +31°, $[\Phi]_{400}$ + 123°, $[\Phi]_{350}$ +4°, $[\Phi]_{315}$ −773°, $[\Phi]_{300}$ −19° (*c* 0.3, dioxane).

Anal. Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 73.99; H, 9.90.

Chromatography of the mother liquors on 150 g. of neutral alumina gave, after elution with ethyl acetate, an additional 1.7 g. of the 5β isomer IIa and 0.16 g. of 17β,19-dihydroxy-5α-androstan-3-one (IIb). Several crystallizations of the latter product from acetone provided the analytical sample: m.p. 150–151°; $[\alpha]_D$ +44°; ν_{max} 3350 and 1700 cm.$^{-1}$; R.D. $[\Phi]_{700}$ +108°, $[\Phi]_{589}$ +192°, $[\Phi]_{400}$ +246°, $[\Phi]_{315}$ +1025°, $[\Phi]_{295}$ +292° (*c* 0.08, dioxane).

Anal. Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 73.97; H, 9.89.

17β,19-Dihydroxy-5β-androstan-3-one 17,19-Diacetate (IIg).—A mixture of the 5β-diol IIa (1 g.), dry pyridine (1 ml.), and acetic anhydride (3 ml.) was heated on the steam bath for 2 hr. then poured into water and the product was isolated by extraction with ether. Several crystallizations from hexane and methanol afforded the diacetate IIg: m.p. 127–128°; $[\alpha]_D$ +16°; ν_{max} 1720 and 1250 cm.$^{-1}$; R.D. $[\Phi]_{700}$ ±0°, $[\Phi]_{589}$ ±0°, $[\Phi]_{400}$ ±0°, $[\Phi]_{340}$ −163°, $[\Phi]_{315}$ −853°, $[\Phi]_{300}$ +254°, $[\Phi]_{292.5}$ +942° (*c* 0.09, dioxane).

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

5β-Androstane-3α,17β,19-triol (IIIc).—A solution of 0.1 g. of 17β,19-dihydroxy-5β-androstan-3-one (IIa) in 20 ml. of ether–tetrahydrofuran (4:1) was added dropwise with stirring to a suspension of 0.2 g. of lithium aluminum hydride in 25 ml. of ether. After standing for 1 hr. at room temperature, moist acetone and water were added successively to the reaction to destroy the excess of hydride and the product was isolated with ethyl acetate. Several crystallizations from acetone afforded an analytical sample of the triol IIIc: m.p. 237–238°, $[\alpha]_D$ +33°, ν_{max} 3350 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 73.98; H, 10.48.

5α-Androstane-3β,17β,19-triol (IIId).—The reduction of 0.2 g. of 17β,19-dihydroxy-5α-androstan-3-one (IIb) with 0.4 g. of lithium aluminum hydride, as described in the preceding experiment, gave the 5α-triol IIId: m.p. 233–234°, $[\alpha]_D$ +15°, ν_{max} 3350 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 73.94; H, 10.57.

3β,19-Dihydroxy-5α-androstan-17-one (IIIb).—A solution of 1 g. of 3β,19-dihydroxyandrost-5-en-17-one[18] (IIIa) in 100 ml. of methanol was hydrogenated with 0.2 g. of prereduced 10% palladium-on-charcoal catalyst at atmospheric pressure[22] for 8 hr. After removal of the catalyst, the filtrate was concentrated to a small volume, cooled, and filtered to afford 0.8 g. of the dihydro compound IIIb, m.p. 234–237°. Two additional crystallizations from methanol gave a pure sample: m.p. 237–238°, $[\alpha]_D$ +89°, ν_{max} 3350 and 1740 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{30}O_3 \cdot 0.25CH_3OH$: C, 73.59; H, 9.94; O, 16.48. Found: C, 73.95; H, 9.94; O, 16.48.

Oxidation of 3β,19-Dihydroxy-5α-androstan-17-one (IIIb).—A solution of 0.2 g. of the foregoing diol IIIb in 30 ml. of acetone was oxidized with 0.7 ml. of 8 *N* chromium trioxide–sulfuric acid reagent[14] for 1.3 hr. at 20°. The reaction mixture was diluted with water and extracted with several portions of ethyl acetate. The acid fraction was separated from the organic phase by shaking with 5% sodium bicarbonate, acidification, and isolation with methylene chloride. Crystallization of the crude acid (0.07 g.) from acetone afforded 0.03 g. of 3,17-dioxo-5α-androstan-19-oic acid (IIc) with m.p. 196–198°, which was raised to 199.5–201.5° after two additional crystallizations: $[\alpha]_D$ +111°; ν_{max} 3350, 1740, and 1715 cm.$^{-1}$; R.D. $[\Phi]_{700}$ +295°, $[\Phi]_{589}$ +295°, $[\Phi]_{400}$ +1350°, $[\Phi]_{320}$ +10,200°, $[\Phi]_{300}$ +2197° (*c* 0.1, dioxane).

Anal. Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23; O, 20.10. Found: C, 71.70; H, 8.03; O, 20.32.

Concentration of the original ethyl acetate extract afforded a neutral product (0.09 g.) which was chromatographed on 15 g. of silica gel with a mixture of ethyl acetate–chloroform (1:4). Fractions 5–8 contained 0.04 g. of pure crystalline 3β-hydroxy-17-oxo-5α-androstan-19-oic acid 3β,19-lactone (IV): m.p. 272–274° (unchanged after several crystallizations from acetone–hexane), $[\alpha]_D$ +79°, ν_{max} 1760–1710 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 75.46; H, 8.67; O, 15.87. Found: C, 75.65; H, 8.67; O, 15.85.

Lithium Aluminum Hydride Reduction of the Lactone IV.—A solution of 0.1 g. of the lactone IV and 0.5 g. of lithium aluminum hydride in 250 ml. of tetrahydrofuran was heated under reflux for 1 hr. and after cooling was treated with aqueous acetone to destroy the excess hydride. Saturated sodium sulfate solution and solid sodium sulfate were added successively; the resulting solution was filtered and then concentrated to dryness. Crystallization of the solid product from methanol gave 0.04 g. of 5α-androstane-3β,17β,19-triol (IIId), m.p. 233–234°, identical in all respects with the sample prepared by reduction of 17β,19-dihydroxy-5α-androstan-3-one (IIb).

Lithium Aluminum Hydride Reduction of 3β,19-Dihydroxy-5α-androstan-17-one (IIIb).—The reduction of 0.25 g. of the diol IIIb with 0.4 g. of lithium aluminum hydride afforded 0.2 g. of 5α-androstane-3β,17β,19-triol (IIId), m.p. 233–234°, identical in all respects with the triol from the preceding experiment.

Catalytic Hydrogenation of 19-Hydroxyandrost-4-ene-3,17-dione (Ib).—A solution of Ib (20 g.) in ethanol (200 ml.) was hydrogenated over a 5% palladium-on-charcoal catalyst (6 g.) at an initial pressure of 50 p.s.i. and after 5 min. the hydrogen uptake ceased. Fractional crystallization of the crude product from ethyl acetate afforded 13.4 g. of the 5β-dihydro derivative IId and 2.3 g. of the 5α isomer isolated as the hemiketal V.

A pure sample of 19-hydroxy-5β-androstane-3,17-dione (IId) exhibited m.p. 208–209°; $[\alpha]_D$ +103°; ν_{max} 3380, 1735, and 1705 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 75.08; H, 9.22.

An analytically pure sample of the hemiketal V had m.p. 137–138°, $[\alpha]_D$ +115°, ν_{max} 1735 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 75.20; H, 9.25.

Several recrystallizations of the hemiketal V from acetone afforded pure 19-hydroxy-5α-androstane-3,17-dione IIo: m.p. 178–181°; $[\alpha]_D$ +111°; ν_{max} 3350, 1735, and 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 75.10; H, 9.31.

Lithium Aluminum Hydride Reduction of 19-Hydroxy-5β-androstane-3,17-dione (IId).—Reduction of 0.2 g. of 19-hydroxy-5β-androstane-3,17-dione (IId) with 0.2 g. of lithium aluminum hydride provided 5β-androstane-3α,17β,19-triol (IIIc), m.p. 236–238°, identical with an authentic sample by mixture melting point and infrared spectral comparison.

Lithium Aluminum Hydride Reduction of the Hemiketal V.—Reduction of 0.2 g. of the hemiketal V with 0.2 g. of lithium aluminum hydride furnished 5α-androstane-3β,17β,19-triol (IIIb), m.p. 233–234°, identical in all respects with an authentic sample.

Catalytic Hydrogenation of 17-Cycloethylenedioxy-19-hydroxy-androst-4-en-3-one (Ic).—The hydrogenation of 0.4 g. of the ketal Ic[15] in 15 ml. of methanol with 0.08 g. of 10% palladized charcoal at atmospheric pressure[22] gave, after the usual processing and crystallization from acetone–hexane, 0.29 g. of the 5β isomer IIe: m.p. 154–155°; $[\alpha]_D$ ±0°; ν_{max} 3500–3300 and 1710 cm.$^{-1}$; R.D. $[\Phi]_{700}$ ± 0°, $[\Phi]_{589}$ −146°, $[\Phi]_{400}$ −146°, $[\Phi]_{350}$ −515°, $[\Phi]_{315}$ −1413°, $[\Phi]_{300}$ −661° (*c* 0.1, dioxane).

Anal. Calcd. for $C_{21}H_{32}O_4 \cdot 0.25H_2O$: C, 71.48; H, 9.29; O, 19.23. Found: C, 71.29; H, 9.48; O, 19.23.

Hydrolysis of 17-Cycloethylenedioxy-19-hydroxy-5β-androstan-3-one (IIe).—A solution of 0.08 g. of the foregoing ketal IIe in 3 ml. of methanol containing 0.3 ml. of concentrated hydrochloric acid was heated under reflux for 45 min. and then poured into water. Crystallization of the dried precipitate (m.p. 206–208°) provided 0.04 g. of 19-hydroxy-5β-androstane-3,17-dione (IId), m.p. 208–209°, identical in all respects with the sample prepared

(22) Atmospheric pressure refers to 570 mm.

by catalytic hydrogenation of 19-hydroxyandrost-4-ene-3,17-dione (Ib).

Catalytic Hydrogenation of 17β,19-Dihydroxyandrost-4-en-3-one 17,19-Diacetate (Id).—A solution of 7.7 g. of the diacetate Id[9a] in 100 ml. of ethanol was hydrogenated over 3 g. of 5% palladized charcoal at an initial pressure of 50 p.s.i. The product was isolated in the usual manner and recrystallized several times from methanol to give 0.6 g. of 17β,19-dihydroxy-5α-androstan-3-one 17,19-diacetate (IIf): m.p. 140–141°; $[\alpha]_D$ +5°; ν_{max} 1735 and 1240 cm.$^{-1}$; R.D. $[\Phi]_{700}$ ±0°, $[\Phi]_{589}$ −38°, $[\Phi]_{400}$ −82°, $[\Phi]_{350}$ −100°, $[\Phi]_{330}$ +199°, $[\Phi]_{317.5}$ +862°, $[\Phi]_{305}$ +372°, $[\Phi]_{300}$ −95° (*c* 0.09, dioxane).

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.91; H, 8.94.

The mother liquors were chromatographed on 300 g. of Florisil and the first crystalline fractions eluted with hexane–ether (7:3) yielded 2.9 g. of 17β,19-dihydroxy-5β-androstan-3-one 17,19-diacetate (IIg). A sample crystallized from methanol showed m.p. 126–128°, undepressed when mixed with the diacetate obtained from the acetylation of 17β,19-dihydroxy-5β-androstan-3-one (IIa). The infrared spectra of the two diacetates were indistinguishable.

Further elution with the same solvent system afforded an additional 1.9 g. of the 5α-diacetate IIf.

Hydrolysis of 17β,19-Dihydroxy-5α-androstan-3-one 17,19-Diacetate (IIf).—The hydrolysis of 1.5 g. of the diacetate IIf with 25 ml. of 5% methanolic potassium hydroxide for 18 hr. at 20° yielded 0.9 g. of crude 17β,19-dihydroxy-5α-androstan-3-one (IIb). This afforded a sample, m.p. 150–152°, on crystallization from methanol which was undepressed in melting point when mixed with the authentic diol IIb prepared by hydrogenation of 19-hydroxytestosterone (Ia).

Hydrolysis of 17β,19-Dihydroxy-5β-androstane-3-one 17,19-Diacetate (IIg).—The hydrolysis of 0.5 g. of the diacetate IIg with 10 ml. of 5% methanolic potassium hydroxide exactly as described in the preceding experiment furnished the diol IIa, m.p. 181–183°, identical in all respects with an authentic sample.

19-Acetoxyandrost-4-ene-3,17-dione (Ie).[16]—19-Hydroxyandrost-4-ene-3,17-dione (Ib)[6d] (10 g.) was acetylated at steam-bath temperature (2 hr.) with 40 ml. of a mixture of pyridine–acetic anhydride (1:3). Isolation of the product in the usual manner with ethyl acetate afforded an oil which was dissolved in hexane and adsorbed on a column of 300 g. of neutral alumina. Elution with hexane–ether (9:1 and 1:1) provided 10.2 g. of oily material which was dissolved in 50 ml. of methanol and added slowly with vigorous stirring to 500 ml. of cold water. The acetate separated as an oil which rapidly crystallized. The solid was collected and dried to afford 7.9 g. of 19-acetoxyandrost-4-ene-3,17-dione (Ie): m.p. 52–53°, raised to 81–82° by recrystallization from hexane; $[\alpha]_D$ +251°; λ_{max} 238 mμ (log ε 4.21); ν_{max} 1730, 1680, 1630, and 1250 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19; O, 18.58. Found: C, 73.33; H, 8.37; O, 18.73.

Catalytic Hydrogenation of 19-Hydroxyandrost-4-ene-3,17-dione 19-Acetate (Ie).—A solution of 13 g. of the crude 19-acetate Ie in 100 ml. of ethanol was hydrogenated with 3 g. of 5% palladized charcoal at an initial pressure of 50 p.s.i. After the usual processing the crude product was crystallized from methanol to afford 3.5 g. of the 5β isomer IIh, m.p. 160–163°. Several additional crystallizations from methanol gave an analytically pure specimen: m.p. 165–167°; $[\alpha]_D$ +87°; ν_{max} 1735, 1725, and 1250 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.62. Found: C, 72.63; H, 8.26.

Hydrolysis of a sample of the 5β isomer IIh with 5% methanolic potassium hydroxide produced 19-hydroxy-5β-androstan-3,17-dione (IId) identical in all respects with an authentic sample.

The mother liquors remaining after removal of the 5β isomer IIh were saponified by heating with 150 ml. of 5% methanolic potassium hydroxide solution and the resulting oil was chromatographed on 150 g. of alumina. The fractions eluted with benzene–ether (1:1) were crystallized from methanol to yield 1.4 g. of the hemiketal V, m.p. 134–137°. It was identical by mixture melting point and infrared spectral comparison with a sample of the hemiketal obtained by catalytic hydrogenation of 19-hydroxyandrost-4-ene-3,17-dione (Ib).

Catalytic Hydrogenation of 17-Cycloethylenedioxy-19-hydroxyandrost-4-en-3-one 19-Acetate (If).—A solution of 1 g. of the acetate If[15] in 75 ml. of methanol was hydrogenated with 0.2 g. of prereduced 10% palladized charcoal at atmospheric pressure[22] and processed in the usual manner. Crystallization of the crude product from ether–hexane gave 0.63 g. of the 5β isomer IIi: m.p. 107–108°, raised to 110–111° after several additional crystallizations; $[\alpha]_D$ +1°; ν_{max} 1740, 1710, and 1250 cm.$^{-1}$; R.D. $[\Phi]_{700}$ ±0°, $[\Phi]_{589}$ ±0° $[\Phi]_{400}$ −312°, $[\Phi]_{350}$ −515°, $[\Phi]_{315}$ −1528°, $[\Phi]_{300}$ −453° (*c* 0.1, dioxane).

Anal. Calcd. for $C_{28}H_{34}O_5$: C, 70.74; H, 8.78; O, 20.49. Found: C, 70.77; H, 8.81; O, 20.23.

Hydrolysis of 17-Cycloethylenedioxy-19-hydroxy-5β-androstan-3-one 19-Acetate (IIi).—A solution of 0.5 g. of the foregoing 5β isomer in 50 ml. of 2% methanolic sodium hydroxide solution was heated under reflux for 1 hr. The reaction mixture was diluted with water and the product was isolated by extraction with ethyl acetate. Crystallization from acetone–ether gave 0.28 g. of the 5β-alcohol IIe, m.p. 151–152°, identical in all respects with an authentic sample.

Catalytic Hydrogenation of 17-Cycloethylenedioxy-19-hydroxyandrost-4-en-3-one 19-Tetrahydropyranyl Ether (Ig). A.—The hydrogenation of the pyranyl ether Ig[15] (1 g.) with prehydrogenated 10% palladized charcoal (0.2 g.) in methanol (100 ml.) at atmospheric pressure[22] was complete after 40 min. Crystallization of the product from hexane provided 0.71 g. of 5β isomer IIj, m.p. 127–129°. An analytically pure sample exhibited m.p. 137–138°, $[\alpha]_D$ −43°, ν_{max} 1710 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32; O, 18.49. Found: C, 71.85; H, 9.55; O, 18.94.

B.—The hydrogenation of the pyranyl ether Ig (1.7 g.) in 165 ml. of ethanol containing 0.5 g. of palladium-on-charcoal catalyst at 3 atm. resulted in the partial reduction of the 3-carbonyl grouping as indicated by thin layer chromatographic analysis of the crude product. This mixture was dissolved in 80 ml. of methanol containing 8 ml. of concentrated hydrochloric acid and heated under reflux for 45 min. The reaction mixture was evaporated to a small volume, diluted with ethyl acetate, and washed with saturated sodium carbonate solution and water. Evaporation of the sodium sulfate dried extract followed by crystallization from ethyl acetate furnished 0.33 g. of 19-hydroxy-5β-androstane-3,17-dione (IId), m.p. 204–205°. Concentration of the mother liquors afforded as a second crop 0.25 g. of 3β,19-dihydroxy-5α-androstan-17-one (IIIb), m.p. 228–230°, identical in all respects with an authentic sample. Chromatography of the remaining mother liquors on 20 g. of alumina gave an additional 0.26 g. of the 5β-hydroxy diketone IId (eluted with benzene–ethyl acetate 4:1) and 0.18 g. of the diol IIb (eluted with pure ethyl acetate).

Catalytic Hydrogenation of 19-Hydroxyandrost-4-en-3,17-dione 19-Tosylate (Ih).—A solution of 1.7 g. of the 19-tosylate Ih[6a] in 100 ml. of ethyl acetate was reduced with 0.5 g. of prereduced 10% palladized charcoal at atmospheric pressure[22] and processed in the usual manner. On the basis of thin layer chromatography, the crude product was estimated to contain *ca.* 70% of the 5α-dihydro compound admixed with the 5β isomer. Several crystallizations from acetone–hexane afforded a pure sample of 19-hydroxy-5α-androstane-3,17-dione 19-tosylate (IIk): m.p. 151–152°; $[\alpha]_D$ +56°; λ_{max} 226, 264, and 273 mμ (log ε 4.12, 2.82, and 2.74); ν_{max} 1740, 1715, 1600, 1365, and 1180 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{34}O_5S$: C, 68.18; H, 7.48; O, 17.86. Found: C, 68.21; H, 7.53; O, 17.29.

Lithium Aluminum Hydride Reduction of the 5α-Tosylate IIk.—A solution of the tosylate IIk (0.02 g.) was heated under reflux with 0.1 g. of lithium aluminum hydride in 5 ml. of anhydrous dioxane for 18 hr. Work-up by the sodium sulfate procedure afforded 5α-androstane-3β,17β,19-triol (IIId), m.p. 228–230°, identical by mixture melting point determination and infrared comparison with an authentic sample.

2,19-Cyclo-5α-androstane-3,17-dione (VI).—The isomeric mixture obtained from the hydrogenation of 0.5 g. of 19-hydroxyandrost-4-ene-3,17-dione 19-tosylate (Ih) was dissolved in 25 ml. of ethylene glycol and treated with a solution of 2.5 g. of potassium hydroxide in 2.5 ml. of water. The resulting solution was heated under reflux for 4 hr., cooled, diluted with saturated sodium chloride solution, and extracted with ethyl acetate. The organic phase was washed with water, dried (Na_2SO_4), and concentrated *in vacuo*. This gave an amorphous foam which was chromatographed on 15 g. of alumina. Elution with hexane–benzene (4:1) furnished 0.17 g. of the 2,19-cyclo compound VI which exhibited m.p. 129–130° after several crystallizations from acetone–hexane; $[\alpha]_D$ +97°; λ_{max} 282 mμ (log ε 1.87); ν_{max} 1730 and 1710 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15; O, 11.17. Found: C, 79.69; H, 9.08; O, 10.97.

Lithium Aluminum Hydride Reduction of the Isomeric Dihydro Tosylate Mixture.—The dihydro tosylate mixture (0.5 g.) was reduced with lithium aluminum hydride (2 g.) in anhydrous dioxane (75 ml.) as described previously. The resulting triol mixture was dissolved in chloroform and adsorbed on 25 g. of silica gel. Elution with chloroform–methanol (49:1) afforded 5β-androstane-3α,17β,19-triol (IIIc), m.p. 230–232°, identical in all respects with an authentic sample.

Further elution afforded a mixture of alcohols from which a pure sample of 5α-androstane-3β,17β,19-triol (IIId), m.p. 228–230°, was obtained by fractional crystallization.

Catalytic Hydrogenation of 3,17-Dioxoandrost-4-en-19-oic Acid (Ii).—A solution of the Δ⁴-3-keto acid Ii (4.7 g.)[6c] in ethanol (50 ml.) was reduced over 5% palladium-on-charcoal catalyst (1.5 g.) at an initial pressure of 50 p.s.i. and processed in the usual manner. Crystallization of the crude product from acetone afforded a homogeneous acid (3 g.), m.p. 199–201°, identical in all respects with a sample of 3,17-dioxo-5α-androstan-19-oic acid (IIc).

3,17-Dioxo-5β-androstan-19-oic Acid (III).—A solution of 2 g. of 19-hydroxy-5β-androstane-3,17-dione (IId) in 250 ml. of acetone was stirred for 1.5 hr. with 3 ml. of 8 *N* chromium trioxide–sulfuric acid reagent[14] and then diluted with 500 ml. of ethyl acetate. The resulting solution was washed with water, dried (Na_2SO_4), and concentrated to dryness *in vacuo*. Crystallization of the solid residue from acetone–hexane furnished 0.9 g. of the *cis* acid III: m.p. 229–231°, raised to 244–245° after several additional crystallizations from acetone; $[\alpha]_D$ +15°; ν_{max} 1730–1700 cm.$^{-1}$; R.D. $[\Phi]_{700}$ ±0°, $[\Phi]_{589}$ ±0°, $[\Phi]_{400}$ +533°, $[\Phi]_{320}$ +5850°, $[\Phi]_{300}$ −444° (*c* 0.1, dioxane).

Anal. Calcd. for $C_{19}H_{26}O_4$: C, 71.76; H, 8.23; O, 20.10. Found: C, 71.63; H, 8.28; O, 20.28.

Lithium Liquid Ammonia Reduction of 19-Hydroxytestosterone (Ia).—A solution of 19-hydroxytestosterone (Ia, 9.7 g.) in dioxane (300 ml.) and ether (300 ml.) was added rapidly to a stirred solution of lithium metal (1.5 g.) in liquid ammonia (1.5 l.). After 4 min. solid ammonium chloride was added to discharge the blue color and the ammonia was evaporated. Isolation with chloroform gave an oily product (9.8 g.) which was chromatographed on neutral alumina (500 g.). Elution with ethyl acetate provided 5.1 g. of 17β,19-dihydroxy-5β-androstan-3-one (IIa), m.p. 178–180°, identical in all respects with a sample of the 5β isomer IIa prepared by catalytic hydrogenation of 19-hydroxytestosterone (Ia).

Further elution with acetone yielded 1.8 g. of 5α-androstane-3β,17β,19-triol (IIId), m.p. 233–234°, undepressed in melting point when mixed with an authentic sample of IIId. The infrared spectra of the two samples were indistinguishable.

Lithium Liquid Ammonia Reduction of 17-Cycloethylenedioxy-19-hydroxyandrost-4-en-3-one 19-Tetrahydropyranyl Ether (Ig).—A solution of 2 g. of the pyranyl ether derivative Ig in 50 ml. of anhydrous tetrahydrofuran was added with stirring to a solution of 0.31 g. of lithium in 100 ml. of liquid ammonia and after 10 min. the blue color was discharged with solid ammonium chloride. The residue obtained after evaporation of the ammonia was treated with water and the resulting mixture was extracted with ethyl acetate. The usual processing gave a crude product (2 g.) which was oxidized with 2 ml. of 8 *N* chromium trioxide reagent[14] at 10° for 5 min. Water was added to the reaction mixture and the product was isolated with ethyl acetate. Crystallization from hexane furnished 1.6 g. of 17-cycloethylenedioxy-19-hydroxy-5α-androstan-3-one 19-tetrahydropyranyl ether (IIm), m.p. 108–111°. Several additional crystallizations from hexane gave an analytical sample: m.p. 144.5–145.5, $[\alpha]_D$ −41°, ν_{max} 1710 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32. Found: C, 72.48; H, 9.34.

Alternatively, oxidation of 0.22 g. of the crude Birch reduction product in 25 ml. of dry benzene with 4.4 g. of activated manganese dioxide[18] for 15 hr. with efficient stirring furnished 0.18 g. of the ketone IIm, m.p. 108–111°.

Hydrolysis of 17-Cycloethylenedioxy-19-hydroxy-5α-androstane-3,17-dione 19-Tetrahydropyranyl Ether (IIm).—A solution of the foregoing ketone IIm (0.1 g.) in a mixture of acetic acid (6 ml.), acetone (4 ml.), water (2 ml.), and concentrated sulfuric acid (2 drops) was boiled for 1.5 hr. Sodium acetate and water were added and the product was isolated with ethyl acetate. This gave 0.05 g. of the hemiketal V, m.p. 136.5–137.5°, identical in all respects with an authentic sample.

19-Chloro-3β-hydroxy-5α-androstan-17-one 3-Acetate (IIIf).—A solution of 1.5 g. of 19-chloro-3β-hydroxyandrost-5-en-17-one 3-acetate[6c] (IIIe) was hydrogenated in 30 ml. of ethyl acetate with 0.5 g. of 10% palladium-on-charcoal catalyst at atmospheric pressure.[22] After the absorption of 0.9 molar equiv. of hydrogen, the reaction was stopped and processed in the usual manner. This yielded an amorphous product which was chromatographed on 60 g. of alumina. Elution with hexane–benzene (3:1) afforded 1 g. of the dihydro compound IIIf, m.p. 110–113°. A pure sample prepared by crystallization from ethyl acetate–hexane exhibited m.p. 127–128°, $[\alpha]_D$ +46°, ν_{max} 1740 and 1250 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{31}ClO_3$: C, 68.73; H, 8.52; Cl, 9.66; O, 13.08. Found: C, 68.76; H, 8.57; Cl, 9.59; O, 13.00.

19-Chloro-3β-hydroxy-5α-androstan-17-one (IIIg).—A solution of 0.1 g. of the acetate IIIf in methanol (10 ml.) was treated with a solution of potassium carbonate (0.25 g.) in water (2 ml.) and then heated under reflux for 2 hr. The reaction mixture was neutralized with 5% aqueous hydrochloric acid and the product was precipitated with water. This gave 0.09 g. of 19-chloro-3β-hydroxy-5α-androstan-17-one (IIIg) which exhibited m.p. 214–215° after several crystallizations from ethyl acetate–hexane; $[\alpha]_D$ +60°; ν_{max} 3350 and 1730 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{29}ClO_2$: C, 70.23; H, 8.99; Cl, 10.92; O, 9.85. Found: C, 70.56; H, 9.14; Cl, 11.08; O, 9.75.

19-Chloro-5α-androstane-3,17-dione (IIn).—A solution of 1.6 g. of the alcohol IIIg in 170 ml. of acetone was treated dropwise with 2.8 ml. of 8 *N* chromium trioxide–sulfuric acid reagent[14] and the reaction mixture was stirred for 10 min. at 20°. Water was then added and the product was isolated by extraction with ethyl acetate. Several crystallizations from acetone–hexane gave an analytical sample of 19-chloro-5α-androstane-3,17-dione (IIn): m.p. 114–115°; $[\alpha]_D$ +81°; ν_{max} 1740 and 1725 cm.$^{-1}$; R.D. $[\Phi]_{700}$ +286°, $[\Phi]_{589}$ +319°, $[\Phi]_{400}$ +1038°, $[\Phi]_{320}$ +8050°, $[\Phi]_{300}$ +1068° (*c* 0.09, dioxane).

Anal. Calcd. for $C_{19}H_{27}ClO_2$: C, 70.69; H, 8.44; Cl, 10.98; O, 9.91. Found: C, 70.80; H, 8.54; Cl, 11.23; O, 9.73.

Catalytic Hydrogenation of 19-Chloroandrost-4-ene-3,17-dione (Ij).—A solution of the 19-chloro Δ⁴-3-ketone Ij[6c] (0.14 g.) in ethyl acetate (30 ml.) was hydrogenated over prereduced platinum oxide catalyst (0.01 g.) at atmospheric pressure.[22] After the absorption of 1 molar equiv. of hydrogen the product was isolated in the usual manner. Thin layer chromatography revealed the presence of the 5α- and 5β-dihydro compounds in approximately equal amounts. Chromatography of this mixture on 15 g. of alumina and elution with hexane–benzene (1:1) afforded a pure sample of the 5α isomer IIn, identical in all respects with an authentic sample prepared in the preceding experiment. Further elution afforded a mixture of the 5α- and 5β-dihydro compounds, rich in the latter isomer. Rechromatography of these fractions failed to provide a pure sample of the 5β compound.

Lithium–Liquid Ammonia Reduction of 19-Chloroandrost-4-ene-3,17-dione (Ij).—A solution of the 19-chloro Δ⁴-3-ketone Ij (0.5 g.) in a mixture of dioxane (10 ml.) and ether (15 ml.) was added dropwise with stirring to a solution of lithium (0.08 g.) in liquid ammonia (100 ml.). Ammonium chloride was added immediately to destroy the excess of lithium, then the ammonia was evaporated, and the residue was dissolved in ethyl acetate and water. The organic phase was separated, washed well with water, dried (Na_2SO_4), and evaporated. The resulting solid was dissolved in acetone (50 ml.) and oxidized with 2 ml. of 8 *N* chromic acid[14] for 15 min. at 20°. Chromatography of the crude oxidation product on 15 g. of alumina afforded 0.25 g. of 5β,19-cycloandrostane-3,17-dione (VII) on elution with pure hexane. This substance exhibited m.p. 133–134° when crystallized from acetone–hexane and was identical in all respects with an authentic sample[19] prepared by an unambiguous synthesis. Crystallization of the mother liquors afforded 0.02 g. of 19-chloro-5α-androstane-3,17-dione (IIn), m.p. 114–115°, identical with an authentic sample by mixture melting point and infrared comparison.

19-Chloro-3-ethoxyandrosta-3,5-dien-17-one (VIII).—A solution of 1 g. of 19-chloroandrost-4-ene-3,17-dione (Ij) in 9 ml. of anhydrous dioxane and 1.1 ml. of ethyl orthoformate was treated with 0.07 g. of *p*-toluenesulfonic acid and stirred for 1 hr. at 20°. Addition of saturated sodium bicarbonate solution precipitated

1.1 g. of the dienol ether derivative VIII which exhibited m.p. 159–161° after several crystallizations from acetone–methanol; $[\alpha]D$ −109°; λ_{max} 244 mμ (log ε 4.28); ν_{max} 1740, 1640, and 1600 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{29}ClO_2$: C, 72.27; H, 8.38; Cl, 10.16; O, 9.17. Found: C, 72.17; H, 8.39; Cl, 10.43; O, 9.26.

Catalytic Hydrogenation of 19-Chloro-3-ethoxyandrosta-3,5-dien-17-one (VIII).—A solution of 1 g. of the foregoing dienol ether VIII in 150 ml. of ethyl acetate was hydrogenated with 0.5 g. of prereduced platinum oxide at atmospheric pressure.[22] The experiment was terminated after the absorption of 4.3 molar equiv. of hydrogen and processed in the usual manner to give a crystalline solid which was dissolved in hexane and adsorbed on 100 g. of silica gel. Elution with hexane–benzene (9:1) afforded 0.1 g. of 19-chloro-5α-androstan-17-one (IIIh) which exhibited m.p. 118–120° after crystallization from acetone–methanol; $[\alpha]D$ +75°; ν_{max} 1740 cm.$^{-1}$; n.m.r. 18-methyl at 55 c.p.s. and 19-chloromethyl (2 protons) at 231 c.p.s.

Anal. Calcd. for $C_{19}H_{29}ClO$: C, 73.85; H, 9.46; Cl, 11.47; O, 5.18. Found: C, 73.89; H, 9.37; Cl, 11.53; O, 5.23.

Continued elution with benzene–chloroform (1:1) afforded 0.03 g. of 19-chloro-3β-ethoxy-5α-androstan-17-one (IIIi) with m.p. 93–95° after crystallization from acetone–methanol; $[\alpha]D$ +80°; ν_{max} 1740 cm.$^{-1}$; n.m.r. 18-methyl at 55 c.p.s., methyl of 3β-ethoxy group (3 protons) at 64, 72, and 79 c.p.s., methylene of 3β-ethoxy group (2 protons) at 201, 209, 215, and 222 c.p.s., and 19-chloromethyl (2 protons) at 228 c.p.s.

Anal. Calcd. for $C_{21}H_{33}ClO_2$: C, 71.45; H, 9.42; O, 9.07. Found: C, 71.33; H, 9.52; O, 9.12.

Continued elution with the same mixture provided 0.42 g. of 19-chloro-5α-androstan-3,17-dione (IIn), identical in all respects with an authentic sample.

1-Phenylcyclopenten-3-one Derivatives and Their Conversion into Bis-π-(1-methyl-3-phenylcyclopentadienyl)titanium Dichlorides

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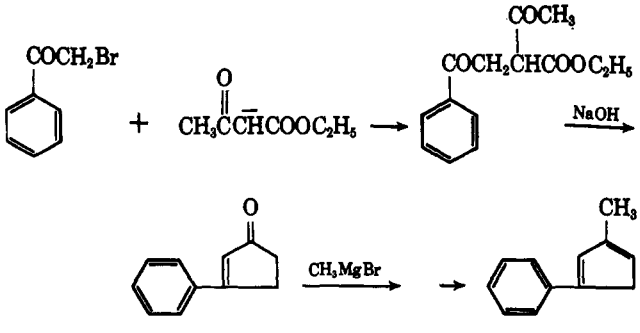
Bis-π-(1-methyl-3-phenylcyclopentadienyl)- and bis-π-(1-methyl-3-*p*-bromophenylcyclopentadienyl)titanium dichlorides were prepared from the lithium salts of the corresponding cyclopentadienes and titanium tetrachloride. The cyclopentadienyl compounds were obtained by the reaction of methylmagnesium bromide with 1-phenyl- or 1-*p*-bromophenylcyclopenten-3-ones. Attempts to prepare the related *p*-methoxy and *p*-methyl derivatives were unsuccessful.

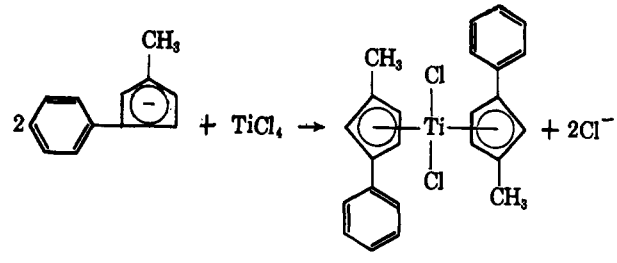
A series of substituted bis-π-cyclopentadienyltitanium dichlorides was needed to determine how changing substituents in the cyclopentadienyl rings would affect the ability of these complexes, in combination with alkylaluminum halides, to polymerize ethylene.[1,2] To keep steric factors constant and also to keep the synthesis simple, we chose to prepare a series of bis-π-(1-methyl-3-phenylcyclopentadienyl)titanium dichlorides. The general method of preparation of these compounds from titanium tetrachloride and cyclopentadienide salts is well known[3] and the preparation of 1-methyl-3-phenylcyclopentadiene had already been described in the literature.[4a] It also appeared that *para*-substituted phenyl compounds could be used in this synthesis as well.

Results

1-Methyl-3-phenylcyclopentadiene was prepared by the procedure of Borsche and Menz.[4a] The position of the double bonds in the product has not been determined with certainty.



The 1-methyl-3-phenylcyclopentadiene appeared to be quite unstable in air. The titanium complex was prepared from the freshly prepared diene by first making the lithium salt by reaction with 1 equiv. of *n*-butyllithium in ether solution and then adding 0.5 equiv. of titanium tetrachloride. The compound formed stable, red-purple prisms melting at 224°.[4b]



A similar series of reactions was carried out with *p*-bromophenacyl bromide. Reactions were much slower with the *p*-bromo compound. The acetoacetic ester alkylation required refluxing overnight to go to completion rather than the 30 min. necessary for phenacyl bromide itself to react. The intermediate *p*-bromophenacylacetoacetic ester crystallized and was characterized. This product also reacted much more slowly with aqueous sodium hydroxide than the unsubstituted compound did. Under conditions where the unsubstituted compound cyclized completely, *viz.*, boiling with 2% aqueous sodium hydroxide for 1 min., the *p*-bromo derivative gave a mixture of products. The mixture was separated into two components by fractional crystallization. The more soluble compound,

(1) D. S. Breslow and N. R. Newburg, *J. Am. Chem. Soc.*, **81**, 81 (1959).
(2) W. P. Long and D. S. Breslow, *ibid.*, **82**, 1953 (1960).
(3) G. Wilkinson and J. M. Birmingham, *ibid.*, **76**, 4281 (1954).
(4) (a) W. Borsche and W. Menz, *Ber.*, **41**, 190 (1908). (b) A referee has pointed out that this compound and the *p*-bromo analog described below should exist in *meso* and racemic forms. No attempt was made to separate isomers and consequently the products are probably mixtures of the two forms.