Oxasteroids. II.[1] 6-Oxaandrostane Derivatives

By Norman W. Atwater

5,6-Seco-B-nor keto esters, prepared by ozonization of the corresponding Δ^5-7-ketones, were reduced with sodium borohydride to a complex mixture of B-ring lactones and lactols. The course of the reduction has been deduced by preparing various of the supposed intermediates and observing their behavior. An explanation for the unusual formation of the hemiacetals has been advanced on the basis of studies with analogous compounds. The configurations at C-5 of the reduction products have been established by relating them to the Baeyer–Villiger reaction product of B-norcoprostan-6-one.

Although the literature contains many examples of the replacement of steroidal nuclear carbon atoms with atoms of oxygen and nitrogen or the expansion of one or the other of the rings with inclusion of these elements, the preparation of 6-oxasteroids had until recently not been reported.[2] In a continuing effort to examine the effect of nuclear changes on the biological activity of steroids, a number of new 6-oxaandrostane derivatives were prepared. Their chemistry is described in this paper.

3β - Acetoxy - 17β - benzoyloxyandrost - 5 - ene (I)[3] was oxidized to its known 7-keto derivative II[4] with anhydrous sodium chromate[5] and this in turn was ozonized in methylene chloride–methanol with subsequent hydrogen peroxide treatment to give the B-nor seco ester IVa in a yield of 73% along with small amounts of the acid IVb and the hydroxy ester IVc. Earlier attempts to ozonize II in ethyl acetate–acetic acid followed by base extraction of the acidic product (a method used very successfully for Δ^4-3-ketones[1,6]) had led to very low yields of the unsaturated keto acid IIIb (cf. ref. 2).

The acetoxy group in compound IVa was extremely labile, being eliminated with great ease to give the α,β-unsaturated keto ester IIIa. Attempts to hydrolyze IVa to its hydroxy derivative IVc with dilute methanolic hydroxide, bicarbonate or hydrogen chloride[7] were all unsuccessful for this reason. Infrared studies of these reactions indicated that at no time was a 3-hydroxy species present but rather that the acetoxy group was eliminated as such without prior cleavage to the alcohol. In the light of these data the isolation of IVc in small quantity from the ozonization reaction is difficult to explain except by assuming that hydrolysis (or alcoholysis) occurred prior to the formation of the 5-ketone, i.e., before oxidation or at the ozonide stage. The difference in behavior of IVa and the acetoxy keto-acid V of Dauben and Fonken[8] which can be hydrolyzed with bicarbonate

Chart I

I

II

IIIa, R = CH₃, R' = Bz
b, R = H, R' = Bz
c, R = CH₃, R' = H

IVa, R = CH₃, R' = Ac
b, R = H, R' = Ac
c, R = CH₃, R' = H

V

VI

probably lies in the fact that in IVa the carboxyl carbon atom is more favorably situated to stabilize the carbanion intermediate (see VI) in the elimination.

Methyl 17β-benzoyloxy-5-oxo-5,6-seco-B-norandrost-3-en-7-oate (IIIa) was best prepared from IVa by a short duration base treatment in a two-phase aqueous dioxane system; the use of aqueous methanol resulted in much lower yields. The 17-hydroxy keto ester IIIc was formed in moderate yield when IVa was allowed to react with methanolic hydrogen chloride for a longer period.

When IVa was treated with sodium borohydride in an attempt to produce lactones VIIa and Xa (cf. ref. 1 for formation of similar A-ring lactones) a complex mixture of products was obtained which contained only a minor amount of compound Xa and no VIIa. The constituents of the mixture which were isolated by a combination of chromatography and separation procedures based on their chemical properties are depicted in Chart II. Evidence for the structures of these products as well as their manner of formation will be described

(1) Paper I, N. W. Atwater and J. W. Ralls, J. Am. Chem. Soc., **82**, 2011 (1960).

(2) For a listing of leading references to the field of heterocyclic steroid analogs and a description of the preparation of 6-oxa- and 6-azacholestane derivatives see T. L. Jacobs and R. B. Brownfield, ibid., **82**, 4033 (1960).
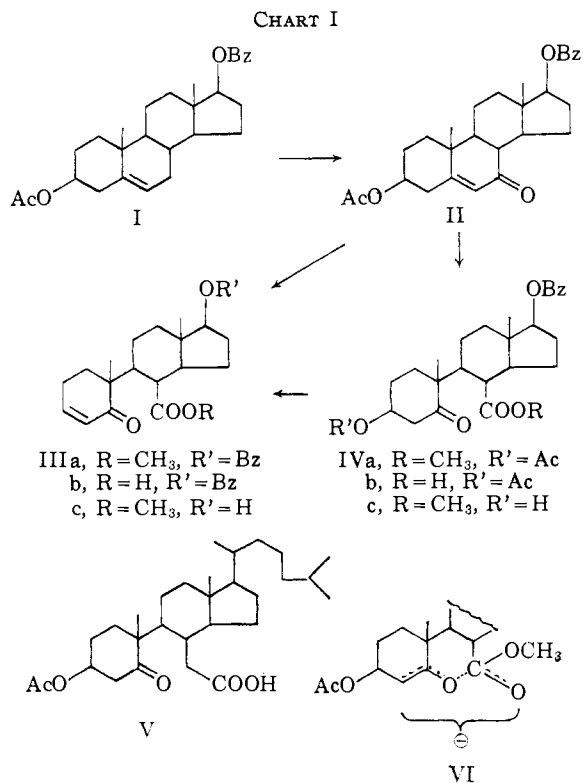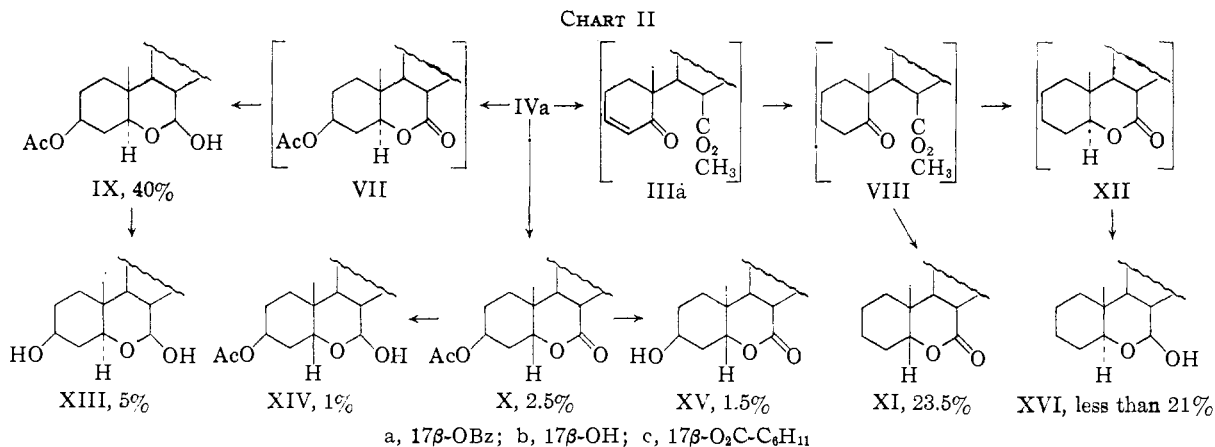
(3) The mixed 3,17-diester was chosen as starting material so as to facilitate the carrying out of selective reactions at later stages in the synthetic scheme.

(4) D. K. Fukushima, S. Lieberman and B. Praetz, J. Am. Chem. Soc., **72**, 5205 (1950), prepared this compound by an alternate method.

(5) C. W. Marshall, R. E. Ray, I. Laos and B. Riegel, ibid., **79**, 6308 (1957); W. C. Meuly, U. S. Patent 2,505,646 (1950).

(6) R. B. Turner, J. Am. Chem. Soc., **72**, 579 (1950).

(7) R. B. Turner, ibid., **75**, 3489 (1953).

(8) W. G. Dauben and G. J. Fonken, ibid., **78**, 4736 (1956).

CHART II

IX, 40%   VII   ←IVa→   IIIá   →   VIII   →   XII

XIII, 5%   XIV, 1%   X, 2.5%   XV, 1.5%   XI, 23.5%   XVI, less than 21%

a, 17β-OBz; b, 17β-OH; c, 17β-O₂C-C₆H₁₁

in the following paragraphs. Discussion of their C-5 configurations will be deferred until a later section of the paper.

The large portion of the total product accounted for by materials having no oxygen function at C-3 was postulated to have arisen by dehydroacetoxylation of IVa prior to reduction. In support of this idea it was found that the unsaturated keto ester IIIa gave, under the conditions of the original reduction, the same mixture of 3-desoxy products (XIa and XVIa) as were obtained from IVa along with some saturated keto ester VIIIa. Furthermore VIIIa itself, which was best produced by hydrogenation of IIIa, could also be reduced to these same products. The rather unexpected saturation of the double bond of the 5-oxo-Δ^3 system as in IIIa by sodium borohydride had also been noted by Jacobs and Brownfield[2] in their cholestane derivatives. This reaction finds its closest analogy in the reduction of the 1,2 and 4,5 double bonds of steroidal 3-ketones under similar conditions[9] and in particular it resembles the former where reaction is complete.

The structures of the lactols IXa and XIVa were proved as follows. They were oxidized to the isomeric lactones VIIa and Xa, respectively, and in the case of IXa, the transformation was accomplished with manganese dioxide[10] (a method reported to oxidize cyclic hemiacetals but not saturated secondary alcohols) as well as with more conventional reagents. They also readily formed methyl ethers with concomitant alcoholysis of the acetoxy group on standing in methanolic p-toluenesulfonic acid. Compound XVII (see Chart III) was isolated directly from XIVa while the acetoxy derivative XVIIIb was obtained by reacetylation in the case of IXa. The n.m.r. spectra of these ethers both showed the presence of the methoxy group at $\tau = 6.667$.

The parent substances IXa and XIVa also had n.m.r. spectra consistent with their structures and in particular the broad absorption at about $\tau = 5.25$–5.30 due to protons on oxygen-bearing carbon had in each case an area corresponding to four such atoms. Additional evidence for the hemiacetal structure in IXa was provided by its acetylation

and subsequent vacuum pyrolysis to the dihydropyran XIX, easily identifiable as such by its characteristic infrared absorption at 6.04 μ.[11]

Compound XVIb, obtained by hydrolysis of a mixture of substances containing XVIa, underwent similar transformations to give the lactone XXI and the methyl ether XX. This ether provided the link between the 3-oxygenated and 3-desoxy compounds since it could also be obtained from the 3-acetoxy hemiacetal IXa by the sequence: ether formation with acetate hydrolysis, oxidation to the 3-ketone, benzoate hydrolysis and Wolff–Kishner reduction[12] (IXa → XVIIIa → XXIIIa → XXIIIb → XX). Thus compounds IXa and XVIb were shown to correspond in stereochemistry at C-5. Since lactone XIa could be transformed by hydrolysis and oxidation into a 17-keto lactone XXII isomeric with compound XXI, it obviously was related to the acetoxy compounds Xa and XIVa and hence of the opposite stereochemistry from the hemiacetals IXa and XVIb.

The presumed intermediacy of the lactones VIIa, Xa and XIIa in the formation of the lactols IXa, XIVa, and XVIa was indicated when it was found that both VIIa and XXI easily were reduced to the hemiacetals with sodium borohydride.

The structures of the minor 3-hydroxy products XIIIa and XVa, which apparently were formed by base-catalyzed hydrolysis (or alcoholysis) of the corresponding acetoxy compounds (IXa and Xa) during the reaction or subsequent work-up, were proved as follows. The hemiacetal XIIIa was oxidized to the 3-keto lactone XXIV which proved identical with the compound obtained from VIIa by acetate hydrolysis and oxidation. The hydroxy lactone XVa was acetylated to give compound Xa.

The recently reported instance[2] of the isolation of diol XXVI from the sodium borohydride reduction of keto ester XXV, while in accord with reported cases of the reduction of carboalkoxy groups to carbinols[13] with this reagent, was at variance with the findings reported here and therefore bore reinvestigation. The ozonization, dehydroacetoxylation and hydrogenation starting with 3-acetoxycholest-5-en-7-one to produce XXV were car-
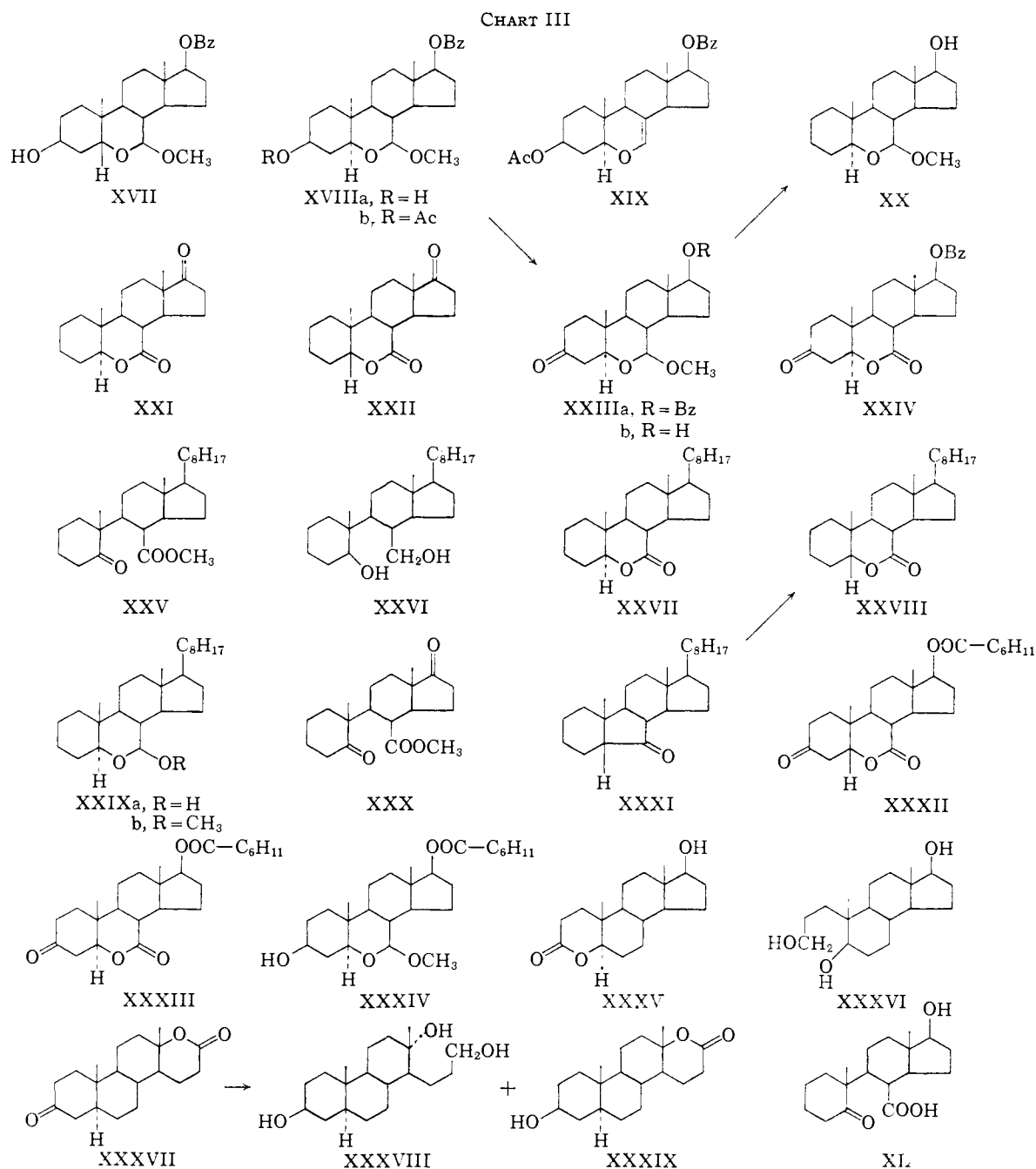
(9) F. Sondheimer, M. Velasco, E. Batres and G. Rosenkranz, Chemistry & Industry, 1482 (1954).

(10) R. J. Highet and W. C. Wildman, J. Am. Chem. Soc., 77, 4399 (1955).

(11) G. D. Meakins, J. Chem. Soc. 4170 (1953).

(12) Huang-Minlon, J. Am. Chem. Soc., 68, 2487 (1946).

(13) H. Heymann and L. F. Fieser, ibid., 73, 5252 (1951); M. L. Wolfrom and K. Anno, ibid., 74, 5583 (1952); N. J. Leonard, K. Conrow and R. W. Fulmer, J. Org. Chem., 22, 1445 (1957).

Chart III

ried out as with the 17-benzoyloxy compounds and repetition of the sodium borohydride reaction conditions of the other authors gave both the lactone and the non-lactonic neutral product reported by them to have structures XXVII and XXVI, respectively. The fact that the diol structure XXVI was incorrect for the latter material and should be replaced by the hemiacetal structure XXIXa was ascertained by formation from it of the methyl ether XXIXb on standing in methanolic p-toluenesulfonic acid and its ready oxidation to a lactone isomeric with that formed in the original reduction. Furthermore the material was not identical with the single diol produced from the keto ester XXV by reduction with lithium aluminum hydride.

The reduction of XXV is thus seen to take the same course as the similar reaction of the benzoyloxy keto ester VIIIa, giving a lactone and a cyclic hemiacetal differing from one another in their configuration about C-5. It was reasonable then to assume that the products of similar structural type in the two series corresponded in their stereochemistry and thus that the lactone produced in the reduction of XXV should be represented as XXVIII and the structure XXVII assigned by Jacobs and Brownfield to this material should instead be assigned to the product of oxidation of the hemiacetal XXIXa. Table I presents rotational data in support of this assumption. The molecular rotation differences of the lactones from the keto esters XXV and XXX[14] are shown to

demonstrate that large negative values are obtained regardless of the C-5 configuration of the lactone.

TABLE I

	Keto ester M_D	5β lactone M_D	5α lactone M_D	$\Delta M\beta$	$\Delta M\alpha$
Cholestane series					
XXV, XXVIII, XXVII	+356	−68	−41	−423	−397
17-Keto series					
XXX, XXII, XXI	+594	+58	+99	−536	−495

The solution of the problem of making definite configurational assignments was accomplished when it was found that Baeyer–Villiger oxidation[15] of B-norcoprostan-6-one[16] (XXXI) gave the same lactone (XXVIII) that was obtained directly in the sodium borohydride reduction of the keto ester XXV. Since this oxidative rearrangement was well known to occur with retention of configuration at the migrating center[17] and the configuration of the starting material had been firmly established, this result made it possible to assign the A:B *cis* structure to XXVIII and the related materials XIa, etc., and the *trans* arrangement to XXVII, XXI, etc.

An earlier attempt to resolve this question of stereochemistry was based on the known distinction[18] between the optical rotatory dispersion curves of saturated 3-ketones in the "normal" and "allo" series and required the preparation of suitable 6-oxa-3-ketones for dispersion measurements. The cyclohexanecarboxy lactone XXXII was prepared by hydrogenation of the benzoyloxy group of XVa to give XVc and then oxidation at C-3; its epimer XXXIII was obtained from XIIIa in a three-step sequence involving hydrogenation in acidified methanol to the ether, hydrolysis of the ether and finally oxidation at positions 3 and 7 (XIIIa → XXXIV → XIIIc → XXXIII).

The R.D. curve of the 5α-compound XXXIII was virtually without a Cotton effect while that of XXXII showed a strong positive effect. These results, while they were somewhat indicative of a conclusion opposite to the subsequently discovered fact, really allowed no definite assignment to be made. The determination of the curve of the methyl ether XXIIIb shed no further light on the question since it also showed a positive Cotton effect. The explanation of the differences between these findings with 6-oxasteroids and the data for normal saturated 3-ketones may be a polar effect of the oxygen at position 6 or, in the case of the 5β-derivative where a positive Cotton effect is quite unexpected, an unusual conformation in the B-ring may be responsible.

Various means have been used to reduce lactones to their corresponding lactols including sodium amalgam, Raney nickel and electrolytic treat-

(14) The diketo ester XXX was prepared from compound XL by diazomethane treatment and oxidation.

(15) W. D. Emmons and G. B. Lucas, *J. Am. Chem. Soc.*, **77**, 2287 (1955).

(16) T. Goto, *ibid.*, **82**, 2005 (1960).

(17) R. B. Turner, *ibid.*, **72**, 878 (1950); T. F. Gallagher and T. H. Kritchevsky, *ibid.*, **72**, 882 (1950); K. Mislow and J. Brenner, *ibid.*, **75**, 2318 (1953).

(18) C. Djerassi and W. Closson, *ibid.*, **78**, 3761 (1956).

ment.[19] Sodium borohydride itself when used in acid solution has been reported to effect this transformation with carbohydrate γ-lactones[20] although at higher pH only the more fully reduced glycitols were obtained. Examples of lactol formation by treatment of a lactone with this reagent under the conditions described in this paper are lacking, however, and it was felt necessary to investigate the reaction of related steroidal δ-lactones before a rational explanation could be advanced for the results observed with the 6-oxa compounds.

The two readily available substances 17β-hydroxy-4-oxa-5α-androstan-3-one[1] (XXXV) and dihydrotestololactone[21] (XXXVII) were treated under the same conditions in which VIIa had been reduced to IXa. The 4-oxa compound gave a single product, the triol XXXVI, nearly quantitatively[22] while the lactone function of XXXVII was attacked to an extent of less than 50% giving the triol XXXVIII. The other product of this reaction was the hydroxy lactone XXXIX.[21] Thus both lactones while attacked at different rates gave the fully reduced products.

From these results and those with the 6-oxa compounds it was evident that two effects had to be considered: the rate at which the lactone carbonyl was reduced to the hemiacetal anion A
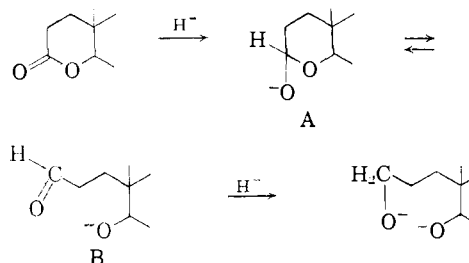
and the rate at which this intermediate further reacted to give the seco diol dianion. The second stage of any reduction of this type undoubtedly occurs by reaction of the aldehyde B which is in equilibrium with the hemiacetal anion A as shown in the equation. Thus any structural feature in the molecule which could cause the equilibrium to shift toward form A would suppress the tendency for the reduction to proceed beyond its initial phase and foster the production of the lactol as the final product. On examination of spatial models of the 5,6-seco-B-nor compounds it could be easily seen that rotation about the 9,10-bond was virtually impossible due to the bulk of the groups involved. The functions attached to carbons 5 and 7 were, as a consequence, forced to remain close to one another and hence in the equilibrium A $\rightleftarrows$ B the left hand member was greatly favored as com-

(19) E. Fischer, *Ber.*, **22**, 2204 (1889); T. Sato, *J. Chem. Soc., Japan*, **71**, 194 (1950); E. London, A. Robertson and H. Worthington, *J. Chem. Soc.*, 3431 (1950).

(20) M. L. Wolfrom and H. B. Wood, *J. Am. Chem. Soc.*, **73**, 2933 (1951). For other references see N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, p. 532.

(21) H. Levy and R. P. Jacobsen, *J. Biol. Chem.*, **171**, 71 (1947).

(22) The 4-oxa lactones were produced by sodium borohydride reduction of 3,5-seco-A-nor keto acids (*cf.* ref. 1). No seco diols were isolated in this reaction since the lactone ring was not closed until the reducing agent was destroyed. The product before acidification was the salt of the hydroxy acid.

pared to the situation which obtained in the compounds XXXV and XXXVII. In these latter cases several conformational possibilities existed for the aldehyde intermediate B. In fact, the initial reduction product of the 6-oxa lactones might better be represented as the mesomeric species C partaking of the character of the two forms shown.
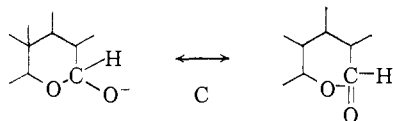
Obviously the high concentration of negative charge in the vicinity of C-7 would render further attack by the borohydride ion on this position unlikely and hence cause the reaction to stop at this stage.

The slower rate of initial lactone carbonyl reduction in dihydrotestololactone (XXXVII) relative to that in the other cases could be explained by considering the steric features in the substrates as they affected both the approach of the borohydride ion to the carbonyl and the thermodynamic stability of the lactol anions. Thus in both the 6-oxa and 4-oxa lactones (cf. XLI and XLII) of the A:B trans series, attack from the unhindered α-face of the molecule led to products in which the oxygen function assumed the equatorial position and, as expected, the reactions were relatively rapid. In the 17a-oxo-D-homo lactone (cf. XLIII), on the other hand, approach of the reducing agent from the β-side leading to equatorial placement of the oxygen was considerably blocked by the angular methyl group and attack from the open lower face was unfavorable because of the relative instability

CHART IV

of the product (due to axial–axial interaction between C-18 and the oxygen function). As a consequence reduction of this material was less rapid. On this limited evidence it was concluded that the transition state in the initial phase of these reduc-

tions resembled the hemiacetal, since if it did not XLIII would have been reduced by attack from the α-face with as great facility as were XLI and XLII.

The 6-oxa lactone Xa in the A:B cis series was only partially converted into the lactol form (cf. yields Chart II) while in the same reaction its epimer VIIa was converted completely to IXa. This fact could be rationalized by considering the increased hindrance to attack from the lower side of the molecule afforded by the C-4 methylene group (cf. XLIV). This factor certainly would account for the decreased reaction rate relative to that of XLI where only the axial hydrogens on C-5, C-9 and C-14 interfere.

One other aspect concerning the yields of the products from the reduction of IVa requiring interpretation was the difference in ratio of A:B cis to A:B trans products depending on whether or not an acetoxy group was present at C-3. Thus, as shown in Chart II, in the 3-acetoxy series a ratio of 1:9 was observed while with the desoxy compounds the ratio was at best 1:1. This effect obviously reflected the difference in behavior of the seco esters IVa and VIIIa in the reaction with sodium borohydride. These starting materials might be considered to react in one or the other of the conformations represented by XLV and XLVI, the former being attacked predominantly from the lower side to produce the 5α-lactones and the latter reacting on the β-side to give the epimeric compounds. Clearly, conformation XLVI would be less stable when R is acetoxy because of the axial position that this group is required to occupy and hence IVa would exist nearly completely in form XLV. This factor no doubt accounts for the small amount of 5β-product formed with the 3-acetoxy group present. The energy difference between forms XLV and XLVI when R is hydrogen, however, would be significantly less so that subtle factors such as differences in the strength of dipole–dipole attraction between the carbomethoxy and carbonyl groups could cause one or the other form to predominate. The results of the reduction would seem to indicate that the conformers are of equal stability or that XLVI is somewhat favored.
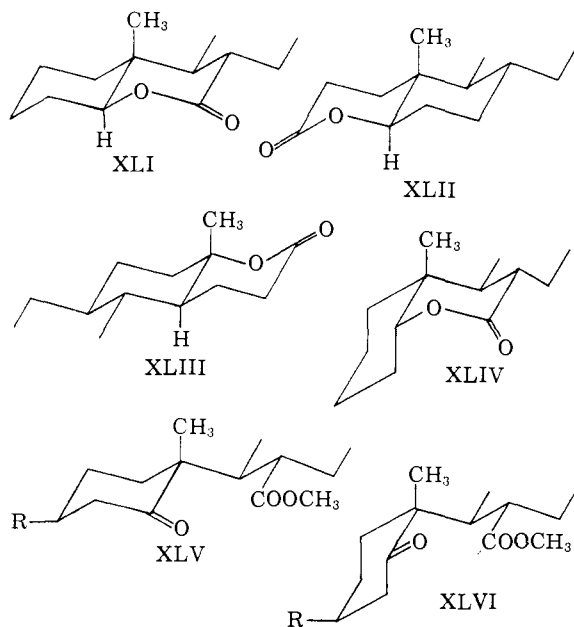
Acknowledgments.—The author wishes to express his appreciation to: Professor William Klyne of Westfield College, University of London, for determining the rotatory dispersion curves and giving his comments on them; Dr. Neal McNiven of the Worcester Foundation for Experimental Biology for determining the n.m.r. data; Dr. H. L. Dryden, Jr., of this Laboratory for helpful discussions concerning the interpretation of the results of the lactone reductions.

Experimental[23]

3β-Acetoxy-17β-benzoyloxyandrost-5-en-7-one (II).—3β-Acetoxy-17β-benzoyloxy-androst-5-ene (I, 54.5 g.) in acetic acid (425 ml.) and acetic anhydride (250 ml.) was

warmed to 40° and anhydrous sodium chromate (37.6 g.) was added portionwise over a short period. The mixture was stirred until homogeneous, then allowed to stand at 40–45° for 3 days after which the solution was added to water (3 l.) and the product collected by filtration. The crude solid was dissolved in ethyl acetate and the solution washed with water, 5% aqueous sodium carbonate and again with water. Removal of the solvent under vacuum and trituration of the residue in boiling methanol (400 ml.) followed by cooling gave the product, 30.0 g. (53.5%), m.p. 201–204°. An analytical sample prepared by further crystallization from methylene chloride–methanol had m.p. 203–204.5°, $[\alpha]$D −59.5°; infrared spectrum: 5.80 broad, 5.98, 6.13, 7.73, 7.81, 7.98 μ; ultraviolet max. 231 mμ, ϵ 27,200.

Anal. Calcd. for $C_{28}H_{34}O_5$ (450.55): C, 74.64; H, 7.60. Found: C, 74.55; H, 7.43.

Ozonization of the Unsaturated Ketone II.—Compound II (100 g.) in methylene chloride (1760 mL) and methanol (660 ml.) was treated with ozone containing oxygen at −78° in two equal portions until the solution assumed a blue color. Each portion was then warmed to room temperature, treated with 30% hydrogen peroxide (14 ml.) and water (28 ml.) and allowed to stand for 16 hr. The combined portions were diluted with methylene chloride (1 l.), washed twice with water and freed of solvent at reduced pressure. The residue dissolved in ether was extracted twice with 5% aqueous sodium carbonate and once with water and was dried with anhydrous sodium sulfate before being evaporated to dryness. The residue on crystallization from isopropyl alcohol and recrystallization from methanol yielded 66.7 g. of IVa, m.p. 170–172°. Another 11.5 g. (m.p. 170–172°) of IVa was obtained on chromatography of the mother liquors over silica gel (total yield 73%). The analytical sample obtained by recrystallization from acetone–isopropyl ether had m.p. 175–176°, $[\alpha]$D +80.5°; infrared spectrum: 5.80 broad, 7.80, 7.97 μ.

Anal. Calcd. for $C_{28}H_{36}O_7$ (484.57): C, 69.40; H, 7.49. Found: C, 69.50; H, 7.64.

After compound IVa, which was eluted from the column with benzene–ethyl acetate (4:1), there was obtained the keto acid IVb (4.9 g., 4.5%) eluted with benzene–ethyl acetate (3:1). An analytical sample obtained by recrystallization from acetone–isopropyl ether had m.p. 195–196.5° dec., $[\alpha]$D +83°; infrared spectrum, 2.73 weak, 5.74–5.82, 7.79, 7.93 μ.

Anal. Calcd. for $C_{27}H_{34}O_7$ (470.54): C, 68.92; H, 7.28. Found: C, 69.25; H, 7.52.

A sample of the acid IVb when treated with an excess of ethereal diazomethane gave the ester IVa, m.p. 171–172.5°, m.p. of mixture with IVa obtained above 171–172°. The infrared spectra of the two samples were identical.

The last compound eluted from the column was the 3-hydroxy keto ester IVc (0.73 g., 1%) eluted with benzene–ethyl acetate 1:1. The analytical sample obtained by crystallization from acetone had m.p. 194.5–197.5°, $[\alpha]$D +99°; 2.73, 5.78 broad, 7.79 μ.

Anal. Calcd. for $C_{28}H_{34}O_6$ (442.53): C, 70.56; H, 7.75. Found: C, 70.19; H, 8.05.

When compound IVc was acetylated the acetoxy keto ester IVa was produced, m.p. 166.5–170°, m.p. of mixture with authentic IVa (see above) 167.5–170°. The infrared spectra of the two samples were identical.

Methyl 17β-Benzoyloxy-5-oxo-5,6-seco-B-norandrost-3-en-6-oate (IIIa).—The keto ester (IVa, 15.0 g.) was dissolved in purified dioxane (230 ml.) and the solution was added all at once to a second solution of potassium hydroxide (8.6 g.) in water (150 ml.) and dioxane (370 ml.). The two-phase mixture then was stirred rapidly at room temperature for 30 min. and poured into water (2.5 l.). The solid was collected by filtration, and then resuspended in water and refiltered. Overnight drying gave 12.0 g. (91%), m.p. 124–130° and 147–149° (double m.p.). Recrystallization from methanol gave analytical material, m.p. 149.5–151°, $[\alpha]$D +106°; ultraviolet max. 229 mμ, ϵ 21,600; infrared spectrum (KBr): 5.81, 5.98, 6.23 μ.

Anal. Calcd. for $C_{26}H_{32}O_5$ (424.52); C, 73.56; H, 7.60. Found: C, 73.29; H, 7.60.

Methyl 17β-Hydroxy-5-oxo-5,6-seco-B-norandro-3-en-6-oate (IIIc).—The keto ester (IVa, 5.0 g.) was dissolved in methanol (350 ml.) and was treated with 50 ml. of a

saturated methanolic solution of hydrogen chloride. The reaction mixture was refluxed for 22 hr. and then was poured into a large excess of dilute ammonium hydroxide. The product was extracted with methylene chloride and the extracts were washed, dried and evaporated. The residual material next was subjected to chromatography on silica gel. Two recognizable products were obtained. The first was the unsaturated keto ester IIIa (0.38 g.), and the second was the desired 17-hydroxy keto ester IIIc (1.45 g.). One crystallization of the latter material from methanol–isopropyl ether gave 1.07 g. of product, m.p. 160.5–161°. Further crystallization from the same solvent mixture gave the analytical sample, $[\alpha]$D +90°; ultraviolet max. 227 mμ, ϵ 11,000; infrared spectrum (KBr): 2.85, 5.88 shoulder, 5.94, 8.27 μ.

Anal. Calcd. for $C_{19}H_{28}O_4$ (320.41): C, 71.22; H, 8.81. Found: C, 71.26; H, 8.62.

Methyl 17β-Benzoyloxy-5-oxo-5,6-seco-B-norandrostan-6-oate (VIIIa).—The unsaturated keto ester IIIa (3.0 g.) was dissolved in ethanol (200 mL) and shaken in an atmosphere of hydrogen in the presence of 5% palladium-on-carbon (300 mg.). Filtration of the catalyst and evaporation of the solvent left a solid residue, 3.0 g., m.p. 164–168.5°. The analytical sample was obtained by recrystallization of this from isopropyl ether; m.p. 170–171°, $[\alpha]$D +101°; infrared spectrum (KBr): 5.79, 5.84 shoulder, 7.83 μ.

Anal. Calcd. for $C_{26}H_{34}O_5$ (426.53): C, 73.21; H, 8.04. Found: C, 73.32; H, 8.36.

For an alternate preparation of this material see description of sodium borohydride reduction of IIIa below.

Sodium Borohydride Reduction of Seco Ester IVa.—Compound IVa (11.2 g.) in anhydrous ethanol (1350 ml.) was treated with a solution of sodium borohydride (5.6 g.) in the same solvent (450 ml.) and the solution was allowed to stand at 23° for 5 hr. and then acetic acid was added until effervescence ceased. The solution was concentrated under vacuum to small volume then water was added and the product extracted with benzene. After washing the extracts with dilute aqueous sodium bicarbonate and then water, they were dried with anhydrous sodium sulfate and applied to a chromatography column containing 1 kg. of silica gel.

17β-Benzoyloxy-6-oxa-5β-androstan-7-one (XIa, 2.16 g., 23.5%) was eluted with benzene–ethyl acetate 19:1. The analytical sample obtained by crystallization from isopropyl ether had m.p. 198.5–201.5°, $[\alpha]$D +18°; infrared spectrum: 5.74–5.82, 7.79 μ.

Anal. Calcd. for $C_{25}H_{32}O_4$ (396.51): C, 75.72; H, 8.14. Found: C, 75.74; H, 7.99.

The second chromatography peak (2.23 g.) eluted with the same solvent mixture when crystallized several times from methanol gave a small quantity of 3β-acetoxy-17β-benzoyloxy-6-oxa-5β-androstan-7-one (Xa), m.p. 224–225.5°, $[\alpha]$D +33°; infrared spectrum: 5.75, 5.80 shoulder, 7.80, 7.99 μ.

Anal. Calcd. for $C_{27}H_{34}O_6$ (454.54): C, 71.34; H, 7.54. Found: C, 71.33; H, 7.62.

An aliquot of the total chromatography peak (0.53 g.) was hydrolyzed with aqueous methanolic potassium hydroxide and the neutral non-lactonic material removed by extraction of the diluted hydrolysate. The amount of crude lactonic material (45 mg.) obtained by acidification and re-extraction of the aqueous phase indicated that compound Xa was produced in the reduction in about 2.5% yield. The crude neutral material from the hydrolysis (465 mg.) when recrystallized from methanol–water and then several times from acetone gave the analytical sample of 6-oxa-5α-androstane-7β,17β-diol (XVIb), m.p. 215.5–217°; infrared spectrum: 2.74, 9.22, 9.38, 10.00 μ.

Anal. Calcd. for $C_{18}H_{30}O_3$ (294.42): C, 73.43; H, 10.27. Found: C, 73.18; H, 10.09.

Had the total non-lactonic material from the hydrolysis been XVIb, the amount obtained would indicate a 21% yield of 17β-benzoyloxy-6-oxa-5α-androstan-7β-ol (XVIa) in the reduction. The high loss which occurred on purification of XVIb, however, would indicate the presence of other similar materials.

The third chromatography peak (4.39 g.) eluted with benzene–ethyl acetate 4:1 consisted largely of 3β-acetoxy-17β-benzoyloxy-6-oxa-5α-androstan-7β-ol (IXa) with a small amount of its C-5 epimer 3β-acetoxy-17β-benzoyloxy-6-oxa-5β-androstan-7β-ol (XIVa) in the later fractions. This latter material was isolated by virtue of its slight solubility in ace-

tone; 0.10 g. (1%), m.p. 230.5–233.5°. The analytical sample obtained by recrystallization from acetone had m.p. 234–237°; infrared spectrum: 2.74, 5.78 broad, 7.78, 7.92 μ; n.m.r.[23] spectrum: 9.042 (C-18, C-19), 7.958 (acetate CH₃), 5.25 (4 R₂CHO–).

Anal. Calcd. for $C_{27}H_{36}O_6$ (456.56): C, 71.02; H, 7.95. Found: C, 70.96; H, 8.15.

The good recovery (2.90 g., m.p. 200–202°) of IXa from the material remaining after removal of its epimer indicated that it was probably the only other compound present in the chromatography peak and therefore was formed in the reduction in about 40% yield. The analytical sample was obtained by recrystallization from acetone–isopropyl ether, m.p. 201.5–202.5°; infrared spectrum: 2.77, 5.78, 5.82 shoulder, 7.80, 7.94 μ; n.m.r.,[23] spectrum: 9.050 (C-18, C-19), 7.975 (acetate CH₃), 5.30 (4 R₂CHO–).

Anal. Calcd. for $C_{27}H_{36}O_6$ (456.56): C, 71.02; H, 7.95. Found: C, 71.15; H, 7.86.

17β-Benzoyloxy-3β-hydroxy-6-oxa-5β-androstan-7-one (XVa, 0.14 g., 1.5%) was eluted with benzene–ethyl acetate 3:2 and was purified by recrystallization from acetone–isopropyl ether, m.p. 233.5–235°; infrared spectrum: 2.74, 5.73, 5.81, 7.73, 7.79 μ.

Anal. Calcd. for $C_{25}H_{32}O_5$ (412.50): C, 72.79; H, 7.82. Found: C, 73.01; H, 8.05.

Acetylation of XVa gave compound Xa, m.p. 223.5–224.5°. The infrared spectrum was identical with that of the sample described above.

17β-Benzoyloxy-6-oxa-5α-androstane-3β,7β-diol (XIIIa, 0.45 g., 5%) was eluted from the column with benzene–ethyl acetate 1:4. The analytical sample obtained by recrystallization from ethyl acetate had m.p. 254–257.5°; infrared spectrum: 2.73, 5.81, 7.79 μ.

Anal. Calcd. for $C_{25}H_{34}O_5$ (414.52): C, 72.43; H, 8.27. Found: C, 72.68; H, 8.61.

Sodium Borohydride Reduction of Keto Esters IIIa and VIIIa.—Compound IIIa (0.50 g.) was dissolved in anhydrous ethanol (60 ml.) and the solution was treated with sodium borohydride (0.25 g.) in 20 ml. of the same solvent. After the solution had stood at room temperature for 4.5 hr. it was treated with acetic acid until the reducing agent was destroyed and then was diluted with water. Ether extraction of the mixture followed by drying and removal of the solvent under vacuum left a yellow oil which crystallized on treatment with methanol. Three crystallizations of this solid from methanol and three from isopropyl ether gave the analytical sample of the saturated keto ester VIIIa (0.09 g.), m.p. 171.5–173.5°. The infrared spectra of this material and of that prepared by hydrogenation of IIIa (see above) were identical.

In another experiment 5.7 g. of IIIa was treated under the same conditions with 2.85 g. of the reducing agent and the total product was hydrolyzed in aqueous methanolic potassium hydroxide and separated into acidic, lactonic and neutral non-lactonic fractions. The acidic material (2.25 g.) after being freed of benzoic acid by heating under vacuum was crystallized from isopropyl ether to give 17β-hydroxy-5-oxo-5,6-seco-B-norandrostan-6-oic acid (XL), m.p. 229.5–231.5°, $[\alpha]\text{D}$ +105.5°; infrared spectrum (KBr): 2.88, 5.80, 5.90, 5.99, 8.34, 9.40, 9.76 μ.

Anal. Calcd. for $C_{18}H_{28}O_4$ (308.40): C, 70.10; H, 9.15. Found: C, 69.92; H, 8.94.

The same product was obtained by hydrolysis of the benzoyloxy ester VIIIa.

The lactonic material (1.15 g.) gave 17-hydroxy-6-oxa-5β-androstan-7-one (XIb) on crystallization from isopropyl ether; m.p. 149° with resolidification and remelting at 161–162.5°, $[\alpha]\text{D}$ −30°; infrared spectrum: 2.74, 5.75, 8.43 μ.

Anal. Calcd. for $C_{18}H_{28}O_3$ (292.40): C, 73.93; H, 9.65. Found: C, 73.81; H, 9.77.

The same hydroxy lactone was obtained on hydrolysis of the benzoyloxy lactone XIa.

The neutral non-lactonic fraction (0.42 g.) when crystallized from methanol–water and then acetone gave a small amount of lactol XVIb, m.p. 215.5–216.5°. A mixture with material obtained as described above melted at 216–217°.

The saturated keto ester VIIIa gave the same products in approximately the same yields when treated as described above for IIIa.

3β-Acetoxy-17β-benzoyloxy-6-oxa-5α-androstan-7-one (VIIa). A. By Chromium Trioxide Oxidation of IXa.—Hemiacetal IXa (0.50 g.) was oxidized in acetone solution (15 ml.) with a slight excess of aqueous 8 N chromium trioxide–8 N sulfuric acid. After 10 min., isopropyl alcohol was added to destroy the excess oxidant and the mixture diluted with water. The product (0.40 g.) was collected by filtration and recrystallized from methanol; m.p. 186–189.5°. The analytical sample obtained by further recrystallization from methanol exhibited a double melting point at 190° and 220–221°, $[\alpha]\text{D}$ +15.5°; infrared spectrum: 5.77, 7.79, 7.95, 8.91, 9.72 μ.

Anal. Calcd. for $C_{27}H_{34}O_6$ (454.55): C, 71.34; H, 7.54. Found: C, 71.46; H, 7.93.

B. By Treatment of IXa with Manganese Dioxide.—Compound IXa (150 mg.) was dissolved in chloroform (50 ml.) and the solution stirred at room temperature for 22 hr. with manganese dioxide.[24] The solid reagent then was removed by filtration and washed thoroughly with additional solvent. The combined solutions were taken to dryness *in vacuo* and the residue chromatographed on silica gel. The solid (30 mg.) eluted with benzene–ethyl acetate (19:1) displayed an infrared spectrum identical to the lactone VIIa prepared as described above.

Oxidation of Lactol XIVa.—Compound XIVa (15 mg.) when treated with aqueous chromium trioxide–sulfuric acid in acetone solution as described above gave lactone Xa whose infrared spectrum was identical with that of the sample obtained directly from the reduction of IVa.

3β-Acetoxy-17β-benzoyloxy-7β-methoxy-6-oxa-5α-androstane (XVIIIb).—Lactol IXa (0.50 g.) dissolved in methanol (35 ml.) was treated with p-toluenesulfonic acid monohydrate (60 mg.) and allowed to stand 16 hr. at room temperature. Solid potassium hydroxide in excess of that required to neutralize the acid was added and allowed to dissolve. The mixture then was diluted with water and the product collected by filtration; infrared spectrum: 2.73, 5.81, 7.78 μ. After drying, this material was acetylated with acetic anhydride and pyridine by heating on the steam-plate for 3 hr. The product was obtained by dilution with water and filtration. Recrystallization from methanol–water and then hexane gave the analytical sample, 0.13 g., m.p. 147–147.5°; infrared spectrum: 5.76–5.81, 7.78, 7.90 μ; n.m.r.[23] spectrum: 9.075 (angular CH₃'s), 7.958 (acetate CH₃), 6.667 (methoxy CH₃).

Anal. Calcd. for $C_{28}H_{38}O_6$ (470.58): C, 71.46; H, 8.14; OCH₃, 6.60. Found: C, 71.64; H, 8.09; OCH₃, 6.62.

17β-Benzoyloxy-7β-methoxy-6-oxa-5β-androstan-3β-ol (XVII).—The hemiacetal XIVa (300 mg.) was treated with p-toluenesulfonic acid in methanol as described above and the crude product submitted to chromatography on silica gel. Elution with 9:1 benzene–ethyl acetate gave the methoxy compound XVII (107 mg.). Two recrystallizations from acetone–hexane gave the hemiacetonate, m.p. 187.5–189.5° after softening at 160–170° and resolidifying; infrared spectrum: 2.74, 5.81, 7.77, 8.91 μ; n.m.r.[23] spectrum: 9.137, 9.078 (angular CH₃'s), 7.837 (acetone CH₃'s), 6.667 (methoxy CH₃).

Anal. Calcd. for $C_{26}H_{36}O_5 \cdot 0.5 C_3H_6O$ (457.59): C, 72.18; H, 8.59. Found: C, 72.19; H, 8.51.

3β-Acetoxy-17β-benzoyloxy-6-oxo-5α-androst-7-ene (XIX).—Hemiacetal IXa (0.15 g.) was dissolved in pyridine (2 ml.) and treated with acetic anhydride (1 ml.). The mixture stood at room temperature for 7 hr. and then was diluted with water. The amorphous solid was collected by filtration, washed and air-dried; infrared spectrum (KBr): 5.72–5.81, 7.81, 8.05 μ. The crude acetylation product then was pyrolyzed at 220° and a pressure of 0.1 mm. The material which sublimed had m.p. 175–183°; infrared spectrum (KBr): 3.25, 5.80, 5.85, 6.04 μ.

Anal. Calcd. for $C_{27}H_{34}O_5$ (438.54): C, 73.94; H, 7.82. Found: C, 73.68; H, 7.69.

6-Oxa-5α-androstan-7,17-dione (XXI).—The hemiacetal XVIb (50 mg.) in acetone (5 ml.) was treated with excess 8N chromium trioxide–8 N sulfuric acid according to the procedure previously described. The crude product after two

(24) The manganese dioxide was prepared according to J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and T. Walker, *J. Chem. Soc.*, 1094 (1952).

crystallizations from acetone (18 mg.) had m.p. 270–272°, [α]D +34°; infrared spectrum: 5.73, 8.42 μ.

Anal. Calcd. for C₁₈H₂₆O₃ (290.38): C, 74.44; H, 9.03. Found: C, 74.54; H, 8.89.

17β-Benzoyloxy-7β-methoxy-6-oxa-5α-androstan-3-one (XXIIIa).—Crude hydroxy ether XVIIIa (0.70 g.) prepared as described above was dissolved in pyridine (22 ml). and treated with a previously prepared mixture of chromium trioxide (1.00 g.) in pyridine (15 ml.). The mixture was allowed to stand 16 hr. at room temperature then diluted with ethyl acetate and filtered. The filtrate was distilled to dryness and the product (0.27 g.), m.p. 190–192°, obtained by crystallization of the residue from acetone–isopropyl ether. The analytical sample obtained on further crystallization from the same solvents had m.p. 199.5–202°; infrared spectrum: 5.80, 7.79, 8.92, 9.53 μ.

Anal. Calcd. for C₂₆H₃₄O₅ (426.53): C, 73.21; H, 8.04. Found: C, 73.33; H, 7.72.

17β-Hydroxy-7β-methoxy-6-oxa-5α-androstan-3-one (XXIIIb).—Compound XXIIIa (239 mg.) in methanol (20 ml.) was treated with 10% KOH (5 ml.) and the mixture was kept at reflux for 4.5 hr. The mixture was extracted with methylene chloride and the extracts washed with water and the solvent removed at reduced pressure. The residue (173 mg.) on crystallization from acetone–isopropyl ether had m.p. 193–195.5°; infrared spectrum: 2.76, 5.81, 9.58 μ; R.D. in CH₃OH (mμ, *M*D × 10⁻²) 500, + 3; 400, +2; 326, −3; 321, −1.5; 280, −12.5; 270, −8.

Anal. Calcd. for C₁₉H₃₀O₄ (322.43): C, 70.77; H, 9.38. Found: C, 70.77; H, 9.58.

7β-Methoxy-6-oxa-5α-androstan-17β-ol (XX). A. From Lactol XVIb.—Compound XVIb (0.31 g.) was treated in methanol with *p*-toluenesulfonic acid as previously described for other lactols. The product was extracted with ether and the extracts were washed, dried with sodium sulfate and taken to dryness *in vacuo.* The residue was recrystallized from acetone–hexane to give the product (0.30 g.), m.p. 157–159°. The analytical sample obtained by further recrystallization from the same solvents had infrared spectrum: 2.73, 8.81, 9.60, 10.09 μ.

Anal. Calcd. for C₁₉H₃₂O₃ (308.45): C, 73.98; H, 10.46. Found: C, 73.95; H, 10.56.

B. From Ketone XXIIIb.—Compound XXIIIb (114 mg.) was dissolved in a 20% solution of potassium hydroxide in diethylene glycol (5 ml.) and 95% hydrazine (1 ml.) was added. The mixture was kept at reflux (130°) for 1 hr. then the condenser was removed and the temperature allowed to increase to 200–210°. After 1 hr. at this temperature gas evolution ceased and the solution began to darken. After cooling, the reaction mixture was poured into water and the product collected by filtration. Chromatography on Florisil gave 48 mg. of solid material on elution with benzene, which after recrystallization from methanol–water and acetone–hexane gave material of m.p. 156.5–159°. A mixture with material produced by the other route had m.p. 157–159°. The infrared spectra of the two samples were identical.

6-Oxa-5β-androstan-7,17-dione (XXII).—Compound XIb (20 mg.) was dissolved in acetone (2 ml.) and the resulting solution treated with an aqueous solution 6 *N* in chromium trioxide and 6 *N* in sulfuric acid until an excess of oxidant was present. After 1 min. a drop of isopropyl alcohol was added to destroy this excess and the mixture was diluted with water. The solid then was filtered, washed and dried, m.p. 161.5–162.5°. The analytical sample was obtained by recrystallization from isopropyl ether; infrared spectrum: 5.75, 8.39 μ.

Anal. Calcd. for C₁₈H₂₆O₃ (290.38): C, 74.44; H, 9.03. Found: C, 74.70; H, 9.11.

Sodium Borohydride Treatment of Lactones XXI and VIIa.—The 3-desoxy compound XXI (55 mg.) was dissolved in ethanol (10 ml.) and treated with a solution of sodium borohydride (50 mg.) in ethanol (5 ml.). After 4.5 hr. at 23° acetic acid was added to destroy the reducing agent and the mixture was poured into water. After evaporation of the ethanol the product was collected by filtration (54 mg.), m.p. 211–214°. Recrystallization from acetone gave material of m.p. 217.5–218°; mixture with authentic material (see above) m.p. 217–218°.

The acetoxy lactone VIIa (1.90 g.) when similarly treated (3 hr.) gave a somewhat impure solid product. Recrystallization from isopropyl ether gave 1.25 g. (66%) of lactol

IXa having an infrared spectrum identical to that of the material obtained in the reduction of IVa.

17β-Benzoyloxy-6-oxa-5α-androstan-3,7-dione (XXIV).—The compound VIIa (0.40 g.) in ethanol (35 ml.) was treated with a solution of potassium hydroxide (0.056 g.) in water (1 ml.). After standing at 25° for 16 hr. the mixture was diluted with water (250 ml.) and the product filtered. Recrystallization from acetone gave 0.20 g. of material, m.p. 277–278°. A portion (0.2 g.) of this material was oxidized in acetone solution with aqueous 8 *N* chromium trioxide–8 *N* sulfuric acid according to the procedure used for the formation of lactone XXII. The product (0.19 g.), m.p. 261–270°, was obtained from the crude solid by recrystallization from acetone–isopropyl ether. The analytical sample prepared by one further recrystallization had m.p. 269–273°; infrared spectrum: 5.79, 7.80, 8.49, 8.90, 9.51 μ.

Anal. Calcd. for C₂₅H₃₀O₅ (410.49): C, 73.15; H, 7.36. Found: C, 73.08; H, 7.45.

Hemiacetal XIIIa when similarly oxidized gave the same product as demonstrated by the identity of their infrared spectra.

Preparation and Reduction of Methyl 5-Oxo-5,6-seco-B-norcholestan-6-oate (XXV).—20.25 g. 7-ketocholesteryl acetate was ozonized in methylene chloride–methanol and the crude neutral product dehydroacetoxylated with potassium hydroxide in dioxane as with the 17-benzoyloxy compound to give an oily product (13 g.); infrared spectrum: 5.78, 5.95 μ; ultraviolet max. 226 mμ, ε 6700. A portion of this material was hydrogenated and the reduced material (keto ester XXV) subjected to the action of sodium borohydride in isopropyl alcohol as described by Jacobs and Brownfield.[2] The two products isolated had constants in agreement with those obtained by the other authors. The lactone XXVIII had m.p. 132.5–134° [α]D −17.5°; infrared spectrum: 5.75, 8.43, 8.78, 9.81, 9.90 μ; the non-lactonic material XXIXa had m.p. 159.5–160.5°; infrared spectrum: 2.76, 2.95 μ and no carbonyl absorption.

7β-Methoxy-6-oxa-5α-cholestane (XXIXb).—6-Oxa-5α-cholestan-7β-ol (XXIXa, 100 mg.) in 35 ml. of methanol was treated with *p*-toluenesulfonic acid monohydrate (50 mg.) and allowed to stand 16 hr. at room temperature. The mixture was neutralized with solid potassium hydroxide and diluted with water. The oily product was obtained by hexane extraction and washing, drying and evaporating the extracts; infrared spectrum: 8.79, 9.57, 10.10 μ and no hydroxyl absorption.

Anal. Calcd. for C₂₇H₄₈O₂ (404.65): CH₃O, 7.67. Found: CH₃O, 7.52.

6-Oxa-5α-cholestan-7-one (XXVII).—The lactol XXIXa (50 mg.) was oxidized in acetone solution with aqueous chromium trioxide–sulfuric acid as described above. The product after two recrystallizations from acetone–isopropyl ether had m.p. 171–172°, [α]D −10.5°; infrared spectrum: 5.79, 8.40, 9.53 μ.

Anal. Calcd. for C₂₆H₄₄O₂ (388.61): C, 80.35; H, 11.41. Found: C, 80.29; H, 11.01.

5,6-Seco-B-norcholestane-5ξ,6-diol (XXVI).—Crude seco ester XXV (2.5 g.) was kept at reflux 28 hr. in a tetrahydrofuran solution (300 ml.) containing lithium aluminum hydride (2.0 g.). The excess reducing agent was destroyed with acetone and the mixture was diluted with water and acidified. The crude product was obtained by ether extraction followed by washing, drying and vacuum removal of the solvent. The residue was chromatographed on silica gel and the diol XXVI (1.5 g.) was eluted with benzene–hexane (3:1). The analytical material obtained by recrystallization from acetone–water and then isopropyl ether had m.p. 155–157.5°; infrared spectrum: 2.71, 9.63 μ.

Anal. Calcd. for C₂₆H₄₈O₂ (392.64): C, 79.53; H, 12.32. Found: C, 79.54; H, 12.06.

Methyl 5,17-Dioxo-5,6-seco-B-norandrostan-6-oate (XXX).—The keto acid XL (0.8 g.) in benzene (150 ml.) was treated with excess ethereal diazomethane. After 16 hr. at room temperature the solution was evaporated to dryness and the residue crystallized first from acetone–water and then acetone–hexane to give methyl 17-hydroxy-5-oxo-5,6-seco-B-norandrostan-6-oate (VIIIb), m.p. 139.5–140.5°, [α]D +94.5°; infrared spectrum: 2.75, 5.79, 5.87, 8.52 μ.

Anal. Calcd. for C₁₉H₃₀O₄ (322.43): C, 70.77; H, 9.38. Found: C, 71.18; H, 9.31.

This material then was oxidized with chromium trioxide–sulfuric acid in acetone as described above to give compound XXX, m.p. 173–174°, $[\alpha]$D +185°; infrared spectrum: 5.77, 5.87, 7.62, 8.49, 8.71 μ.

Baeyer–Villiger Oxidation of B-Norcoprostan-7-one (XXXI).—Compound XXXI was prepared from B-norcoprostan-3,7-dione (11.4 g.) by the sequence lithium tri-*t*-butoxyaluminum hydride reduction, tosylation, lithium aluminum hydride treatment and chromic acid oxidation using modifications of the conditions of Goto[16] and without isolation of intermediates. Part of the product (1.0 g., m.p. 90–92.5°) was isolated by direct crystallization and a further quantity (2.4 g., infrared spectrum identical with analytical sample) was obtained after chromatography on silica gel (total yield 30%). The analytical sample had m.p. 96–98°, $[\alpha]$D +30°, infrared absorption at 5.77 μ.

A solution of the ketone XXXI (0.464 g.) in methylene chloride (10 ml.) was cooled to Dry Ice temperature and treated with a solution of trifluoroperacetic acid prepared from 68% hydrogen peroxide (0.12 ml.) and trifluoroacetic anhydride (0.84 ml.). The mixture stood overnight at 5° and then was diluted with ether and washed successively with dilute aqueous sodium bicarbonate, dilute aqueous sodium thiosulfate and saturated aqueous sodium chloride. The ether solution was dried with anhydrous sodium sulfate and the solvent removed to leave a solid residue. Recrystallization from isopropyl ether gave 0.16 g. of material, m.p. 122–128°. Further crystallization from methanol gave pure XVIII, m.p. 132–134°, infrared absorption identical with that of material prepared by reduction of keto ester XXV (see above), m.p. of mixture with this material 132–134°.

17β-Cyclohexanecarboxy-3β-hydroxy-6-oxa-5β-androstan-7-one (XVc).—The corresponding benzoate XVa (130 mg.) was hydrogenated at one atmosphere of hydrogen pressure with platinum oxide (200 mg.) in an ethanol solution (25 ml.) containing 60% perchloric acid (0.1 ml.). When hydrogen uptake ceased the catalyst was filtered and the filtrate diluted with water. The mixture was extracted with benzene and the extracts were washed with dilute sodium bicarbonate and water with removal of the solvent at reduced pressure. The residue on repeated crystallization from acetone–isopropyl ether gave XVc (80 mg.), m.p. 199–200°; infrared spectrum: 2.73, 5.77, 7.98, 8.49 μ.

Anal. Calcd. for $C_{25}H_{38}O_5$ (418.56): C, 71.74; H, 9.15. Found: C, 71.95; H, 9.06.

17β-Cyclohexanecarboxy-6-oxa-5β-androstane-3,7-dione (XXXII).—Compound XVc (100 mg.) in acetone (5 ml.) was treated dropwise with an aqueous solution 8 N in chromium trioxide and 8 N in sulfuric acid at room temperature until an excess of oxidant was present. After 15 min. a drop of isopropyl alcohol was added and the mixture was diluted with 5 volumes of water. After removing the acetone at reduced pressure the product was filtered. Recrystallization from isopropyl ether gave XXXII, m.p. 174.5–176.5°; infrared spectrum: 5.73 shoulder, 5.79, 7.99, 8.52 μ; R.D. in CH_3OH (mμ, MD × 10⁻²); 500, −2; 400, 0; 325, + 12.5; 320, +11.5; 307, + 24; 285, −5; 268, 0.

Anal. Calcd. for $C_{25}H_{36}O_5$ (416.54): C, 72.08; H, 8.71. Found: C, 71.88; H, 8.85.

17β-Cyclohexanecarboxy-7β-methoxy-6-oxa-5α-androstan-3β-ol (XXXIV).—Compound XIIIa (650 mg.) dissolved in methanol (125 ml.) was treated with 60% perchloric acid (0.1 ml.) and the solution allowed to stand for 16 hr. at 25°. A slurry of prereduced platinum oxide (700 mg.) in methanol (10 ml.) was added and the mixture hydrogenated at 25° and 1 atmosphere pressure until no more gas was absorbed. The catalyst was removed by filtration and solid potassium hydroxide was added to the filtrate. Two volumes of water was added and the methanol removed at reduced pressure. The product was collected by filtration and purified by recrystallization from acetone–isopropyl ether; 0.23 g., m.p. 182–185°; infrared spectrum: 2.73, 5.78, 7.98, 8.48, 8.80, 9.53 μ.

Anal. Calcd. for $C_{26}H_{42}O_5$ (434.60): C, 71.85; H, 9.74; OCH_3, 7.14. Found: C, 71.48; H, 9.38; OCH_3, 7.69.

17β - Cyclohexanecarboxy - 6 - oxa - 5α - androstane-3β,7β-diol (XIIIc).—Ether XXXIV (250 mg.) in dioxane (20 ml.) was treated with a solution of concentrated HCl (0.3 ml.) in water (5 ml.). The mixture was warmed for 40 min. on the steam-plate, diluted with water and the product filtered. Recrystallization from acetone–petroleum ether gave material of m.p. 186–190°; infrared spectrum: 2.74, 5.79, 7.98, 8.80, 9.53 μ.

Anal. Calcd. for $C_{25}H_{40}O_5$ (420.57): C, 71.39; H, 9.59. Found: C, 71.11; H, 9.19.

17β-Cyclohexanecarboxy-6-oxa-5α-androstane-3,7-dione (XXXIII).—Compound XIIIc (100 mg.) in reagent acetone (40 ml.) was treated dropwise with an aqueous chromium trioxide–sulfuric acid solution (8 N in both components) until an excess of oxidant was present. After 20 min. a small quantity of isopropyl alcohol was added and the mixture diluted with 5 volumes of water. The product was collected by filtration and purified by recrystallization from acetone–isopropyl ether to give material of m.p. 221.5–225.5°; infrared spectrum: 5.78, 8.49, 9.50 μ; R.D. in CH_3OH (mμ, MD × 10⁻²) 500, +6; 400 +2; 345, −2; 319, +3.5; 313, +1; 309, +5; 294, −3.5; 280, +4.

Anal. Calcd. for $C_{25}H_{36}O_5$ (416.54): C, 72.08; H, 8.71. Found: C, 71.95; H, 8.56.

Borohydride Reduction of 17β-Hydroxy-4-oxa-5α-androstan-3-one (XXXV).—Compound XXXV (1.25 g.) in anhydrous ethanol (60 ml.) was treated with a solution of sodium borohydride (0.63 g.) in the same alcohol (30 ml.). The solution stood at room temperature for 3 hr. and then was treated cautiously with acetic acid until effervescence ceased. After dilution to 350 ml. with water the ethanol was removed under vacuum and the 3,5-seco-A-norandrostane-3,5β,17β-triol (XXXVI) collected by filtration; 1.20 g., m.p. 204–207.5°. The analytical sample was prepared by recrystallization from ethyl acetate, m.p. 205–208°; infrared spectrum (KBr): 2.97, 9.49, 9.72 μ.

Anal. Calcd. for $C_{18}H_{32}O_3$ (296.44): C, 72.92; H, 10.88. Found: C, 72.87; H, 10.74.

The triacetate showed m.p. 119.5–121°; infrared spectrum: 5.77, 7.90, 9.68 μ.

Anal. Calcd. for $C_{24}H_{38}O_6$ (422.54): C, 68.22; H, 9.06. Found: C, 68.46; H, 8.74.

Borohydride Reduction of Dihydrotestololactone (XXXVII).—This material (20 g.) was treated with the reducing agent in the same manner as XXXV. The crude product was dissolved in methanol (450 ml.) and treated with a solution of potassium hydroxide (15 g.) in water (50 ml.). The mixture was heated at reflux for 5 hr. and then diluted with water (600 ml.). After cooling, the basic mixture was extracted exhaustively with ethyl acetate and the extracts were washed with water and the solvent removed under vacuum. The moist residue (8.0 g.) was recrystallized from methanol to give 13,17-seco-5α-androstane-3β,13α,17-triol (XXXVIII), 4.70 g., m.p. 223–224°. The analytical sample obtained by further crystallization from methanol had m.p. 226–227°; infrared spectrum (KBr): 3.04 broad, 9.18, 9.47, 9.63, 9.77 μ.

Anal. Calcd. for $C_{19}H_{34}O_3$ (310.46): C, 75.50; H, 11.04. Found: C, 73.57; H, 10.67.

The hydroxy diacetate from XXXVIII was prepared; m.p. 108.5–110°; infrared spectrum: 2.73, 5.77, 7.88–7.96 μ.

Anal. Calcd. for $C_{23}H_{38}O_5$ (394.53): C, 70.01; H, 9.71. Found: C, 70.15; H, 9.53.

The aqueous solution from which XXXVIII had been extracted was acidified with concentrated hydrochloric acid and the solid filtered and dried (10.4 g.). The infrared spectrum of this material was identical with that of an authentic specimen of the hydroxy lactone XXXIX.