Steroids. CLXXXVII.[1] Transannular Reactions at Saturated Carbon Atoms. Part 2.[2] C-19 Oxygenation[3]

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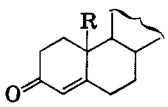
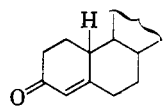
Received October 19, 1961

The importance of C-19 oxygenated steroids is discussed. Androstane-3β,6β,17β-triol 3,17-diacetate (Xa) readily formed the 6β,19-oxide XIIa upon treatment with lead tetraacetate in benzene solution. Oxidation of the oxide XIIa with chromium trioxide led to the lactone XIa and cleavage of the oxide with acetic anhydride and boron trifluoride afforded the tetraacetate XIII. Analogous work with 6β-hydroxytigogenin afforded the 6β,19-oxidosapogenin (XVI) which was converted into some 6β,19-oxidoallopregnane derivatives.

Steroidal C-19 oxygenated Δ^4-3-ketones have great potential as useful intermediates for the preparation of the important C-19 norsteroids since the C-19 alcohols Ia[4] aldehydes Ib,[5,6] and acids



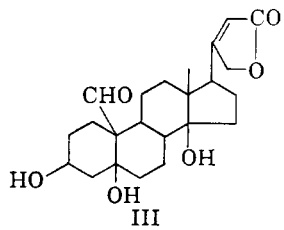
Ia. R = CH_2OH
b. R = CHO
c. R = COOH



II

Ic[6] are known to undergo conversion with base Ia and Ib or acid Ic to the corresponding C-19-nor compounds II.

Certain naturally occurring C-19 oxygenated compounds have been isolated. Of these perhaps strophanthidine (III) is the best known but in



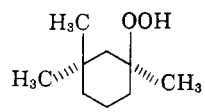
III

spite of extensive and detailed studies by Ehrenstein and his collaborators to utilize this cardiac aglycone, certain difficulties inherent in its polyfunctional nature have so far precluded its efficient conversion into useful 19-nor compounds.[7]

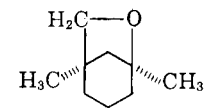
In principle, enzymatic oxygenation methods offer a promising approach for the C-19 hydroxylation of C-19 methyl steroids, and in fact this has been achieved by both adrenal incubation and perfusion[8] and microbiological hydroxylation[9] methods. However, so far these methods have been characterized by low yields due to nonselective attack of the enzyme systems on the steroid substrate.

This paper describes the direct oxygenation at C-19 by a chemical method[10,11] involving a transannular attack on the angular methyl group by a 6β-orientated oxygen cation (or free radical).

Recently, interest has been focused on the controlled transannular oxygenation of saturated carbon atoms with cationic or radical oxygen species. Corey and White[12] reported the conversion of 1,3,3-trimethyl cyclohexyl peroxide (IV) into the bicyclic ether V by treatment with *p*-nitrobenzenesulfonyl chloride in pyridine. Shortly



IV



V

(1) Part CLXXXVI. R. Varela and F. A. Kincl, *Ciencia*, in press.

(2) Part 1. A. Bowers and E. Denot, *J. Am. Chem. Soc.*, 82, 4956 (1960).

(3) A preliminary account of part of this work has been published: A. Bowers, L. C. Ibáñez, M. E. Cabezas, and H. J. Ringold, *Chem. & Ind.*, (London), 1299 (1960).

(4) G. Winston Barber and M. Ehrenstein, *J. Org. Chem.*, 20, 1253 (1955).

(5) A. S. Meyer, *Experientia*, 11, 99 (1955).

(6) H. Hagiwara, S. Noguchi, and M. Nishikawa, *Chem. Pharm. Bull., Japan*, 8, 84 (1960).

(7) (a) For a complete coverage of the literature through to 1958, *cf.* Fieser and Fieser, "Steroids," Reinhold Publishing Corp., New York, 1959, pp. 586–588 and 727–809; (b) In addition, *cf.* M. E. Ehrenstein and K. Otto, *J. Org. Chem.*, 24, 2006 (1959); E. P. Oliveto *et al.*, *J. Am. Chem. Soc.*, 81, 2831, 2833 (1959).

(8) *Cf.*, for example, H. Levy and S. Kushinsky, *Arch. Biochem. and Biophys.*, 55, 290 (1955); 58, 245 (1955); R. Neher and A. Wettstein, *Helv. Chim. Acta*, 39, 2062 (1956) and ref. 5.

(9) M. Nishikawa and H. Hagwara, *Chem. Pharm. Bull., Japan*, 6, 226 (1958).

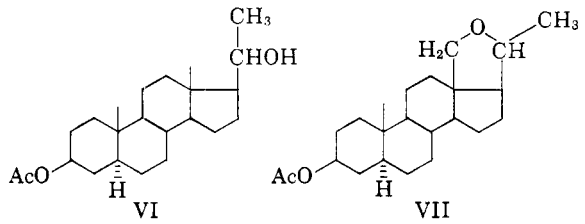
(10) The first reported chemical oxygenation at C-19 involved formation of the oxime of the C-19 aldehyde *via* photolysis of the nitrite ester of a 6β-alcohol. *Cf.* D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Am. Chem. Soc.*, 82, 2640 (1960).

(11) After the appearance of our preliminary communication[3] two groups reported alternate pathways to C-6β,19-oxide steroids *via* transannular attack at C-19 from 6β-substituted steroids; M. Akhtar and D. H. R. Barton, *J. Am. Chem. Soc.*, 83, 2213 (1961); J. S. Mills and V. Petrow, *Chem. & Ind.* (London), 946 (1961).

(11a) ADDED IN PROOF. See also Ch. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein, *Experientia*, 17, 475 (1961).

(12) E. J. Corey and R. W. White, *J. Am. Chem. Soc.*, 80, 6686 (1958).

afterward Cainelli, Mihailovic, Arigoni, and Jeger[13] showed that treatment of allopregnane-3β,20β-diol-3-acetate (VI) with lead tetraacetate in benzene solution led to oxygenation of the C-18 methyl group by formation of the C-18,20-oxide VII.



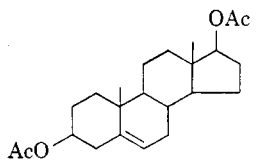
VI VII

In particular, the latter reaction has found important utility in the partial synthesis of aldosterone.[14]

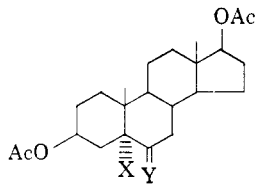
Studies with 3α-hydroxypregnanes and lead tetraacetate have afforded 3α,9α-oxides[2,15] and studies with other steroid secondary alcohols and lead tetraacetate have shown that three different reaction pathways are possible, the nature of product being dependent on the environment of the alcohol.[2]

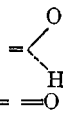
With this background it was considered that a rational approach to oxygenation at C-19 lay in a study of the action of lead tetraacetate on a 6β-hydroxy steroid and accordingly Δ5-androstene-3β,6β,17β-triol 3,17-diacetate (Xa) was prepared.

Addition of hypobromous acid to Δ5-androstene diacetate[16] (VIII) according to the method of Grenville[17] gave the corresponding 5α-bromo-6β-hydroxy bromohydrin[17] (IXa) which was oxidized to the bromo ketone IXb with 8 *N* chromic acid[18] in acetone solution.



VIII



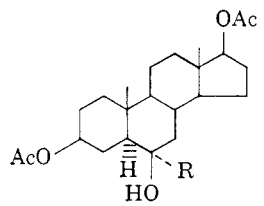
IXa X = Br, Y = 

b X = Br, Y = =O
c X = H, Y = =O
d X = H, Y = =NOH

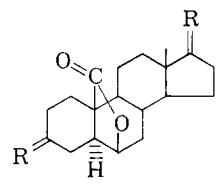
Reductive removal of the bromine with zinc dust in acetic acid then led to androstane-3β,17β-diol-6-one diacetate (IXc)[16,17,19] characterized as its oxime IXd. Hydrogenation of IXc under pressure in ethanol–acetic acid solution in the presence of platinum oxide smoothly afforded the 6β-alcohol Xa.[19] This hydrogenation procedure was much superior to the one carried out at atmospheric pressure.[19] Treatment of Xa with lead tetraacetate in benzene solution under reflux for eighteen hours and chromatography of the product over alumina led to the isolation of three compounds. The least polar compound towards alumina, isolated in 68% yield, was shown to be the 6β,19-oxide XIIa. The second product (7.5% yield) was androstane-3β,17β-diol-6-one diacetate (IXc) and finally 4.5% of starting material was eluted from the column.

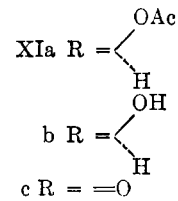
It was interesting to note that the 6α-methyl analog Xb of IXa (prepared by reaction of the 6-ketone IXc with methylmagnesium bromide followed by acetylation under mild conditions) did not afford a 6,19-oxide under conditions where a good yield of XIIa was obtained from Xa.

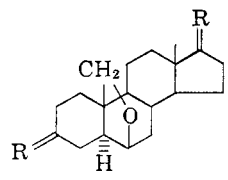
Mild alkaline hydrolysis of XIIa gave the corresponding 3β,17β-diol XIIb which reafforded

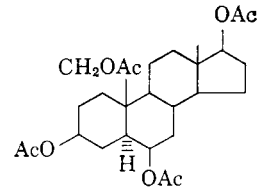


Xa R = H
b R = CH_3

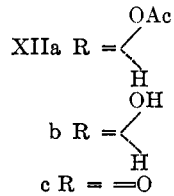








XIII



(13) G. Cainelli, M. Lj. Mihailovic, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **42**, 1124 (1959).

(14) (a) K. Heusler, J. Kalvoda, Ch. Meystre, P. Wieland, G. Anner, A. Wettstein, G. Cainelli, D. Arigoni, and O. Jeger, *Experientia*, **16**, 21 (1960); (b) L. Velluz, G. Muller, R. Bardoneschi, and A. Poitevin, *Compt. rend.*, **250**, 725 (1960).

(15) H. Immer, M. Lj. Mihailovic, K. Schaffner, D. Arigoni, and O. Jeger, *Experientia*, **16**, 530 (1960).

(16) H. B. MacPhillamy and C. R. Scholz, *J. Am. Chem. Soc.*, **74**, 5512 (1952).

(17) V. Grenville, D. K. Patel, V. Petrow, I. A. Stuart-Webb, and D. M. Williamson, *J. Chem. Soc.*, 4105 (1957).

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

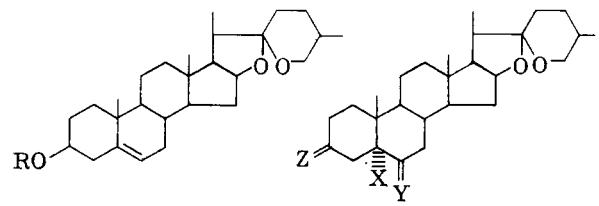
(19) D. L. Garmaise and C. W. Shoppee, *J. Chem. Soc.*, 245 (1953).

XIIa upon acetylation with acetic anhydride in pyridine. Oxidation of XIIb with 8 *N* chromic acid[18] led to the 3,17-diketone XIIc. These data, taken in conjunction with the analytical data and infrared spectra for XIIa, b, and c, and the low order of polarity of XIIa towards alumina were only consistent with XIIa being formulated as a diacetoxy ether. It was readily seen that the ether bridge had formed from the 6β-position across to the C-19 angular methyl group when oxidation of XIIa with chromium trioxide in acetic acid at 90° for ninety minutes gave a five-membered ring lactone XIa (λ_{max}^{KBr} 1755, 1725, and 1238 cm.$^{-1}$) which could only have arisen from structure XIIa.[20] Mild alkaline hydrolysis of XIa followed by treatment with hydrochloric acid gave the lactone diol XIb which regenerated the diacetate XIa upon reacetylation. Oxidation of XIb then gave the 3,17-diketolactone XIc.

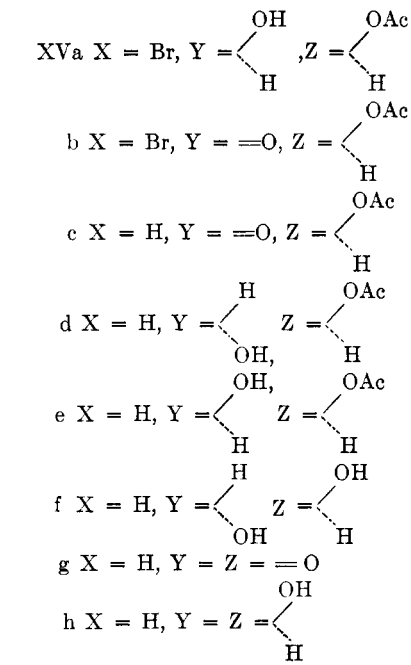
Various approaches were now open to complete the first phase of this work, namely the conversion of a C-19 methyl group to the corresponding hydroxymethyl, formyl, or carboxyl group. After a certain amount of experimentation it was found that treatment of the 6β,19-oxide diacetate XIIa with acetic anhydride containing boron trifluoride led to cleavage of the oxide bridge to afford the tetraacetate XIII.

Having demonstrated the feasibility of oxygenation at C-19 in the androstane series by chemical methods, it was of interest to explore the potential of this reaction for the preparation of C-19-oxygenated pregnanes.

Although several different 6β-hydroxypregnanes were considered, a very versatile starting material was 6β-hydroxytigogenin acetate (β-chlorogenin acetate) (XVe) providing: (a) the spiroketal side chain was stable to the conditions of the lead tetraacetate reaction and (b) the standard procedure for the degradation of the spiroketal side chain to the corresponding Δ^{16}-20-ketone could be carried out in the presence of a 6β,19-oxide bridge. It was felt that both of these requirements could be met and thus the preparation of XVe was investigated. Marker and his colleagues[21] in their structure elucidation studies had previously converted diosgenin XIVa into 6β-hydroxytigogenin (XVh) but two alternate preferred routes to XVe were developed. The first followed the method used for the preparation of IXc: addition of hypobromous acid to diosgenin acetate XIVb to give the bromohydrin XVa which was oxidized with chromium trioxide in pyridine to the bromo ketone XVb and then debrominated with zinc and acetic acid to afford the 6-ketone XVc. Stereospecific reduction of the 6-ketone XVc to the 6β-alcohol XVe with preservation of the C-3 acetate group was readily carried out in good yield with lithium tri-*t*-butoxyaluminohydride.[22] The second route to XVe involved a Brown hydration[23] of diosgenin XIVa to 6α-hydroxytigogenin (chlorogenin) (XVf). This product was identical in every respect with naturally occurring chlorogenin[21,24] and thus this represents an independent structure proof of this natural product.



XIVa R = H
b R = Ac



XVa X = Br, Y = OH, Z = OAc
b X = Br, Y = =O, Z = OAc
c X = H, Y = =O, Z = OAc
d X = H, Y = H, Z = OAc
OH,
e X = H, Y = OH, Z = OAc
f X = H, Y = H, Z = OH
OH
g X = H, Y = Z = =O
h X = H, Y = Z = OH

Oxidation of XVf gave chlorogenone[21,25] XVg which was reduced with lithium tri-*t*-butoxyaluminohydride[22] in tetrahydrofuran to 6β-hydroxytigogenin XVh. Preferential acetylation of XVh with 1.1 moles of acetic anhydride in pyridine solution afforded XVe.

(20) For a similar conversion of a C-18, 20-oxide to the corresponding lactone *cf.* footnote 12.

(21) R. E. Marker *et al.*, *J. Am. Chem. Soc.*, **62**, 2537 (1940).

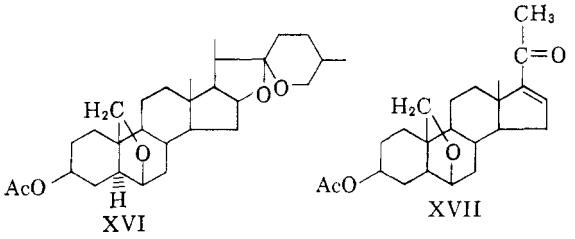
(22) H. C. Brown and R. F. McFarlin, *J. Am. Chem. Soc.*, **80**, 5372 (1958); for the use of this reagent with a wide variety of steroids, *cf.*, J. Fajkos, *Coll. Czech. Chem. Comm.*, **24**, 2284 (1959).

(23) For an excellent review of this reaction see H. C. Brown, *Tetrahedron*, **12**, 117 (1961) and for an example of its use in the hydration of a Δ^5-steroid olefin *cf.* W. J. Wechter, *Chem. & Ind.* (London), 294 (1959) and S. Wolfe, M. Nussim, Y. Mazur, and F. Sondheimer, *J. Org. Chem.*, **24**, 1034 (1959).

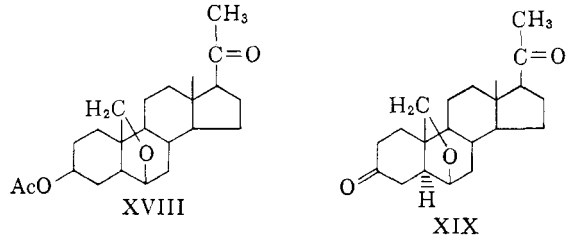
(24) (a) P. Liang and C. R. Noller, *J. Am. Chem. Soc*, **57**, 525 (1935). (b) M. E. Wall, M. M. Krider, E. S. Rothman, and C. R. Eddy, *J. Biol. Chem.*, **198**, 533 (1952).

(25) I. I. Salaman and K. Dobriner, *J. Biol. Chem.*, **207**, 323 (1954).

Reaction of this 6β-alcohol XVe with lead tetraacetate in benzene solution under reflux gave in 40% yield the corresponding 6β,19-oxide XVI which underwent the usual three step side chain degradation[26] to the Δ^{16}-20-ketone XVII. Hydrogenation of the Δ^{16}-double bond in ethyl acetate solution in the presence of a 5% palladium-on-carbon catalyst readily gave the saturated ketone XVIII. Alkaline hydrolysis of XVIII followed by oxidation of the resulting 3β-alcohol with 8 *N* chromic acid[18] afforded 6β,19-oxidoallopregnane-3,20-dione (XIX).



XVI XVII



XVIII XIX

Further reactions with some of these 6,19-oxides and lactones and some work directed towards their conversion to 19-nor steroids will be forthcoming shortly.

EXPERIMENTAL[27]

(27) Melting points were determined on a Fisher-Johns hot stage and are uncorrected. The specific rotations were determined in chloroform and ultraviolet light absorption spectra in 95% ethanol solution. We are grateful to Dr. J. Matthews and his staff for these measurements and for the infrared spectra which were obtained with a Perkin-Elmer Model 21 spectrophotometer. The alumina used in this work had been suspended in ethyl acetate for 18 hr. and then dried at 100°. The elemental analyses were carried out by Dr. A. Bernhardt, Mülheim (Ruhr), Germany, and the Midwest Microlabs., Indianapolis 20, Ind.

5α-Bromoandrostane-3β,6β,17β-triol 3,17-diacetate (IXa). *N*-Bromoacetamide (8.65 g.) was added portionwise over 10 min., with stirring, to a solution of Δ^5-androstene-3β,17β-diol diacetate (VIII) in dioxane (195 cc.) containing aqueous perchloric acid (1.73 cc. of 70% and 24 cc. of water) at 20°. After stirring at 20° for a further 30 min., sodium thiosulfate solution (10 cc. of 1%) was added and the reaction mixture diluted with ice water. Removal of the precipitate by filtration and crystallization from methylene dichloride–methanol afforded 5α-bromoandrostane-3β,6β,17β-triol 3,17-diacetate (IXa) (9.22 g.), m.p. 172–174°, raised by crystallizations from the same solvent system to 174–175°, $[\alpha]_D$ −35°. Lit.,[17] m.p. 159°, $[\alpha]_D$ −58°.

5α-Bromoandrostane-3β,17β-diol-6-one diacetate (IXb). An excess of 8 *N* chromic acid (permanent orange color)[18] was added over 2 min. to a solution of 5α-bromoandrostane-3β,6β,17β-triol diacetate (IXa) (18.5 g.; m.p. 170–172°) in acetone (500 cc.) at 10°. After an additional 3 min. at 10°, addition of ice water and filtration afforded the keto diacetate IXb (16.7 g.) m.p. 186–190°, raised by several crystallizations to 188–191° (variable m.p.) $[\alpha]_D$ −160°. Lit.,[17] m.p. 190–191°.

Anal. Calcd. for $C_{23}H_{33}O_5Br$: C, 58.83; H, 7.08; Br, 17.02. Found: C, 59.20; H, 7.07; Br, 17.29.

Androstane-3β,17β-diol-6-one diacetate (IXc). Zinc dust (50 g.) was added to a solution of the bromo ketone IXb (50 g.) in acetic acid (750 cc.). The reaction mixture was stirred vigorously for 1 hr. at 90° when the insoluble inorganic material was removed by filtration over Celite. Addition of water to the filtrate and isolation with ether afforded a product which was adsorbed from benzene–hexane (50:50) onto alumina (1.3 kg.). Elution with benzene (3.5 l.) and benzene–ether (90:10; 6 l.) and one crystallization from acetone–hexane afforded androstane-3β,17β-diol-6-one (IXc) (21.7 g.); m.p. 173–176°, $[\alpha]_D$ −35°. Lit.[19] m.p. 176–178°, $[\alpha]_D$ −37°.

The corresponding oxime IXd was obtained by heating a solution of the ketone IXc (1.5 g.) in pyridine (40 cc.) and water (10 cc.) containing hydroxylamine hydrochloride (1.5 g.) under reflux for 18 hr. Addition of water and filtration afforded the oxime (IXd) (1.46 g.) m.p. 244–246° raised by crystallizations from methanol to 250–251°, $[\alpha]_D$ −68°.

Anal. Calcd. for $C_{23}H_{35}O_5N$: C, 68.12; H, 8.70; O, 19.73; N, 3.45. Found: C, 67.89; H, 8.70; O, 19.83; N, 3.70.

Androstane-3β,6β,17β-triol 3,17-diacetate (Xa). Platinum oxide (4.0 g.) was added to a solution of androstane-3β,17β-diol-6-one (IXc) (30 g.) in acetic acid (300 cc.) and ethyl alcohol (200 cc.). The mixture was shaken in a Parr hydrogenator under a hydrogen pressure of 40–50 p.s.i.^{2} for 48 hr. Removal of the catalyst by filtration and evaporation of the solvent gave a product which was adsorbed from benzene–hexane (1:1) onto alumina (1 kg.). Elution with benzene (3.6 l.) and benzene–ether (90:10; 4.8 l.) and one crystallization from acetone–hexane afforded androstane-3β,6β,17β-triol 3,17-diacetate (Xa) (20.4 g.) m.p. 130–132°, $[\alpha]_D$ −24°. Lit.,[19] m.p. 128–130°, $[\alpha]_D$ −30°.

6β,19-Oxidoandrostane-3β,17β-diol diacetate (XIIa). Lead tetraacetate[28] (18 g.) was added to a solution of androstane-3β,6β,17β-triol 3,17-diacetate (Xa) (9.5 g.) in dry benzene (475 cc.). After heating under reflux for 18 hr., the precipitate was removed by filtration and washed well with benzene. The combined benzene solutions were washed with water, (the insoluble lead dioxide was removed by filtration) dried over sodium sulfate, concentrated to 200 cc., diluted with hexane (200 cc.), and adsorbed onto alumina (350 g.). Elution with benzene–hexane (50:50; 1800 cc.) and benzene (600 cc.) afforded 6β,19-oxidoandrostane-3β,17β-diol diacetate (XIIa) (6.44 g.) m.p. 130–133° raised by crystallizations from hexane to m.p. 136–137°, $[\alpha]_D$ −14°.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78; O, 20.49. Found: C, 70.49; H, 8.69; O, 21.02.

Further elution with benzene (900 cc.) afforded androstane-3β,17β-diol-6-one diacetate (IXc) (760 mg.) m.p. 168–170° undepressed on admixture with an authentic sample. The infrared spectra of the two samples were identical. Further elution with benzene–ether (90:10, 600 cc.) afforded 460 mg. of Xa m.p. 123–126° undepressed on admixture with starting material.

6β,19-Oxidoandrostane-3β,17β-diol (XIIb). A solution of the diacetate (XIIa) (2.0 g.) in methanol (80 cc.) containing potassium hydroxide (800 mg.) was heated under reflux for 1 hr. Neutralization of the solution with acetic acid and addition to ice water afforded a precipitate of 6β,19-oxidoandrostane-3β,17β-diol (XIIb) (1.12 g.) m.p. 181–183° raised by crystallizations from acetone–hexane to 184–186°, $[\alpha]_D$ −2°.

(26) R. E. Marker and E. Rohrmann, *J. Am. Chem. Soc.*, 61, 3592 (1939); 62, 518 (1940).

(28) The lead tetraacetate used in this work was freshly crystallized from acetic acid and then dried in a vacuum desiccator over potassium hydroxide.

Anal. Calcd. for $C_{19}H_{30}O_3 \cdot (CH_3)_2CO$: C, 72.49; H, 9.96; O, 17.56. Found: C, 72.76; H, 9.72; O, 17.60.

6β,19-Oxidoandrostane-3,17-dione (XIIc). An excess of 8 *N* chromic acid (permanent orange color)[18] was added over 1 min. to a solution of 6β,19-oxidoandrostane-3β,17β-diol (XIIb) (970 mg.) in acetone (75 cc.) at 0°. The reaction mixture was then poured into an ice cold saturated solution of sodium chloride. Extraction with ether gave a product which was adsorbed from hexane–benzene (5:1) onto alumina (30 g.). Elution with hexane–benzene (7:3; 480 cc.) and hexane–benzene (1:1; 560 cc.) and one crystallization from acetone–hexane afforded 6β,19-oxidoandrostane-3,17-dione (XIIc) (290 mg.) m.p. 163–165°, raised by crystallizations from acetone–hexane to 165–167°, $[\alpha]_D$ +130°; λ_{max}^{KBr} 1725 cm.$^{-1}$ (broad).

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67; O, 15.87. Found: C, 75.35; H, 8.71; O, 16.01.

Androstane-3β,6β,17β-triol-19-oic acid 6β,19-lactone 3,17-diacetate (XIa). A solution of chromium trioxide (340 mg.) in water (1.0 cc.) and acetic acid (10 cc.) was added to a solution of 6β,19-oxidoandrostane-3β,17β-diol diacetate (XIIa) (340 mg.) in acetic acid (11 cc.) and heated at 90–95° for 1–1.5 hr. Addition of ice water and filtration afforded the lactone diacetate (XIa) (250 mg.) m.p. 187–190°, raised by crystallizations from acetone–hexane to 212–214°, $[\alpha]_D$ +8°; λ_{max}^{KBr} 1755, 1725, and 1238 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97; O, 23.73. Found: C, 67.81; H, 7.87; O, 24.05.

Androstane-3β,6β,17β-triol-19-oic acid 6β,19-lactone (XIb). A solution of the diacetate XIa (1.30 g.) in methanol (55 cc.) containing potassium hydroxide (550 mg.) was heated under reflux for 1 hr. when the solution was acidified with concd. hydrochloric acid and then refluxed for a further 15 min. Addition of ice water saturated with sodium chloride and extraction with ethyl acetate afforded the lactone diol XIb (800 mg.) m.p. 185–188° raised by crystallizations from acetone–hexane to 187–189°, $[\alpha]_D$ ±0°.

Anal. Calcd. for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81; O, 19.97. Found: C, 70.96; H, 8.61; O, 20.31.

Acetylation of XIb (100 mg.) by heating in pyridine solution (10 cc.) containing acetic anhydride (1.0 cc.) at 90° for 1 hr. afforded the diacetate (XIa) identical (melting point, mixture melting point, and infrared comparison) with an authentic specimen.

Androstane-6β,ol-3,17-dione-19-oic acid 6β,19-lactone (XIc). An excess of 8 *N* chromic acid (permanent orange color)[18] was added over 1 min. to a solution of the diol lactone XIb (1.50 g.) in acetone (70 cc.) at 0°. The reaction mixture was then poured into ice water. Extraction with ethyl acetate and one crystallization from acetone–hexane gave androstane-6β-ol-3,17-dione-19-oic acid 6β,19-lactone (XIc) (1.09 g.) m.p. 191–194°, raised by crystallizations from acetone–hexane to 194–196°, $[\alpha]_D$ +71°; λ_{max}^{KBr} 1755, 1730 (sh.), and 1725 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65; O, 20.23. Found: C, 71.86; H, 7.91; O, 20.40.

Androstane-3β,6β,17β,19-tetrol tetraacetate (XIII). Boron trifluoride etherate (0.5 cc.) was added to a solution of 6β,19-oxidoandrostane-3β,17β-diol diacetate (XIIa) (1.0 g.) in acetic anhydride (10 cc.). After 1 hr. at room temperature the dark brown reaction mixture was added to ice water. Isolation with ethyl acetate afforded a product which was adsorbed from benzene–hexane (70:30) onto alumina (50 g.). Elution with benzene–hexane (80:20, 240 cc.) and one crystallization from acetone–hexane gave the tetraacetate XIII (210 mg.) m.p. 128–132° raised by crystallizations from acetone–hexane to 155–157°, $[\alpha]_D$ +37°.

Anal. Calcd. for $C_{27}H_{40}O_8$: C, 65.83; H, 8.19; O, 25.99. Found: C, 66.14; H, 8.28; O, 26.32.

6α-Methylandrostane-3β,6β,17β-triol 3,17-diacetate (Xb). A solution of androstane-3β,17β-diol-6-one diacetate (IXc) 5.0 g.) in dry tetrahydrofuran (150 cc.) was added dropwise over 45 min. with stirring to a mixture of 3 *N* methylmagnesium bromide in ether (50 cc.) and tetrahydrofuran (100 cc.) under reflux in an atmosphere of nitrogen. It was then heated under reflux for a further 8 hr. when an excess of a saturated solution of ammonium chloride was added slowly to the cooled reaction mixture. Ethyl acetate (350 cc.) was added and the combined organic layer was washed with water and dried over sodium sulfate. Removal of the solvent gave a product which was dissolved in pyridine (50 cc.) containing acetic anhydride (10.0 cc.) and kept at room temperature for 18 hr. Addition of water containing hydrochloric acid and extraction with ethyl acetate afforded a product which was adsorbed from benzene–hexane (1:1) onto alumina (250 g.). Elution with benzene (1400 cc.) and one crystallization from acetone–hexane afforded 6α-methylandrostane-3β,6β,17β-triol 3,17-diacetate (Xb) (2.92 g.) m.p. 155–157°, raised by crystallizations from acetone–hexane to 158–160°, $[\alpha]_D$ −15°.

Anal. Calcd. for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42; O, 19.68. Found: C, 71.02; H, 9.16; O, 19.46.

5α-Bromo-6β-hydroxytigogenin acetate (XVa). *N*-Bromoacetamide (33.0 g.) was added in three portions over 45 min. to a stirred suspension of diosgenin acetate (XIVa) (100 g.) in dioxane (1400 cc.) containing 0.46 *N* aqueous perchloric acid (103 cc.) at room temperature. Stirring at room temperature was continued for a further hour when the reaction mixture was poured into ice water (6 l.). Removal of the precipitate by filtration and crystallization from methylene dichloride–hexane afforded the bromohydrin (XVa) (59.2 g.) m.p. 212–217°, raised by crystallizations from methylene dichloride–methanol to 220–222°, $[\alpha]_D$ −100°; lit.,[29] m.p. 223–226°, $[\alpha]_D$ −107°.

Anal. Calcd. for $C_{29}H_{45}O_5Br$: C, 62.92; H, 8.19; Br, 14.64. Found: C, 62.97; H, 8.24; Br, 14.87.

5α-Bromo-6-ketotigogenin acetate (XVb). Bromohydrin (XVa) (43.7 g.) in pyridine (437 cc.) was added slowly with stirring to a mixture of chromium trioxide (43.7 g.) in pyridine[30] (437 cc.). After stirring for 24 hr. at room temperature, the reaction mixture was diluted with ethyl acetate filtered over Celite and the residue washed with ethyl acetate (500 cc.). The combined ethyl acetate solutions were washed with an excess of 5 *N* hydrochloric acid and then water to neutrality. The dried solution (Na_2SO_4) was evaporated to dryness and the residue was crystallized from methanol to afford the bromo ketone XVb (29.6 g.) m.p. 225–231°, raised by crystallizations from methanol to 230–233°, $[\alpha]_D$ − 145°. Lit.,[29] m.p. 211–212°, $[\alpha]_D$ −173°.

6-Ketotigogenin acetate (XVc). Zinc powder (30 g.) was added to a solution of the bromo ketone XVb (29.2 g., m.p. 225–232°) in glacial acetic acid (300 cc.). The reaction mixture was stirred vigorously at 90° for 45 min. Removal of the zinc by filtration addition of ice water and extraction with ethyl acetate afforded a product which crystallized from methanol to afford 6-ketotigogenin acetate (XVc) (12.2 g.) m.p. 213–22 °, $[\alpha]_D$ −79°. A further crystallization from methylene dichloride–methanol gave 10.1 g. having m.p. 222–224°; $[\alpha]_D$ −86°. Lit.,[29] m.p. 222–224°, $[\alpha]_D$ −93°.

6α-Hydroxytigogenin (chlorogenin) (XVf). Boron trifluoride etherate (32 cc.) was added over 1 hr. with stirring to a mixture of diosgenin (XIVa) (100 g.) and sodium borohydride (41.2 g.) in tetrahydrofuran (1.5 l.) at room temperature. Stirring was then continued for a further 24 hr. Slow addition of ice water (2 l.) afforded a precipitate which was removed by filtration, dried and then dissolved in ethanol (2.5 l.) containing potassium hydroxide (50 g.) and cooled to 10°. Hydrogen peroxide (250 cc. of 35%) was added to this solution over 30 min. The reaction mixture was then poured into ice water (4 l.). Filtration afforded crude 6α-hydroxytigogenin (XVf) (96.1 g.), m.p. 238–248°. A portion of this material was crystallized from methylene dichloride–hexane to afford pure XVf, m.p.

(29) D. Burn, B. Ellis, V. Petrow, I. A. Stuart-Webb, and D. M. Williamson, *J. Chem. Soc.*, 4092 (1957).

(30) G. I. Poos, G. E. Arth, R. E. Beyler, and L. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

281–283°, [α]D −42°. The melting point was undepressed on admixture with an authentic sample[31] of naturally occurring chlorogenin and the infrared spectra were identical. Lit.,[24b] m.p. 276°, [α]D −45°.

6-Ketotigogenone (chlorogenone) (XVg). An excess of 8 *N* chromic acid (permanent orange color)[18] was added to a well stirred suspension of 6α-hydroxytigogenin (XVf) (96 g. m.p. 238–248°) in acetone (1 l.) at 10°. After a further 5 min. at 10° the reaction mixture was added to ice water (2 l.). Filtration afforded the 3,6-dione XVg (86.7 g.), m.p. 222–231°. A portion of this product had m.p. 233–235°, [α]D −84° after two crystallizations from acetone–hexane, Lit.,[25] m.p. 220–226°, [α]D −76°.

6β-Hydroxytigogenin (XVh). Lithium tri-*t*-butoxyaluminohydride[22] (60 g.) was added with stirring to a solution of 6-ketotigogenone (XVg.) (25 g.) in tetrahydrofuran (1 l.). After 48 hr. at room temperature the reaction mixture was added to ice cold dilute acetic acid (5 l. of 5%). The precipitate was removed by filtration and crystallized from methylene dichloride–hexane to yield 6β-hydroxytigogenin (XVh) (19 g.) m.p. 235–239°. A portion crystallized from acetone had m.p. 245–247°, [α]D −72°. Lit., m.p. 244–248°, [α]D −73°.

6β-Hydroxytigogenin acetate (XVe). (a) Lithium tri-*t*-butoxyaluminohydride[22] (32 g.) was added with stirring to a solution of 6-ketotigogenin acetate (XVc) (10.0 g., m.p. 221–224°) in tetrahydrofuran (400 cc.). After 60 hr. at room temperature the reaction mixture was added to ice cold dilute acetic acid (3 l. of 5%). The precipitate was removed by filtration, dried and crystallized from ethyl acetate–hexane to afford 6β-hydroxytigogenin acetate (XVe) (8.9 g.,) m.p. 232–238°, raised by several crystallizations from methylene dichloride–hexane to 236–239°, [α]D −95°.

Anal. Calcd. for $C_{29}H_{46}O_5$: C, 73.38; H, 9.77; O, 16.85. Found: C, 73.15; H, 9.46; O, 16.92.

(b) 6β-Hydroxytigogenin (XVh) (410 mg.) was dissolved in pyridine (4.1 cc.) containing acetic anhydride (0.10 cc.) at 0° and kept at the same temperature for 48 hr. Addition of water, filtration and chromatography of the product over alumina (20 g.), afforded XVe (270 mg.), m.p. 230–235°, raised by one crystallization to 236–238°, undepressed upon admixture with the product obtained in method (a).

6β,19-Oxidotigogenin acetate (XVI). Lead tetraacetate (10.0 g.) was added to a solution of 6β-hydroxytigogenin acetate (XVe) (5.0 g.) in dry benzene (125 cc.). After heating under reflux for 18 hr. the precipitate was removed by filtration and washed well with benzene. The combined benzene solutions were washed with water (the insoluble lead dioxide was removed by filtration) dried over sodium sulfate and adsorbed onto alumina (300 g.). Elution with benzene–ether (90:10; 1.5 l.) and one crystallization from methylene dichloride–hexane gave the 6β,19-oxide (XVI) 1.96 g.), m.p. 193–195°, raised by crystallizations from methanol–water to 197–199°, [α]D −65.5°.

(31) Kindly donated by Dr. O. Mancera from his steroid collection.

Anal. Calcd. for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38; O, 16.93. Found: C, 73.99; H, 9.29; O, 16.80.

Further elution with benzene–ether (80:20, 750 cc.) and one crystallization from methylene dichloride–hexane gave 6-ketotigogenin acetate (XVc) (430 mg.), m.p. 219–221°, undepressed upon admixture with an authentic sample.

6β,19-Oxido-Δ[16]-allopregnene-3β-ol-20-one acetate (XVII). A solution of 6β,19-oxidotigogenin acetate (XVI) (2.5 g.) in acetic anhydride (12.5 cc.) was heated in a sealed glass tube at 200° for 3 hr. The reaction mixture was poured into ice water containing an excess of sodium bicarbonate. Extraction with methylene dichloride afforded a product (2.7 g.) which was dissolved in a mixture of acetic acid (37 cc.), methylene dichloride (30 cc.), and water (1.5 cc.) and cooled to 0°. A solution of chromium trioxide (1.15 g.) in 90% acetic acid (82 cc.) was then added dropwise over 45 min. and stirring was continued for 2 hr., keeping the temperature below 10°. Addition of water and extraction with methylene dichloride gave a product which was dissolved in acetone (21 cc.) and water (4.3 cc.) containing sodium hydroxide (1.07 g.) and heated under reflux for 30 min. Acidification with acetic acid, dilution with water, and filtration afforded a solid (1.51 g.) which was dissolved in pyridine (30 cc.) containing acetic anhydride (5 cc.) and heated at 90° for 45 min. Addition of water and filtration gave a precipitate (1.47 g.), m.p. 170–187°, which was crystallized twice from methylene dichloride–hexane to afford 6β,19-oxido-Δ[16]-allopregnene-3β-ol-20-one acetate (XVII) (810 mg.) m.p. 228–231° raised by crystallizations from methylene dichloride–hexane to 238–239°, [α]D +19°; $\lambda_{max}^{C_2H_5OH}$ 240 mμ (log ε 4.02).

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66; O, 17.18. Found: C, 74.36; H, 8.66; O, 17.44.

6β,19-Oxidoallopregnane-3β,ol-20-one acetate (XVIII). A solution of 6β,19-oxido-Δ[16]-allopregnene-3β-ol-20-one acetate (XVII) (260 mg.) in ethyl acetate (25 cc.) was hydrogenated at atmospheric pressure in the presence of 5% palladium on carbon (100 mg.) for 15 min. Removal of the catalyst by filtration and evaporation of the solvent afforded 6β,19-oxidoallopregnane-3β-ol-20-one acetate (XVIII) (260 mg.) m.p. 134–137° raised by crystallizations from methanol–water to 141–142°, [α]D +66°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.97; H, 9.24.

6β,19-Oxidoallopregnane-3,20-dione (XIX). A solution of the oxide acetate (XVIII) (570 mg.) in methanol (25 cc.) containing potassium hydroxide (500 mg.) was heated under reflux for 1 hr. Neutralization with acetic acid removal of most of the methanol on the steam bath and addition of water afforded a product (370 mg.) m.p. 206–220° (no acetate band in the infrared) which was dissolved in acetone (15 cc.) at 10° and treated with an excess of 8 *N* chromic acid in the usual manner. Addition of water and filtration afforded the dione (XIX) (290 mg.), m.p. 208–214°, raised by crystallizations from methylene dichloride–hexane to 216–218°, [α]D +121°.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.22; H, 9.11; O, 14.41. Found: C, 76.32; H, 9.15; O, 14.53.