18,19,20β-Trihydroxypregn-4-en-3-one (1b).—Zinc dust (75 g) and sufficient 3 *N* HCl to make a paste were heated on the steam bath for 30 min. The zinc was filtered off, washed with water and ethanol, and the resulting cake ground in a mortar under ethanol. The powdered zinc was then suspended in dilute acetic acid, filtered, and washed with water and acetic acid.

A solution of the 6,19-oxido compound (350 mg) in acetic acid (10 cc) was heated with vigorous agitation on the steam bath. Zinc, prepared as above, was then added (7 g, in portions over 13 min). The reaction mixture was cooled, filtered, and worked up as usual to afford the crude product, which was chromatographed on silica gel (30 g). Elution with 8–16% methanol in methylene chloride gave the title compound **1b** recrystallized from methylene chloride–ether (220 mg), mp 194–197°. An analytical sample had mp 198–204°, $[\alpha]D$ +78°, λ_{max}^{MeOH} 243 mμ (ε 14,000).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.37; H, 9.25; O, 18.36. Found: C, 72.32; H, 9.35; O, 18.22.

Registry No.—**1a,** 15833-26-8; **1b,** 15833-27-9; **2a,** 15833-28-0; **2b,** 15833-29-1; **4a,** 15833-30-4; **6a,** 15833-31-5; 5α-bromopregn-3β,20α-diol 6β,19-oxide 20-acetate, 15833-32-6; **7a,** 15833-33-7; **7b,** 15833-34-8; **8a,** 15833-35-9; **8b,** 15856-42-5; **12,** 15833-40-6; **14,** 15833-37-1; 18,19,20α-trihydroxypregn-4-en-3-one 18,20-diacetate, 15833-38-2; **18,** 15833-39-3.

A Rearrangement Reaction of 17-α-Hydroperoxypregnan-20-ones

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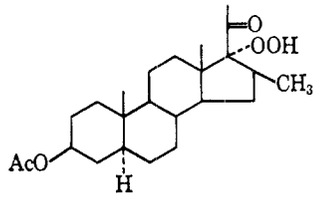
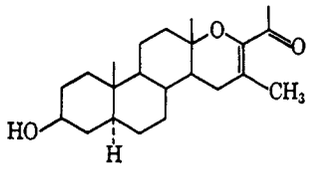
17α-Hydroperoxy-16β-methylpregnan-20-ones have been found to rearrange to 17a-oxa-D-homopregnan-20-ones upon acetylation or treatment with mineral acid. The structure, stereochemistry, and mode of formation of the products are discussed.

Although the preparation of 17α-hydroperoxypregnan-20-ones has been described,[2] their acylation has not been reported. While attempting the acetylation of 17α-hydroperoxy-16β-methyl-5α-pregnan-3β-ol-20-one 3-acetate (I) with a pyridine–acetic anhydride mixture, we were surprised to find that the crude product absorbed in the ultraviolet, having a band at λ_{max} 278 mμ.



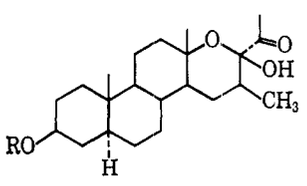
I



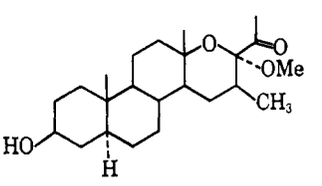
II

Chromatographic analysis revealed the presence of several materials and an investigation of their nature was undertaken.

Chromatography of the mixed acetates failed to resolve the mixture into its components and it was therefore subjected to hydrolysis with excess potassium hydroxide in aqueous methanol at room temperature. From the resulting mixture of alcohols three crystalline materials, II, III, and IV, were readily obtained by partition chromatography. Their structures were assigned on the basis of the following evidence.

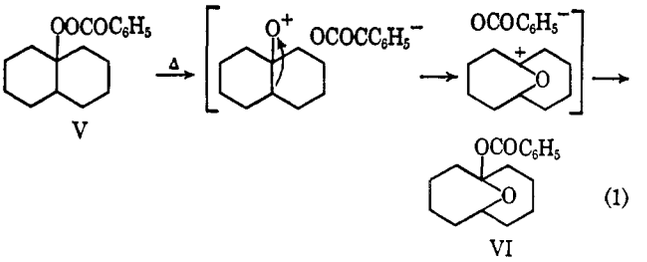


III, R = H
VII, R = $COCH_3$



IV

The major product (II), obtained in *ca.* 25% yield, had an ultraviolet absorption maximum at 278 mμ (ε 5900) and analyzed for $C_{22}H_{34}O_3$, whereas infrared maxima at 1700 and 1620 cm^{-1} indicated the presence of a conjugated carbonyl group. As the Criegee rearrangement of hydroperoxide esters is a well-documented reaction,[3] a typical example being the conversion of the decalin hydroperoxide benzoate V into the isomeric compound VI (eq 1), it was apparent early in the investigation that structure II was mechanistically



V → VI (1)

logical and fitted much of the available evidence. Although no good model could be found for the chromophore in II, the observed absorption did not seem inconsistent with such a structure. The nmr spectrum of II (see Table I) was also in agreement with the pro-

TABLE I
NMR DATA[a]

Compd	Chemical shift C-16 Me	C-18 Me	C-19 Me	C-21 Me	17-OH	17-OMe	3-OAc	C-6 Me
II	1.90	1.02	0.77	2.14				
XVIII	1.98	1.06	0.98	2.22			2.04	1.64
III	0.66	1.25	0.77	2.20	4.15			
	0.77							
XIX	0.68	1.25	0.95	2.20	4.15		1.98	1.58
	0.77							
IV	0.93	1.08	0.75	2.13		3.22		
	1.04							
XV	0.77	1.25	0.77	2.13		3.12		
	0.90							

[a] Expressed in parts per million.

(1) Author to whom correspondence should be addressed at Hoffmann-La Roche, Inc., Nutley, N. J. 07110.

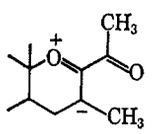
(2) E. J. Bailey, D. H. R. Barton, J. Elks, and J. F. Templeton, *J. Chem. Soc.*, 1578 (1962).

(3) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart, and Winston, Inc., New York, N. Y., 1959, p 633.

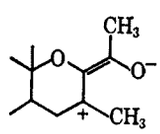
posed structure, with the exception that the resonance at 1.02 ppm which had to be ascribed to the C-18 methyl group was clearly too far upfield for methyl on carbon bearing oxygen. In addition, II did not undergo reactions typical of an enol ether or of an αβ-unsaturated ketone (for example, it was unaffected by mineral acid or zinc in acetic acid).

Attention was now directed to compound III, obtained in *ca.* 10% yield. This material did not absorb in the ultraviolet, analyzed for $C_{22}H_{36}O_4$, and had a single carbonyl absorption at 1730 cm^{-1}. On acetylation it yielded a monoacetate (VII) which had an infrared absorption at 3450 cm^{-1} showing that it still contained hydroxyl. These data were all consistent with structure III whose genesis *via* the Criegee rearrangement is obvious. The nmr spectrum was also in agreement. Notably the resonance at 1.25 ppm assigned to the C-18 methyl was in an acceptable position, and the only band in the spectrum which could not be unequivocally assigned was that at 4.15 ppm. This was tentatively ascribed to the proton of the hydroxyl group at 17, and it was shown that the band was absent from the spectrum after exchange with deuterium oxide. The stereochemistry at 17 remained unknown at this time.

The relationship of II to III was firmly established when it was discovered that III was converted into II on treatment with dilute mineral acid. This at once suggested that the anomalous position of the C-18 methyl resonance in the nmr spectrum of II was due to diamagnetic shielding by the 16 double bond. This conclusion was supported by an examination of models which revealed that the relative positions of the methyl group and the double bond were similar to those in other compounds where such shieldings have been reported.[4] In view of these developments it seemed reasonable to account for the lack of reactivity of the D ring in II as being due to contributions from canonical forms such as VIII and IX.

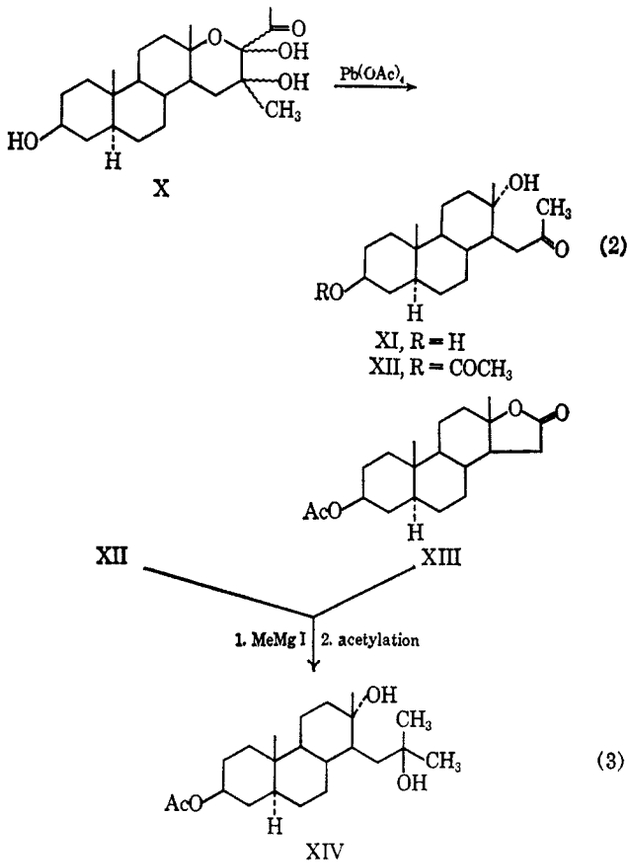


VIII



IX

As the structure of II seemed fairly secure on the basis of the evidence cited, degradation was undertaken. Reaction with osmium tetroxide yielded a mixture of glycols (X) which had spectral properties in accord with the proposed structure. In particular the C-18 methyl resonance occurred at 1.25 ppm and, as in III, there was a peak at 4.10 ppm assignable to the 17-hydroxyl. Reaction of X with lead tetraacetate, followed by alkaline hydrolysis, gave a methyl ketone (XI) which was converted into its 3-acetate (XII) with acetic anhydride in pyridine[5] (eq 2). An attempted iodoform degradation of XI to XIII was inconclusive, the lactone being formed in too small a yield to be obtained pure. An authentic sample of the lactone (XIII) was therefore prepared[6] and both it and XII were treated withe xcess methylmagnesium iodide followed by acetic anhydride–pyridine, affording thereby the same product, the triol acetate XIV (see eq 3). The structure of II is thus firmly established.



X

XI, R = H
XII, R = $COCH_3$

XII

XIII

1. MeMgI | 2. acetylation

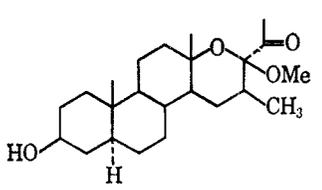
XIV

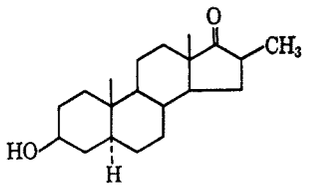
The third rearrangement product (IV), obtained from I in *ca.* 1% yield, was now examined. The compound analyzed for $C_{23}H_{38}O_4$, it had an infrared absorption band at 1725 cm^{-1}, and its nmr spectrum (see Table I) contained a band at 3.22 ppm ascribable to a methoxyl group. These data suggested that the compound might be a methyl ether of III, a hypothesis which was supported by its conversion into II on treatment with dilute mineral acid. An explanation of the formation of IV was then sought and it was thought that it might have been formed from III when the methanolic hydrolysis mixture of the crude rearrangement product was acidified with acetic acid. Compound III was therefore warmed with methanolic acetic acid and an isomeric ether (now assigned structure XV) was isolated. This material was identical with IV in chromatographic mobility, but whereas its infrared and nmr spectra showed similarities to those of IV, there were also profound differences. It was especially notable that in the nmr spectra (see Table I) of III and XV the C-18 methyl resonances occurred at 1.25 ppm whereas in IV this resonance was at 1.08 ppm. An examination of models of 17a-oxa-D-homopregnan-20-ones indicates that in a compound with a 17β-acetyl group the C-18 methyl should be diamagnetically shielded by the 20-ketone, whereas a 17α-acetyl group should have relatively little effect at C-18. As the C-18 methyl resonance in IV is shifted upfield relative

(4) R. R. Fraser, *Can. J. Chem.*, **40**, 78 (1962).

(5) The nmr absorption of the C-18 methyl group in XII is worthy of comment as it occurs at 1.00 ppm, the same position as in II. Examination of models reveals that if a hydrogen bond is formed between the 13α-hydroxyl and the 16-carbonyl, then the latter group is in a position to diamagnetically shield the C-18 methyl. Although the hydrogen bond postulated would form part of a seven-membered ring, the proposed explanation is supported by the fact that in XIV, where the carbonyl group is absent, the three methyl groups on carbon bearing oxygen lie in the range 1.12–1.25 ppm.

(6) S. Rakhit and M. Gut, *J. Org. Chem.*, **29**, 229 (1964).


XV

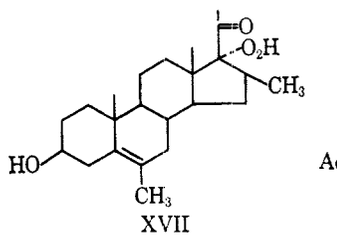

XVI

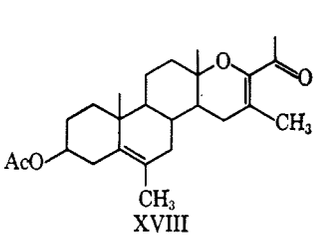
to the usual position for methyl on carbon bearing oxygen, IV was tentatively assigned the 17β-acetyl structure. If this is correct, III and XV should have the more stable 17α-acetyl configuration, in which the acetyl group is equatorial. These assignments were then confirmed by showing that IV yields XV in high yield on treatment with methanolic acetic acid.

The aforegoing stereochemical arguments are supported by examination of the positions of the resonances due to the 16β-methyl group in the nmr spectra of III, IV, and XV. In IV the doublet ascribed to this group is centered at 0.99 ppm whereas in XV, evidently as the result of diamagnetic shielding by the 17α-acetyl group, this resonance is centered at 0.83 ppm. In III the doublet in question is observed at even higher field than in XV (0.71 ppm) an effect that is perhaps due to the influence of hydroxyl *vs.* methoxyl on the preferred rotational position of the 17α-acetyl group.

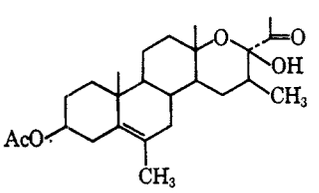
Before discussing the mechanism of the rearrangement, some further facts about the reaction and its products may be cited. It was found that if the acetylation of I was conducted with a limited amount of acetic anhydride and methanol was then added to the reaction mixture, the yield of IV could be raised to 22%. In contrast, if a large excess of anhydride was used, II was obtained in 62% yield and neither III nor IV could be isolated, while the best yield of II (*ca.* 80%) was obtained by acetylation of I with *p*-toluenesulfonic acid–isopropenyl acetate. Rearrangement of I could also be accomplished by treatment with perchloric acid in dioxane, and in this case II was isolated in 40% yield, together with a 14% yield of the 17-ketone XVI. It was also found that IV and XV yield III on treatment with trifluoroacetic acid in aqueous tetrahydrofuran, but prolonged exposure to these conditions can result in the formation of II.

When the hydroperoxide XVII was used as the substrate for the rearrangement, the reaction took the


XVII

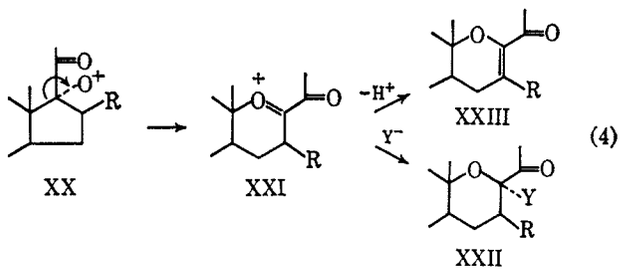

XVIII

expected course and XVIII and XIX were isolated. However, with 17α-hydroperoxy-5-pregnen-3β-ol-20-

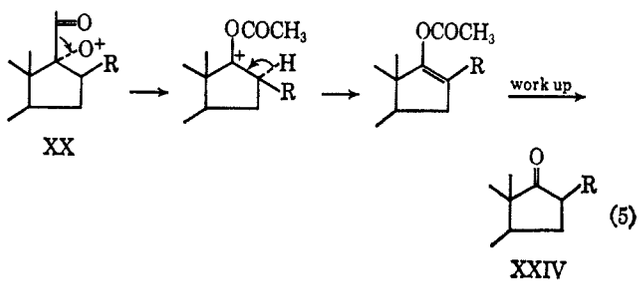

XIX

one the major product isolated was 5-androsten-3β-ol-17-one acetate, together with a small amount of 5-pregnene-3β,17α-diol-20-one 3-acetate. In this case the crude reaction product had an ultraviolet absorption maximum at 262 mμ, but we were unable to isolate the compound containing this chromophore as it appeared to decompose during chromatography. It was observed that variation of the amount of acetic anhydride used had no detectable effect on the course of this reaction.

The D-homo products isolated from the rearrangements discussed are most easily rationalized in terms of a Criegee rearrangement[3] of the intermediate XX leading *via* XXI to XXII and XXIII (see eq 4). This


(4)

explanation defines neither the species which gives rise to XX nor the nature of Y in XXII. In addition, XX may undergo an alternative decomposition to yield the 17-ketone XXIV (eq 5), and the extent to which either


(5)

process predominates is evidently largely dependent on the nature of the substituent at 16. When a 16β-methyl group is present (XX, R = CH_3), the compression between this and the C-18 methyl group results in ring enlargement being the favored reaction. When the reaction is brought about with strong acid, XX presumably arises by protonation of the hydroperoxy function and subsequent loss of water. Likewise, it seems logical to assume that under acetylation conditions the acetate of the hydroperoxide forms and decomposes to XX. We have, however, been unable to detect the presence of this acetate. The formation of IV in *ca.* 20% yield, when methanol is added to an acetylation of I in which a limited amount of acetic anhydride is used, would appear to indicate that the reactive intermediate is present in appreciable amounts up to the time the methanol is added. Further, it is known that a steroidal 10β-hydroperoxyacetate has a carbonyl absorption at 1775 cm^{-1} in the infrared;[7] yet, examination of acetylations of I prior to quenching failed to detect any carbonyl absorption in this region. In addition, the thermodynamically unstable ether IV was originally isolated from a reaction mixture which had been quenched with water prior to coming into

(7) E. L. Shapiro, T. Legatt, and E. P. Oliveto, *Tetrahedron Lett.*, 663 (1964).

contact with methanol, suggesting that traces of the intermediate even survived water treatment. (That IV was not formed in this last experiment from II or III was established by showing that these compounds were stable in the presence of methanol and potassium hydroxide, and II was also shown to be stable in acidic methanol.) If XX does arise from the acetate of the hydroperoxide, then during the rearrangement of I, Y in XXII should be acetate prior to alkaline hydrolysis and epimerization to yield III. However, our inability to resolve the mixture of acetates prior to hydrolysis has left this point undetermined, and we have, therefore, no direct evidence for the formation of the acetate of the hydroperoxide, although its intermediacy does seem to offer a plausible explanation of the observed results.

Experimental Section

Melting points were determined on a Kofler hot-stage microscope. Ultraviolet data refer to solutions in methanol, infrared data to Nujol mulls and rotations to approximately 1% solutions in dioxane. Nmr spectra were measured at 60-Mc for solutions in deuteriochloroform with tetramethylsilane as internal standard.

17α-Hydroxyperoxy-16β-methyl-5α-pregnan-3β-ol-20-one Acetate (I).—Sodium hydride (50% in oil; 3.75 g) was dissolved at room temperature in a mixture of *t*-butyl alcohol (50 ml) and dimethylformamide (75 ml). Dimethylformamide (125 ml) was added, the solution was cooled to −25° and a solution of 16β-methyl-5α-pregnan-3β-ol-20-one acetate (25 g) in tetrahydrofuran (60 ml) was added in one lot. A brisk stream of oxygen was blown through the solution while maintaining the temperature at −25°, and the reaction was monitored by thin layer chromatography using the system benzene–methanol (99:1). After 25 min when only a trace of starting material was detected, the solution was acidified with acetic acid. The product (28 g) was isolated by dilution with water and filtration. It was virtually homogeneous on thin layer chromatography. Two crystallizations from acetone–hexane gave an analytical sample: mp 170–173°; $[\alpha]_D$ +63.9°; ν_{max} 3300, 1750, 1700, and 1250 cm^{-1}.

Anal. Calcd for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 71.12; H, 9.38.

Acetylation of 17α-Hydroperoxy-16β-methyl-5α-pregnan-3β-ol-20-one 3-Acetate. A. With Excess Acetic Anhydride.—The hydroperoxide (I) (1.22 g) in pyridine (7 ml) and acetic anhydride (3.5 ml) was left at room temperature for 18 hr. The mixture was poured into water and the crude product was isolated by extraction with ethyl acetate. The solvent was evaporated, and the residue hydrolyzed in a nitrogen atmosphere at room temperature for 1 hr with excess potassium hydroxide in aqueous methanol. The reaction mixture was acidified with acetic acid, and the product was precipitated by addition of water. After drying at 50°, this material was chromatographed on Chromosorb (100 g) in ligroin–propylene glycol, fractions of 30 ml being collected. Fractions 32–64 afforded 16-methyl-17a-oxa-D-homo-5α,16-pregnen-3β-ol-20-one (II) (649 mg). The analytical sample, crystallized from acetone–hexane, had mp 159–162°: $[\alpha]_D$ −79.5°; ν_{max} 1700 and 1620 cm^{-1}; λ_{max} 278 mμ (ε 5900). A second crystalline modification, mp 128–132°, was also obtained on some occasions.

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 75.99; H, 9.96.

B. With a Limited Amount of Acetic Anhydride.—The preceding experiment was repeated with the quantity of acetic anhydride reduced to 610 mg.

Fractions 23–32 afforded 17α-methoxy-16β-methyl-17a-oxa-D-homo-5α-pregnan-3β-ol-20-one (IV) (112 mg) which crystallized from ether–hexane and had mp 128–135°. Several recrystallizations gave an analytical sample: mp 142–145°; $[\alpha]_D$ −30°; ν_{max} 3500 and 1725 cm^{-1}.

Anal. Calcd for $C_{23}H_{38}O_4$: C, 72.97; H, 10.12. Found: C, 72.54; H, 10.44.

Fractions 38–54 afforded II (333 mg).

Fractions 67–78 yielded 16β-methyl-17a-oxa-D-homo-5α,17-isopregnane-3β,17β-diol-20-one (III) (112 mg). This material crystallized from ether–hexane and had mp 173–178° with a change of crystal form in the range 130–150°. Two crystalline modifications with distinctly different infrared absorption spectra were encountered: $[\alpha]_D$ −42.5°; ν_{max} 1730 cm^{-1}.

Anal. Calcd for $C_{22}H_{36}O_4$: C, 76.26; H, 9.89. Found: C, 75.99; H, 9.96.

C. With a Limited Amount of Acetic Anhydride and Subsequent Addition of Methanol.—The hydroperoxide I (2.44 g) in pyridine (14 ml) and acetic anhydride (1.22 g) was left at room temperature for 18 hr. The reaction mixture under a nitrogen atmosphere, was diluted with excess potassium hydroxide in methanol and maintained at room temperature for 1 hr. Water was added and the product was isolated by extraction with ethyl acetate and chromatographed as in method A. Fractions 28–40 afforded IV (490 mg) and fractions 48–58 yielded II (625 mg).

16β-Methyl-17a-oxa-D-homo-5α,17-isopregnane-3β,17β-diol-20-one 3-Acetate (VII).—The diol III (110 mg) was acetylated in pyridine–acetic anhydride at room temperature for 18 hr. Water was added and the product was isolated by extraction with ethyl acetate and crystallized from aqueous ethanol to yield the 3-acetate (VII) (40 mg): mp 127–130°; $[\alpha]_D$ −46°.

Anal. Calcd for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 70.80; H, 9.43.

Treatment of III with Mineral Acid.—The diol III (50 mg) in methanol (2 ml) was treated with a few drops of 2 *N* hydrochloric acid and left at room temperature for 48 hr. The product was precipitated by addition of water and chromatographed in ligroin–propylene glycol on Chromosorb (25 g) to yield II (10 mg) identical with an authentic specimen as evidenced by mixture melting point and ultraviolet and infrared spectra.

16ζ-Methyl-17a-oxa-D-homo-5α-pregnane-3β,16ζ,17ζ-triol-20-one (X).—The olefin II (717 mg) in ether (30 ml) and pyridine (1 ml) was treated with a solution of osmium tetroxide (500 mg) in ether (15 ml). The mixture was stored in the dark for 3 days when the precipitate (1.25 g) was isolated by filtration and washed with ether. This material was dissolved in ethanol (125 ml) and 2% sodium metabisulfite solution (100 ml) was added. The reaction mixture was heated under reflux for 1.25 hr, filtered, and concentrated by boiling. It was then cooled and the product isolated by extraction with ethyl acetate. The resultant gum (shown by thin layer chromatography in chloroform–ethyl acetate 4:1 to be a mixture of two materials) was crystallized from aqueous ethanol to yield X (127 mg). Recrystallization from the same solvent gave an analytical sample: mp 166–177°; $[\alpha]_D$ −87°; ν_{max} 1700 cm^{-1}; nmr, 0.77 (C-19 methyl), 1.1 (16β-methyl), 1.24 (C-18 methyl), 2.26 (C-21 methyl), and 4.08 ppm (17-hydroxyl).

Anal. Calcd for $C_{22}H_{36}O_5 \cdot H_2O$: C, 66.30; H, 9.61. Found: C, 66.36; H, 9.78.

13,17-Seco-5α-androstane-3β,13α-diol-16-one (XI).—A solution of the triol (X) (981 mg) and lead tetraacetate (1.96 g) in chloroform (50 ml) was stirred at room temperature for 3.5 hr. The chloroform solution was washed with aqueous ethylene glycol and with water, and then dried over sodium sulfate. Evaporation of the solvent gave an oil which was treated with excess potassium hydroxide in aqueous methanol at room temperature for 1.5 hr. The reaction mixture was poured into dilute aqueous acetic acid and the product was isolated by extraction with dichloromethane. This material was chromatographed in toluene–propylene glycol on Chromosorb (50 g) and crystallized from acetone–hexane to yield XI (144 mg), mp 187–200°. A further crystallization gave an analytical sample: mp 190–204°; $[\alpha]_D$ −7.9°; ν_{max} 1700 cm^{-1}.

Anal. Calcd for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 74.00; H, 10.09.

13,17-Seco-5α-androstane-3β,13α-diol-16-one 3-Acetate (XII).—The diol (XI) (80 mg) was acetylated in a pyridine–acetic anhydride mixture at room temperature for 18 hr to yield 34 mg of the 3-acetate (XII): mp 151–154° after two crystallizations from acetone–hexane; $[\alpha]_D$ −26°; ν_{max} 3500, 1710, and 1270 cm^{-1}; nmr, 0.73 (C-19 methyl), 1.00 (C-18 methyl), 1.94 (3β-acetate), and 2.10 ppm (C-16 methyl).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.75. Found: C, 71.92; H, 9.72.

16-Methyl-13,17-seco-5α-androstane-3β,13α,16-triol 3-Acetate (XIV) from XII.—The ketone XII (250 mg) in tetrahydrofuran (50 ml) was added to an excess of methylmagnesiumi odide in ether. The mixture was stirred 2.5 hr at room temperature, then poured into aqueous ammonium chloride solution. The product was isolated by filtration, dried, and acetylated in a

pyridine–acetic anhydride mixture at room temperature for 18 hr to yield XIV, mp 190–194° after two crystallizations from acetone–hexane: $[\alpha]D$ −32°; ν_{max} 1750 cm^{-1}; nmr, 0.77 (C-19 methyl), 1.12, 1.17, 1.25 (C-18 methyl and 16,16-dimethyl), and 2.00 ppm (3β-acetate).

Anal. Calcd for $C_{22}H_{38}O_4$: C, 72.09; H, 10.45. Found: C, 71.97; H, 10.66.

From 17-oxa-5α-androstan-3β-ol-16-one Acetate (XIII).—The lactone (XIII)[6] (60 mg) in tetrahydrofuran (10 ml) was added to an excess of methylmagnesium iodide in ether. The product was isolated, acetylated, and crystallized as described above to yield XIV (8 mg), mp 188–192°, identical with the product obtained from XII as evidenced by mixture melting point and infrared absorption.

Treatment of IV with Mineral Acid.—The methyl ether IV (63 mg) in tetrahydrofuran (8 ml) was treated with a few drops of 2 *N* hydrochloric acid, and the solution was warmed on the steam bath for 1 hr. The product was precipitated by addition of water and crystallized from acetone–hexane to yield II (29 mg) identical with an authentic specimen.

17β-Methoxy-16β-methyl-17a-oxa-D-homo-5α,17-isopregnan-3β-ol-20-one (XV). A. From IV.—A solution of IV (88 mg) in methanol (6 ml) containing a few drops of acetic acid was warmed on the steam bath for 3 hr. Addition of water and crystallization of the resultant precipitate from acetone–hexane gave XV (45 mg): mp 180–192°; $[\alpha]D$ −110°; ν_{max} 3550, 3450, 1750, and 1730 cm^{-1}.

Anal. Calcd for $C_{23}H_{38}O_4$: C, 72.97; H, 10.12. Found: C, 73.05; H, 10.28.

B. From III.—A solution of III (110 mg) in methanol (5 ml) containing a few drops of acetic acid was warmed on the steam bath for 3 hr. Water was added, and the product was isolated by extraction with ethyl acetate and chromatographed in ligroin–propylene glycol on Chromosorb (36 g), fractions of 15 ml being collected. The material in fractions 12–18 was crystallized from acetone–hexane to yield XV (18 mg), mp 178–188°.

Rearrangement of I with Perchloric Acid.—The hydroperoxide I (3 g) suspended in dioxane (80 ml) and perchloric acid (70%; 8 ml) was stirred at room temperature for 18 hr. The product was precipitated with water and hydrolyzed and chromatographed as described for the rearrangement using acetic anhydride–pyridine. In addition to II (1.02 g), there was isolated from subsequent chromatogram fractions XVI (307 mg), mp 153–156° after crystallization from acetone–hexane. This material was identical with an authentic sample of 16β-methyl-5α-androstan-3β-ol-17-one.[8]

Rearrangement of I with Isopropenyl Acetate *p*-Toluenesulfonic Acid.—The hydroperoxide I (5.2 g) suspended in acetic acid (150 ml) and isopropenyl acetate (20 ml) was stirred at room temperature for 18 hr with *p*-toluenesulfonic acid (520 mg). The crude product was isolated by dilution with water and extraction with ethyl acetate. It was hydrolyzed and chromatographed as described for the rearrangement using acetic anhydride–pyridine to yield II (4.05 g).

Treatment of IV with Aqueous Trifluoroacetic Acid.—The methyl ether IV (1.06 g) in tetrahydrofuran (45 ml) and water (5 ml) was treated with trifluoroacetic acid (1 ml) and left at room temperature for 60 hr. The reaction mixture was poured into water, and the precipitate was isolated and crystallized from ether–hexane to yield III (630 mg), mp 168–173°.

(8) P. de Ruggieri, C. Ferrari, and C. Gandolfi, *Gazz. Chim. Ital.*, **91**, 672 (1961).

6,16-Dimethyl-17a-oxa-D-homo-5,16-pregnadiene-3β-ol-20-one 3-Acetate (XVIII).—6,16β-Dimethyl-17α-hydroperoxy-5-pregnen-3β-ol-20-one[9] (3.1 g) was acetylated in a pyridine–acetic anhydride mixture for 18 hr at room temperature. The mixture of acetates was crystallized twice from aqueous methanol to yield XVIII (1.03 g), mp 175–178°. Four further crystallizations from methanol gave an analytical sample with mp 180–183°; $[\alpha]D$ −169°; λ_{max} 278 mμ; (ε 6200); ν_{max} 1740, 1700, 1630, and 1250 cm^{-1}.

Anal. Calcd for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 74.90; H, 9.17.

6,16β-Dimethyl-17a-oxa-D-homo-17-iso-5-pregnene-3β,17β-diol-20-one 3-Acetate (XIX).—The mother liquors from the first two crystallizations of XVIII were hydrolyzed with excess potassium hydroxide in aqueous methanol at room temperature. The crude product was chromatographed in ligroin–propylene glycol on Chromosorb (140 g), fractions of 50-ml volume being collected. The gum in fractions 53–72 (481 mg) was acetylated in the usual manner, and the product was crystallized from aqueous ethanol to yield XIX: mp 149–153°; ν_{max} 3450, 1720, and 1250 cm^{-1}.

Anal. Calcd for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.39; H, 8.78.

Rearrangement of 17α-Hydroperoxy-5-pregnen-3β-ol-20-one.[2]—The hydroperoxide (1 g) was acetylated in a pyridine–acetic anhydride mixture at room temperature for 18 hr. The crude product, which had a band at λ_{max} 262 mμ (ε 500–1000), was chromatographed on Chromosorb (130 g) in heptane–methyl Cellosolve, fractions of 25 ml being collected.

Fractions 25–39.—This material (800 mg), which on paper chromatography in heptane–methyl Cellosolve appeared to be homogeneous and to absorb in the ultraviolet, was hydrolyzed in aqueous methanol at room temperature with excess potassium hydroxide. The product was chromatographed on Chromosorb (75 g) in ligroin–propylene glycol. The material in fractions 19–33, which likewise appeared to be homogeneous and to absorb in the ultraviolet, was crystallized from hexane–ether and then from aqueous methanol to yield 5-androsten-3β-ol-17-one (155 mg) identical with an authentic specimen. (Subsequent attempts to isolate the compound containing the chromophore failed due to its apparent decomposition.)

Fractions 40–60.—This material (275 mg) was hydrolyzed in aqueous methanol at room temperature with excess potassium hydroxide. The product was crystallized from methanol to give 5-pregnene-3β,17α-diol-20-one (70 mg) identical with an authentic specimen.

Registry No.—I, 15815-49-3; II, 15815-51-7; III, 15815-50-6; IV, 15811-05-9; VII, 15811-04-8; X, 15811-06-0; XI, 15811-07-1; XII, 15811-08-2; XIV, 15811-09-3; XV, 15811-10-6; XVIII, 15811-11-7; XIX, 15811-12-8.

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(9) J. N. Gardner, F. E. Carlon, C. H. Robinson, and E. P. Oliveto, *Steroids*, **7**, 234 (1966).