halogenated product (II), on the bases of increased chlorine percentage. A small sample was placed in a microevaporative still. A colorless oil collected at 64° (0.5–1 mm.). After standing overnight the oil crystallized to a white solid which was washed with hexane leaving the analytical sample, m.p. 69–70°. Alternatively, chromatography on activated alumina with a hexane–ether eluent gave 80% recovery of an oil which required several weeks to crystallize. The infrared spectrum of the compound showed a sharp peak at 2.8 μ with disappearance of the broad O–H band found in the starting material.

Anal. Calcd. for $C_{11}H_9Cl_2NO_2$: C, 51.19; H, 3.52. Found: C, 51.30; H, 3.72.

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The Hydrogenation of Dihydrolanosteryl and Dihydroagnosteryl Acetates[1]

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We wish to report that both dihydrolanosterol, 3β-hydroxy-5α-lanost-8-ene, and dihydroagnosterol, 3β-hydroxy-5α-lanost-7:8,9:11-diene, acetates are hydrogenated to an easily separable mixture of the saturated acetate, 3β-acetoxy-5α-lanostane (67% yield), and saturated ether, 3β-ethoxy-5α-lanostane (24% yield). The identity of these products was established by a comparison of their melting points and mixture melting points, specific rotation, and infrared spectra with authentic samples.[2]

The hydrogenations proceed slowly at atmospheric pressure, when relatively large amounts of Adams, catalyst (PtO_2) are employed and a few drops of perchloric acid have been added to the solvent, acetic acid. These findings are in contrast to the numerous reports concerning the nonhydrogenability, under a variety of conditions, of either the Δ7- or Δ8-lanosten-3-ol, and dihydroagnosterol.[3] The hydrogenation of the 9:11 double bond of 3β-acetoxy-5α-lanost-9-ene has been accomplished[4] (PtO_2, acetic acid, 60°), albeit with some difficulty. The stereochemistry of the hydrogens at C-8 and C-9, β and α, for both the saturated acetate and the saturated ether has been established.[4-7] These observations coupled with the known stability[8] of the 9:11 double bond as contrasted to the ready intraconvertibility[9] of the 7:8 and 8:9 double bond isomers of 3β-acetoxy-5α-lanostene under acid conditions indicate that addition of hydrogen to the 9:11 and 7:8 double bonds take place at the α and β faces, respectively, and, in fact, it is the isomer (7:8-ene) derived from dihydrolanosterol which is hydrogenated.[10] The last consideration follows from the steric course of the hydrogenation of dihydrolanosterol. The relative rates of saturation of the double bonds has not as yet been investigated.

The catalytic reduction of an ester to an ether under the conditions employed is striking. The recently reported[11] catalytic hydrogenation of succinic anhydride to butyrolactone and butyric acid bears a formal resemblance to our findings. The role of the solvent and acidity as well as possible intermediates in the conversion of the acetate to an ether remains to be elucidated.

Experimental[12]

3β-Acetoxy-5α-lanost-8-ene, dihydrolanosteryl acetate, m.p. 120–121°, lit.[14] m.p. 120–121°, prepared by hydrogenation, over PtO_2, of crude lanosteryl acetate dissolved in ethyl acetate–acetic acid mixture, was recrystallized from methanol–petroleum ether (b.p. 30–60°). 3β-Acetoxy-5α-lanost-7:8,9:11-diene, dihydroagnosteryl acetate [m.p. 164–165°; λ_{max} 236 mμ (ϵ 12,500), 244 (14,830), and 252 (9800)], was prepared by oxidation of dihydrolanosteryl acetate with N-bromosuccinimide, according to Dorée, *et al.*,[15] and recrystallized several times from acetone and methanol (lit.[3] m.p. 168–169°).

3β-Acetoxy-5α-lanostane and 3β-Ethoxy-5α-lanostane. A.—Dihydroagnosteryl acetate (340 mg.) dissolved in glacial acetic acid (200 ml.) containing 12 drops of perchloric acid (70%) was hydrogenated, at atmospheric pressure and room temperature in the presence of PtO_2 (300 mg.). After 48 hr. fresh catalyst (200 mg.) was added and the hydrogenation continued for *ca.* an additional 48 hr.[17] After removal of spent catalyst, the hydrogenation mixture was poured into ice–water, and the precipitated solid collected by filtration and dried *in vacuo* over phosphorus pentoxide. The dried material, dissolved in petroleum ether (b.p. 30–60°), was chromatographed on Woelm alumina (34 g.). The alumina, initially of activity I, had been partially deacti-

(1) This work was supported by National Science Foundation Grant G-24019, Office of Naval Research Contract NR-107543, and National Institutes of Health Grant A-6180.

(2) We wish to thank Professor George Petit for supplying us with these samples.

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(10) Dihydrolanosteryl acetate was hydrogenated under the same conditions as are given in the Experimental section, except that perchloric acid was omitted. As shown by infrared analysis and chromatography, 80% of final product consisted of a 70/30 mixture of the acetates of lanost-8-en-3-ol and lanost-7-en-3-ol, respectively, while 20% was identified as the fully hydrogenated lanostanyl acetate. In the absence of catalyst, a solution (acetic acid + perchloric acid, *cf.* Experimental) of the acetate of lanost-8-en-3-ol, after standing for 2 days at room temperature, is converted, as shown by infrared analysis and chromatography, into a 60/40 mixture of the Δ7- and Δ8-ene, respectively.

(11) (a) R. McCrindle, K. H. Overton, and R. A. Raphael, *Proc. Chem. Soc.*, 313 (1961); (b) Professor John T. Edward (private communication) has informed us that in his laboratories a number of lactones derived from steroids have been hydrogenated (PtO_2) to the corresponding ethers.

(12) All melting points were taken on a Fisher-Johns melting point apparatus. Rotations were determined in chloroform; ultraviolet spectra were determined in ethanol (95%), and infrared spectra of solutions in carbon disulfide and carbon tetrachloride, employing a Beckman DU and Perkin Elmer 421 infrared spectrophotometer, respectively.

(13) L. Ruzicka, R. Denss, and O. Jeger, *Helv. Chim. Acta*, **28**, 759 (1945).

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(15) C. F. Dorée, J. F. McGhie, and F. Kurzer, *J. Chem. Soc.*, 570 (1949).

(16) R. G. Curtis, *ibid.*, 1017 (1950).

(17) The uptake of hydrogen was in great excess over that calculated for 2 moles of hydrogen. Subsequently it was shown that acetic acid also is hydrogenated when perchloric acid is present.

vated by the addition of 4% of its weight of acetic acid (10%). Elution was effected with petroleum ether (b.p. 30–60°), 50-ml. fractions, followed by petroleum ether (b.p. 72–78°). The course of the chromatography was followed by noting the presence or absence of an acetyl band in the infrared, as indicated in Table I. Recrystallization of the combined fractions, 2 and 3 (negative tetranitromethane test), from ethyl acetate and methanol yielded 3β-ethoxy-5α-lanostane (56 mg.) as plates, m.p. 133.5–135°, $[\alpha]^{25}D$ 44.7°; lit.[7] m.p. 133.5°, $[\alpha]^{25}D$ 53.2°. Mixture melting point with an authentic sample, m.p. 133.5°, showed no depression while their infrared spectra in carbon tetrachloride were superimposable, with the strong characteristic ether band at 1101 cm.$^{-1}$.

TABLE I

Fraction	Solvent	Infrared band at 1733	Material	Weight, mg.
1	Pet. ether (b.p. 30–60°)	Neg.	Oil	*ca.* 10
2,3	Pet. ether	Neg.	Ether	75
4	Pet. ether			
5–12	Pet. ether	Pos.	Lanostanyl acetate	
13–21	Pet. ether (b.p. 72–78°)	Pos.	Lanostanyl acetate	210 ...

Recrystallizations of the combined fractions, 5–21, from petroleum ether–methanol mixture afforded pure 3β-acetoxy-5α-lanostane (180 mg., negative tetranitromethane test) of $[\alpha]^{25}D$ +41.2°. The saturated acetate so prepared exhibits a double melting point. It melts at 151–152°, resolidifies, and remelts at 156.5–157°. The authentic sample exhibited the same behavior on melting and mixture melting point gave no depression. The infrared spectra (carbon tetrachloride and carbon disulfide) of both samples were identical in all respects (lit.[4] m.p. 151–152°, $[\alpha]^{20}D$ 41°; lit.[18] m.p. 156–157°, $[\alpha]^{20}D$ 46°).

B.—Dihydrolanosteryl acetate was hydrogenated and worked up as for dihydroagnosteryl acetate. 3β-Acetoxy- and 3β-ethoxylanostane were isolated in essentially the same proportions, as above.

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17-Oxa-5α-Androstan-3-one[1]

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The study of the effects of structural modifications of natural steroid hormones upon their biological activities has received much attention in the last few years and has led to a number of highly active synthetic modifications. A review of the publications in this field reveals examples of the insertion of oxygen in the D-ring,[2,3] although no steroid analog has been prepared in which that ring remained five-membered. This paper describes the synthesis of a 17-oxa compound with a five-membered D-ring. Our interest in such a compound is due to the fact that a modification of the procedure could lead to 17-aza steroids.[4]

This paper describes two routes leading to the elimination of C-17, followed by ring closure to a five-membered lactone and reduction to a diol which, in turn, could be ring-closed to the desired 17-oxa steroid.

The required lactone II, possessing an oxygen function at C-16, and thereby readily amenable to oxidative degradation, was obtained by a Baeyer–Villiger oxidation of the known 3β,16β-diacetoxy-5α-androstan-17-one[5] (I). Its reduction with lithium aluminum hydride gave the tetrol III which was oxidized with periodic acid to the aldehyde IV, with the desired oxygen function at C-13 and the C-17 eliminated. The crude aldehyde was oxidized with chromic acid to its acid which lactonized spontaneously to V. Attempts to reduce the lactone directly to the desired ether with either lithium aluminum hydride and boron trifluoride or with sodium borohydride and boron trifluoride led[6] only to the triol. Therefore, the lactone V was transformed to the 3-ketal and then reduced with lithium aluminum hydride to give 13α,16-dihydroxy-13,16-seco-17-nor-5α-androstane 3-ethylene ketal (VII). Ring closure with *p*-toluenesulfonyl chloride–pyridine, followed by hydrolysis of the ketal function gave the desired 17-oxa-5α-androstan-3-one (VIII).

An alternative approach to the preparation of VIII starts with the readily available lactone[7] IX, which was formylated to the 3β-hydroxy-16-hydroxymethylene-17α-oxa 5α-D-homoandrostan-17-one[8] (X). Acetylation of the lactone X furnished the diacetate XI and the latter was ozonized to yield, after decomposition of the ozonide and usual work-up, 3β-acetoxy-17-oxa-5α-androstan-16-one. Hydrolysis[6] of the acetate with sodium carbonate and oxidation[6] of the resulting alcohol with chromic acid gave 17-oxa-5α-androstane-3,16-dione, identical in all respects with V obtained previously.

Experimental[9]

3β,16β-Diacetoxy-17a-oxa-5α-D-homoandrostan-17-one (II).—To a solution of 5 g. of 3β,16β-diacetoxy-5α-androstan-17-one[5] (I) in 80 ml. glacial acetic acid, 500 mg. of *p*-toluenesulfonic acid and 30 ml. of 40% peracetic acid were added; the mixture was stored at room temperature in the dark for 24 hr. The solution was then poured into cold water and the precipitate collected and thoroughly washed with water. Upon drying 5.05 g. (96.5% yield) of II, m.p. 212–215°, was obtained. Thin layer chromatography of the crude product showed it to be a single compound. An analytical sample was crystallized from dichloromethane–ether to yield needles, m.p. 217–219°; $[\alpha]^{22}D$ −39° (*c* 1.0, chloroform); ν_{max} 1760 (16-acetoxy), 1745 (δ-lactone), and 1730 cm.$^{-1}$ (3-acetoxy).

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 67.72; H, 8.26.

13,17-Seco-5α-androstane-3β,13α,16,17-tetrol (III).—A solution of 5 g. of the lactone II in 100 ml. of absolute tetrahydrofuran was added with stirring over a period of 20 min. to a slurry of 5 g. of lithium aluminum hydride in 350 ml. of absolute tetrahydrofuran. The mixture was refluxed for 18 hr., then cooled, and the excess reagent decomposed by ethyl acetate. A saturated solution of sodium sulfate was added and the precipitated inorganic material filtered off. The inorganic material was thoroughly extracted with ethyl acetate, the extracts were

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