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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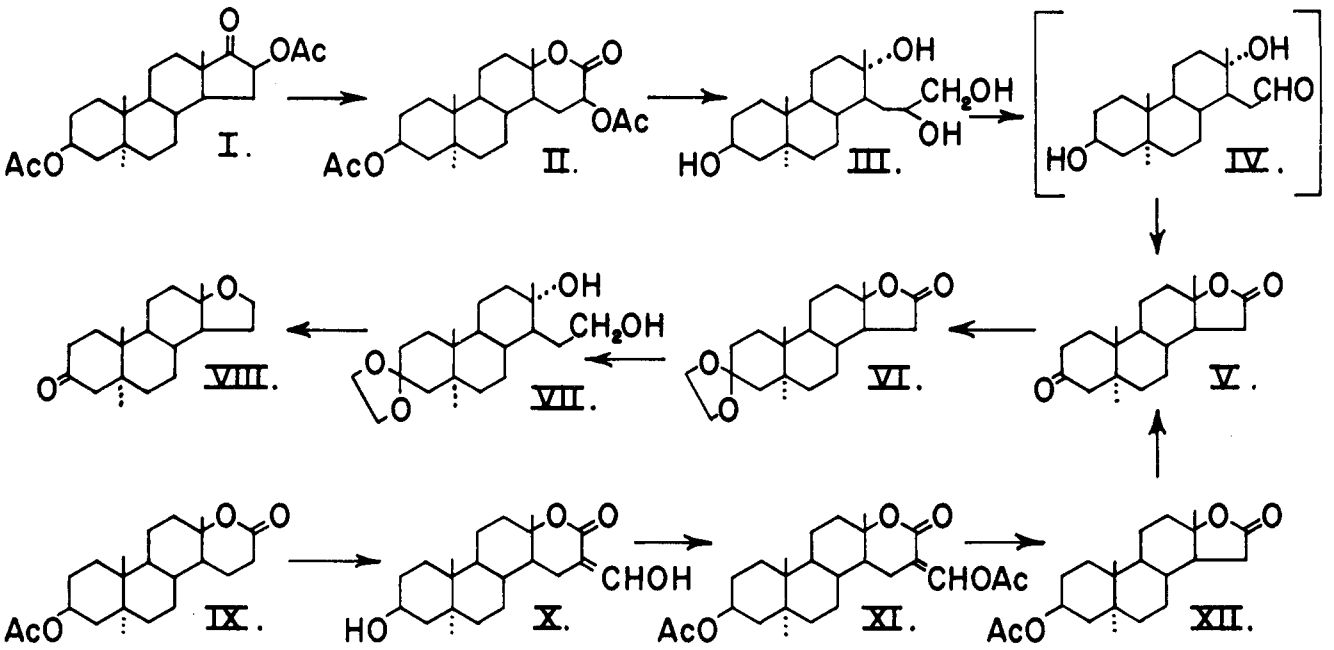
(9) Melting points were determined on a Fisher-Johns apparatus and are not corrected. The ultraviolet absorption spectra were taken in methanol and the infrared spectra in a potassium bromide pellet (Infracord). For chromatographic purifications, the silica gel used was Davison Type 923, 100–200 mesh. Analyses were carried out by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.



added to the original filtrate, and the combined solutions dried over sodium sulfate. Removal of the solvents gave 3.9 g. (97%) of the tetrol III, m.p. 201–203°. The infrared spectrum of the crude material showed no absorption in the carbonyl region. Recrystallization from methanol–ether furnished an analytical sample of prisms, m.p. 207–208°; $[\alpha]^{22}D$ −13° (*c* 1.0, dioxane).

Anal. Calcd. for $C_{19}H_{34}O_4$: C, 69.90; H, 10.50. Found: C, 69.73; H, 10.73.

17-Oxa-5α-androstane-3,16-dione (V).—To a solution of 4 g. of the tetrol III in 200 ml. of dioxane was added 8 g. of periodic acid in 20 ml. of water. The solution was allowed to stand at room temperature in the dark for a period of 23 hr. The solution was then neutralized with sodium hydrogen carbonate solution and most of the solvent was removed *in vacuo*. The residue was poured into cold water and the precipitate was extracted with ether. The ether extract was washed with water and dried over sodium sulfate. Removal of solvent yielded 3.5 g. of oily aldehyde IV, demonstrated by the presence of a carbonyl absorption at 1730 cm.$^{-1}$ in the infrared spectrum. This oil resisted all attempts at crystallization, and was, therefore, directly oxidized to the lactone IX as described subsequently.

The crude aldehyde IV, *vide supra*, was dissolved in 100 ml. of absolute acetone and cooled to 0–5°. A solution of chromic acid[10] was added until the brown color persisted. The mixture was stirred for 5 min. at 0–5° and then for another 5 min. at room temperature. Excess reagent was decomposed by adding a few ml. of methanol and then the mixture was poured into water. The precipitate was extracted with methylene chloride; the organic layer was washed with a solution of sodium hydrogen carbonate and with water, and dried over sodium sulfate. Removal of solvent yielded 3.35 g. of an oil. Upon trituration with ether, 1.0 g. of the lactone V, m.p. 165–167°, was obtained. The mother liquors were adsorbed on a column of silica gel. Elution with ethyl acetate–benzene mixtures (1:9 and 1:7) yielded another 800 mg. of V, m.p. 168–169°. Total yield of lactone was 1.8 g. (50.7%). Further elution of the column with solvent mixtures of higher polarity failed to yield any clearly defined product. A portion of the lactone was crystallized for analysis three times from dichloromethane–ether to give needles, m.p. 170–171°; $[\alpha]^{22}D$ −24° (*c* 1.0, chloroform); ν_{max} 1775 (γ-lactone) and 1705 cm.$^{-1}$ (3-ketone).

Anal. Calcd. for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.60; H, 8.88.

17-Oxa-5α-androstan-16-one 3-Ethylene Ketal (VI).—To a solution of 1.0 g. of 17-oxa-5α-androstane-3,16-dione (V) in 200 ml. of 2-methyl-2-ethyl-1,3-dioxolane was added 18 mg. of *p*-toluenesulfonic acid and the solution refluxed for 5 hr. Ether was added after cooling and the organic phase was washed with sodium hydrogen carbonate solution and with water, and finally dried over sodium sulfate. Removal of solvent under reduced pressure (benzene being added to remove last traces of dioxolane by codistillation), gave 1.1 g. of an oil which upon trituration with ether yielded 950 mg. of 17-oxa-5α-androstan-16-one 3-ethylene ketal, m.p. 179–181° (82% yield). An analytical sample was obtained by successive recrystallizations from ether to give colorless needles, m.p. 187–188°; $[\alpha]^{22}D$ −44° (*c* 1.0, chloroform); ν_{max} 1775 cm.$^{-1}$ (γ-lactone).

Anal. Calcd. for $C_{20}H_{30}O_4$: C, 72.03; H, 9.16. Found: C, 71.82; H, 9.04.

13,16-Seco-17-nor-5α-androstane-13α,16-diol 3-Ethylene Ketal (VII).—To a slurry of 500 mg. of lithium aluminum hydride in 300 ml. of absolute tetrahydrofuran was added with stirring over a period of 20 min. a solution of 520 mg. of 17-oxa-5α-androstan-16-one 3-ethylene ketal (VI) in 50 ml. tetrahydrofuran, and the mixture refluxed for 20 hr. After cooling, the excess reagent was decomposed by ethyl acetate, a saturated solution of sodium sulfate was added, and the precipitated inorganic material filtered off. The residue was then thoroughly washed with ethyl acetate and the washings were added to the original filtrate. The solution was dried over sodium sulfate, and the solvent removed under reduced pressure to yield 500 mg. of crystalline 13α,16-dihydroxy-13,16-seco-17-nor-5α-androstane 3-ethylene ketal (VII), m.p. 144–146° (95% yield). A portion of this was crystallized twice from methanol–ether for analysis to give needles, m.p. 152–153°; $[\alpha]D$ −7° (*c* 1.0, chloroform).

Anal. Calcd. for $C_{20}H_{34}C_4$: C, 70.97; H, 10.13. Found: C, 71.28; H, 10.18.

17-Oxa-5α-androstan-3-one (VIII).—To 350 mg. of 13α,17-dihydroxy-13,16-seco-17-nor-5α-androstane 3-ethylene ketal (VII) in 10 ml. of dry pyridine was added 500 mg. of *p*-toluenesulfonyl chloride. The solution was stored at room temperature for 24 hr. and then heated on a steam bath for 3 hr. Pyridine was removed under reduced pressure and the oily residue taken up in ether and washed with cold 2 *N* hydrochloric acid, water, sodium hydrogen carbonate solution, and with water, and then dried over sodium sulfate. Removal of solvent yielded 300 mg. of an oil, which showed in the infrared absorption spectrum no hydroxyl band and a weak carbonyl band indicating partial hydrolysis of the ketal function. The oil was dissolved in 40 ml. of acetone and refluxed with 50 mg. of *p*-toluenesulfonic acid for 1 hr. Most of the solvent was removed under reduced pressure and the residue diluted with water. The precipitate was extracted with ether. The ether extract was washed with water and dried over sodium sulfate. Removal of the solvent gave 250 mg. of crystalline 17-oxa-5α-androstan-3-one (VIII), m.p. 100–102°, 87% yield. An analytical sample, obtained by a recrystallization from hexane, gave plates, m.p. 109–110°; $[\alpha]D$ +42° (*c* 1.0, chloroform); ν_{max} 1700 cm.$^{-1}$ (3-ketone).

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.47; H, 10.25.

3β-Acetoxy-17a-oxa-5α-D-homoandrostan-17-one (IX).—This

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substance was prepared from 3β-acetoxyandrost-5-en-17-one as described by Levy and Jacobsen[7] in an over-all yield of 85%. The melting point of the lactone was found to be 169–170°, lit. m.p. 169.7–169.9°.

3β-Hydroxy-16-hydroxymethylene-17a-oxa-5α-D-homoandrostan-17-one[8] (X).—A mixture of 2.5 g. of IX, 150 ml. of dry thiophene-free benzene, 10 ml. of ethyl formate, and 2 g. of sodium hydride (50% in oil) was stirred in an atmosphere of nitrogen for a period of 5 hr. Excess reagent was decomposed by a few milliliters of methanol, and water added to the mixture. The aqueous alkaline layer was separated and the organic phase washed with water. The aqueous washing and the alkaline extract were mixed and acidified with cold 2 *N* hydrochloric acid. The precipitate was collected and dried to yield 2.55 g. of X, m.p. 291–292°, lit. m.p. 292–294°; ν_{max} 3340 (OH), 1690 (δ-lactone carbonyl), and 1610 cm.$^{-1}$ (hydroxymethylene); λ_{max} 250 mμ (log ε 4.05).

3β-Acetoxy-16-acetoxymethylene-17α-oxa-5α-D-homoandrostan-17-one (XI).—A solution of 2 g. of X in 25 ml. of pyridine and 5 ml. of acetic anhydride was kept at room temperature for 18 hr. Excess acetic anhydride was decomposed by adding a few ml. of methanol and the solution was poured into ice–water. The precipitate was collected and dried to give 2.4 g. of the diacetate XI, m.p. 105–105°. A sample was crystallized three times from ether–hexane for analysis to give needles, m.p. 108–110°; $[\alpha]^{22}D$ −122° (*c* 1.0, chloroform); λ_{max} 237 mμ (log ε 4.12); ν_{max} 1760 (16-acetoxy), 1740 (3-acetoxy), 1708 (conjugated δ-lactone), and 1630 cm.$^{-1}$ (double bond of acetoxymethylene).

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 69.02; H, 8.45.

3β-Acetoxy-17-oxa-5α-androstan-16-one (XII).—A solution of 2 g. of XI in a mixture of 30 ml. of ethyl acetate and of 30 ml. of acetic acid was cooled to −10° and then ozonized for a period of 75 min. After addition of 5 ml. of a 30% solution of hydrogen peroxide and 5 ml. of water the mixture was stored at 25° for 24 hr. It was then diluted with ether, washed with water, with sodium hydrogen carbonate solution, and water, and dried over sodium sulfate. Removal of solvent gave 2 g. of an oil which was dissolved in 10 ml. of benzene and adsorbed on a column of silica gel. Elution with mixtures of ethyl acetate, benzene (5% and 10%) yielded fractions melting in the range of 139–142°. These fractions were combined to give a total of 1.42 g. of XII (85%). No other compound of definite nature could be isolated by further elution of the column. An analytical sample was prepared by crystallizing from dichloromethane–hexane to give prisms, m.p. 146–148°; $[\alpha]^{23}D$ −59° (*c* 1.0, chloroform); ν_{max} 1776 (γ-lactone), 1730 (3-acetate), and 1236 cm.$^{-1}$ (3-acetate).

Anal. Calcd. for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.68; H, 9.17.

Quinazolines and 1,4-Benzodiazepines. XVI.[1] Synthesis and Transformations of 5-Phenyl-1,4-benzodiazepine-2-thiones

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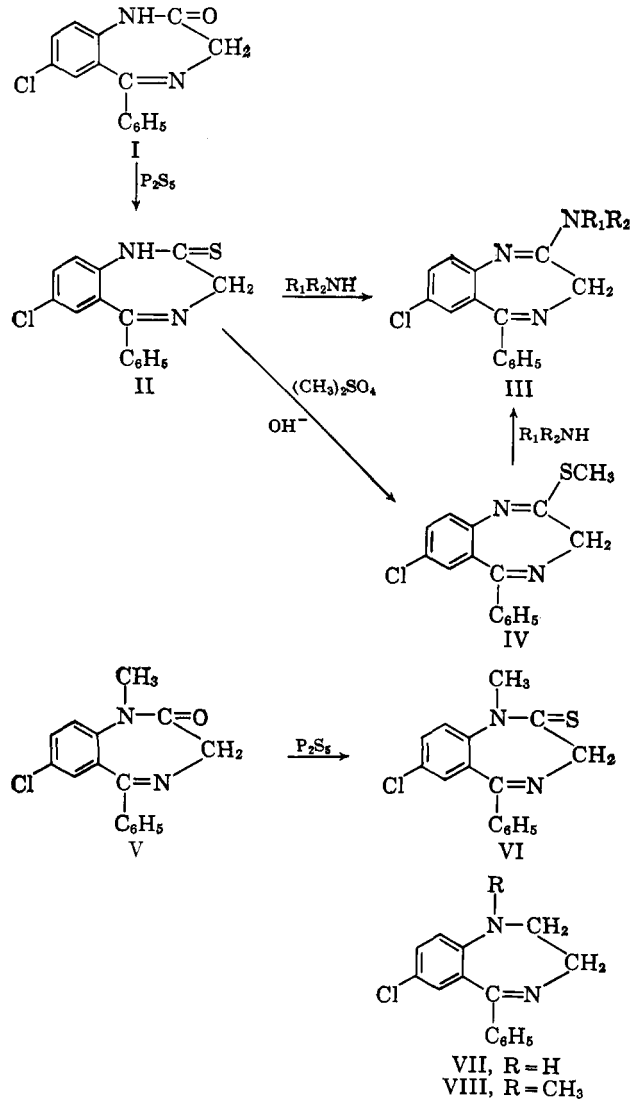
In continuation of our studies of the chemistry of 5-phenyl-1,4-benzodiazepin-2-ones, we examined methods for effecting transformations of the carbonyl grouping in position 2. Firstly we turned our attention to the synthesis and reactions of the thiolactam II. We expected the thione group in II to undergo nucleophilic replacement, when treated with a primary or secondary amine, to give aminobenzodiazepines of type III. This type of reaction has been used for the preparation of amino compounds from the corresponding thionamides, in the pyrimidine,[2] purine,[3] and quinazoline,[4,5] series, but had not been applied to 1,4-benzodiazepines.

Thiation of the lactam I was readily achieved by treatment with phosphorus pentasulfide in refluxing pyridine, to give the desired thiolactam II. Reaction of II with primary or secondary aliphatic amines, or with secondary heterocyclic amines, resulted in formation of compounds of type III, with evolution of hydrogen sulfide. Since it has been reported[6] that S-alkylthiopyrimidines react with amines more readily than do the corresponding thiopyrimidines, we were led to methylate II to the methylmercapto derivative (IV). That the product was in fact the S-methyl derivative, and not the isomeric N-methylthiolactam (VI), was proved by its ready acid hydrolysis to I and also by the unequivocal synthesis of VI from the N-methylbenzodiazepinone (V).



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