well with water, and dried *in vacuo* over P_2O_5 at 100°; yield 0.26 g. (91%), m.p. 255–260° (dec.). Calcd. for $C_{21}H_{23}O_3NI_2$: C, 36.70; H, 3.40; N, 2.04; I, 36.94. Found: C, 36.41; H, 3.60; N, 2.05; I, 36.27.

Fluorine analysis on the free glucoside was carried out as described for VII and XI. Again, the results indicated that not more than 1% of the trifluoroacetyl groups could have resisted the hydrolytic treatment.

N-Trifluoroacetyl-DL-thyroxine Methyl Ester.—DL-Thyroxine (Hoffmann–La Roche)[32] was esterified according to Ashley and Harington.[31] 0.73 g. of thyroxine methyl ester (m.p. 148–151° dec.) was suspended in 30 cc. of 1:1 ethyl acetate–chloroform, treated with 0.4 cc. of trifluoroacetic anhydride, and worked up as described for V; yield 0.76 g. (93%), m.p. 203–206°. *Anal.* Calcd. for $C_{18}H_{12}O_5NF_3I_4$: C, 24.37; H, 1.35; N, 1.58; I, 57.24. Found: C, 24.46; H, 1.54; N, 1.55; I, 57.8.

This derivative of thyroxine failed to couple with either acetobromoglucose or acetobromoglucuronic acid methyl ester by the methods described here.

N-Benzoyl-L-thyroxine Methyl Ester.—L-Thyroxine[30] was esterified in the same manner as the DL-isomer (treatment of a methanol suspension of the amino acid with dry HCl gas and removal of HCl from the resulting hydrochloride with an equivalent amount of NaOH). The ester prepared by this procedure was not entirely satisfactory. It started to melt at approximately 100°, but melted over a range of 10–15° to give a sticky, non-flowing melt. Several different preparations all behaved in this manner, differing somewhat in the temperature at which melting first started. The preparation used for the N-benzoyl derivative gave the following analysis. Calcd. for $C_{16}H_{13}O_4NI_4$: C, 24.28; H, 1.66. Found: C, 24.40; H, 1.70.

1.32 g. of L-thyroxine methyl ester (1.67 mmoles) was dissolved in 50 cc. of chloroform in a separator funnel. Six cc. of 2 *N* Na_2CO_3 was added, and then in portions, 0.25 cc. of benzoyl chloride (2.1 mmoles) contained in several cc. of chloroform, was added with shaking. The chloroform layer was drawn off, washed with 10 cc. of 2 *N* Na_2CO_3, twice with water, and dried with $CaCl_2$. The chloroform solution was concentrated *in vacuo* at room temperature, and the residue was redissolved in a small volume of warm benzene. After charcoal treatment and concentration *in vacuo* the benzene solution was treated with several volumes of petroleum ether, whereupon the product started to crystallize. Precipitation was completed by standing in the refrigerator overnight; yield 1.22 g. (82%), m.p. 200–206°. *Anal.* Calcd. for $C_{23}H_{17}O_5NI_4$: C, 30.82; H, 1.91. Found: C, 31.44; H, 2.13.

An attempt to couple the above thyroxine derivative with acetobromoglucuronic acid methyl ester was not successful.

BERKELEY, CALIF.

(32) We are indebted to Dr. A. E. Heming of Smith, Kline and French Laboratories, for a supply of DL-thyroxine.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

Synthesis of 11-Keto Steroids

BY E. M. CHAMBERLIN, W. V. RUYLE, A. E. ERICKSON, J. M. CHEMERDA, L. M. ALIMINOSA, R. L. ERICKSON, G. E. SITA AND M. TISHLER

RECEIVED DECEMBER 9, 1952

A general synthesis of 11-keto steroids is described in which the prerequisite $\Delta^{7,9(11)}$-*allo*-steroid is converted through successive stages to a Δ^7-9α,11α-epoxide, a Δ^8-7ξ,11α-diol, a Δ^8-7,11-dione, and finally to a 7,11-dione. The latter can be reduced preferentially at the 7-position to an 11-keto steroid. By means of this procedure ergosterol, stigmasterol and diosgenin can be converted to *allo*-pregnan-3β-ol-11,20-dione acetate (XV) which can be used for the synthesis of cortical steroids.

In an earlier communication, we described briefly the synthesis of *allo*pregnan-3β-ol-11,20-dione acetate (XV) from ergosterol, stigmasterol and diosgenin.[1] Since that time other investigators have also reported the preparation of 11-oxygenated steroids from $\Delta^{5,6}$-steroids devoid of functional groups in ring C.[2] Of these publications only two have described the synthesis of the diketo *allo*pregnane (XV).[1,2b] We now wish to describe the results presented in our first communication and additional pertinent data.

In the course of research on the introduction of 11-oxygen into the above-mentioned steroids, the oxidation of $\Delta^{7,9(11)}$-steroid dienes by peracids was studied. In contradistinction to earlier literature on the action of perbenzoic acid on conjugated dienes[3] we observed that $\Delta^{7,9(11)}$-dienes react in an orderly stepwise manner with perbenzoic acid. Thus, from the reaction between $\Delta^{7,9(11),22}$-ergostatrien-3β-ol acetate (I) (ergosterol-D acetate)[4] and perbenzoic acid in benzene at 10° a mono-epoxide, a di-epoxide, and a tri-epoxide can be isolated by the use of one, two or three moles of the peracid, respectively. Of these various derivatives, the mono-epoxide proved most useful for the synthesis of 11-keto steroids.

Since the mono-epoxide obtained from ergosterol-D acetate exhibits end absorption only in the ultraviolet above 220 mμ, it is evident that the 7,9(11)-diene system is attacked in preference to the side-chain function. In fact the dienic function is attacked with such rapidity that the mono-epoxide is obtained almost exclusively from the reaction of I with one mole of perbenzoic acid. Similarly $\Delta^{7,9(11)}$-5α,22a-spirostadien-3β-ol acetate (XVI) can be selectively oxidized to a mono-epoxide and to a di-epoxide.

After our initial communication,[1] Jeger and his co-workers[2e] reported the conversion of I into the mono-epoxide and ascribed to the latter a Δ^7-9α,11α-epoxide structure (II). Our experience likewise indicates that these mono-epoxides from $\Delta^{7,9(11)}$-*allo*-steroids are best described as Δ^7-9α,11α-mono-epoxides.[5]

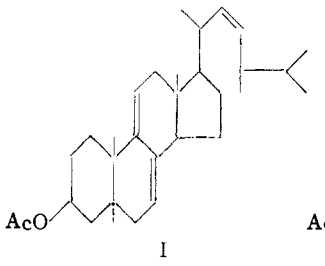
(1) E. M. Chamberlin, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, L. M. Aliminosa, R. L. Erickson, G. E. Sita and M. Tishler, THIS JOURNAL, **73**, 2396 (1951).

(2) (a) L. F. Fieser, J. E. Herz and Wei-Yuan Huang, *ibid.*, **73**, 2397 (1951); (b) G. Stork, J. Romo, G. Rosenkranz and C. Djerassi, *ibid.*, **73**, 3546 (1951); (c) L. F. Fieser, J. C. Babcock, J. Herz, Wei-Yuan Huang and W. P. Schneider, *ibid.*, **73**, 4053 (1951); (d) C. Djerassi, O. Mancera, G. Stork and G. Rosenkranz, *ibid.*, **73**, 4496 (1951); (e) H. Heusser, K. Eichenberger, P. Kurath, H. R. Dällenbach and O. Jeger, *Helv. Chim. Acta*, **34**, 2106 (1951); (f) R. C. Anderson, R. Budziarek, G. T. Newbold, R. Stevenson and F. S. Spring, *Chemistry and Industry*, 1035 (1950); *J. Chem. Soc.*, 2892 (1952).

(3) A. Windaus and A. Lüttringhaus, *Ann.*, **481**, 119 (1930); A. Windaus, O. Linsert and H. J. Eckhardt, *ibid.*, **534**, 22 (1938).

(4) An improved method of synthesis of this substance and other $\Delta^{7,9(11)}$-steroids will be presented later in THIS JOURNAL.

(5) A report covering additional reactions of the mono-epoxide will be presented later.



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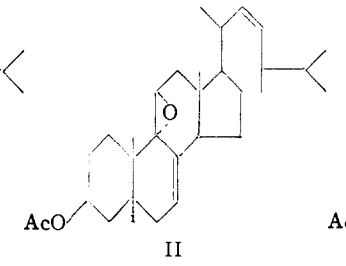

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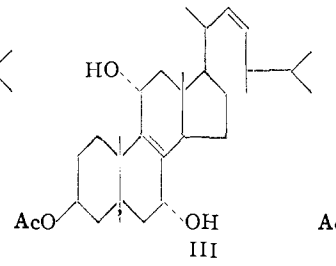

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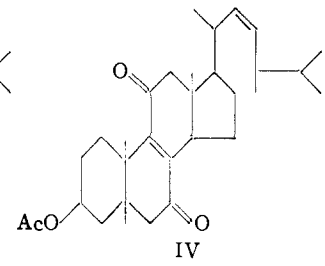

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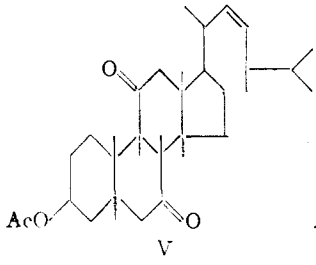

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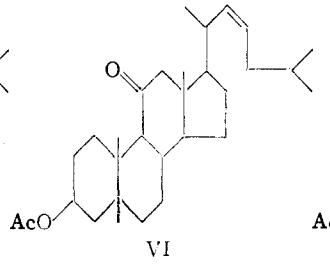

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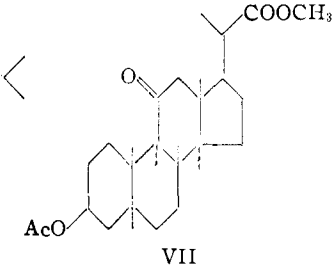

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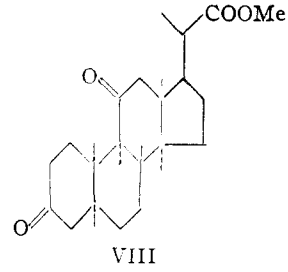

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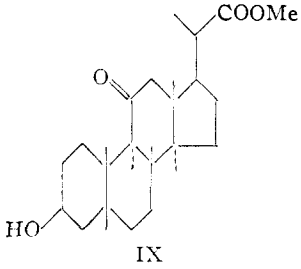

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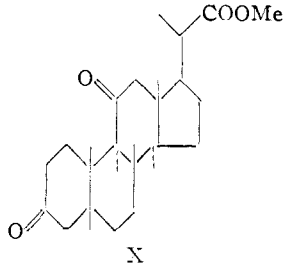

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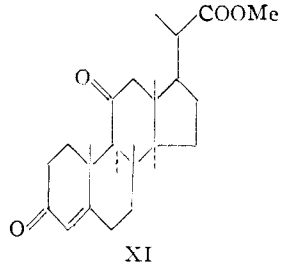

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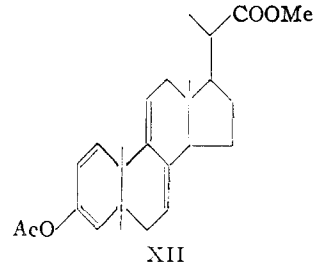

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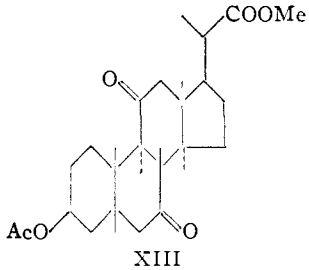

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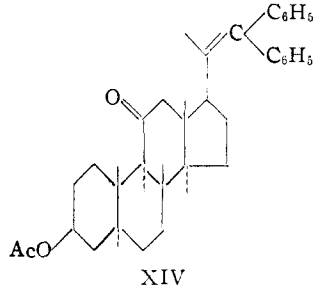

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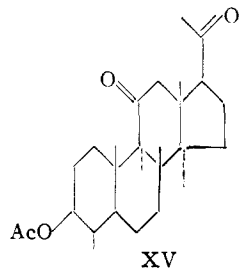

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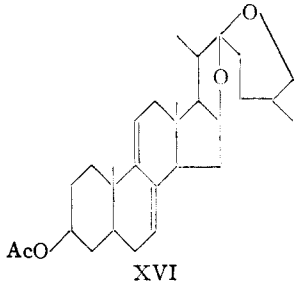

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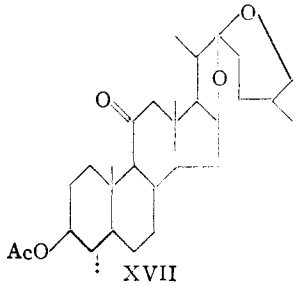

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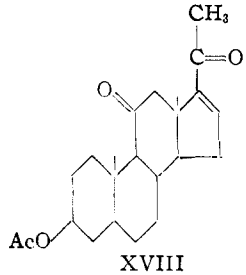

XVIII

Although the epoxide ring of the mono-epoxides is stable toward alcoholic alkali under ordinary conditions, it is extremely labile toward acidic reagents. When the levorotatory mono-epoxide (II) from $\Delta^{7,9(11),22}$-ergostatrien-3β-ol acetate[1] is subjected to prolonged chromatography over acid-washed alumina cleavage of the oxide ring occurs and a strongly adsorbed dextrorotatory substance is formed. Analysis of the cleavage product indicates hydration of the mono-epoxide II. The active hydrogen determination together with the formation of a tri-acetate by the action of acetic anhydride–pyridine at room temperature suggested that the dextrorotatory hydration product of II is a derivative of a tri-secondary triol, namely, $\Delta^{8,22}$-ergostadien-3β,7ξ,11α-triol 3-monoacetate (III). The formulation of the hydrolysis rearrangement product as III was confirmed further by the oxidation of III to $\Delta^{8,22}$-ergostadien-3β-ol-7,11-dione acetate (IV) by chromic acid. As expected, IV exhibits an absorption maximum at 270 mμ (alcohol) or 266 mμ (isoöctane) which can only be explained in terms of a 1,4-diketone conjugated through a 2,3-double bond. The observed shift of 15 mμ from the absorption maximum of Δ^4-cholestene-3,6-dione[6] is not unexpected in view of the presence of an additional substituent in IV except for the fact

(6) W. Ross, *J. Chem. Soc.*, 737 (1946).

that a similarly constituted 1,4-enedione, $\Delta^{8(14)}$-ergosten-3β-ol-7,15-dione has been reported to absorb at 255 mμ.[7] However, Δ^{9}-octalin-1,5-dione,[8] a more precise counterpart of the absorbing entity in IV, has been reported to possess an absorption maximum at 263 mμ. Subsequent transformations of IV and similar products described in this paper provide rigorous proof of the structure of the cleavage product of III and its oxidation product IV.

The hydrolytic rearrangement of II catalyzed by acidic alumina is also readily applicable to the conversion of the monoepoxides prepared from methyl $\Delta^{7,9(11)}$-3β-acetoxy-*allo*bisnorcholadienate (XII) and $\Delta^{7,9(11)}$-5α,22a-spirostadiene-3β-ol acetate (XVI) into the respective triol monoacetates. As might be expected from the reactions of butadiene mono-epoxide,[9] these Δ^{8}-7,11-hydroxylated derivatives can be obtained also by the action of aqueous acids. The Swiss investigators, Jeger and his co-workers,[2e] have described the hydrolytic rearrangement of the mono-epoxide (II) by the action of dilute aqueous sulfuric acid in dioxane for a short period of time at a low temperature. We have likewise observed that the rearrangement of these epoxides can be carried out in homogeneous media.[5] From the standpoint of efficiency of operation, the alumina-catalyzed hydrolysis possesses considerable advantage over the use of homogeneous media particularly if the epoxide preparation is contaminated with the Δ^{7}-*allo*-steroids.[10] The latter are difficult to remove by crystallization and hence complicate the purification of subsequent reaction products derived from the epoxides. Since the triol monoacetates are strongly adsorbed on alumina, the other less polar impurities are easily and efficiently separated by elution with non-polar solvents. In this manner the epoxide (II) is converted to pure III in yields of 80–85% on the basis of the epoxide present.

The triol monoacetate (III) was readily oxidized by chromic acid in aqueous acetone to the Δ^{8}-7,11-dione (IV). Sodium dichromate in acetic acid produced the ene-dione in a much lower yield. The epoxide, Δ^{22}-ergosten-3β-ol-7,11-dione-8,9-epoxide obtained by the Swiss investigators[2e] by the oxidation of III with chromic acid in acetic acid was not isolated from any of our reaction products despite considerable investigation of the mother liquors. However, the same diketo epoxide was obtained in low yield by the direct action of chromic acid on the epoxide (II) although in this case other unidentified products were formed as well.

$\Delta^{8,22}$-Ergostadien-3β-ol-7,11-dione acetate reacts smoothly with zinc dust–acetic acid to yield Δ^{22}-ergosten-3β-ol-7,11-dione acetate (V). The reduced dione remains unaltered in the presence of sulfuric–acetic acid[11] as one might expect for a normal B/C ring junction.

In accordance with the postulated structures both the reduced 7,11-dione (V) and the parent Δ^{8}-7,11-dione (IV) form only mono derivatives with 2,4-dinitrophenylhydrazine or ethylenebisthiol. The difference in reactivities of the carbonyl functions of Δ^{22}-ergostene-3β-ol-7,11-dione acetate is in fact so great that we were able to effect its selective reduction by the Huang-Minlon modification[12] of the Wolff–Kishner reduction to Δ^{22}-ergostene-3β-ol-11-one which was also characterized as the acetate (VI).

Degradation of the side chain of VI finally provided indisputable proof that a method for the preparation of 11-keto steroids had been achieved. Ozonization of VI, decomposition of the ozonide with zinc dust–acetic acid, oxidation of the intermediate aldehyde and esterification of the acetoxy acid yielded methyl 3β-acetoxy-11-ketobisnor*allo*cholanate (VII). The latter was transformed into methyl 3,11-diketobisnor*allo*cholanate (VIII) by hydrolysis followed by oxidation. By an unequivocal synthesis, methyl 3α-hydroxy-11-ketobisnorcholanate (IX)[13] was also converted to VIII which proved to be identical with the derivative synthesized from ergosterol. Briefly, the synthesis involved oxidation of IX to the 3-keto compound (X) bromination of X to the 4-bromo derivative followed by dehydrobromination using the method of Koechlin, Kritchevsky and Gallagher.[14] The resulting methyl Δ^{4}-3,11-diketobisnorcholenate (XI) was hydrogenated to a mixture of saturated diols which was oxidized to the diketones with chromic acid. Both methyl 3,11-diketobisnorcholanate (X) and the desired *allo* derivative (VIII) were isolated by chromatography over alumina.

By a similar series of transformations Δ^{5}-3β-acetoxybisnor*allo*cholenic acid, derived from stigmasterol and cholesterol, has also been converted into methyl 3β-acetoxy-11-ketobisnor*allo*cholanate (VII). In this series Δ^{5}-3β-acetoxybisnorcholenic acid was first transformed into methyl $\Delta^{7,9(11)}$-3β-acetoxybisnor*allo*choladienate[4] (XII) and the latter was converted to the epoxide. The epoxide derived from XII was converted to the triol monoacetate derivative which upon oxidation and reduction yielded methyl 3β-acetoxy-7,11-diketobisnor*allo*cholanate (XIII). Wolff–Kishner reduction of XIII yielded 3β-hydroxy-11-ketobisnor*allo*cholanic acid which was converted to VII and found to be identical with the product derived from ergosterol.

Methyl 3β-acetoxy-11-ketobisnor*allo*cholanate (VII) reacts with phenylmagnesium bromide in N-ethylmorpholine–benzene to give the diphenylcarbinol which is dehydrated to XIV by the action of refluxing acetic anhydride. As expected the resulting Δ^{20}-3β-acetoxy-11-keto-22,22-diphenyl bisnor*allo*cholen (XIV) exhibits an absorption peak in the ultraviolet, λ_{max} 244 mμ. Ozonization of XIV and reductive decomposition of the ozonide yields *allo*pregnan-3β-ol-11,20-dione acetate (XV).

In a similar fashion, the *allo*diketopregnan (XV) was prepared from diosgenin. The latter was transformed consecutively into $\Delta^{5,7}$-22a-spirosta-

(7) H. E. Stavely and G. N. Bollenback, THIS JOURNAL, **65**, 1285 (1943).

(8) W. P. Campbell and G. C. Harris, *ibid.*, **63**, 2721 (1941).

(9) W. E. Bissinger, R. H. Fredenburg, R. G. Kadesch, F. Kung, J. H. Langston, H. C. Stevens and F. Strain, *ibid.*, **69**, 2955 (1947).

(10) These materials are common contaminants of $\Delta^{7,9(11)}$-*allo*-steroid preparations obtained by the action of mercuric acetate on Δ^{7}-*allo*-steroids. For a discussion of the preparation of $\Delta^{7,9(11)}$-steroids and related problems, see THIS JOURNAL, **75**, 2604 (1953).

(11) V. Prelog and E. Tagmann, *Helv. Chim. Acta*, **27**, 1880 (1944).

(12) Huang-Minlon, THIS JOURNAL, **68**, 2487 (1946).

(13) L. H. Sarett, *J. Biol. Chem.*, **162**, 601 (1946).

(14) B. A. Koechlin, T. H. Kritchevsky and T. F. Gallagher, *ibid.*, **184**, 393 (1950); THIS JOURNAL, **74**, 485 (1952).

dien-3β-ol acetate,[15] Δ⁷-5α,22a-spirosten-3β-ol acetate[16] and finally into Δ⁷,⁹(¹¹)-5α,22a-spirostadien-3β-ol acetate[4] (XVI). The mono-epoxide prepared from XVI was ultimately converted into the 5α,22a-spirostane-3β-ol-11-one acetate (XVII) by the procedures already described above. Pyrolysis of XVII with acetic anhydride at 200° yielded the pseudo-sapogenin which was oxidized directly with chromic acid. Cleavage of the oxidation product with sodium hydroxide in aqueous tetrahydrofuran yielded Δ¹⁶-*allo*pregnen-3β-ol-11,20-dione acetate (XVIII). Hydrogenation of XVIII yielded *allo*-pregnan-3β-ol-11,20-dione acetate identical with the material derived from ergosterol or stigmasterol.

Acknowledgment.—We wish to acknowledge the aid of Mr. Richard Boos and his staff for the analyses recorded and Dr. N. R. Trenner and Mr. F. Bacher and their staffs for the physical measurements reported. In addition we wish to thank Dr. J. van de Kamp for the generous supply of methyl 3α-hydroxy-11-ketobisnorcholanate.

Experimental

All melting points are corrected. Rotations are determined in 1% chloroform unless otherwise noted.

I. **Transformations in Ergosterol Series. Reaction of Δ⁷,⁹(¹¹),²²-Ergostatrien-3β-ol Acetate with Perbenzoic Acid.** (a) **Formation of Mono-epoxide** (II).—To a solution of 17.5 g. of Δ⁷,⁹(¹¹),²²-ergostatrien-3β-ol acetate (I) in 100 cc. of benzene was added 100 cc. of 0.42 *M* perbenzoic acid in benzene[17] over a period of one hour while maintaining the temperature of the reaction mixture at 10°. Shortly after the addition of all of the perbenzoic acid solution, the starch–iodide test was negative and the reaction mixture was extracted successively with 5% sodium hydroxide and water. Upon concentration of the benzene extract to dryness *in vacuo*, a semi-solid residue was obtained from which 8.87 g. of mono-epoxide (II) was obtained by crystallization from acetone; m.p. 205–206°, $[\alpha]_D$ −26.6°, sufficiently pure for utilization in subsequent reactions. Pure **Δ⁷,²²-ergostadien-3β-ol-9α,11α-epoxide acetate** (II) was obtained by rapid chromatography of this material over acid-washed alumina followed by recrystallization of the petroleum ether–benzene eluate from acetone; m.p. 211.5–213.5°, $[\alpha]_D$ −39.3°; and end absorption in the ultraviolet above 220 mμ.

Anal. Calcd. for $C_{30}H_{46}O_3$: C, 79.25; H, 10.20. Found: C, 79.37; H, 10.04.

Four grams of Δ⁷,⁹(¹¹),²²-ergostatrien-3β-ol in 65 cc. of benzene was treated with 27.5 cc. of 0.39 *M* perbenzoic acid as described above. After all of the perbenzoic acid was consumed, the insoluble product was filtered off. One recrystallization from benzene yielded pure Δ⁷,²²-ergostadien-3β-ol-9α,11α-epoxide; m.p. 188–189°, $[\alpha]_D$ −34°. The same product was obtained in practically quantitative yield by heating under reflux a mixture of II in benzene–5% methanolic sodium hydroxide.

Anal. Calcd. for $C_{28}H_{44}O_2$: C, 81.50; H, 10.75. Found: C, 81.25; H, 10.79.

(b) **Di-epoxide.**—To one gram of Δ⁷,⁹(¹¹),²²-ergostatrien-3β-ol acetate in 25 cc. of benzene was added 15 cc. of 0.39 *M* perbenzoic acid in benzene. The mixture was held at room temperature for 1.5 hours at which time two molar proportions of perbenzoic acid had been consumed. The reaction mixture was then extracted with 5% aqueous sodium hydroxide and concentrated *in vacuo*. The solid residue was crystallized from methanol and a *di-epoxide* was obtained; m.p. 174–175°, $[\alpha]_D$ −18°.

Anal. Calcd. for $C_{30}H_{46}O_4$: C, 76.55; H, 9.90. Found: C, 75.86; H, 9.90.

(c) **Tri-epoxide.**—Upon reaction of 1.0 g. of Δ⁷,⁹(¹¹),²²-ergostatrien-3β-ol acetate with excess perbenzoic acid (30 cc. of 0.39 *M* perbenzoic acid) for five days at room temperature three molar proportions of perbenzoic were ultimately consumed. After work-up of the reaction mixture as described above, the crude reaction product was crystallized from methanol and tri-epoxide was isolated m.p. 197–198°, $[\alpha]_D$ +6°.

Anal. Calcd. for $C_{30}H_{46}O_5$: C, 74.03; H, 9.53. Found: C, 73.31; H, 9.31.

Δ⁸,²²-Ergostadiene-3β,7ξ,11α-triol 3-Acetate (III).—Early experiments indicated that the mono-epoxide (II) could be purified by chromatography over acid-washed alumina if the epoxide was eluted in a short time (two to three hours). Even under these conditions a small amount of the dextrorotatory triol monoacetate was formed as indicated by a final elution of the column with methanol–chloroform. Practically, it proved more feasible to carry out the desired rearrangement by a batch procedure as described below.

A solution of 150 g. of Δ⁷,²²-ergostadien-3β-ol-9α,11α-epoxide acetate in 1,800 cc. of benzene was thoroughly mixed with 2,400 g. of acid-washed alumina[18] and the paste maintained at room temperature for five days. At the end of this period unreacted epoxide (II) and inert impurities were removed by filtration of the slurry followed by extraction of the filter-cake with two 750-cc. portions of benzene. In this case 21 g. of material was obtained and proved suitable for recycling on alumina. The alumina residue was packed into a canvas bag and the triol monoacetate (III) eluted by extraction with a mixture of 2,500 cc. of methanol and 2,000 cc. of chloroform in a Soxhlet extractor for 16 hours. Upon concentration of the methanol–chloroform extract to a thick slurry, the product was filtered off and washed with methanol. In this manner 106 g. of practically pure triol monoacetate was obtained; m.p. 251–254°, a yield of 86% based on the reacted epoxide. One recrystallization of this material from acetone afforded pure **Δ⁸,²²-ergostadien-3β-7ξ,11α-triol 3-acetate** (III); m.p. 253–255°, $[\alpha]_D$ +83° (0.5%, $CHCl_3$).[19]

Anal. Calcd. for $C_{30}H_{48}O_4$: C, 76.22; H, 10.24. Found: C, 76.28; H, 10.19.

One gram of III was refluxed with 50 cc. of methanol, 20 cc. of benzene and 5 cc. of *N* methanolic potassium hydroxide for one-half hour. On cooling, 820 mg. of pure **Δ⁸,²²-ergostadien-3β,7ξ,11α-triol** was obtained; m.p. 273–274°.

Anal. Calcd. for $C_{28}H_{46}O_3$: C, 78.13; H, 10.77. Found: C, 77.99; H, 10.91.

To 1.0 g. of III dissolved in 5 cc. of pyridine 1.25 cc. of acetic anhydride was added and the solution kept at room temperature for 24 hours. Upon dilution with water a crystalline triacetate precipitated which on recrystallization from methanol yielded pure Δ⁸,²²-ergostadien-3β,7ξ,11α-triol triacetate; m.p. 171–173°, $[\alpha]_D$ +90°.

Anal. Calcd. for $C_{34}H_{52}O_6$: C, 73.34; H, 9.41; active H, 0.0. Found: C, 73.35; H, 9.03; active H, 0.0.

Δ⁸,²²-Ergostadien-3β-ol-7,11-dione Acetate (IV).—To a stirred suspension of 1.36 g. of III in 25 cc. of acetic acid was added 570 mg. of sodium dichromate dihydrate dissolved in 25 cc. of acetic acid. A clear solution was obtained immediately and the temperature was maintained at 23°. After 18 hours at room temperature, the green solution was concentrated to a small volume, water added and the precipitated gum was extracted with benzene. The filtered benzene extract was concentrated *in vacuo* and the yellow gummy residue was crystallized from methanol to give 190 mg. of

(15) G. Rosenkranz, J. Romo and J. Berlin, *J. Org. Chem.*, **16**, 290 (1951).

(16) G. Rosenkranz, J. Romo, E. Batres and C. Djerassi, *J. Org. Chem.*, **16**, 298 (1951); W. V. Ruyle, E. M. Chamberlin, J. M. Chemerda, G. E. Sita, L. M. Aliminosa, R. L. Erickson and M. Tishler, THIS JOURNAL, **74**, 5929 (1952).

(17) I. M. Kolthoff, T. S. Lee and M. A. Mairs, *J. Polymer Sci.*, **2**, 198 (1947).

(18) The acidity of the alumina is significant for optimum yields. The acidity can be conveniently evaluated by slurrying 1.0 g. of alumina with 50 cc. of water and examining the *p*H of the supernatant liquor. In our best preparations, the alumina-free liquor possessed a *p*H of 4.3.

(19) O. Jeger, *et al.*,[2e] report a m.p. 270–272° *in vacuo* for this compound. The m.p. of our triol monoacetate is 267–269.5° *in vacuo*. Mixed melting point determinations of our material with a sample kindly supplied by Dr. Jeger demonstrated the identity of the materials.

lemon yellow needles, m.p. 121–133°. By chromatography over alumina, pure **$\Delta^{8,22}$-ergostadien-3β-ol-7,11-dione acetate (IV)** was obtained as fine pale yellow needles after crystallization of the petroleum ether–ether eluate from methanol; m.p. 135–136°, $[\alpha]D$ +18.5°, $\lambda_{max}^{isooctane}$ 266 mμ (E_M 9400), λ_{max}^{EtOH} 270 mμ (E_M 8700).

Anal. Calcd. for $C_{30}H_{44}O_4$: C, 76.88; H, 9.46. Found: C, 76.91; H, 9.58.

Better yields of IV were obtained if the oxidation was carried out in aqueous acetone with chromic acid. Since the properties of the diene dione (IV) are not such as to permit its ready isolation, it is more advantageous to carry out the reduction of the Δ^8-function without purification and isolate the more insoluble enedione (V) as described below.

Treatment of $\Delta^{8,22}$-ergostadiene-3β-ol-7,11-dione acetate with excess 2,4-dinitrophenylhydrazine yields the **7-mono-2,4-dinitrophenylhydrazone** of IV; m.p. 203.5–206°, after recrystallization from ethanol–ethyl acetate; $\lambda_{max}^{CHCl_3}$ 380 mμ (E_M 32,600).

Anal. Calcd. for $C_{36}H_{48}O_7N_4$: N, 8.64. Found: N, 8.48.

Reaction of 1.0 g. of IV with 5 cc. of ethanedithiol in the presence of gaseous hydrogen chloride for two hours resulted in the formation of the **7-monoethylenethioketal** derivative of IV; m.p. 164.5–165.5°, after recrystallization from acetone–methanol.

Anal. Calcd. for $C_{32}H_{48}O_2S_2$: C, 70.54; H, 8.88; S, 11.71. Found: C, 70.32; H, 8.60; S, 12.41.

Δ^{22}-Ergostene-3β-ol-7,11-dione Acetate (V).—A solution of 100 mg. of IV in 5 cc. of acetic acid and 0.1 cc. of water was heated with zinc dust on the steam-bath for three hours. The initial yellow color of the solution was discharged immediately on addition of zinc dust. The reduction product after filtration from unused zinc was precipitated with water, extracted into benzene and the benzene-free residue crystallized from methanol. Pure **Δ^{22}-ergosten-3β-ol-7,11-dione acetate** was obtained as fine white needles, m.p. 196–198°, $[\alpha]D$ −30°.

Anal. Calcd. for $C_{30}H_{46}O_4$: C, 76.55; H, 9.85. Found: C, 76.68; H, 9.59.

V was more conveniently prepared by direct reduction of the crude triol monoacetate oxidation product. A suspension of 9.46 g. of III in 200 cc. of purified acetone (distilled from chromic acid) was treated with a solution of 2.66 g. of chromic acid in 18 cc. of water and 2 cc. of concentrated sulfuric acid over a three-hour period while maintaining the temperature at 20°. After an additional hour at 20°, the insoluble chromium salts were filtered off, the cake washed with acetone and the crude diketone (IV) precipitated by the addition of 200 cc. of water. In this manner 8.57 g. of crude IV was obtained; m.p. 109–119°, λ_{max} 2690 (E_M 6450) corresponding to a yield of 67.5% of IV. Without further purification, 8.1 g. of the total crude diketone in 60 cc. of acetic acid and 4.6 cc. of water was heated with 18.3 g. of zinc dust for one hour and the mixture was worked up as described above. Upon crystallization of the reduction product from methanol, 5.49 g. of V was obtained, m.p. 195–199°, in a yield of 62% based on triol monoacetate (III).

Treatment of V with 0.1 *M* sulfuric acid in acetic acid for three hours at 85° does not effect any isomerization[11] since the material was recovered quantitatively upon dilution with water.

With excess 2,4-dinitrophenylhydrazine in acidic methanol, V formed the **7-mono-2,4-dinitrophenylhydrazone**; m.p. 150–155, 208–210°, after recrystallization from ethanol–ethyl acetate.

Anal. Calcd. for $C_{36}H_{50}O_7N_4$: N, 8.61. Found: N, 8.53.

Upon reaction of V with ethanedithiol in the presence of gaseous hydrogen chloride the **7-monoethylenethioketal** of V was obtained; m.p. 230–233°, after crystallization from methanol.

Anal. Calcd. for $C_{32}H_{50}O_3S_2$: C, 70.28; H, 9.21; S, 11.72. Found: C, 70.24; H, 8.90; S, 12.19.

Δ^{22}-Ergosten-3β-ol-11-one.—Five grams of Δ^{22}-ergosten-3β-ol-7,11-dione acetate (V), 2.275 g. of powdered potassium hydroxide, 25 cc. of redistilled diethylene glycol and 2.5 cc. of 85% hydrazine hydrate were heated with stirring in an open flask for one hour at 130–140°. The temperature of the reaction mixture was then raised to 195–200° and held at this temperature for 2 hours. The product was then isolated from the reaction mixture by the addition of water and 50% sulfuric acid and extraction into benzene. The washed and dried benzene solution was concentrated to small volume and diluted with methanol whereupon the product crystallized on cooling in 70% yield. **Δ^{22}-Ergosten-3β-ol-11-one** was obtained pure after one more crystallization from methanol; m.p. 170–171°, $[\alpha]D$ +26.6°.

Anal. Calcd. for $C_{28}H_{46}O_2$: C, 81.10; H, 11.17. Found: C, 81.43; H, 11.25.

Upon refluxing 1.0 g. of Δ^{22}-ergostene-3β-ol-11-one with 5 cc. of acetic anhydride for one hour, the **3-acetate** was obtained in 80% yield; m.p. 129–131°, $[\alpha]D$ +11.9°, after crystallization from methanol.

Methyl 3β-Acetoxy-11-keto-bisnor*allo*cholanate (VII).—A solution of 2.36 g. of Δ^{22}-ergostene-3β-ol-11-one acetate (VI) in 75 cc. of chloroform was cooled to 0° and ozonized until one molar proportion of ozone had been absorbed. After this amount of ozone had reacted, the solution was light blue and ozone was no longer absorbed completely. The reaction mixture was then diluted with 100 cc. of glacial acetic acid, 3 g. of zinc was added and the mixture stirred at room temperature for one hour to effect reduction of the ozonide. The intermediate steroid aldehyde was directly oxidized to the desired acid by the action of 1.0 g. of chromic acid in 1.0 cc. of water and 50 cc. of acetic acid for 16 hours. After destruction of excess chromic acid by the addition of methanol, the reaction mixture was concentrated *in vacuo* and the residue distributed between benzene and 5% sulfuric acid. Upon concentration of the benzene extract and dissolution of the residue in acetone, **3β-acetoxy-11-keto-bisnor*allo*cholanic acid** was obtained in 45% yield; m.p. 197–200°, $[\alpha]D$ +16.5°.

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.24; H, 8.85.

Saponification of a sample of 3β-acetoxy-11-keto-bisnor-*allo*cholanic acid with 5% methanolic potassium hydroxide afforded **3β-hydroxy-11-keto-bisnor*allo*cholanic acid**; m.p. 260–262°, $[\alpha]D$ +31°.

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 73.07; H, 9.42.

The 3β-acetoxy-11-keto-bisnor*allo*cholanic acid was dissolved in ether and esterified with diazomethane. On concentrating to a small volume the methyl 3β-acetoxy-11-keto-bisnor*allo*cholanate (VII) crystallized; m.p. 191–194°, $[\alpha]D$ +24.3°.

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.73; H, 8.91. Found: C, 71.89; H, 9.15.

A solution of 750 mg. of methyl 3β-acetoxy-11-ketobisnor-*allo*cholanate was refluxed for 0.5 hour with 30 cc. of 5% alcoholic potassium hydroxide, water was added and the precipitated product, methyl 3β-hydroxy-11-keto-bisnor-*allo*cholanate, filtered and washed with water; recrystallized from methanol–water, m.p. 177.5–180.5°, $[\alpha]D$ +41.5°.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.66; H, 9.76.

$\Delta^{20(22)}$-3β-Acetoxy-11-keto-22,22-diphenylbisnor*allo*cholene (XIV).—Phenylmagnesium bromide was prepared in the usual manner from 3 g. of magnesium metal and 14 cc. of bromobenzene in 14 cc. of absolute ethyl ether. To the phenylmagnesium bromide solution was first added 23 cc. of dry N-ethylmorpholine and 12 cc. of dry benzene and then a solution of 4.7 g. of methyl 3-hydroxy-11-keto-bisnor*allo*-cholanate in 23 cc. of dry N-ethylmorpholine and 12 cc. of dry benzene, over a period of 45 minutes at 15°. When the addition of the ester was complete a further 23 cc. of N-ethylmorpholine and 12 cc. of benzene was added. The reaction was stirred for four days until all solid material had dissolved. The reaction mixture was then poured into a mixture of 500 g. of ice and 71 cc. of concentrated hydrochloric acid; the *p*H was adjusted to between 6.5–7.5 by the addition of solid sodium carbonate and the mixture steam distilled for four hours. The product was filtered, dissolved in hot benzene, the benzene solution concentrated to the point of crystallization and the crystalline diol filtered off. Pure 3,22-dihydroxy-11-keto-22,22-diphenylbisnor-*allo*cholane was obtained after an additional recrystallization from methanol; m.p. 244.5–249°, $[\alpha]D$ −22.5°.

Anal. Calcd. for $C_{34}H_{44}O_2$: C, 81.55; H, 8.86. Found: C, 81.79; H, 8.96.

A mixture of 6.5 g. of 3,22-dihydroxy-11-keto-22,22-diphenylbisnor*allo*cholane and 40 cc. of acetic acid–acetic anhydride (2:1) was refluxed for six hours. On cooling, the crystalline product was filtered and pure $\Delta^{20(22)}$-3β-acetoxy-11-keto-22,22-diphenylbisnor*allo*cholene (XIV) was obtained after recrystallization from methanol–chloroform; m.p. 267–268.5°, $[\alpha]_D$ +228°, λ_{max}^{EtOH} 244 mμ (E_M 12,440).

Anal. Calcd. for $C_{36}H_{44}O_3$: C, 82.40; H, 8.45. Found: C, 82.27; H, 8.56.

*Allo***pregnan-3β-ol-11,20-dione Acetate (XV).**—A solution of 1.5 g. of Δ^{20}-3β-acetoxy-11-keto-22,22-diphenylbisnor*allo*cholene in 100 cc. of chloroform was ozonized at −50 to −70°. The ozonide was decomposed by the addition of 5 cc. of glacial acetic acid and 2 g. of zinc dust to the resulting solution at room temperature. After removal of zinc, the solution was concentrated *in vacuo* and the residue moistened with a little methanol to induce crystallization. Upon recrystallization of the product from aqueous methanol, pure ***allo*pregnan-3β-ol-11,20-dione** acetate (XV) was obtained; m.p. 141–143°, $[\alpha]_D$ +88°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.79; H, 8.90.

2,4-Dinitrophenylhydrazone, m.p. 234–235°, after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{29}H_{37}O_7N_4$: C, 62.91; H, 6.74; N, 10.12. Found: C, 62.93; H, 6.90; N, 10.13.

II. **Synthesis of Methyl 3,11-Diketobisnor*allo*cholanate from Methyl 3α-Hydroxy-11-keto-bisnorcholanate. Methyl 3,11-Diketobisnorcholanate (X).**—To a solution of 1.88 g. of methyl 3α-hydroxy-11-keto-bisnorcholanate in 50 cc. of methanol and 0.5 cc. of pyridine was added 3.9 g. of N-bromoacetamide (0.014 mole of active bromine) in 50 cc. of methanol and the resultant solution maintained at room temperature for 20 hours. At the end of this period, 1 cc. of allyl alcohol was added and the oxidation product was precipitated by the addition of 150 cc. of water. Practically pure **methyl 3,11-diketo-bisnorcholanate** (X) was obtained in 93% yield; m.p. 198.6–202°. For analysis a sample was recrystallized twice from acetone; m.p. 202–202.8°, $[\alpha]_D$ +51°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.77; H, 9.15. Found: C, 73.69; H, 8.86.

2,4-Dinitrophenylhydrazone; m.p. 237–238° after recrystallization from ethyl acetate–ethanol.

Anal. Calcd. for $C_{29}H_{38}N_4O_7$: C, 62.80; H, 6.91; N, 10.10. Found: C, 62.65; H, 6.93; N, 9.82.

Methyl 4-Bromo-3,11-diketo-bisnorcholanate.—To a solution of 39.0 g. of X in 1,000 cc. of acetic acid was added successively 21 cc. of 0.95 *N* hydrogen bromide in acetic acid followed by dropwise addition of a mixture of 104 cc. of 1 *M* bromine in acetic acid and 104 cc. of 1 *M* sodium acetate in acetic acid. The reaction mixture was stirred vigorously during the bromination and the addition of the bromine–sodium acetate solution required 28 minutes. Immediately after all of the bromine solution had been added, the 25 cc. of 1 *M* sodium acetate in acetic acid was added and the reaction mixture was concentrated *in vacuo* to a volume of 200 cc. while maintaining the internal temperature at 40°. The crude bromo derivative, obtained by dilution of the concentrate with water, was dissolved in hot acetone and crystallized by the addition of ether–petroleum ether (2:1); yield 19.9 g., m.p. 171–174°. Pure **methyl 4-bromo-3,11-diketo-bisnorcholanate** was obtained as diamond shaped massive prisms upon recrystallization from ethyl acetate; m.p. 174–175.6°, $[\alpha]_D$ +79°.

Anal. Calcd. for $C_{23}H_{33}O_4Br$: C, 61.06; H, 7.32; Br, 17.63. Found: C, 61.26; H, 7.27; Br, 17.48.

Methyl Δ^4-3,11-Diketo-bisnorcholenate (XI).—To a solution of 7.0 g. of methyl 4-bromo-3,11-diketo-bisnorcholanate in 80 cc. of acetic acid was added 3.0 g. of semicarbazide hydrochloride and 2.1 g. of sodium acetate in 48 cc. of water and the resultant solution maintained at room temperature for 2.5 hours (carbon dioxide atmosphere). At the end of this period, 14 g. of sodium acetate in 28 cc. of water was added together with 25 cc. of 90% pyruvic acid and the solution was refluxed for one hour. Upon dilution with 300 cc. of water at reflux temperature, an oil precipitated which gradually solidified on cooling. The dried solid was dissolved in 15 cc. of benzene and 20 cc. of absolute ether and chromatographed over 150 g. of acid-washed alumina and the product eluted by 600 cc. of 2:1 ether–petroleum ether and 5600 cc. of ether. Recrystallization of the composited fractions from acetone–petroleum ether yielded 3.75 g. of XI in two crops, m.p. 169–175°. Pure methyl **Δ^4-3,11-diketo-bisnorcholenate** (XI) was obtained upon further recrystallization from methanol; m.p. 173.5–175.2°, $[\alpha]_D$ +165°, λ_{max}^{EtOH} 238 mμ (E_M 15,600).

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.15; H, 8.66. Found: C, 73.90; H, 8.41.

2,4-Dinitrophenylhydrazone, red needles; m.p. 261.8–262.4°, after recrystallization from chloroform–methanol, $\lambda_{max}^{CHCl_3}$ 259 mμ (E_M 19,000), 292 mμ (E_M 12,000), 385 mμ (E_M 32,000).

Anal. Calcd. for $C_{29}H_{36}N_4O_7$: C, 63.03; H, 6.58; N, 10.14. Found: C, 63.06; H, 6.50; N, 9.94.

Methyl 3,11-Diketo-bisnor*allo*cholanate (VIII). (a) Synthesis from XI.—One gram of methyl Δ^4-3,11-diketo-bisnorcholenate in 100 cc. of 95% ethanol was hydrogenated over 0.13 g. of platinum oxide catalyst (Adams) at slightly more than one atmosphere pressure and 25°. Two moles of hydrogen was absorbed in 17 minutes and the hydrogenation was interrupted. The catalyst-free solution was concentrated to dryness. The residue was dissolved in 50 cc. of acetone and the solution oxidized with 300 mg. of chromic acid in 10 cc. of 2 *N* sulfuric acid. After one hour excess chromic acid was then discharged with isopropyl alcohol; the precipitated chromium solvents removed by filtration and the product was isolated by the addition of water. The dried residue was dissolved in 5 cc. of benzene and 10 cc. of ether and chromatographed over 60 g. of acid washed alumina. Elution was carried out with ether–petroleum ether 2:1, ether and ether–acetone (20:1). The ether eluted material amounted to 440 mg.; m.p. 201–204°, from which pure **methyl 3,11-diketobisnor*allo*cholanate** was obtained on repeated recrystallization from acetone; m.p. 203–205.2°, $[\alpha]_D$ +66°.

Anal. Calcd. for $C_{23}H_{34}O_2$: C, 73.77; H, 9.15. Found: C, 73.64; H, 9.17.

2,4-Dinitrophenylhydrazone; m.p. 246–247°, after recrystallization from ethyl acetate–ethanol.

Anal. Calcd. for $C_{29}H_{38}N_4O_7$: C, 62.80; H, 6.91; N, 10.10. Found: C, 62.67; H, 7.03; N, 9.98.

From the ether–acetone eluates, 207 mg. of methyl 3,11-diketo-bisnorcholanate was obtained; m.p. 201–202°. Mixed melting point determinations of VIII and X as well as comparison through the 2,4-dinitrophenylhydrazones demonstrated the non-identity of the two compounds.

(b) Synthesis from VII.—The total product from the hydrolysis of 750 mg. of methyl 3-acetoxy-11-keto-bisnor*allo*cholanate (as described above) was dissolved in acetone and oxidized by the addition of 200 mg. of chromic acid in 5 cc. of *N* sulfuric acid at room temperature. Excess oxidant was destroyed by the addition of methanol and the precipitated chromium salts were filtered off. The filtrate was diluted with water and the precipitated product was crystallized from methanol to give pure **methyl 3,11-diketo-bisnor*allo*cholanate** (VIII); m.p. 201–204°, mixed m.p. with an authentic sample synthesized from methyl 3,11-diketocholanate, m.p. 201–204°; mixed m.p. with methyl 3,11-diketocholanate, 171–192°; $[\alpha]_D$ +63°; infrared spectra and X-ray diffraction patterns of the two specimens were identical. Hence it was conclusively demonstrated that an 11-keto*allo*-steroid had been synthesized by the transformations indicated.

III. **Transformation of Stigmasterol to *allo*Pregnane-3β-ol-11,20-dione Acetate. Methyl Δ^7-3β-Acetoxy-9α,11α-epoxybisnor*allo*cholenate.**—As indicated above for I, methyl $\Delta^{7,9(11)}$-3β-acetoxybisnor*allo*choladienate (XII) was converted to the mono-epoxide by oxidation with one molar proportion of perbenzoic acid; m.p. 198–201°, $[\alpha]_D$ −21°, after recrystallization from acetone. The mono-epoxide retained acetone of crystallization tenaciously even though dried at 100° for eight hours *in vacuo*.

Anal. Calcd. for $C_{25}H_{36}O_5 \cdot C_3H_6O$: C, 70.85; H, 8.92. Found: C, 70.73; H, 8.48.

Methyl Δ^8-3β-Acetoxy-7ξ,11α-dihydroxybisnor*allo*cholenate.—A solution of 1 g. of the epoxide in 10 cc. of benzene

was placed on a column of 30 g. of acid-washed alumina and kept for five days at room temperature. After this period, the column was eluted successively with 200 cc. of ether, 200 cc. of acetone–ether (1:2), 220 cc. of acetone–ether (2:1), 200 cc. of acetone and 250 cc. of methanol, whereupon the pure triol monoacetate was eluted by the acetone–ether eluates. Pure **Δ^8-3β-acetoxy-7ξ,11α-dihydroxybisnor*allo*cholenate** exhibited a melting point which varied with the solvent used for recrystallization and the rate of heating. From the methanol, the sample melted at 218–230° whereas from ethyl acetate, the preparation melted at 237–248°. For analysis, the product from methanol was dried at 100° *in vacuo*; $[\alpha]_D$ +92°.

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 69.13; H, 9.02.

Methyl Δ^8-3β-Acetoxy-7,11-diketo-bisnor*allo*cholenate.—A solution of 1.0 g. of the triol monoacetate was oxidized with 730 mg. of sodium dichromate in 30 cc. of acetic acid as already described above and 550 mg. of crude dione was obtained, m.p. 183–185°. Pure methyl Δ^8-3β-acetoxy-7,11-diketo-bisnor*allo*cholenate was obtained after two recrystallizations from methanol; m.p. 186.5–187.5°, $[\alpha]_D$ +38.7°, λ_{max}^{EtOH} 270 mμ (E_M 9110).

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 70.00; H, 8.12.

Methyl 3β-Acetoxy-7,11-diketo-bisnor*allo*cholanate (XIII).—Four hundred milligrams of the above enedione was reduced with zinc dust and acetic acid as already described. Pure **methyl 3β-acetoxy-7,11-diketobisnor*allo*cholanate** (XIII) was obtained after two recrystallizations of the crude product from methanol; m.p. 230.5–231.5°, $[\alpha]_D$ −14.5°.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.41; H, 8.39. Found: C, 69.70; H, 8.40.

Wolff–Kishner Reduction of XIII.—A suspension of 2.0 g. of XIII, 15 cc. of diethylene glycol, 1.5 g. of powdered potassium hydroxide and 1.5 cc. of 85% hydrazine hydrate was stirred while heating the reaction mixture to 135–140°. After 45 minutes at 135–140°, the temperature was raised to 190–195° and maintained at that point for 1 hour. The cooled reaction mixture was acidified with 2 *N* sulfuric acid, diluted with water and the product filtered. After preliminary treatment with Darco in benzene–ethanol, pure **3-hydroxy-11-ketobisnor*allo*cholanic acid** was obtained by two further crystallizations of the initial product from benzene; m.p. 258–261°.

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.82; H, 9.34.

The free acid reacted with ethereal diazomethane to yield methyl 3β-hydroxy-11-keto-bisnor*allo*cholanate; m.p. 175–177.5°, $[\alpha]_D$ +42.3°, which proved to be identical with the specimen prepared from ergosterol.

IV. Transformation of Diosgenin Acetate to *Allo*pregnane-3β-ol-11,20-dione Acetate. Δ^7-5α,22a-Spirosten-3β-ol-9α,11α-epoxide Acetate.—As already described above, 3.25 g. of $\Delta^{7,9(11)}$-5α,22a-spirostadien-3β-ol acetate in 50 cc. of benzene was oxidized with 25 cc. of 0.34 *N* perbenzoic acid solution at room temperature. After 20 minutes, the reaction mixture was worked up and 2.60 g. of pure **monoepoxide** was obtained after crystallization from acetone; m.p. 265–271°, $[\alpha]_D$ −73°.

Anal. Calcd. for $C_{29}H_{42}O_5$: C, 74.00; H, 9.00. Found: C, 73.75; H, 8.82.

In a separate experiment, we ascertained that the diene required two hours to react with 1.8 moles of perbenzoic acid. From this reaction mixture we isolated **5α,22a-spirostan-3β-ol-7,8,9α,11α-diepoxide acetate**; m.p. 311–316° (bath preheated to 300°); end absorption above 220 mμ.

Anal. Calcd. for $C_{29}H_{42}O_6$: C, 71.57; H, 8.70. Found: C, 71.86; H, 8.50.

Δ^8-5α,22a-Spirosten-3β,7ξ,11α-triol 3-Monoacetate.—A solution of 780 mg. of the mono-epoxide in 20 cc. of benzene was mixed with 25 g. of acid-washed alumina and kept at room temperature for five days. The reaction mixture was filtered, the alumina washed with benzene and the triol monoacetate eluted with hot chloroform–methanol. Δ^8-5α,22a-Spirosten-3β,7ξ,11α-triol monoacetate was obtained as fine needles, m.p. 250–254°, $[\alpha]_D$ +21°.

Anal. Calcd. for $C_{29}H_{44}O_6$: C, 71.28; H, 9.38. Found: C, 71.08; H, 9.30.

Δ^8-5α,22a-Spirosten-3β-ol-7,11-dione Acetate.—A suspension of 346 mg. of the triol monoacetate in 10 cc. of acetone was treated with 106 mg. of chromium trioxide in 0.8 cc. of 3.6 *N* sulfuric acid. The mixture was stirred for 15 minutes, the chromium salts filtered and the crude dione precipitated by addition of water. After two recrystallizations from methanol, pure Δ^8-5α,22a-spirosten-3β-ol-7,11-dione acetate was obtained as pale yellow needles; m.p. 226–227°, $[\alpha]_D$ −14°, λ_{max}^{EtOH} 270 mμ (E_M 8700).

Anal. Calcd. for $C_{29}H_{44}O_6$: C, 71.87; H, 8.32. Found: C, 71.73; H, 8.34.

5α,22a-Spirostan-3β-ol-7,11-dione Acetate.—Reduction of the enedione with zinc–acetic acid as previously described above yielded pure 5α,22a-spirostan-3β-ol-7,11-dione acetate after crystallization from methanol; m.p. 241–243°, $[\alpha]_D$ −72°.

Anal. Calcd. for $C_{29}H_{46}O_6$: C, 71.57; H, 8.70. Found: C, 71.38; H, 9.00.

5α,22a-Spirostan-3β-ol-11-one (XVII).—A mixture of 420 mg. of 5α,22a-spirostane-3β-ol-7,11-dione acetate, 2 ml. of diethylene glycol, 200 mg. of powdered potassium hydroxide and 0.2 cc. of 85% hydrazine hydrate reacted as described above. The product was precipitated by the addition of water to the reaction mixture and recrystallized successively from ethyl acetate–petroleum ether and methanol whereupon pure 5α,22a-spirostane-3β-ol-11-one was obtained; m.p. 224–229°, $[\alpha]_D$ −39.4°.

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 75.40; H, 10.20.

Δ^{16}-*Allo*pregnen-3β-ol-11-one Acetate (XVIII).—A mixture of 2.9 g. of 5α,22a-spirostane-3β-ol-11-one and 10 cc. of acetic anhydride was heated at 200° for ten hours. The mixture was cooled, concentrated to a thick sirup, the sirup dissolved in benzene and the solution decolorized with alumina. The benzene solution was concentrated *in vacuo* to dryness, the pseudo-sapogenin dissolved in 20 cc. of ethylene dichloride and 1.4 g. of chromic acid in 30 cc. of 90% acetic acid added to the resultant solution. After two hours at room temperature, the excess oxidant was discharged with ethanol, water was added, the product extracted into ether, and the ethereal extracts washed with sodium bicarbonate solutions. The ether-free residue was refluxed with 30 cc. of 2.5 *N* sodium hydroxide in 30 cc. of tetrahydrofuran for one-half hour and the tetrahydrofuran distilled off. The pregnene was extracted into chloroform and finally crystallized from methanol to give 1.07 g. of practically pure XVIII; m.p. 181–184°. Pure **Δ^{16}-*allo*pregnen-3β-ol-11,20-dione acetate** was obtained after an additional crystallization from methanol, m.p. 183–185°, $[\alpha]_D$ +64.5°; λ_{max}^{EtOH} 235 mμ (E_M 9250).

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 73.93; H, 8.83.

Hydrogenation of XVIII to XV.—In the course of studies on the hydrogenation of XVI to XV, we encountered two polymorphic modifications of XV other than the form obtained originally from ergosterol. Thus, 40 mg. of XVIII in 25 cc. of methanol was hydrogenated overnight with 50 mg. of palladium on barium sulfate (5%); 3 cc. of hydrogen was absorbed (theory—3 cc.). The mixture was filtered and the compound (XV) crystallized from aqueous methanol in needles, m.p. 124–127°. This same material was obtained from petroleum ether but at other times, recrystallization of XV from aqueous methanol yielded plates, m.p. 135–136°. With material obtained from ergosterol, m.p. 141–143°, no melting point depression was observed on mixing the various specimens. The optical rotation of these preparations was $[\alpha]_D$ +86°, and their carbon tetrachloride solutions possessed identical infrared absorption spectra, which resolved all doubt as to the identity of the *allo*pregnan-3β-ol-11,20-dione acetate (XV) prepared from all three steroids. In addition, the 2,4-dinitrophenylhydrazones prepared from the lower melting forms were identical with the 2,4-dinitrophenylhydrazone obtained previously in the case of the sample, m.p. 141–143°.

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