sealed tube at 100° for 16 hr. Concentration *in vacuo*, trituration and recrystallization from ethyl acetate–methanol afforded 0.16 g. (46%) of recovered starting material, m.p. 170.0–173.2°.

(b) **8(14)-Ergostenol Acetate** (III).—One gram of III was treated for 16 hr. in a medium consisting of 0.050 g. of hydroquinone, 1.25 ml. of pyridine, 5 ml. of benzene and 5 ml. of sulfur dioxide. Concentration of the reaction mixture yielded 0.92 g. of yellow crystals, m.p. 109.2–110.0°, undepressed on admixture with starting material.

Attempted Basic and Acidic Rearrangements. (a) **Sulfur Dioxide in Non-basic Medium.**—To a suspension of 1 g. of ergosterol in a small bomb tube in 5 ml. of chloroform containing 0.050 g. of propyl gallate as a stabilizer was added 5 ml. of liquid sulfur dioxide by condensation at −70° without special precautions to exclude moisture. The reaction mixture was heated to 90° for 2 hr., then allowed to stand at room temperature overnight. The dark yellow solution was evaporated *in vacuo* and the green tarry residue was triturated with 15 ml. of methanol to yield 0.58 g. of white granular residue m.p. 135–136°. Recrystallization from ether–methanol yielded 0.225 g., m.p. 137.5–139.5°, $[\alpha]^{25}D$ −39.9° ($CHCl_3$), $\lambda_{max}^{CHCl_3}$ 250.5 mμ (log ε 4.17).

(b) **Hydrochloric Acid.**—A solution of 0.5 g. of dehydroergosterol acetate (V), m.p. 148.2–151.0°, was dissolved in 15 ml. of dry chloroform and treated with gaseous hydrochloric acid for 15 minutes at 0°. Concentration afforded a black tar, which was not brought to crystallization by trituration or chromatography.

(c) **Boron Fluoride Etherate.**—A solution of 0.50 g. of V in 10 ml. of ether containing 0.5 ml. of boron fluoride etherate was refluxed for 13 hr. Extraction and concentration afforded 0.47 g. of impure starting material, $[\alpha]^{25}D$ +94° ($CHCl_3$), λ_{max}^{ether} 326 mμ (log ε 3.86).

(d) **Pyridine.**—A solution of 1.0 g. of V in 5 ml. of pyridine and 5 ml. of benzene containing 0.1 g. of hydroquinone was refluxed for 20 hr. Concentration *in vacuo* followed by trituration with cold methanol yielded 0.920 g. of starting material, $[\alpha]^{25}D$ +142.5° ($CHCl_3$).

(e) **Pyridine Hydrochloride.**—Addition of 0.5 g. of pyridine hydrochloride to the reaction mixture (d) resulted in an identical product, 0.925 g., $[\alpha]^{25}D$ +144.5° ($CHCl_3$).

Attempted Dehydrogenation of 8(14)-Ergostenol Acetate (III).—A solution of 3.25 g. of mercuric acetate and 2.0 g. of III in 50 ml. of glacial acetic acid and 25 ml. of chloroform was stirred for 1.5 hr. in a closed flask without evidence of reaction. The solution was then refluxed for 20 hr., the precipitated mercury salts filtered off and the black filtrate concentrated to dryness *in vacuo*, weight 1.78 g., m.p. 100–105°. Recrystallization from methanol afforded 1.0 g. (50% recovery) of pure starting material, m.p. 110–111°, melting point not depressed on admixture with an authentic sample.

Attempted Dehydrogenation of 7,14,22-Ergostatrienol Acetate 7,14-Maleic Anhydride Adduct.—7,14,22-Ergostatrienol acetate, m.p. 131.0–132.2°, $[\alpha]^{25}D$ −17.6° ($CHCl_3$), was prepared in 29% yield by the method of Windaus.[9a] Reaction with maleic anhydride afforded the 7,14-adduct, m.p. 191.0–195.2°.

A solution of 0.300 g. of the adduct and 0.49 g. of mercuric acetate in 3.75 ml. of chloroform and 7.5 ml. of glacial acetic acid was stirred for 19 hr. without evidence of reaction. The reaction mixture was evacuated to dryness, extracted with benzene and reconstituted in 25 ml. of dioxane containing 0.30 g. of freshly sublimed selenium dioxide. The mixture was heated at reflux temperature for 70 minutes without evidence of reaction.

BROOKLYN 6, N. Y.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF CHAS. PFIZER AND CO., INC.]

Corticosteroid Intermediates. IV. Synthesis of 11-Oxygenated Steroids from Ergosterol

BY G. D. LAUBACH, E. C. SCHREIBER, E. J. AGNELLO AND K. J. BRUNINGS

RECEIVED APRIL 5, 1956

A new route for the synthesis of 11-ketoergostenol from ergosterol involving 11,14-epidioxide and ketol intermediates has been developed.

The discovery of a selective rearrangement of steroid polyenes[1] made available from simple sterols a new type of C-ring unsaturated intermediate which appeared to be functionally adaptable to corticosteroid synthesis. Like the 7,9(11)-diene precursors which have been successfully transformed to 11-oxygenated derivatives in the bile acid, sterol and genin series,[2,3] the trienic intermediates from the rearrangement reaction possess a double bond at the 9(11)-position potentially suitable for the introduction of the 11-oxygen function. However, the unique structural feature of the 6,8(14),9(11)-triene I on which the present work is based is the presence in the C-ring of a homoannular diene system. Such steroidal diene systems are known to undergo photochemical 1,4-addition of molecular oxygen[4] under mild conditions with yield and a degree of facility that has been rarely observed in non-steroid series. The photoöxidation reaction has already been made the basis of an efficient preparation of a 7,9(11)-intermediate for cortisone synthesis.[5] The goal of the present work was to explore the possibility of using the photoöxidation reaction applied in the C-ring as a means of actually introducing the 11-oxygen function.

The C-Ring Epidioxide and Derived Diols.—The classical photoperoxidation reaction as applied to sterol dienes is in general carried out by lengthy irradiation of dilute alcoholic solutions of the diene and a photosensitizing dye with visible light. The earliest attempts to prepare the C-ring peroxide from I by such methods resulted in disappointing yields, a result in harmony with the distinct instability which was later demonstrated to be the most salient characteristic of the desired product. Studies directed to the systematic variation of the several parameters of the photoperoxidation reaction met with only moderate success,

(1) G. D. Laubach, E. C. Schreiber, E. J. Agnello and K. J. Brunings, THIS JOURNAL, **78**, 4743 (1956).

(2) C. Djerassi, *Vitamins and Hormones*, **11**, 205 (1953).

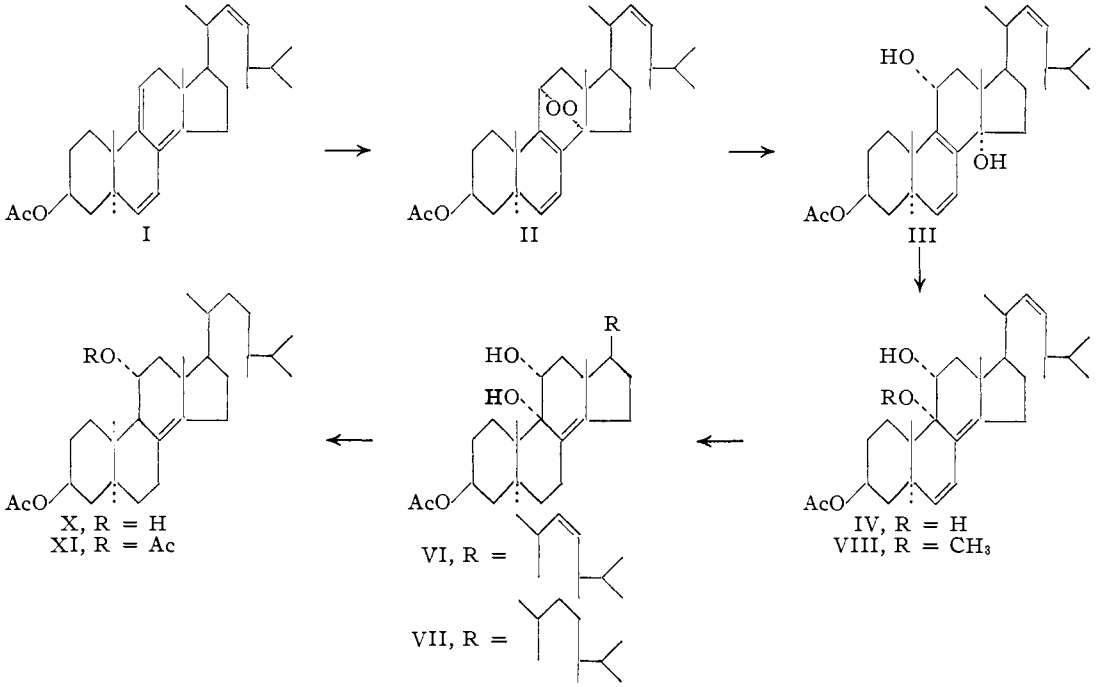
(3) G. Rosenkranz and F. Sondheimer, *Fortschritte Chem. Org. Naturstoffe*, **10**, 274 (1953).

(4) W. Bergmann and M. J. McLean, *Chem. Revs.*, **28**, 367 (1941).

(5) P. Bladon, R. B. Clayton, C. W. Greenhalgh, H. B. Henbest, E. R. H. Jones, B. J. Lovell, G. Silverstone, G. W. Wood and G. F. Woods, *J. Chem. Soc.*, 4883 (1952); P. Bladon, H. B. Henbest, E. R. H. Jones, B. J. Lovell and G. F. Woods, *Chem. and Ind.*, 945 (1953).

the most valuable innovation proving in the end to be the simple expedient of substituting benzene–alcohol for the usual alcoholic reaction medium. Under these conditions, with intense lighting, reaction was complete in 30 minutes at 0–10° with a minimal production of by-products.[6]

However, reduction of the peroxide proved to involve certain unexpected difficulties, traceable in the case of most catalytic hydrogenation procedures to partial loss of the allylic oxygen functions(s).[5] The more obvious chemical methods[9] were precluded by marked and quite obvious instability of



Neglecting for the moment stereochemical considerations, the structure of the photoöxidation product II isolated by chromatography and crystallization was based chiefly on the absence of ketonic carbonyl absorption in the infrared and the characteristic ultraviolet spectrum, λ_{max}^{ether} 272 mμ (log ε 3.6), comparable in both wave length and intensity to 6,8-cholestadiene[7] and the maleic anhydride adduct previously prepared from I.[1] Consistent with the peroxidic structure, II readily liberated iodine from acidified iodide solution.[4]

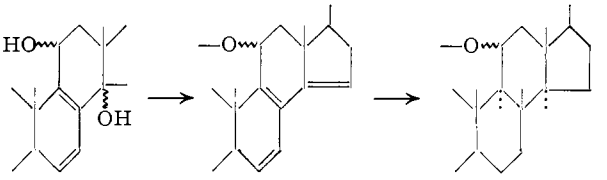
As a means of unequivocally corroborating the structure assigned the epidioxide, the most straightforward route appeared at the onset to be the conversion of II to a nuclear unsubstituted 11-hydroxy sterol. The transformation envisaged for this purpose involved reduction of the epidioxide to an 11,14-diol, followed by selective dehydration of the tertiary hydroxyl and clearing of the nuclear unsaturation by catalytic perhydrogenation. Although this procedure offered little promise for the retention of the synthetically essential side-chain unsaturation, it did allow some degree of assurance that the *trans-anti-trans* configuration of the natural steroid nucleus would obtain in the ultimate product.[8]

(6) These modified conditions were found equally applicable to other photoperoxidations of synthetic interest. For instance, complete conversion of dehydroergosterol acetate to the epidioxide was carried out in less than 30 minutes, compared to 45 hours irradiation reported by others, reference 5.

(7) A. Windaus, O. Linsert and H. J. Eckhardt, *Ann.*, **534**, 22 (1938).

(8) R. B. Turner, in L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd Ed., Reinhold Publ. Corp., New York, N. Y., p. 670.

the peroxide to both acid and base.[10] Eventually,



a highly deactivated palladium–lead catalyst[11] was found to be sufficiently inert to allow selective cleavage of only the highly susceptible –O–O– linkage of the epidioxide with absorption of one equivalent of hydrogen, without attack of either the allylic oxygen substituents, or the usually reactive 6,7-unsaturation of the B-ring diene. The successful retention of the side-chain unsaturation in the reduction product III was, of course, potentially significant in considerations involving syntheses of side-chain degraded corticoid intermediates. Although the unchanged ultraviolet spectrum and the appearance of strong hydroxyl absorption in the infrared seemed to be consistent with the simple 11,14-diol formulation of III, earliest attempts to characterize further the oxygen functions by oxidation or mild acid-catalyzed dehydration of the 14-hydroxyl group resulted in obvious changes in the ultraviolet chromophore and isolation of varying yields of a new product IV, $C_{30}H_{46}O_4$; λ_{max}^{ether} 247.5 mμ (log ε 4.43).

(9) A. Windaus, E. Auhagen, W. Bergmann and H. Butte, *Ann.*, **477**, 268 (1930).

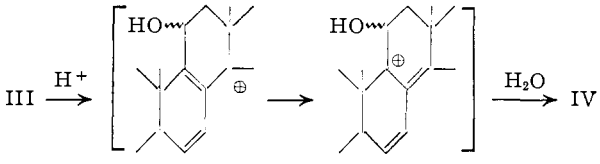
(10) E. J. Agnello, Rex Pinson, Jr., and G. D. Laubach, THIS JOURNAL, **78**, 4756 (1956).

(11) H. Lindlar, U. S. Patent 2,681,938 (June 16, 1950),

Since absence of new carbonyl absorption eliminated ketonic structures from consideration, the ultraviolet spectrum of IV was indicative of a heteroannular diene system for which the 6,8(14)-formulation seemed most likely on grounds of the striking similarity to 6,8(14),22-ergostatrienol acetate (V)[1] in both position and intensity of absorption. In addition, III (like V) readily absorbed one mole of hydrogen over Raney nickel catalyst under conditions not adequate for reduction of the isomeric 8,14-diene system in the ergostatriene series.[12]

An active hydrogen determination demonstrated that the transformation product IV was, like III, a triol monoacetate. Only one of the free hydroxyls proved acylable under mild conditions (pyridine–acetic anhydride at room temperature). The dihydro derivative VI absorbed a further equivalent of hydrogen over palladium–charcoal catalyst, but the remaining double bond of the product VII proved completely inert to noble-metal hydrogenation in neutral media.

In view of the structural data, the isomeric diol seemed adequately formulated as the product of simple anionotropic rearrangement of III.

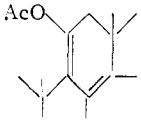


Consistent with this probable mode of formation, it was found that in very dilute aqueous acid media IV could be prepared synthetically from III in quantitative yield. Also consistent with this interpretation of the rearrangement, it was found that mild acid treatment of III in anhydrous methanol afforded a methoxy analog of IV. The product VIII was characterized by an ultraviolet spectrum essentially identical to that of IV, readily formed a monoacetate and was readily reduced to a tetrahydro derivative VII transparent above 230 mμ in the ultraviolet. It appeared, therefore, that the methoxyl substituent had replaced the original tertiary hydroxyl function and that the secondary hydroxyl group of III was not involved in the rearrangement.

At this stage of the studies with the oxygenated products, it seemed possible to assign stereochemical configurations to the epidioxide and its derived diols. It had appeared probable from the first that addition of molecular oxygen would take place on the sterically less encumbered α-face of I. The view derived in part from consideration of the very general phenomenon of attack from the back side of 9(11)-unsaturated steroids[2,3,13–15] and of the C-11 carbon itself.[16] In addition, transannular additions to the somewhat sterically comparable 5,7 B-ring diene systems have in general been found to take place on the α-face.[5,17,18]

Experimental support for the α-configuration of the epidioxide is based on the reactions of the rearranged diols IV, VI and VII, the relationship deriving from the fact that the non-rearranging 11-hydroxyl function must retain the steric configuration of the parent diol III and hence, of the epi-dioxide itself. It has been mentioned that the secondary hydroxyl function of the rearranged diols was readily acetylated under conditions that are not adequate for acylation of the 11β-hydroxyl of a steroid with the normal (9α) BC-ring juncture. That the BC-ring fusion was normal in IV seemed highly probable on the basis of the stereochemistry of the 9-position observed in other acid-catalyzed rearrangements of 8-unsaturated steroids.[8,19] Experimental support of this view, at least to the extent of demonstrating the 9,11-*cis*-orientation of IV, was obtained from the facile formation of a cyclic sulfite ester IX in the reaction of VII with thionyl chloride in pyridine, a reaction which proceeds with facility in the case of a 5,8-oxido-9α,11α-diol.[20]

The rearrangement of the 11,14-diol to the 9,11-isomer under acid conditions indicated the probable equivalence of either precursor under more vigorous dehydration conditions. The 11-acetates of IV, VI and VII seemed particularly suited for study, since loss of the 11-hydrogen would give rise directly to an enol derivative of an 11-ketone.



However, no conditions of acid-catalyzed dehydration examined resulted in the demonstrable formation of the desired enol acetate. The instability of the secondary hydroxyl of the 9α,11α-diols to relatively mild acid-catalyzed dehydration corresponds to similar experiences in a nuclear saturated case, where a 9α,11α-dihydroxy genin was re dily dehydrated to a 7,9(11)-diene.[21]

The typical products XII obtained by the acid treatment of either of the 8(14)-ergostene-9,11-diols (VI or VII) were isolated in good yield from acetic anhydride treatment at reflux temperature. In both cases, the ultraviolet spectra, λ_{max}^{EtOH} 227 mμ (log ε 4.04), 235 mμ (log ε 3.97), 265 mμ (log ε 3.96), suggested at first a mixture of nuclear trienes, but chromatographic and crystallization procedures failed to result in even partial resolution of the chromophore.

Reaction of XIIa with maleic anhydride was carried out in an attempt to demonstrate the presence of 6,8(14),9(11),22-ergostatetraenol acetate (I), suspected as a component of the dehydration "mixture" because of the strong 227, 235 mμ ab-

(12) G. D. Laubach and K. J. Brunings, THIS JOURNAL, **74**, 705 (1952).

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

(14) H. Heusser, K. Eichenberger, P. Kurath, H. R. Dallenbach and O. Jeger, *Helv. Chim. Acta*, **34**, 2106 (1951).

(15) J. Fried and E. F. Sabo, THIS JOURNAL, **75**, 2273 (1953).

(16) L. F. Fieser and M. Fieser, ref. 8, p. 410.

(17) L. F. Fieser, *Experientia*, **6**, 312 (1950).

(18) P. E. Marlatt, A. R. Hanze, A. V. McIntosh and R. H. Levin, U. S. Patent 2,621,181 (December 9, 1952).

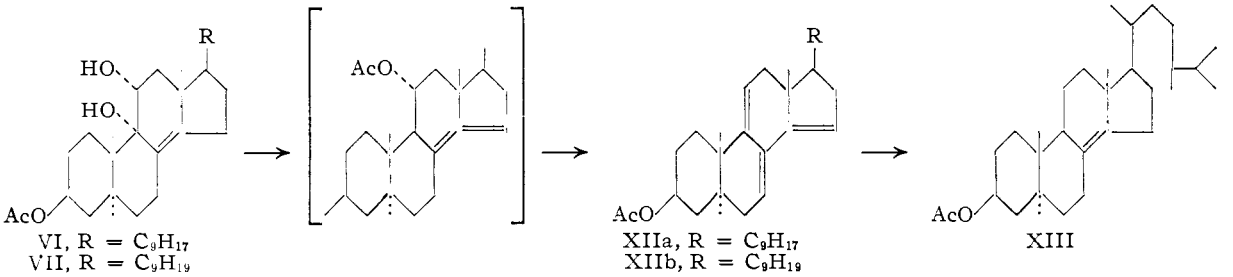
(19) D. H. R. Barton and J. D. Cox, *J. Chem. Soc.*, 783 (1948).

(20) R. B. Clayton, A. Crawshaw, H. B. Henbest, E. R. H. Jones, B. J. Lovell and G. W. Wood, *ibid.*, 2009 (1953).

(21) R. Hirschmann, C. S. Snoddy, Jr., and N. L. Wendler, THIS JOURNAL, **75**, 3252 (1953).

sorption. This reaction resulted in fair yield of an adduct XIVa with ultraviolet absorption (λ_{max}^{EtOH} 273 mμ, log ϵ 3.62) expected of the maleic anhydride adduct of I, but whose infrared spectrum was different from that of the authentic adduct of I.

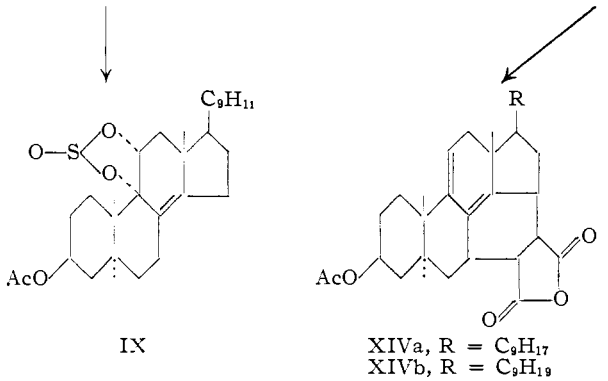
Hydrogenation of XIIb over platinum in acetic acid proceeded with absorption of two equivalents of hydrogen to yield a product shown to be identical to 8(14)-ergostenol acetate (XIII), prepared by a similar hydrogenation of ergosterol acetate. This result indicated that rearrangement of the carbon skeleton had not occurred and, in conjunction with the maleic anhydride experiment, suggested the 7,9(11),14-formulation for the anhydro products XII.



VI, R = C_9H_{17}
VII, R = C_9H_{19}

XIIa, R = C_9H_{17}
XIIb, R = C_9H_{19}

XIII



IX

XIVa, R = C_9H_{17}
XIVb, R = C_9H_{19}

The location of the ultraviolet absorption maximum of the maleic anhydride adduct XIV at 273 mμ was far different from the calculated maximum (295 mμ)[22a] for the 8(14),9(11)-diene chromophore. However, the recent report by Graber, *et al.*,[22b] of the synthesis of an 8(14),9(11)-diene in the corticosteroid series which exhibited similar absorption ($\lambda_{max.}^{MeOH}$ 271 mμ, log ϵ 3.66) added support to the structure XIV which had been assigned to the maleic anhydride adduct.

Although the dehydration experiments were unsuccessful in the sense of leading to the desired 11-monohydroxy intermediate, the fortuitous rearrangement of the 11,14-diol system presented the possibility of selective hydrogenolysis as an alternative to selective dehydration of the tertiary hydroxyl function. When the mono-unsaturated 9,11-diol VII was catalytically hydrogenated over platinum in acetic acid, a further mole of hydrogen was smoothly absorbed, and from the reaction mixture a major product X (55% yield) was isolated by fractional crystallization. Analysis demonstrated the loss of one oxygen function, presumably the acid labile, allylic 9-hydroxyl. A minor product (18% yield) was isolated and identified as 8(14)-ergostenol acetate by comparison with an authentic sample, a result which also demonstrated non-rearrangement of the carbon skeleton in the isomerization III → IV. Loss of the second non-allylic hydroxyl function parallels a similar reaction of a 2,6-diacetoxy genin on catalytic hydrogenation.[23] The 9-hydroxy-11-acetates of IV and VII were similarly hydrogenolyzed in excellent yield to the corresponding 9-desoxy-11-acetate XI without demonstrable loss of the 11-oxygen function. However, attempts to complete the transformation of XI to ergostane-3β,11α-diol diacetate by rearrangement and hydrogenation in the presence of mineral acid resulted consistently in the recovery of unchanged starting material under conditions that resulted in nearly quantitative conversion of 8(14)-ergostenol acetate to ergostanol acetate.[24] The singular resistance of the 8(14)-double bond to migration to the reducible 14,15-position must result from the presence of the 11α-oxygen function and has at least one parallel in a similar effect of the side chain in the genin series.[25]

The unexpected resistance of the 8(14)-double bond to catalytic hydrogenation effectively vitiated attempts to arrive at nuclear unsubstituted 11-hydroxy steroids from the unsaturated diol intermediates, and approaches involving preliminary formation of the 11-ketone were therefore undertaken.

It has been mentioned that initial attempts to oxidize the 11,14-diol III with chromic acid resulted in rearrangement of the acid-sensitive tertiary hydroxyl function rather than formation of the desired 11-ketone. Further attempts to oxidize either III, IV or VI with chromic acid in acidic medium proved completely fruitless, only traces of ketonic material being identifiable in the crude reaction mixtures. Non-acidic oxidants, such as chromic acid in pyridine[26] and manganese dioxide[27] were likewise unsuccessful, indicating that the acid sensitivity of the diols was not alone responsible for the difficulties of oxidation. 11α-Hydroxy steroids are known to be resistant to oxidation and, in particular, 9α,11α-diols have been found to readily undergo oxidative cleavage and afford the desired 9,11-ketol in only low yield.[21] As in the case of the approach by saturation of the

(22) (a) L. F. Fieser and M. Fieser, ref. 8, p. 187; (b) R. P. Graber, C. S. Snoddy and N. L. Wendler, *Chem. and Ind.*, 57 (1956).

(23) O. Mancera, G. Rosenkranz and C. Djerassi, *J. Org. Chem.*, **16**, 192 (1951).

(24) F. Schenck, K. Buchholz and O. Wiese, *Ber.*, **69**, 2696 (1936).

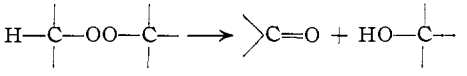
(25) O. Mancera, D. H. R. Barton, G. Rosenkranz and C. Djerassi, *J. Chem. Soc.*, 1021 (1952).

(26) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

(27) F. Sondheimer, C. Amendolla and G. Rosenkranz, *ibid.*, **75**, 5930 (1953).

nuclear bonds, the oxidative route to known 11-oxygenated products was perforce also abandoned.

11-Keto Cortisone Intermediates from Rearrangement of the Epidioxide.—Although steroidal epidioxides in which both ends of the transannular oxygen function are linked to tertiary carbon exhibit remarkable stability, secondary-tertiary and disecondary epoxides in the steroid[28,29] and non-steroid[30] series exhibit a marked tendency to undergo rearrangements, in most cases to ketonic products. An extreme case of this type of reactivity has recently been observed by Barton and Laws,[29] in the attempted photoöxidation of the non-cyclic steroidal 7,14-diene system, wherein the products isolated were chiefly 7- and 15-ketones presumably arising from rearrangement *in situ* of the initially formed unstable peroxide. The classic example involving a homocyclic steroid peroxide is that of 2,5-peroxido-3-cholestene, which may be prepared by conventional methods but undergoes facile rearrangement catalyzed by base or sunlight to several different ketonic products.[28] In a reinvestigation of the structural assignments[31] published almost simultaneously with our original communication,[32] all of the ketonic products derived from cholestene peroxide were shown to involve ketonization of the secondary carbon–oxygen bond in an intramolecular oxidation–reduction reaction, a type of reaction that has also been observed in the case of a non-cyclic secondary-tertiary dialkyl peroxide.[33]



The marked lability of the C-ring epidioxide II and its close structural resemblance to the 2,5-peroxido-3-cholestene of Bergmann, *et al.*, early suggested direct rearrangement as a possible alternative to the reduction–reoxidation sequence that had been considered previously for the conversion of II to the 11-keto intermediate XV. Initial studies involving treatment of the epidioxide with dilute aqueous-alcoholic potassium hydroxide did indeed result in the formation of ketonic products, as evidenced by the infrared absorption of the crude reaction mixture. However, the complexity of the base-catalyzed reaction was not investigated in detail at the time, since it was fortuitously discovered that rearrangement of III under heterogeneous conditions using slightly alkaline chromatographic alumina yielded (with unchanged starting material) an essentially homogeneous product, which proved to be the desired 14-hydroxy-11-ketone XV. Assignment of the 11-keto structure was based on the infrared and ultraviolet absorption λ_{max}^{ether} 308 mμ (log ϵ 3.84) indicative of a diunsaturated ketone, in conjunction with nonformation of ketone derivatives under the usual conditions. The free hydroxyl function of XV could not be acylated with acetic anhydride–pyridine but was readily dehydrated in excellent yield to a product which likewise failed to react with ketone reagents. The double maximum of the ultraviolet spectrum of the dehydration product strengthened the cross conjugated formulation[34] for XVI made on the basis of its mode of formation.

The presence of the 11-keto function in XV and XVI was unambiguously confirmed by hydrogenation experiments. Consistent with the assigned structure, catalytic hydrogenation of XV over palladium in *neutral* medium resulted in absorption of two moles of hydrogen to form the unsaturated ketol XVIII in excellent yield. As would be expected from the experiments with the 9,11-diols, further hydrogenation in *acid* medium resulted in loss of the 14-hydroxyl function with absorption of two additional equivalents of hydrogen. The physical constants of the desoxy ketone XIX isolated as major product after chromatography and crystallization were, however, not identical to those of 11-ketoergostanol acetate XX as prepared by unambiguous means from ergostanol-7,11-dione acetate.[14] However, it was found that catalytic hydrogenation of authentic 8,22-ergostadienol-11-one acetate[14] in acid solution (two equivalents of hydrogen) readily afforded a product identical to XIX. These results are only consistent with formulation of XIX as a stereoisomer of 11-ketoergostanol acetate involving unnatural nuclear configuration. Assuming the reduction to involve attack of hydrogen from the rear (as in the case of the 8-ene-7-ketone[14,35] followed by epimerization adjacent to the ketone, the 8α,9β-structure for XIX seemed most probable. This interpretation was supported by a subsequent preparation of XIX by chemical reduction of an 8-ene-11-ketone in strong basic medium. A similar derivation has since been offered in the analogous hydrogenation in the genin series.[36] A parallel catalytic hydrogenation of XVI over palladium in neutral medium resulted in absorption of three moles of hydrogen to form in excellent yield an unsaturated ketone which was in this case identical to authentic 8-ergosten-3β-ol-11-one acetate (XXI).[14] This result confirmed the interpretation of the experiments with the ketol (XV) and in addition provided the important information that catalytic reduction of the 14-double bond proceeded with generation of the correct stereochemistry at C-14.

Catalytic reduction of the 8-ene-11-ketone function to produce the undesired *cis* BC-ring fusion eliminated catalytic perhydrogenation as a practical route to nuclear saturated 11-ketosteroids from either XV or XVI. In addition to the stereochemical difficulties, none of the products of noble-metal hydrogenation derived from the foregoing structure studies were of synthetic interest because of the loss of the side chain unsaturation es-

(28) E. Skau and W. Bergmann, *J. Org. Chem.*, **3**, 166 (1938); W. Bergmann, F. Hirschmann and E. Skau, *ibid.*, **4**, 29 (1939).

(29) D. H. R. Barton and G. F. Laws, *J. Chem. Soc.*, 52 (1954).

(30) M. Matic and D. A. Sutton, *ibid.*, 349 (1953).

(31) R. J. Conca and W. Bergmann, *J. Org. Chem.*, **18**, 1104 (1953).

(32) G. D. Laubach, E. C. Schreiber, E. J. Agnello, E. N. Lightfoot and K. J. Brunings, THIS JOURNAL, **75**, 1514 (1953).

(33) N. Kornblum and H. E. DeLaMare, *ibid.*, **73**, 880 (1951).

(34) L. F. Fieser, K. Nakanishi and W. Huang, *ibid.*, **75**, 4719 (1953).

(35) C. Djerassi, E. Batres, M. Velasco and G. Rosenkranz, *ibid.*, **74**, 1712 (1952).

(36) F. Sondheimer, R. Yashin, G. Rosenkranz and C. Djerassi, *ibid.*, **74**, 2697 (1952).

sential for ultimate conversion to cortisone. The goal of further hydrogenation experiments was therefore the conversion of XVI to the 8,22-dienic ketone (XXII), of which the remaining nuclear double bond would require reduction by some non-catalytic procedure. Previous hydrogenation experience in the case of nuclear dienes[12] and the dienediols III and IV from ergosterol suggested a probable order of reactivity 6(7)-ene > 22(23)-ene to catalytic hydrogenation over W-2 Raney nickel catalyst. This relationship proved valid in both XV and XVI. The product of Raney nickel hydrogenation of XVI (one mole of hydrogen) was formulated as the 8,14,22-triene-11-ketone XXIII. The same tri-unsaturated ketone could be arrived at by an alternate route from XV that confirmed the assigned structure, *i.e.*, Raney nickel hydrogenation of XV resulted in absorption of one equivalent of hydrogen to yield an unsaturated ketol (shown by infrared and ultraviolet spectra to be the conjugated 8-ene-11-ketone XVII); subsequent acid-catalyzed dehydration of the 14-hydroxyl group afforded XXIII. Under mild conditions, including moderate pressure, the second of the three nuclear double bonds of XVI could not be saturated with W-2 Raney nickel.

Attempted further hydrogenation of the tri-unsaturated ketone XXIII with more active catalysts quickly demonstrated that the nuclear 14-double bond and the side chain 22-double bond did not differ greatly in susceptibility to catalytic hydrogenation. Most noble-metal catalysts promoted complete saturation of both double bonds without an observable change in rate at the mid-point. Strongly deactivated palladium and platinum catalysts (zinc and lead) in general resulted in no hydrogenation at all. Hydrogenation over a very active Raney nickel catalyst[37] (W-7) likewise resulted in saturation of both double bonds to form XXI. However, it was observed in this case that an observable change in rate occurred at the mid-point in the course of the absorption of two equivalents of hydrogen, and from the products of partial hydrogenation poor yields of a dienic ketone XXII[14] could be isolated. This slight but perceptible specificity was found to be greatly enhanced by the addition of base, and hydrogenation

(37) H. Adkins and H. R. Billica, THIS JOURNAL, **70**, 695 (1948).

of XXIII in aqueous alcoholic medium containing 5% of potassium hydroxide abruptly stopped after absorption of one mole of hydrogen. The product isolated in 50% yield after reacetylation was found identical to 8,22-ergostadiene-3β-ol-11-one acetate (XXII) prepared by the peracid–boron fluoride method[14,38] from ergosterol-D-acetate.[39]

Reduction of the remaining nuclear double bond of the 8-ene-11-ketone XXII, not reported in the initial communications of the Ciba group,[14] was required for completion of the synthesis of the known cortisone intermediate 22-ergostenol-11-one acetate (XXV). Preliminary experiments with weak chemical reducing agents such as zinc–acetic acid and sodium hydrosulfite demonstrated that the 8-ene-11-ketone system was not attacked under conditions adequate for reduction of the 8-ene-7,11-diketone or 8,9-oxido-7,11-diketone systems.[13,14,40] More potent reducing agents such as sodium–alcohol resulted in extensive reduction of the 11-carbonyl group, to yield complex mixtures from which (after palladium hydrogenation) 8(14)-ergostenol acetate was the only product identified. Sodium amalgam–acetic acid resulted in incomplete reduction, but sodium amalgam in refluxing ethanol afforded (after reacetylation) in 20% yield a saturated ketone XXVI (infrared maxima 5.79 and 5.90 μ) that was, however, not identical with 22-ergostenol-11-one acetate (XXV). Hydrogenation of XXVI over palladium–charcoal proceeded with absorption of one molar equivalent of hydrogen and formation of the same saturated keto acetate XIX previously prepared by catalytic perhydrogenation of the 8-ene-11-ketones XV and XXII. Sodium amalgam reduction, like catalytic hydrogenation, therefore, proceeded with the generation of unnatural stereochemistry at C-8 and C-9. The formation of XXVI in the strong basic medium of the sodium reduction, which would favor equilibration at 9, supported the 8α,9β-*trans*-structure previously assigned to XIX.

Sodium amalgam reductions were also carried out with the 8-unsaturated ketol XVII in the hope that the 14-hydroxyl might alter the steric course of the reduction. The crystalline product of the reduction in acetic acid was unchanged by attempted dehydration with strong acid and, in fact, proved on analysis to be a desoxy ketone XXVII, not however identical with either of the two 11-keto ergostenols XXII or XXVI previously encountered. The structure of XXVII was elucidated when it was discovered that treatment with either strong acid or strong base in methanol resulted in the formation of a product with the characteristic ultraviolet absorption λ_{max}^{ether} 244 mμ of the 8-ene-14-*epi*-11-ketone XXIV. The product XXVII was, therefore, the 8(14)-unsaturated ketone formed either by dehydration of an initially formed saturated ketone or by initial dehydration of XVII in the acidic medium followed by 1,4-reduction of the resulting 8,14-diene-11-ketone XXIII. Sodium amalgam reduction of XV in basic (alcohol) medium resulted in reduction of the unsaturated ketone system, as indicated by loss of ultraviolet absorption, but no crystalline product could be isolated from the reaction mixture.

Reduction of the unsaturated ketone XXII with sodium in liquid ammonia was also studied and, during the course of our work, simultaneous communications from the Merck[38] and Syntex[36] laboratories reported the successful application of the method to 8-ene-11-ketones using lithium as the preferred reducing agent. In our hands, without developmental studies, the ketone XXII was readily reduced by the lithium reagents to 11-keto ergostenol of correct stereochemistry in good yield. The Merck workers have reported the same transformation in excess of 85–90% yield.

The further conversion of the 11-keto ergostenol acetate to cortisone has been reported by other laboratories.[41,42] Completion of the preparation of XXV from the 6,8(14),9(11),22-tetraene (I), therefore, constitutes an independent route for the synthesis of cortisone from ergosterol.

Experimental[43]

6,8,22-Ergostatriene-3β-ol Acetate 11α,14α-Epidioxide (II).—A solution of 1.00 g. of 6,8(14),9(11),22-ergostatetraen-3β-ol acetate, $[\alpha]^{25}D$ −86° ($CHCl_3$), and 0.010 g. of eosin-Y sodium salt (National Aniline Co.) in 200 ml. of 1:1 benzene–ethanol was irradiated with a single photospot flood lamp under a fine stream of oxygen for 32 minutes in an open beaker. A bath temperature of 0–10° was maintained throughout. The reaction medium was concentrated *in vacuo* to a pink solid, λ_{max}^{ether} 250 mμ (log ε 3.66) and 275 mμ (log ε 3.53), which could be only partially crystallized by methanol trituration. The crude product (1.0 g.) was chromatographed by the method of fractional elution over 50 g. of Florisil in a 34 mm. column. In the 2:3 petroleum ether–benzene through benzene fractions was obtained 0.680 g. (64%) of crude peroxide II, λ_{max}^{ether} 273 mμ (log ε 3.58) (assay purity 90–95%). Recrystallization from methanol afforded 76% recovery, 0.519 g., m.p. 154.0–160.0°.

Recrystallization of a similar sample from methanol–chloroform for analysis resulted in constants m.p. 165.0–167.0°, $[\alpha]^{25}D$ −18.6° ($CHCl_3$), λ_{max}^{ether} 272 mμ (log ε 3.61).

Anal. Calcd. for $C_{30}H_{44}O_4$: C, 76.88; H, 9.45. Found: C, 77.03; H, 9.50.

6,8,22-Ergostatriene-3β,11α,14α-triol 3-Acetate (III). (a).—A solution of 0.472 g. of peroxide II, m.p. 156.1–157.6°, in 30 ml. of ethyl acetate was hydrogenated over 0.200 g. of 4% lead deactivated-5%-palladium on calcium carbonate catalyst.[11] After 2 hr., 102% of one mole of hydrogen had been absorbed and hydrogen uptake ceased. Concentration of the filtered reaction mixture *in vacuo* afforded 0.435 g. of

(38) E. Schoenewaldt, L. Turnbull, E. M. Chamberlin, D. Reinhold, A. E. Erickson, W. V. Ruyle, J. M. Chemerda and M. Tishler, THIS JOURNAL, **74**, 2696 (1952).

(39) The rather poor yield of isolated product from the Raney nickel hydrogenation did not seem consistent with the abrupt break in hydrogen uptake after absorption of one molar equivalent. The possibility that the unnatural 14-isomer was being formed in the presence of strong base suggested itself because of the expected greater stability of a CD-*cis*-hydrindanone system. From the natural 14α-ketone XXII on refluxing with alcoholic potassium hydroxide could be isolated after reacetylation an isomeric keto acetate XXIV for which the 14-*epi* structure seemed the only possibility. Although the ultraviolet spectrum of XXIV was identical to that of the 14α-epimer when measured in alcohol solution, a hypsochromic shift of 6 mμ was observed in ether solution. The position of the maximum could in fact be correlated roughly with the composition of mixtures of the isomers, and by use of this method it was readily demonstrated that the mother liquors of the hydrogenation did not contain appreciable quantities of the unnatural isomer. An exactly analogous epimerization has been demonstrated in the course of studies with 22-isoallospirost-8-ene-3β-ol-11-one, reference 36.

(40) L. F. Fieser, J. E. Herz and W. Huang, THIS JOURNAL, **73**, 2397 (1951).

(41) J. M. Chemerda, E. M. Chamberlin, E. H. Wilson and M. Tishler, *ibid.*, **73**, 4052 (1951).

(42) G. Rosenkranz, C. Djerassi, R. Yashin and J. Pataki, *Nature*, **168**, 28 (1950); G. Rosenkranz, J. Pataki and C. Djerassi, THIS JOURNAL, **73**, 4055 (1951).

(43) Melting points are uncorrected.

white solid product, m.p. 140.6–157.2°. Recrystallization from ether–petroleum ether yielded 0.200 g. (42.5%) of pure diol, m.p. 158.6–162.2°.

An analytical sample was obtained from methanol as colorless silky needles, m.p. 160.8–163.4°, $[\alpha]^{25}D$ −33.6° ($CHCl_3$).

Anal. Calcd. for $C_{30}H_{46}O_4$: C, 76.55; H, 9.86. Found: C, 76.61; H, 9.75.

(b) **Preparative Procedure.**—A solution of 4.0 g. of II in 50 ml. of dry, peroxide-free dioxane was catalytically hydrogenated using 2 g. of lead–palladium catalyst. During a period of 127 minutes the reaction mixture absorbed 208 ml. of hydrogen (theoretical uptake for one mole of hydrogen, 208 ml.) and stopped. Filtration and vacuum concentration to dryness afforded a white solid, which on trituration with 15 ml. of petroleum ether afforded 2.9 g. of semi-pure III, m.p. 146.8–149.0°. Recrystallization from ethyl acetate–petroleum ether afforded 2.6 g. of product, m.p. 160.0–165.0°, $[\alpha]^{25}D$ −27.8° ($CHCl_3$), yield 65%.

Hydrogenatione of 6,8,22-Ergostatriene-3β,11α,14α-triol 3-Acetate (III).—A solution of 0.944 g. (0.002 mole) of III in 35 ml. of dioxane was hydrogenated over 2 g. of Raney nickel catalyst[12] which had been previously saturated with hydrogen. After absorption of slightly more than 1 mole of hydrogen, the gas uptake stopped abruptly. The catalyst was removed by filtration on Filter-Cel, and the filtrate evaporated *in vacuo* to a crisp white solid, weight 0.885 g., m.p. 143.0–175.8°, $[\alpha]^{25}D$ +32.8° ($CHCl_3$). The crude mixture of isomeric monoenic glycols was twice recrystallized from ethyl acetate to afford a single isomer in 30% yield, m.p. 187.0–189.4°.

An analytical sample obtained from ethyl acetate–petroleum ether had a melting point 186.4–187.0°.

Anal. Calcd. for $C_{30}H_{48}O_4$: C, 76.23; H, 10.24. Found: C, 75.88; H, 10.44.

6,8(14),22-Ergostatriene-3β,9α,11α-triol 3-Acetate (IV).—To a solution of 0.20 g. of III in 20 ml. of acetone was added 7 ml. of 0.1 *N* hydrochloric acid. The resulting suspension was allowed to stand at room temperature for 4.25 hr., then diluted with 13 ml. of water, allowed to stand another 15 minutes and cooled in an ice-bath before filtration. The product (0.19 g.) (95% yield) was a faintly yellow powder, m.p. 198.0–203.0°, λ_{max}^{ether} 247.5 mμ (log ε 4.43). Recrystallization of the nearly pure product from methanol containing a trace of pyridine yielded 0.12 g. of small needles, m.p. 207.0–208.0°, $[\alpha]^{25}D$ −24.6° ($CHCl_3$).

An analytical sample obtained from a similar experiment had constants m.p. 203.0–206.0°, λ_{max}^{ether} 248 mμ (log ε 4.42). An active hydrogen analysis using lithium aluminum hydride indicated 1.87 moles of active hydrogen per mole.

Anal. Calcd. for $C_{30}H_{46}O_4$: C, 76.55; H, 9.86. Found: C, 76.68; H, 9.80.

The **11-acetate** was prepared in 63% yield by acetylation of IV in pyridine–acetic anhydride; m.p. 164.6–167.6°. An analytical sample, obtained from methanol, melted 169.2–170.6°, $[\alpha]^{25}D$ −47.4° ($CHCl_3$), λ_{max}^{ether} 248 mμ (log ε 4.43).

Anal. Calcd. for $C_{32}H_{48}O_5$: C, 74.96; H, 9.44. Found: C, 75.05; H, 9.60.

8(14),22-Ergostadiene-3β,9α,11α-triol 3-Acetate (VI).—The diol IV (1.785 g.) was stirred at room temperature and atmospheric pressure in 50 ml. of dioxane (redistilled over sodium) in the presence of **4** g. of Raney nickel catalyst which previously had been saturated with hydrogen. After 76 ml. of hydrogen (82% of one mole) had been absorbed, hydrogen uptake ceased. The filtered reaction mixture was concentrated under vacuum to a white solid, m.p. 190.0–200.0°, which was directly crystallized from methanol–ethyl acetate at 5° to yield 1.62 g. (91%) of VI as two crops of glistening needles, m.p. 195.4–201.8°, $[\alpha]^{25}D$ +6.9° ($CHCl_3$).

An analytical sample was prepared by several recrystallizations of similar material from methanol–ether and ethanol; m.p. 197.6–200.8°, $[\alpha]^{25}D$ +12.3° ($CHCl_3$).

Anal. Calcd. for $C_{30}H_{48}O_4$: C, 76.23; H, 10.24. Found: C, 76.16; H, 10.31.

The **11-acetate** was prepared by acetylation of 1.0 g. of VI in 20 ml. of pyridine and 40 ml. of acetic anhydride. The crude acetate, obtained by dilution with ice and ether extraction, melted at 135.0–136.2°. Recrystallization from methanol–water afforded 0.89 g. (82%), m.p. 146.4–147.8°, $[\alpha]^{25}D$ −11.9° ($CHCl_3$).

Anal. Calcd. for $C_{32}H_{50}O_5$: C, 74.66; H, 9.79. Found: C, 74.57; H, 10.03.

8(14)-Ergostene-3β,9α,11α-triol 3-Acetate (VII).—A solution of 0.118 g. (0.0025 mole) of IV in 12 ml. of ethyl acetate was hydrogenated at room temperature and atmospheric pressure over 0.5 g. of 5% Pd–C catalyst. Over a 10-minute period, 13.5 ml. of hydrogen (110% of 2 moles) was absorbed. The catalyst was removed by filtration and the filtrate concentrated to a mass of colorless needles, weight 0.115 g. (98%), m.p. 165.5–169.5°. An analytical sample was obtained by recrystallization from methanol with 65% recovery, m.p. 170.8–172.5°, $[\alpha]^{25}D$ +36.0 ($CHCl_3$).

Anal. Calcd. for $C_{30}H_{50}O_4$: C, 75.90; H, 10.62. Found: C, 75.71; H, 10.58.

The **11-acetate**, prepared using pyridine–acetic anhydride, was obtained in 95.6% yield, m.p. 121.2–124.8°. An analytical sample was obtained by two recrystallizations from methanol–water; m.p. 128.8–130.0°, $[\alpha]^{25}D$ +10.6° ($CHCl_3$).

Anal. Calcd. for $C_{32}H_{52}O_5$: C, 74.37; H, 10.14. Found: C, 74.26; H, 10.08.

3β,11α-Dihydroxy-9α-methoxyergosta-6,8(14),22-triene 3-Acetate (VIII).—To a stirred mixture of 5 g. of anhydrous sodium sulfate in 110 ml. of methanol (freshly distilled from magnesium methylate) there was added 1.1 g. of III and 0.1 g. of chloroacetic acid. Stirring was continued for 20 hr. while the mixture was protected from atmospheric moisture. Filtration and evaporation of the solvent *in vacuo* yielded a white solid which, after being washed several times with water and dried, weighed 1.11 g. and melted at 128–130°. After two recrystallizations from 90% methanol, 0.70 g. (62%) of the compound was obtained as clusters of flat white needles, m.p. 123.4–125.0°, $[\alpha]^{25}D$ −25.9° ($CHCl_3$). An analytical sample exhibited the following properties: m.p. 137.4–138.4°, $[\alpha]^{25}D$ −19.9° ($CHCl_3$), λ_{max}^{ether} 248 mμ (log ε 4.56).

Anal. Calcd. for $C_{31}H_{48}O_4$: C, 76.81; H, 9.98. Found: C, 76.91; H, 9.86.

This compound exhibited two melting points. Recrystallization of part of the analytical sample yielded material with identical rotation but m.p. 123.0–124.4°.

3β,11α-Dihydroxy-9-methoxyergost-8(14)-ene 3-Acetate.—A solution of 0.46 g. of VII in 25 ml. of sodium-distilled dioxane was stirred in the presence of prereduced platinum (from 0.165 g. of platinum oxide) in the presence of hydrogen at atmospheric pressure. After hydrogen uptake had ceased, the catalyst was removed by filtration, and the solvent was evaporated *in vacuo*. Chromatography of the oily crystalline solid yielded 0.30 g. (65%) of white solid, m.p. 92–95°. Recrystallization from methanol yielded clusters of short needles, m.p. 104.0–105.5°, $[\alpha]^{25}D$ +21.5° ($CHCl_3$).

Anal. Calcd. for $C_{31}H_{52}O_4$: C, 76.18; H, 10.72. Found: C, 75.99; H, 10.63. The infrared spectrum of the product showed a sharp hydroxyl band at 2.79 μ.

The **11-acetate** was prepared in the usual way with acetic anhydride and pyridine. The reaction product was a thick oil which failed to crystallize even when purified by chromatography. The infrared absorption spectrum no longer indicated the presence of a hydroxyl group.

Anal. Calcd. for $C_{33}H_{54}O_5$: C, 74.67; H, 10.25. Found: C, 73.44; H, 9.90.

8(14)-Ergostene-3β,11α-diol 3-Acetate (X). (a).—A solution of 0.118 g. (0.00025 mole) of VI, m.p. 203–206°, in 12 ml. of acetic acid was hydrogenated at room temperature and atmospheric pressure over a platinum catalyst prepared by a reduction of 0.200 g. of platinum oxide. In 2 hr., 18.7 ml. (101% of 3 moles) of hydrogen had been absorbed and hydrogen uptake ceased. The catalyst was removed by filtration and the combined filtrate and washings were concentrated *in vacuo* to a clear oil. Trituration with water followed by crystallization from 3 ml. of methanol afforded in one hour a crop of glistening platelets which were removed by filtration, yield 19.5 mg. (18%), m.p. 100.4–105.0°.

Anal. Calcd. for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found: C, 80.66; H, 11.11. This product did not depress the melting point of an authentic sample of 8(14)-ergostene-3β-ol acetate.[44]

(44) F. Reindel, E. Walter and E. Rauch, *Ann.*, **452**, 34 (1927).

A crop of colorless needles, crystallized from the mother liquors on standing, yield 63.0 mg. (55%), m.p. 122.4–125.2°. Recrystallization from a small volume of methanol afforded an analytical sample of X, m.p. 125.5–126.8°, $[\alpha]^{25}D$ −2.8 ($CHCl_3$).

Anal. Calcd. for $C_{30}H_{50}O_3$: C, 78.55; H, 10.99. Found: C, 78.80; H, 11.05.

(b).—To 0.250 g. of the diol VII, m.p. 161.6–166.8°, $[\alpha]^{25}D$ +31.8° ($CHCl_3$), and 0.100 g. of previously reduced platinum oxide catalyst in 15 ml. of ethanol stirred under hydrogen was added acetic acid (10 ml.) in small portions until hydrogen uptake commenced. After 17 hr., 120% of one molar equivalent of hydrogen had been absorbed.

The crude product, 0.210 g., m.p. 106.6–117.2°, was chromatographed on 0.8 g. of alumina. After elution of 0.024 g. of forerun with 1:4 benzene–petroleum ether, 0.177 mg. (84%) of X was obtained in the 1:9 through 1:1 benzene–ether eluates; m.p. 120.0–124.2°.

8(14)-Ergostene-3β,11α-diol Diacetate (XI).—A solution of 0.129 g. (0.00025 mole) of 8(14)-ergostene-3β,9α,11α-triol 3,11-diacetate in 10 ml. of redistilled acetic acid was hydrogenated at room temperature and atmospheric pressure over 0.200 g. of previously saturated platinum oxide catalyst. Hydrogen absorption equivalent to 105% of 1 mole of hydrogen was observed. Evaporation of the filtered reaction mixture under vacuum yielded a clear oil which spontaneously crystallized. Trituration with 6 ml. of 5:1 methanol–water and filtration afforded 0.115 g. (90%) of crude XI, m.p. 100.0–106.2°. Crystallization from methanol afforded 0.0925 g. (72%), m.p. 105.8–109.0°. The analytical sample obtained from methanol melted at 108.7–111.0°, $[\alpha]^{25}D$ −42.2° ($CHCl_3$).

Anal. Calcd. for $C_{32}H_{52}O_4$: C, 76.75; H, 10.47. Found: C, 77.03; H, 10.25.

8(14)-Ergostene-3β,9α,11α-triol 9,11-Sulfite 3-Acetate (IX).—To 0.300 g. of VII in 8 ml. of dry pyridine was added 0.6 ml. of thionyl chloride. After 45 ml. at 0°, the solution was allowed to warm to room temperature and was then poured into ice-water. Extraction with ether afforded after washing and evaporation to dryness 0.254 g. of crude, m.p. 110–116°. An analytical sample was obtained from ether–methanol; m.p. 133–136°.

Anal. Calcd. for $C_{30}H_{48}O_5S$: C, 69.19; H, 9.29. Found: C, 68.84; H, 9.55.

Dehydration of 9,11-Diols. (a).—8(14)-Ergostene-3β,9α,-11α-triol 3-acetate (VII) (1.0 g.) was heated under reflux for 30 minutes in a mixture of 15 ml. of acetic anhydride and 1 ml. of pyridine. The clear yellow solution was concentrated *in vacuo*, then triturated with methanol to yield 0.715 g. of light yellow crystals, m.p. 109–112°. Recrystallization from ether–methanol afforded an analytical sample of 7,9(11),14-ergostatrien-3β-ol acetate (XIIb), m.p. 115–117°, $[\alpha]^{25}D$ −73.8° ($CHCl_3$), λ_{max}^{EtOH} 227 mμ (log ε 4.04), 235 mμ (log ε 3.97), 268 mμ (log ε 3.96).

Anal. Calcd. for $C_{30}H_{46}O_2$: C, 82.14; H, 10.57. Found: C, 81.89; H, 10.51.

The **maleic anhydride adduct (XIVb)** was prepared from XIIb and an equal weight of maleic anhydride by heating under reflux for 3 hr. in toluene; m.p. 208–214°, λ_{max}^{EtOH} 274 mμ (log ε 3.59).

Anal. Calcd. for $C_{34}H_{50}O_5$: C, 75.80; H, 9.36. Found: C, 75.65; H, 8.90.

(b).—Acetic anhydride dehydration of 8(14),22-ergostadiene-3β,9α,11α-triol 3-acetate (VI) (1.0 g.) by an identical procedure yielded 0.222 g. of 7,9(11),14,22-ergostatetraen-3β-ol acetate (XIIa), m.p. 127–131°, λ_{max}^{EtOH} 227 mμ (log ε 3.96), 235 mμ (log ε 3.80), 268 mμ (log ε 4.00).

The **maleic anhydride adduct (XIVa)**, prepared as described for XIVb was obtained as short needles, m.p. 205–209°, $[\alpha]^{25}D$ −36.7° ($CHCl_3$), λ_{max}^{EtOH} 273 mμ (log ε 3.66).

Anal. Calcd. for $C_{34}H_{46}O_5$: C, 76.37; H, 8.67. Found: C, 76.70; H, 8.70.

Catalytic Hydrogenation of 7,9(11),14-Tetraen-3β-ol Acetate (XIIb).—To 0.100 g. of platinum oxide prereduced in 5 ml. of glacial acetic acid was added 0.185 g. of XIIb in 10 ml. of acetic acid. After 3 hr., 115% of two molar equivalents of hydrogen had been absorbed. Isolation of the product by evaporation of the filtered reaction mixture yielded crystalline 8(14)-ergosterol acetate, m.p. 109–110°, melting point undepressed on admixture with an authentic specimen.

6,8,22-Ergostatriene-3β,14α-diol-11-one 3-Acetate (XV).—The epidioxide II (15 g.), 80% pure by spectrophotometric assay, was adsorbed on 400 g. of alumina from one liter of 75% petroleum ether (30–60°)–25% benzene solution. The starting material was kept in contact with the alumina for 3.5 hr. Unrearranged peroxide was then eluted with 4 l. of benzene and XV was eluted with 3 l. of 50% benzene–50% ether. Evaporation of the benzene–ether eluates afforded 7.2 g. of crisp yellow solid, m.p. 170–177°, λ_{max}^{ether} 308 mμ (log ε 3.73) (assay purity 77%). The yield was 50 at 48% conversion. Several recrystallizations of a similar sample from methanol yielded analytically pure product, m.p. 188.8–192.4°, $[\alpha]^{25}D$ +34° ($CHCl_3$), λ_{max}^{ether} 308 mμ (log ε 3.84).

Anal. Calcd. for $C_{30}H_{44}O_4$: C, 76.88; H, 9.46. Found: C, 76.72; H, 9.65.

8,22-Ergostadiene-3β,14α-diol-11-one 3-Acetate (XVII).—A solution of 0.200 g. (0.000435 mole) of the alumina rearrangement product XV, m.p. 172–182°, in 15 ml. of dioxane, was hydrogenated over 0.6 g. of Raney nickel at room temperature and atmospheric pressure. Hydrogen uptake ceased after 9.0 ml. (slightly less than 1 mole) of hydrogen had been absorbed. From the filtered reaction mixture was isolated by concentration *in vacuo* a crisp white solid, 0.190 g., melting broadly at 160–180°. Recrystallization from methanol afforded 0.085 g. (42.5% yield) of dihydro product XVII, m.p. 169.0–171.5°. An analytical sample was obtained by twice recrystallizing from methanol; m.p. 172.0–175.0°, $[\alpha]^{26}D$ +112.9° ($CHCl_3$), λ_{max}^{ether} 244 mμ (log ε 3.94). The infrared showed strong acetate and conjugated ketone carbonyls.

Anal. Calcd. for $C_{30}H_{46}O_4$: C, 76.55; H, 9.86. Found: C, 76.51; H, 10.02.

8-Ergostene-3β,14α-diol-11-one 3-Acetate (XVIII).—Room temperature hydrogenation of 0.115 g. (0.00025 mole) of XV, m.p. 178–186°, in 10 ml. of ethanol over 0.2 g. of 5% Pd–C catalyst afforded, after filtration, evaporation and methanol trituration, 62.3 mg. of crude tetrahydro product, m.p. 139–160°. Recrystallization from methanol afforded an analytical sample (30 mg.) (yield 26%), m.p. 167.7–169.0°, $[\alpha]^{26}D$ +106.5° ($CHCl_3$), λ_{max}^{ether} 242 mμ (log ε 3.82). The ultraviolet spectrum is indicative of some 1,4-addition at the 6,9-position.

Anal. Calcd. for $C_{30}H_{48}O_4$: C, 76.23; H, 10.24. Found: C, 76.22; H, 10.00.

6,8,14,22-Ergostatetraen-3β-ol-11-one Acetate (XVI).—A solution of 1.0 g. of XV, m.p. 175.0–181.8°, in 230 ml. of methanol was treated with 14 ml. of concentrated hydrochloric acid. After heating at reflux for 10 minutes, the dark reaction mixture was cooled to ice temperature and then neutralized with 150 ml. of cold saturated sodium bicarbonate solution. A flocculent yellow precipitate separated during the dilution. The reaction mixture was cooled in ice for 1 hour, filtered, washed with water and dried *in vacuo*. Recrystallization of the crude product from ether–methanol afforded an analytical sample of 6,8,14,22-ergostatetraen-3β-ol-11-one, m.p. 142.0–145.6°, $[\alpha]^{25}D$ −68.7° ($CHCl_3$).

Anal. Calcd. for $C_{25}H_{40}O_2$: C, 82.30; H, 9.87. Found: C, 82.09; H, 10.01.

The crude product was best isolated as the acetate after treatment with 20 ml. of pyridine and 30 ml. of acetic anhydride for 16 hr. at 30°. Decomposition of excess anhydride with 50 ml. of ice, followed by ether extraction, afforded after washing, drying and evaporation, 0.837 g. (90.5%) of nearly pure XVI, m.p. 138.2–142.0°. Two recrystallizations from methanol for analysis yielded clusters of yellow needles, m.p. 145.0–146.8°, $[\alpha]^{26}D$ −82.2° ($CHCl_3$), λ_{max}^{ether} 233 mμ (log ε 4.19) and 326 mμ (log ε 3.95). The infrared spectrum showed carbonyl absorption at 5.76, 6.04 and 6.19 μ, indicative of acetate and unsaturated ketone functions.

Anal. Calcd. for $C_{30}H_{42}O_3$: C, 79.95; H, 9.40. Found: C, 79.72; H, 9.54.

8,14,22-Ergostatrien-3β-ol-11-one Acetate (XXIII).—A solution of 0.200 g. of the tetraene ketone XVI, m.p. 141.4–144.6°, in 15 ml. of dioxane was hydrogenated over 0.5 g. of previously saturated Raney nickel catalyst. On stirring overnight 17.7 ml. (81% of 2 moles) of hydrogen was absorbed. The reaction mixture was filtered and the filtrate concentrated to a mass of white prisms (0.203 g.), m.p.

120.0–121.8°. This product was recrystallized for analysis from methanol in 60% recovery, m.p. 140–141°, $[\alpha]^{25}D$ +1° ($CHCl_3$), λ_{max}^{ether} 290 mμ (log ε 4.14). The infrared spectrum showed, besides acetate absorption at 5.82 μ, an unusual triple carbonyl peak at 6.08, 6.21 and 6.41 μ.

Anal. Calcd. for $C_{30}H_{44}O_3$: C, 79.60; H, 9.80. Found: C, 79.51; H, 9.92.[45]

8,22-Ergostadien-3β-ol-11-one Acetate (XXII). (a) By Hydrogenation of XXIII over Raney Nickel Catalyst.—A solution of 0.200 g. of XXIII in 10 ml. of dioxane was hydrogenated at atmospheric pressure and room temperature over 0.5 g. of previously saturated Raney nickel catalyst.[37] After absorption of 14.1 ml. of hydrogen (127% of 1 mole), hydrogenation was interrupted and the partial hydrogenation product recovered by filtration and evaporation to dryness. The crude product (0.200 g.), m.p. 114.8–120.0°, showed apparent ultraviolet absorption indicative of 95% 8-ene-11-ketone function and 17% 8,14-diene-11-ketone function. Fractional recrystallization of the product from methanol afforded 0.095 g. of semi-pure XXII, m.p. 122–127°, and eventually 0.0277 g. (14% yield) of pure XXII, m.p. 131.4–131.8°, $[\alpha]^{25}D$ +110.1° ($CHCl_3$), λ_{max}^{ether} 248 mμ (log ε 3.95). The melting point was not depressed on admixture with an authentic sample, m.p. 135.4–136.2°, prepared by an independent method.[38]

(b) By Hydrogenation of XXIII over Raney Nickel in Basic Medium.—In an experiment similar to that of (a) using 0.508 g. of XXIII in which 0.245 g. of potassium hydroxide in 5 ml. of ethanol was substituted as the hydrogenation medium, hydrogen uptake abruptly stopped after absorption of exactly 1 mole. The filtered, acidified reaction mixture was evaporated to dryness and the product reacetylated with 5 ml. of pyridine and 10 ml. of acetic anhydride. Workup by the usual procedure afforded 0.429 g. of crude XXII, m.p. 110–122°, λ_{max}^{ether} 248 mμ (log ε 3.85), indicative of 78% 8-ene-11-ketone function. Recrystallization from methanol afforded 0.243 g. (49%) of pure XXII, m.p. 131.0–132.2°, $[\alpha]^{25}D$ +90.3° ($CHCl_3$), λ_{max}^{ether} 248 mμ (log ε 3.91). The melting point was not depressed on admixture with an authentic sample.

8-Ergostene-3β-ol-11-one Acetate (XXI). (a) By Hydrogenation of XXIII over Raney Nickel.—A solution of 0.400 g. of XXIII in 20 ml. of dry dioxane was hydrogenated over 0.2 g. of freshly prepared Raney nickel catalyst. Hydrogen absorption equivalent to 2 moles was observed and by concentration of the filtered reaction mixture was obtained 0.365 g. (91%) of nearly pure XXI, m.p. 133.4–137.0°, λ_{max}^{ether} 248 mμ (log ε 3.91). Recrystallization from methanol yielded long needles (0.271 g.), m.p. 137.0–139.6°, λ_{max}^{ether} 248 mμ (log ε 3.93). The melting point was not depressed on admixture with an authentic sample.

(b) By Hydrogenation of XXII over Pd–C.—A solution of 0.350 g. of XXII, m.p. 134–135°, $[\alpha]^{25}D$ +108.5° ($CHCl_3$), in 15 ml. of ethanol was hydrogenated at room temperature and atmospheric pressure over 0.200 g. of 5% Pd–C catalyst. Hydrogen uptake equivalent to exactly 1 mole of hydrogen was observed. Filtration, concentration and recrystallization from methanol afforded XXI as 0.260 g. (74.5% yield) of long sturdy needles, m.p. 137.6–138.4°, $[\alpha]^{25}D$ +123.9° ($CHCl_3$). An analytical sample obtained by recrystallization from methanol melted 137.8–138.6°, $[\alpha]^{25}D$ +125.0° ($CHCl_3$), λ_{max}^{ethar} 248 mμ (log ε 3.91), infrared $\lambda\lambda_{max}$ 5.82, 6.09 μ.

Anal. Calcd. for $C_{30}H_{46}O_3$: C, 78.90; H, 10.59. Found: C, 78.91; H, 10.74.

Perhydrogenation of 8-Ene-11-ketones. (a) Hydrogenation of 8,22-Ergostadien-3β-ol-11-one Acetate (XXII).—A solution of 0.226 g. (0.0005 mole) of XXII in 10 ml. of redistilled glacial acetic acid was hydrogenated by stirring over 0.200 g. of 5% Pd–C catalyst. Absorption of 25.8 ml. (105% of 2 moles) of hydrogen was observed. The filtered reaction mixture was concentrated to dryness to yield 0.223 g. of impure product, m.p. 121–150°.

This material, without further manipulation, was chromatographed on 8 g. of alumina. From the 1:4 benzene–petroleum ether through benzene eluates was recovered 128 mg. of crystalline solid, which, on recrystallization from methanol, afforded 100 mg. (44%) of XIX as tiny needles, m.p. 161.2–162.2°. An analytical sample was obtained from methanol, m.p. 162.3–163.6°, $[\alpha]^{25}D$ −4° ($CHCl_3$).

Anal. Calcd. for $C_{30}H_{50}O_3$: C, 78.55; H, 10.99. Found: C, 78.31; H, 10.89.

(b) Hydrogenation of 6,8,22-Ergostatriene-3β,14-diol-11-one 3-Acetate (XV).—A solution of 0.263 g. (0.0005 mole) of XV, m.p. 172–182°, in 10 ml. of acetic acid was hydrogenated over 0.2 g. of previously saturated 5% Pd–C catalyst at room temperature and atmospheric pressure. In 3 hr. between 3 and 4 moles of hydrogen was absorbed and hydrogen uptake ceased. The catalyst was removed by filtration and the filtrate concentrated to a fluid oil which crystallized on trituration with methanol. The melting point, after filtration, was 118–126°.

The total crude product was reconstituted and chromatographed over 7 g. of alumina. After removal of readily eluted fractions, 100.5 g. of crystalline solid was recovered from the 2:3 benzene–petroleum ether through benzene eluates. Recrystallization afforded 29.9 mg. of XIX, m.p. 148.5–151.2°. An analytical sample, obtained from methanol, melted 160.0–161.8°. The melting point was undepressed on admixture with the material obtained in experiment (a).

Anal. Calcd. for $C_{30}H_{50}O_3$: C, 78.55; H, 10.99. Found: C, 78.64; H, 10.97.

Reduction of 8,22-Ergostadien-3β-ol-11-one Acetate (XXII). (a) With Lithium–Ammonia.—In a three-neck flask equipped with stirrer, dropping funnel and gas outlet (protected from atmospheric moisture by drying tubes) 45 mg. of lithium ribbon was dissolved in 100 ml. of liquid ammonia. Dropwise addition of a solution of compound XXII over a period of about 15 minutes caused a decoloration of the blue lithium solution before completion of the addition. A further 20 mg. of lithium was required to produce a blue color which persisted. The stirring was continued for 40 minutes, after which 5 ml. of methanol was added to destroy the excess lithium. Stirring was continued until all the ammonia had evaporated. The residue was taken up in 200 ml. of ether and the ether solution was washed, dried and evaporated to dryness *in vacuo*. The white crystalline product (420 mg.) exhibited the following properties: m.p. 143–145°, $[\alpha]^{25}D$ +18.8° ($CHCl_3$), λ_{max}^{ether} 248 mμ (log ε 3.01), infrared $\lambda\lambda_{max}$ 5.9 and 2.78 μ. Chromatography of the crude 3-hydroxy compound yielded a total of 271 mg. (66% yield) of saturated 11-ketone with melting points ranging between 163 and 168°, and rotations between +23.1 and +33.3°. Schoenewaldt, *et al.*,[38] report m.p. 168.0–169.5°, $[\alpha]^{25}D$ +23° ($CHCl_3$). One of the fractions was recrystallized from acetone–water to give long hair-like needles, m.p. 168–170°, $[\alpha]^{25}D$ +27.5° ($CHCl_3$). The 3-acetate XXV, prepared from the product in another run in the usual way, had m.p. 125–126°, $[\alpha]^{25}D$ +16.7° ($CHCl_3$). Heusser, *et al.*,[14] reported m.p. 125–126°, $[\alpha]^{25}D$ +12.5° ($CHCl_3$).

Anal. Calcd. for $C_{30}H_{48}O_3$: C, 78.89; H, 10.59. Found: C, 78.64; H, 10.88.

(b) With Sodium Amalgam–Ethanol.—To a warm solution of 450 mg. of compound XXII in 50 ml. of ethanol there was added with stirring 18 g. of 2% sodium amalgam, prepared as described by Fieser,[46] in small portions over a period of 1 hr. The reaction mixture was heated under reflux for an additional 3.5 hr. The alcohol solution was decanted, concentrated to about 20 ml. and taken up in 150 ml. of ether. The ether solution was washed, dried (sodium sulfate) and evaporated to dryness *in vacuo*. The product (422 mg.) was a white solid, m.p. 146–150°, $[\alpha]^{25}D$ −1.2° ($CHCl_3$), which had no ultraviolet absorption, infrared $\lambda\lambda_{max}$ 5.9 and 2.73 μ. Acetylation of this product in the usual way yielded 425 mg. of crude 3-acetate, m.p. 110–117°, $[\alpha]^{25}D$ −12.2° ($CHCl_3$), infrared $\lambda\lambda_{max}$ 5.79 and 5.90 μ. (When a sample of the crude reduction product was oxidized with chromic acid, the product exhibited λ_{max}^{ether} 245 mμ (log ε 3.44).) Purification was accomplished by chromatography on 15 g. of alumina. From two petroleum ether–benzene fractions (4:1 and 2:1) there was obtained 208 mg. of white crystalline product which, upon recrystallization from methanol, yielded 100 mg. of pure XXVI. An

(45) The constants reported in our original communication, reference 32, were found in subsequent experimentation to have been incorrect. We are indebted to Prof. F. S. Spring (private communication) for pointing out this fact to us: J. Grigor, G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 1170 (1955).

(46) L. Fieser, "Experiments in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 419.

analytical sample exhibited m.p. 153–155°, $[\alpha]^{25}D$ −24.6° ($CHCl_3$).

Anal. Calcd. for $C_{30}H_{48}O_3$: C, 78.89; H, 10.59. Found: C, 78.73; H, 10.60.

The reduction product (100 mg.) was hydrogenated in 10 ml. of redistilled dioxane over prereduced Pd–C (5%) (theoretical uptake 5.4 ml., actual uptake 7.0 ml.). After filtration, the solution was concentrated to dryness *in vacuo* and crystallization occurred spontaneously. The thick colorless needles, XIX, were recrystallized for analysis from methanol–acetone–ether, m.p. 165–166°, $[\alpha]^{25}D$ −10.5° ($CHCl_3$).

Anal. Calcd. for $C_{30}H_{50}O_3$: C, 78.55; H, 10.99. Found: C, 78.42; H, 11.26. The melting point was not depressed when mixed with the product XIX of acidic Pd–C hydrogenation of XXII.

(c) **With Sodium–Amyl Alcohol.**—To a boiling solution of 200 mg. of compound XXII in 20 ml. of amyl alcohol, 1 g. of sodium was added in small pieces. After refluxing for an additional 0.5 hr. and cooling, 20 ml. of water was added, and the organic material was extracted with 100 ml. of ether. The ether solution was washed, dried (sodium sulfate) and concentrated to dryness *in vacuo*. The crude product was acetylated in the usual manner. The infrared spectrum of the resulting product exhibited a single very strong carbonyl maximum at 5.78 μ and no hydroxyl maximum. This product was combined with the product of a similar experiment. A total of 560 mg. was dissolved again in 40 ml. of ethanol and subjected to hydrogenation in the presence of 500 mg. of 5% Pd–C at atmospheric pressure. Chromatography of the hydrogenation product yielded about 10% of 8(14)-ergosten-3β-ol acetate, m.p. 103–107°.

Anal. Calcd. for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found: C, 81.62; H, 11.37. Mixture with an authentic sample did not depress the melting point. The remainder of the product, which was eluted after the above compound, could not be characterized.

Reduction of 8-Ergosten-3β-ol-11-one Acetate (XXI) with Lithium–Ammonia.—Reduction of 403 mg. of XXI in 20 ml. of dimethoxyethane was carried out using 130 mg. of lithium in 100 ml. of liquid ammonia. (An unusually large amount of lithium was required to give a permanent blue color.) The product, isolated as described for compound XXII, consisted of 362 mg. of ivory-colored crystalline solid, m.p. 148–150°, $[\alpha]^{25}D$ +16.5° ($CHCl_3$), no ultraviolet absorption, infrared $\lambda\lambda_{max}$ 2.78 and 2.90 μ (strong) and 5.90 μ (weak). Chromatography on alumina separated the product into two parts. (a) By benzene elution a white solid (98 mg., m.p. 157–159°) was obtained which, when acetylated, gave 108 mg. of crude acetate, m.p. 130–132°. An analytical sample, obtained by recrystallization from methanol–acetone, melted at 137–140°, infrared $\lambda\lambda_{max}$ 5.79 and 5.90 μ.

Anal. Calcd. for $C_{30}H_{50}O_3$: C, 78.55; H, 10.99. Found: C, 78.74; H, 11.27.

Another sample exhibited m.p. 138–139°, $[\alpha]^{25}D$ +33.5° ($CHCl_3$). The constants reported by Heusser, *et al.*,[14] were m.p. 134.5°, $[\alpha]^{25}D$ +32° ($CHCl_3$).

Anal. Found: C, 78.11; H, 10.86.

(b) Elution with 9:1 benzene–ether gave 141 mg. of white solid with melting points ranging from 154–159°. Acetylation gave 158 mg. of thick oil which was chromatographed on aluminae. Fractions eluted by 9:1 ether–benzene were combined (99 mg., m.p.'s 103 to 112°). Recrystallization from methanol–acetone gave thick flat prisms, m.p. 118–119°.

Anal. Calcd. for $C_{32}H_{54}O_4$: C, 75.86; H, 11.37. Found: C, 76.21; H, 10.89. Infrared $\lambda\lambda_{max}$ 5.79 and 8.0 μ and no other carbonyl band indicating that this was probably impure 3,11-diacetate of ergostane or of 8-ergostene.

Reduction of 8,22-Ergostadiene-3β,14α-diol-11-one Acetate (XVII) with Sodium Amalgam–Acetic Acid.—The reduction of 1 g. of compound XVII with sodium amalgam and acetic acid, as described for compound XXII, yielded a crude product which had practically no ultraviolet absorption. The infrared spectrum contained a strong doublet in the carbonyl region (5.79 and 5.84 μ). The product, purified by chromatography, was isolated in 67% yield, and a sample, recrystallized from methanol, exhibited m.p. 115.2–116.0°, $[\alpha]^{25}D$ +42.0° ($CHCl_3$).

Anal. Calcd. for $C_{30}H_{46}O_3$: C, 79.24; H, 10.20. Found: C, 79.04, 79.00; H, 10.17, 10.24.

After treatment with phosphorous oxychloride and pyridine under the usual dehydrating conditions, the product was recovered unchanged. When the above reduction product was treated with either methanolic hydrochloric acid or methanolic potassium hydroxide, the crude new product exhibited λ_{max}^{ether} 244 mμ (log ϵ 3.60–3.78), infrared λ_{max} 5.8 (broad) and 6.02 μ (moderately strong).

14-Epi-8,22-ergostadien-3β-ol-11-one Acetate (XXIV).—A solution of 0.300 g. of XXII, m.p. 131–132°, $[\alpha]^{25}D$ +105° ($CHCl_3$), in 50 ml. of 5% ethanolic potassium hydroxide solution was heated at reflux for 3 hr. under a nitrogen atmosphere. The reaction mixture was diluted with water and the ethanol partially removed by evaporation *in vacuo*. The organic product was extracted with ether, washed to neutrality, dried over sodium sulfate and concentrated *in vacuo* to a mass of colorless, glistening plates, weight 0.303 g., λ_{max}^{ether} 244 mμ (log ϵ 3.85). The crude product was directly acetylated in 8 ml. of pyridine and 12 ml. of acetic anhydride, from which was recovered by the usual procedure 0.267 g. of nearly pure 14-epi acetate, m.p. 108°, $[\alpha]^{25}D$ +131.7° ($CHCl_3$). An analytical sample was obtained by twice recrystallizing from methanol; m.p. 114.0–114.4°, $[\alpha]^{25}D$ +133.2° ($CHCl_3$), λ_{max}^{ether} 244 mμ (log ϵ 3.98).

Anal. Calcd. for $C_{30}H_{46}O_3$: C, 79.24; H, 10.20. Found: C, 79.21; H, 9.83.

Hydrogenation of the epi-ketone in ethanol over palladium catalyst resulted in absorption of 1 mole of hydrogen to afford a clear oil, λ_{max}^{ether} 243 mμ (log ϵ 3.99), which was not brought to crystallization.

BROOKLYN, N. Y.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF CHAS. PFIZER AND CO., INC.]

Corticosteroid Intermediates. V. Rearrangements of C-Ring Oxygenated Steroids[1]

BY E. J. AGNELLO, REX PINSON, JR., AND G. D. LAUBACH

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The rearrangement of 11α,14α-epidioxido-6,8,22-ergostatrien-3β-ol acetate to 8α(14α),9α(11α)-diepoxido-6,22-ergostadien-3β-ol acetate and the transformation of both of these compounds to 6,8(14),9(11),22-ergostatetraen-3β-ol-15-one acetate are described.

Previous communications[2,3] have described a number of transformations of 11α,14α-epidioxido-6,8,22-ergostatrien-3β-ol acetate (I). Among the reported reactions was the conversion of I to 6,8,22-ergostatrien-3β,14α-diol-11-one 3-acetate (II) by adsorption on basic alumina. The usefulness of II in the synthesis of corticosteroid intermediates,

(1) Presented before the Division of Organic Chemistry, 126th Meeting of the American Chemical Society, September, 1954.

(2) G. D. Laubach, E. C. Schreiber, E. J. Agnello, E. N. Lightfoot and K. J. Brunings, THIS JOURNAL, **75**, 1514 (1953).

(3) G. D. Laubach, E. C. Schreiber, E. J. Agnello and K. J. Brunings, *ibid.*, **78**, 4743 (1956).