953. *Studies in the Steroid Group. Part LVI.* Reduction of Dehydroergosterol Epidioxide.*

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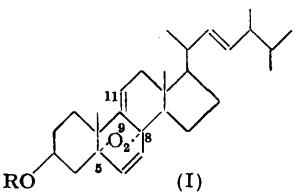
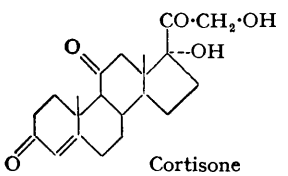
A study of the hydrogenation of dehydroergosterol epidioxide and its esters (I) in the presence of platinum catalysts has shown that the ethylenic bond in ring B is reduced first, this being followed by fission of the epidioxide bridge to yield 5 : 8-dihydroxy-$\Delta^{9(11)}$-steroids (*e.g.*, III); under carefully chosen conditions either of these stages of reduction can be achieved without hydrogenation of the side-chain double bond. Hydrogenation of (I) in the presence of Raney nickel (or palladium) leads to the formation of 5-hydroxy-$\Delta^{7:9(11)}$-steroids, the 22 : 23-bond being unaffected.

THIS paper is the first of a series describing work on the conversion of the comparatively readily available ergosterol into cortisone. During the past two years five schools have described important progress towards the same objective (Chamberlin, Ruyle, Erickson, Chemerda, Aliminosa, Erickson, Sita, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 2396; Fieser, Herz, and Huang, *ibid.*, p. 2397; Stork, Romo, Rosenkranz, and Djerassi, *ibid.*, p. 3546; Heusser, Eichenberger, Kurath, Dallenbach, and Jeger, *Helv. Chim. Acta*, 1951, **34**, 2106; and later papers from these four groups, and Anderson, Budziarek, Newbold, Stevenson, and Spring, *Chem. and Ind.*, 1951, **48**, 1035). All of these workers have, broadly speaking, been studying similar routes, which differ, however, in certain essential particulars from the major route investigated in these laboratories.

In cortisone, the steroid nucleus is modified by the presence of three important structural features, the unsaturated ketone system in ring A, the 11-keto-group in ring C, and the oxygenated side chain. It seemed possible that, starting from dehydroergosterol epidioxide † (I; R = H), procedures could be devised for introducing these features.



(I)



Cortisone

Thus, provided that the side-chain double bond could be retained until an appropriate stage, oxidative fission of this bond could open the way to the cortical side chain by use of known methods. The 9 : 11-ethylenic linkage, either alone or particularly in association with an oxygen atom at $C_{(8)}$, offered promise of a means of introducing the 11-oxygen atom. The 5 : 8-epidioxide system could also afford (by reduction) a 5-hydroxyl group which, after oxidation of the 3-hydroxyl group, should lead readily to the 3-keto-Δ^4-system. The latter possibility could be most advantageous since the introduction of the 3-keto-Δ^4-system, even in the A/B-*cis*-series has presented considerable difficulty (cf. Mattox and Kendall, *J. Biol. Chem.*, 1951, **188**, 287), and was practically impossible in the A/B-*trans*-series until Rosenkranz, Mancera, Gatica, and Djerassi (*J. Amer. Chem. Soc.*, 1950, **72**, 4077) described an elegant, although somewhat roundabout, method.

The starting material in the present work, dehydroergosterol epidioxide, was first prepared by Windaus and Linsert (*Annalen*, 1928, **465**, 148) by photo-activated addition of oxygen to 9(11)-dehydroergosterol. The structure of the epidioxide was then unknown, but, after the formula of ergosterol had been established, Müller (Z. *physiol. Chem.*, 1935,

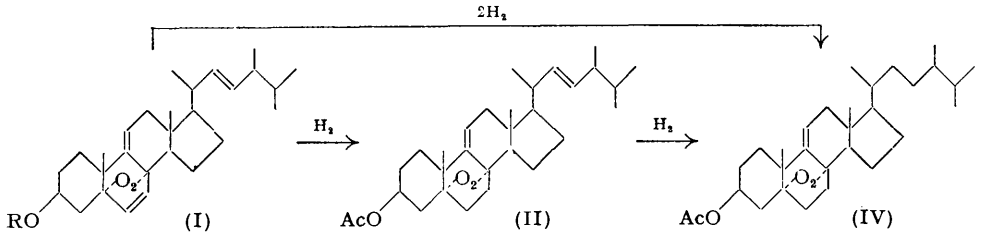
* Part LV, *J.*, 1952, 2737.

† In the steroid field, this group has usually been termed "peroxide"; the more systematic "epidioxide" will be used in this series of papers.

231, 75) suggested that the epidioxide has the (now accepted) structure (I; R = H). Because most reagents attack the centre of the steroid molecule from the rear, and from certain other evidence, Fieser (*Experientia*, 1950, **6**, 312) suggested that the oxygen bridge in ergosterol epidioxide is α-orientated. The closely related dehydroergosterol epidioxide would be expected to have the same configuration [indicated in (I)] as the ergosterol analogue, and this has been confirmed by the present experiments.

Windaus and Linsert's method for preparing the epidioxide from dehydroergosterol involved the passage of oxygen into an irradiated ethanolic solution (containing a little eosin) of the sterol at room temperature. Larger quantities can be more conveniently obtained if the reaction is carried out in boiling ethanol, the yield remaining the same (*ca.* 30%). As the epidioxide is unstable towards traces of acids, small amounts of alkali were added to the oxidation reaction mixture as a prophylactic measure—the effect being to raise the yield to about 80%; it was however also necessary to employ dry ethanol, the use of alkaline 95% ethanol giving yields of the order of 50%.

We investigated first the reduction of the unsaturated epidioxide system (with the possibility of keeping the side-chain double bond intact), and, secondly, the selective oxidation of the 22 : 23-bond in (I). The latter route did not seem very promising since Bergmann and Stevens (*J. Org. Chem.*, 1948, **13**, 10) reported that ozone attacks simultaneously the 6 : 7- and the 22 : 23-bonds in (I)—in contrast, it may be noted, to the ozonolysis of the maleic anhydride adduct of dehydroergosterol, which gives good yields of the side-chain aldehyde retaining the 6 : 7-double bond (cf. Levin, Spero, McIntosh, Wesner, Meinzer, Searcy, and Thompson, Amer. Chem. Soc. 120th Meeting, Abs., 1951, 6L). A preliminary examination showed that (I; R = Ac) and performic acid gave mixtures. However, a similar reaction with perbenzoic acid affords the (two) side-chain epoxides in small yields (personal communication from Dr. D. H. R. Barton and Mr. G. F. Laws—this reaction is described in the Experimental section of this paper).



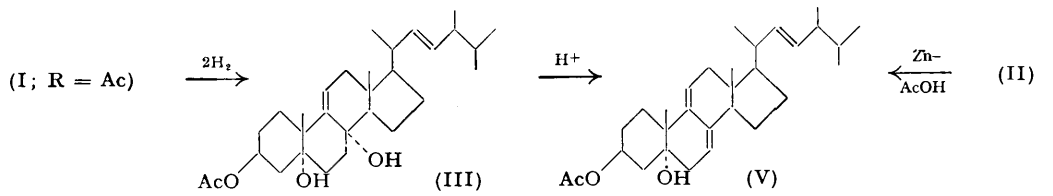
The only previous work on the reduction of dehydroergosterol epidioxide is that of Windaus, Auhagen, Bergmann, and Butte (*Annalen*, 1930, **477**, 268), who reported that zinc–alkali reduction of (I; R = H) gave the 5-hydroxy-7 : 9(11) : 22-triene (V)—evidence for the α-configuration of the 5-hydroxyl group is presented below. Hydrogenation of (I; R = Ac) was first studied in acetic acid solution (platinum catalyst), it being observed that two mols. of hydrogen were rapidly taken up, followed by two more slowly. By stopping the hydrogenation after the uptake of two mols., 3β-acetoxy-5α : 8α-epidioxy-ergost-9(11)-ene (" tetrahydro-acetate ") (IV) was isolated in over 50% yield. Ozonolysis experiments and infra-red absorption measurements with this compound demonstrated the absence of the 22 : 23-bond, and chromatographic behaviour (and also certain colour tests, see Experimental) indicated that the 6 : 7-bond had been reduced without affecting the epidioxide bridge.

Since it was hoped that the 6 : 7-bond might be reduced whilst the 22 : 23-bond (more reactive than the $\Delta^{9(11)}$-bond) remained unaffected and available for side-chain degradation (see following paper), (I; R = Ac) was hydrogenated under a variety of neutral and weakly acidic conditions with platinum catalysts, but in no case was there a definite break in the hydrogenation curve after absorption of 1 mol. Catalyst poisons such as quinoline or thiourea decreased the hydrogenation rate but did not improve the selectivity. From each of these experiments (stopping at one mol. uptake), a mixture of tetrahydro-acetate (IV), the required dihydro-acetate (II), and unchanged (I; R = Ac) was obtained, and on

a small scale this mixture could be separated by chromatography. Separation of the tetrahydro- from the dihydro-acetate was more easy than that of the latter from the starting material, probably because the rigidity of the side chain in (IV) is less than that of the (identical) unsaturated side chain in the other two compounds.

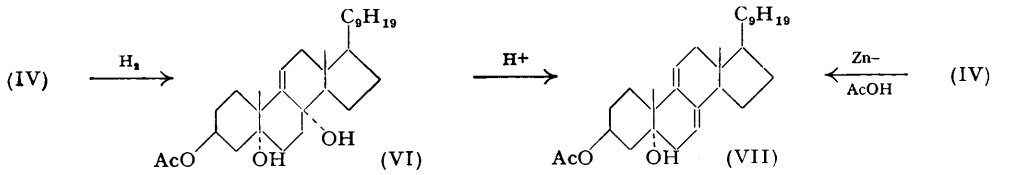
Selective hydrogenation of (I) was finally achieved by using platinum prepared from a variety of hydrated platinic oxide, the dihydro-acetate (II) being then obtained in yields of up to 60%. This is believed to be the first occasion on which hydrogenations have been performed by starting with hydrated platinic oxide of approximate composition, $PtO_2,3H_2O$. The time necessary for pre-reduction of this material (to yield a moderately finely divided form of platinum) is much greater than that required for Adams catalyst. Alternatively, with the steroid present, an " induction period " was observed, hydrogenation then proceeding rapidly until over one mol. had been absorbed. The structure of the dihydro-compound was confirmed by ozonolysis, its chromatographic behaviour, and its further reactions.

Hydrogenation of dehydroergosteryl acetate epidioxide in the presence of palladium and Raney nickel catalysts was also studied. In contrast to the experiments with platinum, the chief product isolated was the 5-hydroxy-7 : 9(11) : 22-triene (V) (80% yield with Raney nickel); this compound had been previously prepared by Windaus *et al.* (*loc. cit.*) by zinc–



alkali reduction of (I; R = H), followed by acetylation. Hydrogenation with palladium and Raney nickel catalysts probably proceeds by rupture of the epidioxide bridge followed by (or possibly simultaneously with) reduction of the 6 : 7-bond, thus affording a 5 : 8-diol of formula (III). We have shown (see below) that diols of this structure are readily dehydrated by acid to 5-hydroxy-7 : 9-dienes; in the present case, the hydrogen adsorbed on the catalyst surface is presumably sufficiently acidic to effect the dehydration.

On hydrogenation of the tetrahydro-acetate (IV) in the presence of Adams catalyst in concentrated *ethyl acetate* solution, uptake of one mol. of hydrogen was accompanied by precipitation of the 5 : 8-diol (VI) in about 80% yield, hydrogenation then virtually ceasing. Similar hydrogenation of the dihydro-acetate or the original epidioxy-acetate (I; R = Ac) led to the uptake of one and two mols. of hydrogen respectively with the simultaneous separation

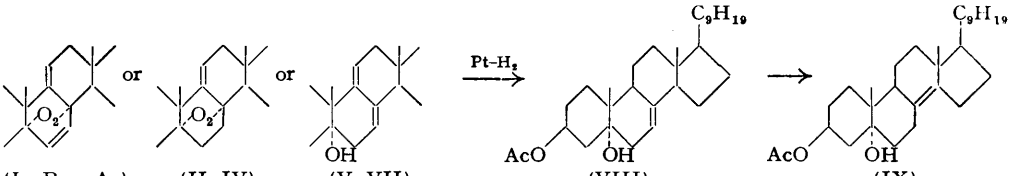


of the side-chain unsaturated 5 : 8-diol (III). These two diols, which showed no selective light absorption in the 2400 Å region, were very easily dehydrated by traces of mineral acids to the corresponding 5-hydroxy-7 : 9-dienes (V and VII). The 5-hydroxyl groups in (V) and VII) had the α-configuration because they could be acylated by the procedure of Plattner, Petrzilka, and Lang (*Helv. Chim. Acta*, 1944, **27**, 518) which, as shown by these authors, does not acetylate 5β-hydroxyl groups. It follows that the epidioxy-bridge in (I) is α-orientated, thus confirming Fieser's suggestion (*loc. cit.*); incidentally, ring B will be in the boat configuration. It has further been observed that 5α-hydroxyl groups may be readily acylated by means of diketen in chloroform solution, giving 5α-acetoacetates.

Another method, more direct and convenient, for converting the partially reduced epidioxides (II) and (IV) into the 5α-hydroxy-7 : 9-dienes (V) and (VII) was by reduction

with zinc dust in warm acetic acid (80% yields); the reaction undoubtedly proceeds *via* the corresponding 5 : 8-diols which are easily dehydrated under these conditions.

The tetrahydro-acetate (IV) also absorbed 1 mol. of hydrogen fairly rapidly in presence of Adams catalyst in *acetic acid* (but without precipitation); a second mol. was then absorbed more slowly, although there was no very well-defined break in the curve. The product after the uptake of two mols. consists mainly of the 5α-hydroxy-Δ^7-compound (VIII), the same product being obtained by hydrogenation of the 5-hydroxy-7 : 9-diene (VII); in this connection, we are much indebted to Drs. E. Mosettig and W. Nes (Washington) for informing us that platinum-catalysed hydrogenation of ergosterol-D in ethyl acetate solution gives ergost-7-enol (cf. also Barton and Cox, *J.*, 1949, 219, who



(I; R = Ac) (II, IV) (V, VII) (VIII) (IX)

describe the isolation of some α-dihydroergosterol from the hydrogenation of dehydroergosterol). Müller (*loc. cit.*) had already described the hydrogenation of the 5-hydroxy-7 : 9 : 22-triene (V) to yield a material (called ergostendiol II) with similar physical constants to our products above, for which the 5-hydroxy-$\Delta^{8(9)}$-structure was (erroneously) suggested. The 5-hydroxy-Δ^7-compound from these experiments proved difficult to purify, even by crystallization of the 3 : 5-diacetate. The structure was indicated by comparison with authentic specimens readily prepared in a pure form from ergosterol epidioxide—a detailed discussion of the reduction of this epidioxide leading to 5-hydroxy-Δ^7-steroids and other products will be presented later. If the reduction of the tetrahydro-acetate under these acidic conditions was stopped after the uptake of 1 mol., a mixture of starting material, 7 : 9-diene (VII), and 5-hydroxy-Δ^7-compound (VIII) was obtained. It is probable that the 5 : 8-diol (VI) is first formed, and that this is rapidly dehydrated under these conditions to the diene (VII), which is then rather more slowly hydrogenated to (VIII). The impure 5-hydroxy-Δ^7-compound was also produced by hydrogenation of the epidioxide (I; R = Ac) or dihydro-acetate (II) with Adams catalyst in acetic acid, four and three mols. of hydrogen being taken up respectively. The isolation of a Δ^7-compound from these platinum–acetic acid hydrogenation experiments indicates that the rate of isomerization to the $\Delta^{8(14)}$-structure normally observed under these conditions is retarded by replacement of 5α-hydrogen by 5α-hydroxyl—the larger group probably hinders the approach of the catalyst. However, longer reaction afforded the 5-hydroxy-$\Delta^{8(14)}$-compound (IX), recognized by its characteristic absorption in the 2050—2250-Å region (Bladon, Henbest, and Wood, *J.*, 1952, 2737).

The above hydrogenation experiments with dehydroergosterol epidioxide parallel to some extent the reduction of the simpler unsaturated epidioxide, ascaridole. Richter and Presting (*Ber.*, 1931, **64**, 878) have shown that hydrogenation of ascaridole in the presence of palladium yields (amongst other products) an unsaturated glycol (1 : 4-dihydroxy-*p*-menth-2-ene) by rupture of the epidioxide ring. On the other hand, Paget (*J.*, 1938, 829) has reported that similar hydrogenation with a platinum catalyst first affords the corresponding saturated epidioxide in good yield.

Experimental

In this and the following two papers m. p.s were determined on a Kofler block and are corrected. Optical rotations were determined in chloroform solutions in a 1-dm. semimicro-tube at room temperature (18—25°) unless stated otherwise. Analytical samples were dried *in vacuo* at 100° or at 20° below the m. p.

Peter Spence (Grade H) alumina was used for chromatography; " deactivated alumina "

signifies that it had been treated with dilute acetic acid as described by Farrar, Hamlet, Henbest, and Jones (*J.*, 1952, 2657).

In all three papers, compounds containing 9 : 11-ethylenic bonds are referred to in the Experimental Sections as Δ^9-compounds.

5α : 8α-*Epidioxy*-3β-*hydroxyergosta*-6 : 9 : 22-*triene* (I; R = H) *and its Esters*.—Dehydroergosterol (50 g.), dissolved in absolute ethanol (3200 c.c., dried by the diethyl phthalate method), containing sodium ethoxide (from 1 g. of sodium) and 10 c.c. of a 10% solution of eosin in ethanol, and contained in a 5-l. flask fitted with a reflux condenser and a sintered glass gas-bubbler, was illuminated from below by a 500-w tungsten lamp placed close to the flask. Oxygen (or dry carbon dioxide-free air) was passed through the irradiated solution, the heat from the lamp keeping the liquid at its b. p. When a sample showed only a downward sloping absorption curve from 3000 to 3400 Å (after about 45 hours), the solvent was removed under reduced pressure. The residual syrup, dissolved in methanol (400 c.c.), was kept overnight at 0°. The separated product was purified by extraction (Soxhlet) with methanol; crystallization then gave the epidioxide (34 g.), m. p. 158—162°, $[\alpha]_D$ +78°. Recrystallization from methanol gave a product of m. p. 161—164·5°, $[\alpha]_D$ +80° (*c*, 1·29). Windaus and Linsert (*loc. cit.*) give m. p. 158°. Acetylation with acetic anhydride and pyridine at 20° overnight gave 3β-*acetoxy*-5α : 8α-*epidioxyergosta*-6 : 9 : 22-*triene*, flat needles (from methanol), m. p. 173·5—175·5°, $[\alpha]_D$ +90° (*c*, 1·75) (Found : C, 77·0; H, 9·85. $C_{30}H_{44}O_4$ requires C, 76·85; H, 9·5%).

Benzoyl chloride in pyridine at 20° (1 hour) gave the 3β-*benzoate*. This separated from acetone–methanol (1 : 1) in a gelatinous form, which slowly crystallized as needles, m. p. 185—189°, $[\alpha]_D$ +87° (*c*, 1·21), when kept overnight in contact with the mother-liquor (Found : C, 79·0; H, 8·8. $C_{35}H_{46}O_4$ requires C, 79·2; H, 8·75%).

3β-*Acetoxy*-5α : 8α-*epidioxyergosta*-9 : 22-*diene* (*Dihydro-acetate*) (II).—A solution of the foregoing epidioxy-acetate (11·25 g.) in dioxan (150 c.c.) was shaken with hydrogen in the presence of yellow hydrated platinic dioxide (100 mg.) (Johnson, Matthey; containing *ca.* 65% of Pt). Uptake of hydrogen was slow at first, but after about 30—45 minutes (during which the catalyst became black) rapid absorption (1 l.) commenced, after which the rate decreased and the hydrogenation was stopped. After evaporation under reduced pressure, the residue was introduced in benzene (200 c.c.) on to a column of alumina (150 g.). Elution with benzene (1·3 l.) gave a product (5 g.), $[\alpha]_D$ −24°, which on recrystallization from methanol gave the *dihydro-acetate* as needles, m. p. 162—164°, $[\alpha]_D$ −28·5° (*c*, 1·14) (Found : C, 76·75; H, 10·15. $C_{30}H_{46}O_4$ requires C, 76·55; H, 9·85%). Further elution with benzene gave steroid (0·6 g.) with $[\alpha]_D$ +20°, and finally elution with ether–methanol (9 : 1) gave 3β-acetoxy-5α : 8α-dihydroxyergosta-9 : 22-diene (6·1 g.) (see below).

The above description is that of a typical experiment. The best yields of dihydro-acetate were obtained when the volume of hydrogen absorbed in the period of rapid uptake was nearest to 1 mol. Some evidence was obtained (see following Table) that better yields of dihydro-acetate were obtained at lower temperatures.

Epidioxide hydrogenated (g.)	Temp.	Hydrogen uptake (mols.)	Dihydro-acetate, yield (%)	Epidioxide hydrogenated (g.)	Temp.	Hydrogen uptake (mols.)	Dihydro-acetate, yield (%)
5·62	20°	1·33	57	25	23°	1·50	39
5·62	23	1·57	47	11·2	21	1·50	49
11·24	24	1·65	40	11·2	15	1·45	
11·08	16	1·50	57				

Alkaline hydrolysis of the dihydro-acetate gave 5α : 8α-*epidioxy*-3β-*hydroxyergosta*-9 : 22-*diene*, leaflets (from methanol), m. p. 162—164°, $[\alpha]_D$ −45° (*c*, 1·30) (Found : C, 78·25; H, 10·4. $C_{28}H_{44}O_3$ requires C, 78·45; H, 10·35%). Its 3β-*benzoate* formed needles (from ethyl methyl ketone–methanol), m. p. 184—189°, $[\alpha]_D$ −18° (*c*, 0·7) (Found : C, 78·8; H, 9·0. $C_{35}H_{48}O_4$ requires C, 78·9; H, 9·1%).

3β-*Acetoxy*-5α : 8α-*epidioxyergost*-9-*ene* (*Tetrahydro-acetate*) (IV).—A solution of 3β-acetoxy-5α : 8α-epidioxyergosta-6 : 9 : 22-triene (1·87 g.) in ethyl acetate–acetic acid (160 c.c.) (19 : 1) was shaken with hydrogen in the presence of Adams platinic oxide (0·18 g.) until 2 mols. of hydrogen had been taken up (35 minutes). Hydrogenation then became considerably slower. Filtration and evaporation of the filtrate to dryness under reduced pressure gave a solid that was introduced in benzene (20 c.c.) on to a column of alumina (180 g.). Elution with light petroleum–benzene (3 : 2) gave the *tetrahydro-acetate* (1·47 g.), which crystallized from ethyl acetate–methanol as needles (1·1 g.), m. p. 167—169° (change of form at 157°), $[\alpha]_D$ −8° (*c*, 1·90) (Found : C, 76·2; H, 10·3. $C_{30}H_{48}O_4$ requires C, 76·2; H, 10·25%). Further elution

with benzene gave 3β-acetoxy-5α-hydroxyergosta-7 : 9-diene (VII) (see later) (0·25 g.), which crystallized from ethyl acetate as plates, m. p. 200—204° (slight decomp.), $[\alpha]_D$ +65° (*c*, 0·96).

Alkaline hydrolysis of the tetrahydro-acetate gave 5α : 8α-*epidioxy*-3β-*hydroxyergost*-9-*ene*, needles (from methanol), m. p. 155·5—157°, $[\alpha]_D$ −28·5° (*c*, 0·79) (Found: C, 77·8; H, 10·7. $C_{28}H_{46}O_3$ requires C, 78·05; H, 10·75%). Benzoyl chloride in pyridine at 20° gave the 3β-*benzoate*, needles (from methanol–ethyl methyl ketone), m. p. 191—192°, $[\alpha]_D$ −9° (*c*, 1·40) (Found: C, 78·4; H, 9·4. $C_{35}H_{50}O_4$ requires C, 78·6; H, 9·45%).

Colour tests. Dehydroergosterol epidioxide and its esters gave an immediate red-brown colour with a solution of antimony trichloride in chloroform, but the dihydro- and the tetrahydro-compound gave no colour. The latter compounds did not react with 2 : 4-dinitrophenylhydrazine in methanol–sulphuric acid, whereas dehydroergosterol epidioxide slowly afforded a dark red precipitate.

3β-*Acetoxy*-5α : 8α-*dihydroxyergost*-9-*ene* (VI).—Hydrogenation of tetrahydro-acetate (20 g.) in ethyl acetate (130 c.c.) in the presence of Adams catalyst (0·5 g.) (uptake 950 c.c. at 18°/760 mm.; theor., 1010 c.c.) gave the diol (17·5 g.), needles, m. p. 174—184°, showing no selective absorption in the 2400 Å region. The diol could be separated from the catalyst by extraction with warm (40°) acetone, ethyl acetate, or dioxan; cooling to 0° afforded the compound as needles in each case. The m. p. of such material was invariably lower (160—170°) but the rotation, $[\alpha]$ +53° (*c*, 0·85), and the chemical properties of the material were unchanged; the proportion of 7 : 9-diene in such purified diol was always less than 2% (estimated spectroscopically). Correct analytical data could not be obtained with the compound; low carbon and high hydrogen values indicated that tenaciously held water was present.

3β-*Acetoxy*-5α : 8α-*dihydroxyergosta*-9 : 22-*diene* (III).—A solution of 3β-acetoxy-5α : 8α-epidioxyergosta-6 : 9 : 22-triene (10 g.) in ethyl acetate (130 c.c.) was shaken with hydrogen in the presence of pre-reduced Adams catalyst (0·5 g.). The product soon began to crystallize out, and after 2 mols. of hydrogen had been absorbed, the mixture was cooled to 6° and filtered. Evaporation under reduced pressure of a filtered chloroform solution of the product gave the *diol* (6·4 g.), m. p. 160—170°, $[\alpha]_D$ +38° (*c*, 1·85). The behaviour of this compound on crystallization and when analysed was similar to that of the 5 : 8-diol with the saturated side chain.

Hydrogenation of the Epidioxide Acetate (I; R = Ac) to 3β-*Acetoxy*-5α-*hydroxyergosta*-7 : 9 : 22-*triene* (V).—A solution of the epidioxide acetate (2·8 g.) in ethyl acetate (200 c.c.) was hydrogenated in the presence of Raney nickel (4 c.c. of thick sludge, prepared according to Pavlic and Adkins, *J. Amer. Chem. Soc.*, 1946, **68**, 1471). The uptake of hydrogen (355 c.c., 2·3 mols.) at 18°/746 mm. was rapid, the solution became warm and solid separated. The solution was diluted with chloroform and filtered, and the solvent removed under reduced pressure. Crystallization from acetone–chloroform gave the triene (2·64 g.), m. p. 203—210° (decomp.), and recrystallization from the same solvent gave plates, m. p. 211—215° (decomp.), $[\alpha]_D$ +47° (*c*, 1·10). Light absorption: Max., 2430 Å; ε = 15,600. Windaus, Auhagen, Bergmann, and Butte (*loc. cit.*) give m. p. 216°, $[\alpha]_D$ +48°.

3β : 5α-*Diacetoxyergosta*-7 : 9 : 22-*triene*.—3β-Acetoxy-5α-hydroxy-compound (200 mg.) was heated with dimethylaniline (1·6 g.), acetyl chloride (1·4 g.), and chloroform (40 c.c.) under reflux for 4½ hours. The cooled solution was washed with sodium carbonate solution, and evaporated. The gummy residue, in light petroleum–benzene, was introduced on to deactivated alumina (20 g.). Elution with light petroleum gave a gum; the *diacetate* was eluted with light petroleum–benzene (4 : 1). Recrystallization from methanol gave it as needles, m. p. 142—143°, $[\alpha]_D$ +92° (*c*, 0·9) (Found: C, 77·3; H, 10·0. $C_{32}H_{48}O_4$ requires C, 77·35; H, 9·7%). Light absorption: Max., 2450 Å; ε = 15,000.

5α-*Acetoacetoxy*-3β-*acetoxyergosta*-7 : 9 : 22-*triene*.—3-Acetoxy-5-hydroxy-steroid (3·2 g.), diketen (4 g.), chloroform (80 c.c.), and a few drops of triethylamine were heated under reflux for 45 minutes. The solution was evaporated under reduced pressure, the residue being dissolved in benzene and chromatographed on deactivated alumina (250 g.). Benzene eluted a product, which after crystallization from methanol afforded needles (2·45 g.), m. p. 127—133°. Recrystallization from methanol gave the 5α-*acetoacetate*, m. p. 134—137°, $[\alpha]_D$ +85° (*c*, 1·15) (Found: C, 75·5; H, 9·6. $C_{34}H_{50}O_5$ requires C, 75·8; H, 9·4%). Addition of neutral ferric chloride solution to a methanolic solution of the steroid gave a purple colour.

Partial hydrolysis of this acetate (2·3 g.) was effected by reflux with 5% potassium hydroxide in 95% ethanol (50 c.c.) for 25 minutes. Cooling and acidification gave a product, which after two recrystallizations from methanol gave the 5α-*acetoacetoxy*-steroid (1·7 g.) as needles, m. p. 125—127°, $[\alpha]_D$ +79° (*c*, 0·86) (Found: C, 76·9; H, 9·8. $C_{32}H_{48}O_4$ requires C, 77·35; H, 9·7%).

3β-*Acetoxy*-5α-*hydroxyergosta*-7 : 9-*diene* (VII) *from* (IV).—Zinc dust (20 g.) was added in small portions to a boiling solution of 3β-acetoxy-5α : 8α-epidioxyergost-9-ene (20 g.), in acetic acid (150 c.c.), the mixture being finally heated under reflux for 15 minutes. The hot solution was filtered, the residue being washed with chloroform. The steroid was isolated with chloroform, acetic acid being removed by washing with aqueous sodium hydrogen carbonate solution. Evaporation of the chloroform, followed by crystallization from acetone or ethyl acetate, gave the 5-*hydroxy-diene* (15 g.) as plates, m. p. 205—208° (slight decomp.), $[\alpha]_D$ +64° (*c*, 0·76) (Found : C, 79·0; H, 10·7. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%). Light absorption : Max., 2430 Å; ε = 15,700.

Similar reduction of the dihydro-acetate (II) afforded 3β-acetoxy-5α-hydroxyergosta-7 : 9 : 22-triene (V) in good yield.

3β : 5α-*Diacetoxyergosta*-7 : 9-*diene*.—The 3β-acetoxy-5α-hydroxy-steroid (5·5 g.), dimethylaniline (38·5 g.), acetyl chloride (38·5 g.), and chloroform (200 c.c.) were heated under reflux for 16 hours. The solution was cooled, diluted with chloroform, washed in turn with dilute acid and alkali, dried and evaporated. The product in light petroleum was chromatographed on deactivated alumina (250 g.). Elution with light petroleum–benzene (4 : 1) followed by crystallization from methanol afforded needles (4·15 g.), m. p. 95—102°, and further recrystallization gave the *diacetate-diene* (3·25 g.), m. p. 100—102°, $[\alpha]_D$ +127° (*c*, 0·8) (Found : C, 77·0; H, 10·1. $C_{32}H_{50}O_4$ requires C, 77·0; H, 10·15%).

Hydrolysis of the diacetate (2·35 g.) with 5% potassium hydroxide in 95% methanol (50 c.c.) for 30 minutes at 50° gave (after isolation with ether) 5α-*acetoxy*-3β-*hydroxyergosta*-7 : 9-*diene* (1·5 g.), needles (from ethyl acetate), m. p. 157—163°, $[\alpha]_D$ +122° (*c*, 0·6) (Found : C, 78·85; H, 10·7. $C_{20}H_{48}O_3$ requires C, 78·85; H, 10·6%).

5α-*Acetoacetoxy*-3β-*acetoxyergosta*-7 : 9-*diene*.—A solution of 3β-acetoxy-5α-hydroxyergosta-7 : 9-diene (2·5 g.) in chloroform (50 c.c.) containing diketen (4 g.) and triethylamine (0·1 c.c.) was heated under reflux for 45 minutes, the product then being isolated as described above for the corresponding Δ^{22}-compound. The 5α-*acetoacetate* crystallized from methanol as needles, m. p. 110—111°, $[\alpha]_D$ +103° (*c*, 0·95) (Found : C, 75·6; H, 9·85. $C_{34}H_{52}O_5$ requires C, 75·5; H, 9·7%).

Hydrogenation of 3β-*Acetoxy*-5α-*hydroxyergosta*-7 : 9-*diene* (VII) *to* 3β-*Acetoxy*-5α-*hydroxy-ergost*-7-*ene* (VIII).—A solution of the diene (0·73 g.) in ethyl acetate (50 c.c.) was fully hydrogenated in the presence of palladium–calcium carbonate (1 g.; 2% Pd). After filtration and removal of the solvent under reduced pressure the residue was twice crystallized from ethyl acetate, to give impure 3β-acetoxy-5α-hydroxyergost-7-ene (230 mg.) as plates, m. p. 215—226° (decomp.), $[\alpha]_D$ +21° (*c*, 1·01) (Found : C, 78·75; H, 10·8. Calc. for $C_{31}H_{51}O_3$: C, 78·55; H, 11·0%) (Müller, *loc. cit.*, records m. p. 196°, $[\alpha]_D$ +22° for this material—the pure acetate has m. p. 224—229°, $[\alpha]_D$ +20° (forthcoming publication).

Hydrolysis yielded the 3 : 5-diol (rectangular plates from ethyl acetate), m. p. 209—223° (decomp.), $[\alpha]_D$ +26·5° (*c*, 1·03) (Müller gives m. p. 219°, $[\alpha]_D$ +23·6°, for this compound called ergostendiol II; the pure compound has m. p. 232—240°, $[\alpha]_D$ +16°). Light absorption : ε_{2050} = 5300, ε_{2100} = 4600; ε_{2200} = 2300 [for ergost-7-enol, Bladon, Henbest, and Wood (*loc. cit.*) give ε_{2050} = 4900; ε_{2100} = 4700; ε_{2200} = 1800].

Acetylation of this material by acetyl chloride–dimethylaniline gave, after chromatographic purification and several crystallizations from methanol, the still somewhat impure 3 : 5-diacetate as needles, m. p. 129—134°, $[\alpha]_D$ +54°—the pure diacetate has m. p. 128—130°, $[\alpha]_D$ +65°. The infra-red spectra of the pure and the impure diacetate were practically identical, both showing peaks at 805, 830, and 847 cm.$^{-1}$ ($C_{(7)}$–H out-of-plane bending frequency region).

3β-*Acetoxy*-5α-*hydroxyergost*-8(14)-*ene* (IX).—Crude 3β-acetoxy-5α-hydroxyergost-7-ene (100 mg.) in acetic acid (10 c.c.) was shaken with hydrogen in the presence of Adams platinic oxide (20 mg.) for 6 hours. The steroid was isolated with ether; crystallization from methanol gave 3β-*acetoxy*-5α-*hydroxyergost*-8(14)-*ene* as rectangular needles, m. p. 161—164°, $[\alpha]_D$ −3·5° (*c*, 1·04) (Found : C, 78·7, H, 11·1. $C_{30}H_{50}O_3$ requires C, 78·5; H, 11·0%).

Alkaline hydrolysis gave the corresponding *diol*, plates (from ethyl acetate), m. p. 208—225° (decomp.), $[\alpha]_D$ +8° (*c*, 1·01) (Found : C, 80·5; H, 11·8. $C_{28}H_{48}O_2$ requires C, 80·7; H, 11·6%). Light absorption: ε_{2100} = 10,000; ε_{2150} = 8500; ε_{2200} = 5700; these values are in good agreement with those for 3β-hydroxyergost-8(14)-ene (Bladon, Henbest, and Wood, *loc. cit.*).

Acetylation of the monoacetate by acetyl chloride–dimethylaniline afforded 3β : 5α-*diacet-oxyergost*-8(14)-*ene*, which after purification by chromatography was crystallized from methanol, from which it separated as a gel that slowly changed into a granular solid, m. p. 99—106°, $[\alpha]_D$ +18° (*c*, 0·6) (Found : C, 76·8; H, 10·5. $C_{32}H_{52}O_4$ requires C, 76·75; H, 10·45%).

3β-*Acetoxy*-5α-*hydroxyergost*-7-*ene* (VIII) *from Dehydroergosteryl Acetate Epidioxide and Intermediate Compounds*.—The epidioxide (1 g.) in ethyl acetate (50 c.c.) containing 10% of acetic acid was hydrogenated in the presence of Adams catalyst (50 mg.). Absorption ceased when 4 mols. had been taken up, the product then being isolated with ether. A single crystallization gave crude 3β-acetoxy-5α-hydroxyergost-7-ene, m. p. 180—208°, $[\alpha]_D$ +27°, after one crystallization. Similar hydrogenation of 3β-acetoxy-5α : 8α-epidioxyergost-9 : 22-ene and 3β-acetoxy-5α : 8α-dihydroxyergost-9-ene resulted in the uptake of 2 and 1 mol. of hydrogen respectively, giving products with m. p. 179—198°, $[\alpha]_D$ +31°, and m. p. 178—197°, $[\alpha]_D$ +33° respectively.

Each of these three samples of crude 3β-acetoxy-5α-hydroxyergost-7-ene when shaken with hydrogen in acetic acid solution in the presence of Adams catalyst gave 3β-acetoxy-5α-hydroxyergost-8(14)-ene in good yield.

Reaction of 3β-*Acetoxy*-5α : 8α-*epidioxyergosta*-6 : 9 : 22-*triene with. Perbenzoic Acid* [Dr. D. H. R. Barton and Mr. G. F. Laws].—A solution of perbenzoic acid (1·5 equivs.) in chloroform (290 c.c.) was added to the epidioxide (20 g.) in chloroform (800 c.c.), both solutions being at 0°. After the mixture had been kept at 0° for 70 hours, the steroid was isolated with chloroform in the usual way. The product was chromatographed on alumina (400 g.; Savory and Moore): (i) elution with light petroleum–benzene (1 : 1) afforded 3β-*acetoxy*-5α : 8α-*epidioxy*-22ξ : 23ξ-*epoxyergosta*-6 : 9-*diene* (0·2 g.), wedges (from methanol), m. p. 164—167°, $[\alpha]_D$ +95° (*c*, 2·0) (Found: C, 73·6; H, 9·0. $C_{30}H_{44}O_5$ requires C, 74·35; H, 9·15%); (ii) elution with benzene gave the isomeric 22ξ : 23ξ-*epoxide* (0·6 g.), needles (from methanol), m. p. 204—205°, $[\alpha]_D$ +79° (*c*, 2·2) (Found: C, 74·4; H, 9·5%). The two oxides showed a m. p. depression on admixture. For proof of structure, both epoxides were reduced to 7 : 9-dienes (cf. Windaus and Linsert, *loc. cit.*): each epoxide (100 mg.) in propanol (10 c.c.) was heated under reflux with potassium hydroxide (0·9 g.) in propanol (15 c.c.) while zinc dust (2 g.) was added intermittently during 3 hours. The steroid was isolated with ether and reacetylated with acetic anhydride in pyridine at 20° overnight. Isolation with ether afforded the two (side chain) isomers of 3β-*acetoxy*-22ξ : 23ξ-*epoxy*-5α-*hydroxyergosta*-7 : 9-*diene*: (i) (from the epidioxide, m. p. 164—167°) crystallized from methanol as plates, m. p. 188—189°, $[\alpha]_D$ +52° (*c*, 2·1) (Found: C, 76·5; H, 9·8. $C_{30}H_{46}O_4$ requires C, 76·55; H, 9·85); light absorption, Max., 2430 Å; ε = 15,700; (ii) (from the epidioxide, m. p. 204—205°) crystallized from methanol as plates, m. p. 202—204°, $[\alpha]_D$ +56° (*c*, 2·0) (Found: C, 77·1; H, 9·9%); light absorption, Max., 2430 Å; ε = 13,500. No further crystalline material was obtained from the original chromatogram of the product from the perbenzoic acid reaction.

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