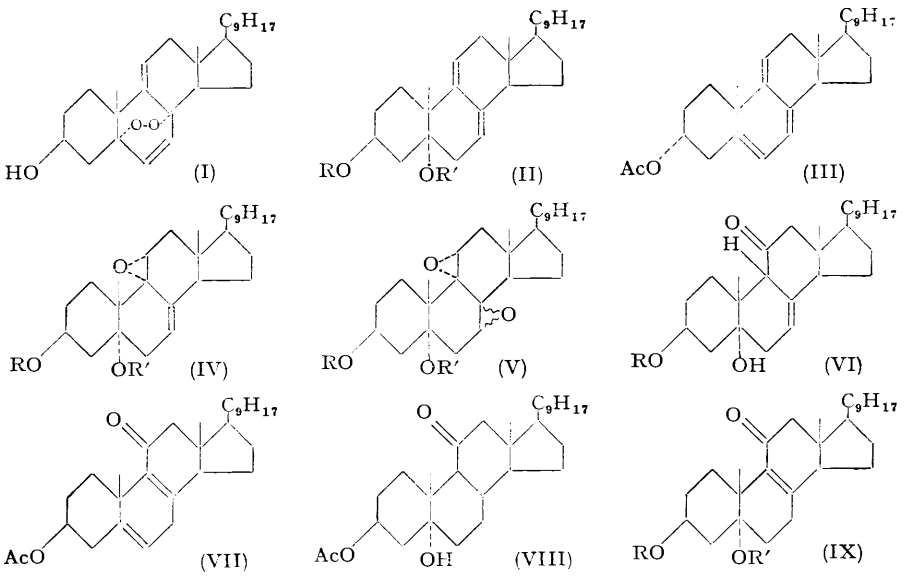
642. *Studies on the Epoxides of 5α-Hydroxy- and 5α-Acetoxy-$\Delta^{7:9}$-steroids.*

By D. C. Burke, J. H. Turnbull, and Walter Wilson.

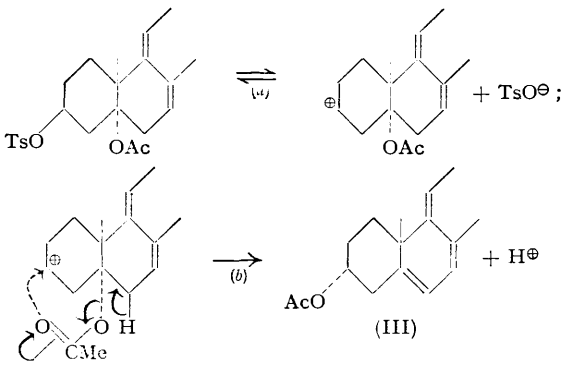
Ergosta-7 : 9 : 22-triene-3β : 5α-diol and its acetates have been converted into the 9α : 11α-monoepoxides. The α-configuration of the 5-hydroxyl group in this series is confirmed by the transformation of 5α-acetoxyergosta-7 : 9 : 22-trien-3β-yl toluene-*p*-sulphonate into *epi*dehydroergosteryl acetate. The mechanism of this reaction is discussed. Acid or alkali treatment of 3β-acetoxy-5-α-hydroxy-9β-ergosta-7 : 22-dien-11-one, obtained by boron trifluoride rearrangement of the 3-acetoxy-5-hydroxy-epoxide, gives a variety of products, including the $\Delta^{8(9)}$-ketone. Reduction of the latter with lithium in liquid ammonia yields 3β-acetoxy-5α-hydroxyergost-22-en-11-one, a valuable potential intermediate for cortisone synthesis. Mineral acid transforms the epoxides into $\Delta^{8(9)}$-7 : 11-diols, then into Δ^{9}-7-ketones. The latter subsequently isomerise to $\Delta^{8(9)}$-ketones, and the 5-substitutent, particularly an acetoxy-group, may be eliminated.

The conversion of ergosterol into cortisone, through dehydroergosterol 5 : 8-epidioxide (I), has been envisaged by E. R. H. Jones and his collaborators (*J.*, 1952, 4883, 4890, 4894; 1953, 2921), who have converted the 7 : 9 : 22-triene alcohol (II; R = R′ = H), obtained by reducing the epidioxide, into 11-keto-steroids by epoxidation reactions similar to those previously described by Swiss and American workers (for references, see Jones *et al.*, *loc. cit.*; Birch, *Ann. Reports*, 1951, **48**, 204). We also have studied the formation and reactions of epoxides of 5-hydroxy- and 5-acetoxy-7 : 9 : 22-trienes.



The 5-hydroxyl group in the triene (II; R = R′ = H) had been assigned the α-configuration, because it can be acetylated (although with difficulty) (Jones *et al.*, *J.*, 1952, 4883). This configuration has been confirmed by means of a reaction discovered by Plattner and Lang (*Helv. Chim. Acta*, 1944, **27**, 1872; Shoppee, *Ann. Reports*, 1946, **43**, 212) : the 5-acetoxytrienyl 3-toluene-*p*-sulphonate (II; R = *p*-C_6H_4·SO_2, R′ = Ac) when refluxed in pyridine afforded a 70% yield of 3α-acetoxyergosta-5 : 7 : 9 : 22-tetraene (*epi*dehydroergosteryl acetate) (III), recognised by the 5 : 7 : 9-triene absorption band at 325 mμ and by hydrolysis to the 3α-hydroxy-steroid which gave no precipitate with

digitonin (cf. *Chem. and Ind.*, 1953, 317). The rate of formation of (III) under different conditions was followed spectroscopically. The reaction proceeded readily in boiling pyridine, but was markedly inhibited by addition of toluene-*p*-sulphonic acid or sodium acetate. When allowance was made for the auto-inhibitory effect of toluene-*p*-sulphonic acid, first-order kinetics were observed. These observations indicate the mechanism illustrated; the rate-determining step is (*b*) and is relatively slow; added acetate ions could compete for the carbonium ions, and thereby inhibit reaction (*b*).



Monoepoxides were obtained in 40—90% yields from the trienediol (II; R = R′ = H) and its acetates with permonophthalic or perbenzoic acid in ether or benzene. Media containing chloroform were unsatisfactory, as strong acid impurities (cf. Kolthoff, Lee, and Mairs, *J. Polymer. Sci.*, 1947, **2**, 199) rearranged some of each epoxide into 7-ketones (see below). The trien-5-ol (II; R = Ac, R′ = H) and monoperphthalic acid in ether–chloroform gave a complex mixture from which two 7-ketones (XI*A*; R = Ac, R′ = H; and XII; R = Ac, R′ = H) were isolated. From a reaction in ether–benzene, the main product (60%) was the monoepoxide (IV; R = Ac, R′ = H); some diepoxide (3%) (V; R = Ac, R′ = H) and a second unconjugated 7-ketone (3%) (XI*B*; R = Ac, R′ = H) were also obtained. The reactions (discussed later) of the monoepoxides are similar to those of other Δ^7-9α : 11α-epoxides reported recently. The structural parallelism of these compounds is confirmed by the fairly uniform large decrease (Δ) in molecular rotation which occurs when a 7 : 9-diene is converted into the monoepoxide (see Table) (cf. Henner, Heusser, Anliker, Eichenberger, and Jeger, *Helv. Chim. Acta*, 1952, **35**, 936).

Molecular rotations.

	Steroid	9α : 11a-Epoxide	Δ
Ergosta-7 : 9 : 22-triene-3β : 5α-diol [1]	+198°	− 17°	−215°
3β-Acetoxyergosta-7 : 9 : 22-trien-5α-ol [1]	+218	+ 19	−200
5α-Acetoxyergosta-7 : 9 : 22-trien-3β-ol [1]	+395	+205	−190
5β : 5α-Diacetoxyergosta-7 : 9 : 22-triene [1]	+471	+256	−215
Ergosta-7 : 9 : 22-trien-3β-ol [2]	+ 83	−140	−223

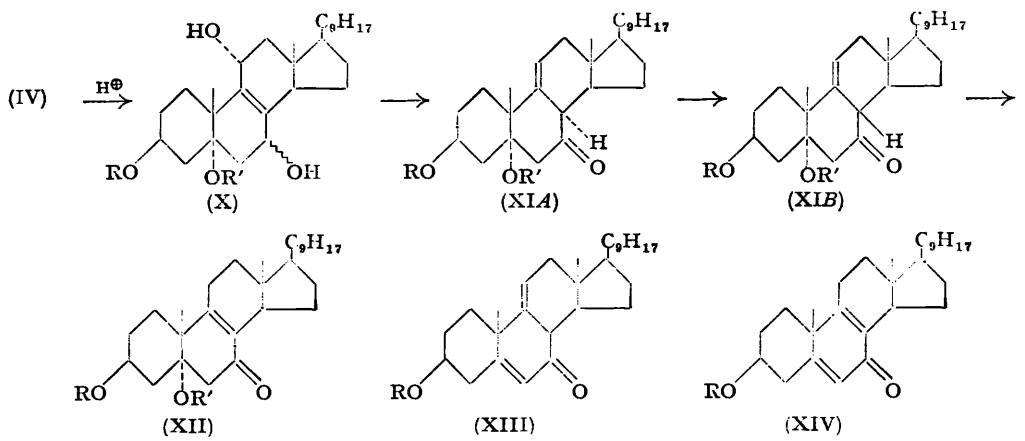
[1] Present work. [2] Schoenewaldt, Turnbull, Chamberlin, Reinhold, Erickson, Ruyle, Chemerda, and Tishler, *J. Amer. Chem. Soc.*, 1952, **74**, 2696.

The diepoxides isolated as by-products from some of these reactions are probably the 7 : 8-9α : 11α-compounds; the alternative keto-epoxide structure is excluded by the stability of the compounds to alkali, whilst the retention of the side-chain double bond is indicated by the nature of the absorption near to 200 mμ (cf. Bladon, Henbest, and Wood, *J.*, 1952, 2737).

Probably for steric reasons, the Δ^7-9 : 11-epoxide system is stable to alkali. In contrast, mineral acids very rapidly produce 7-ketones by allylic rearrangements, whilst boron trifluoride yields 11-ketones. Jones *et al.* (*J.*, 1953, 2921; also Heusler and Wettstein, *Helv. Chim. Acta*, 1953, **36**, 398) recently showed that 7 : 8-unsaturated 9β-11-ketones are the primary products in the latter reaction. 3β-Acetoxy-5α-hydroxy-9β-ergosta-7 : 22-dien-11-one (VI; R = Ac) was made by Jones's method; a substance

$C_{30}H_{44}O_3$, probably (VII), was separated in 14% yield from the crude product by chromatography. The stability of the 9β-ketone (VI; R = Ac) to alumina is noteworthy, as rapid conversion into the 9α-isomer occurs in the analogous 5-hydrogen series (Jones *et al.*, *J.*, 1953, 2921). The Manchester workers isomerised (VI; R = Ac) to the conjugated ketone (IX; R = Ac, R′ = H), using zinc and acetic acid. We have studied the use of mineral acids and alkalis as catalysts in this isomerisation; in addition to compounds (IX), several by-products were obtained, which are being examined further.

The difficult reduction of the ditertiary double bond in Δ⁸⁽⁹⁾11-ketones has been accomplished by use of lithium in liquid ammonia (Schoenewaldt *et al.*, *loc. cit.*; Sondheimer, Yashin, Mancera, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1952, **74**, 2696; Heusler, Heusser, and Anliker, *Helv. Chim. Acta*, 1953, **36**, 652); the products have the normal (8β : 9α-)configuration. Reduction of the ketone (IX; R = Ac, R′ = H) with this reagent gave 3β-acetoxy-5α-hydroxyergost-22-en-11-one (VIII), which is a valuable intermediate for cortisone synthesis.



The conversion of Δ⁷-9 : 11-epoxides into 7-ketones by mineral acids has recently become well known (cf., *e.g.*, Heusser, Eichenberger, Kurath, Dallenbach, and Jeger, *Helv. Chim. Acta*, 1951, **34**, 2106; Chamberlin, Ruyle, Erickson, Chemerda, Aliminosa, Sita, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 2396; Schoenewaldt *et al.*, *loc. cit.*; Budziarek, Newbold, Stevenson, and Spring, *J.*, 1952, 2892). The products obtained in the present experiments are probably formed in the sequence (IV) ⟶ (X) ⟶ (XI*A*) ⟶ (XI*B*) ⟶ (XII). These reactions appear to be slower in the 5α-acetoxy- than in the 5α-hydroxy-series (cf. Jones *et al.*, *J.*, 1953, 2921). In the present experiments, further products [(XIII) and (XIV)] were formed by elimination of the 5-hydroxy- or 5-acetoxy-group. Under acid conditions, the 5-acetoxyl was eliminated much more readily than the 5-hydroxyl group; elimination of both groups occurred rapidly with alkalis. The Δ⁸⁽⁹⁾-7 : 11-diols isolated in these experiments were recognised mainly by their active hydrogen content and by the absence of the absorption bands of conjugated systems. By analogy with similar compounds already described, they have been designated 7ξ : 11α-diols.

The products from experiments already mentioned include two unconjugated 7-ketones, which are probably the $C_{(8)}$-epimers (XI*A*) and (XI*B*); in the ergosterol D series, it appears that the monoepoxide can rearrange similarly to either of the $C_{(8)}$-epimeric 7-ketones (Budziarek, Stevenson, and Spring, *J.*, 1952, 4874). It is believed that the more lævorotatory isomers have the 8β(normal)-configuration (see also Budziarek and Spring, *J.*, 1953, 956). A pair of isomers in a related series described by Djerassi, Mancera, Stork, and Rosenkranz (*J. Amer. Chem. Soc.*, 1951, **73**, 4496) differ by 270° in molecular rotation, and may also be $C_{(8)}$-epimers. The structures (XI*A*) and (XI*B*), which have a 9 : 11-double bond, are consistent with the nature of the absorption near 200 mμ (Bladon, Henbest, and Wood, *loc. cit.*).

Compounds (XII) and (XIII) were characterised by the absorption bands of the αβ-unsaturated ketone systems. Alkali converted both compounds into (XIV), whose structure follows from these two modes of formation and from light-absorption data.

Experimental

Optical rotations were determined on 0·5—2% solutions in chloroform at 15—25°. Infra-red absorptions were measured for 5% solutions in chloroform with a sodium chloride prism and a Grubb–Parsons single-beam spectrophotometer. Ultra-violet absorption measurements were made with a Unicam SP. 500 instrument, "P.I. rectified spirit" being the solvent, and concentrations 1—3 × 10^{-4} mole/l. Hopkin and Williams's alumina was used for chromatographic separations; unless stated otherwise, the alumina was deactivated, by treatment with acetic acid as described by Farrar, Hamlet, Henbest, and Jones (*J.*, 1952, 2657). Light petroleum of b. p. 60—80° was used throughout. Specimens for analysis were dried at 70—80°/0·005 mm. for 12 hr. Chromatograms were eluted with solvents in the conventional order.

Ergosteryl "α"-Acetate.—This was prepared by the published procedure, and had m. p. 132—136°, $[\alpha]_D$ −87° (Heilbron and Sexton, *J.*, 1929, 921, give m. p. 132—133°). Repeated crystallisation from benzene–methanol gave ergosteryl acetate, m. p. 170—172°, $[\alpha]_D$ −86°. The "α"-acetate with digitonin solution gave ergosterol digitonide (40%). The supposed "α"-acetate is therefore a mixture or loose molecular compound of ergosterol and ergosteryl acetate.

Ergosta-7 : 9 : 22-triene-3β : 5α-diol (II; R = R′ = H).—In the preparation of the 3-monoacetate (m. p. 217—218°, $[\alpha]_D$ +50°, $\lambda_{max.}$ 243 mμ, ε 15,800) from ergosterol by the method of Jones *et al.* reproducible yields (75—80%) were obtained at the hydrogenation stage only when fresh ethyl acetate and fresh Raney nickel were employed. The diol (80%; m. p. 215—217°, $[\alpha]_D$ +44°) was prepared by alkaline hydrolysis of the acetate, or (42%) by Windaus, Bergmann, and Butte's method (*Annalen*, 1930, **477**, 268), and was converted by acetic anhydride–pyridine at 20° into the 3-acetate. Benzoyl chloride–pyridine at 20° gave the *3-benzoate*, m. p. 212—213°, $[\alpha]_D$ +47° (Found: C, 81·0; H, 8·9. $C_{35}H_{48}O_3$ requires C, 81·4; H, 9·4%). The 3-acetate (9·55 g.), diethylaniline (22 c.c.), and acetyl chloride (5 c.c.) in chloroform (5 c.c.) were refluxed for 4 hr., and yielded the 3 : 5-diacetate (90%), m. p. 139—140° (from methanol), $[\alpha]_D$ +95°, $\lambda_{max.}$ 242 mμ (ε 15,200), which was similarly obtained (80%) from the 3 : 5-diol [Jones *et al.*, give m. p. 142—143°, $[\alpha]_D$ +92°, $\lambda_{max.}$ 245 mμ (ε 15,000), for the diacetate]. The 3 : 5-diacetate (572 mg.), aqueous 1·2N-potassium hydroxide (5 c.c.) and methanol (75 c.c.) were refluxed for 90 min. Crystallisation from methanol afforded *5α-acetoxyergosta-7 : 9 : 22-trien-3β-ol* (90%) as needles, m. p. 162—163°, $[\alpha]_D$ +87°, $\lambda_{max.}$ 243 mμ (ε 15,100) (Found: C, 79·1; H, 10·4. $C_{30}H_{46}O_3$ requires C, 79·3; H, 10·1%). This contained one active hydrogen atom (Zerewitinoff) and formed a digitonide. Acetic anhydride–pyridine gave the 3 : 5-diacetate; prolonged hydrolysis of the latter gave the 3 : 5-diol (62%).

5α-Acetoxyergosta-7 : 9 : 22-trien-3β-yl Toluene-p-sulphonate (II; R = *p*-C_6H_4·SO_2, R′ = Ac).—The above 5α-acetoxy-sterol (593 mg.) (rigorously dried), pyridine (25 c.c.), and toluene-*p*-sulphonyl chloride (1075 mg.) were left for 16 hr. in the dark. Dioxan (5 c.c.), acetone (20 c.c.), and a little water were added; after 16 hr. at −5°, crystals of the *5α-acetate 3β-toluene-p-sulphonate* (72%), m. p. 130°, $[\alpha]_D$ +77°, $\lambda_{max.}$ 224 (ε 15,900), 242 (ε 14,200), and 325 mμ (ε 140) (Found: C, 73·1; H, 8·9. $C_{37}H_{52}O_5S$ requires C, 73·2; H, 8·6%), were obtained. The ester was somewhat unstable.

3α-Acetoxyergosta-5 : 7 : 9 : 22-tetraene (epi*Dehydroergosteryl Acetate*) (III).—The toluene-*p*-sulphonate (483 mg.) and pyridine (25 c.c.) were refluxed for 24 hr., the solution was poured into dilute hydrochloric acid, and the steroids were isolated with ether and dissolved in light petroleum–benzene (1 : 1) (40 c.c.). Chromatography on alumina (50 g., 2 × 20 cm.) and elution with light petroleum–benzene (4 : 1) gave *3α-acetoxyergosta-5 : 7 : 9 : 22-tetraene* (68%), needles (from methanol), m. p. 137—138°, $[\alpha]_D$ +200°, $\lambda_{max.}$ 324 mμ (ε 11,600) (Found: C, 82·4; H, 10·3. $C_{30}H_{44}O_2$ requires C, 82·6; H, 10·1%). The acetate (96 mg.), methanol (30 c.c.), and aqueous 10% potassium hydroxide (2 c.c.) when refluxed for 40 min. gave the *3α-hydroxy*-compound (epi*dehydroergosterol*), which from methanol formed needles, m. p. 144—145°, $[\alpha]_D$ +194°, $\lambda_{max.}$ 325 mμ (ε 11,600) (Found: C, 83·7; H, 10·8. $C_{28}H_{42}O,0{\cdot}5CH_3$·OH requires C, 83·4; H, 10·7%). The solvate contained 1·3 active hydrogen atoms (calc., 1·5), and gave no precipitate with digitonin in 95% ethanol. Lithium aluminium hydride tended to reduce the 5 : 6-double bond, and was unsuitable for conversion of the acetate into the sterol. The m. p. of the sterol was depressed considerably on admixture with its acetate or with dehydroergosterol.

Rate of Formation of 3α-Acetoxyergosta-5 : 7 : 9 : 22-tetraene.—In these experiments, no attempt was made to isolate products. At suitable intervals, small aliquots of the reaction media were withdrawn and the 5 : 7 : 9-triene absorption band at 325 mμ measured.

(a) *In ethanol.* The above toluene-*p*-sulphonate (23·4 mg.) and ethanol (25 c.c.) were refluxed :

Time (hr.)	0	0·25	0·5	1	1·5	3·5
ε at 242 mμ	14,000	12,400	12,000	11,800	11,700	9,600
ε at 325 mμ	140	150	190	220	260	730

No reaction was observed in a similar experiment in which 10% aqueous potassium hydroxide (5 c.c.) was added.

(b) *In pyridine at* 25°. The sterol (10 mg.) was dissolved in pyridine (50 c.c.) kept at 25° :

Time (days)	0	1	3	14
ε at 325 mμ	120	180	300	550

(c) *In pyridine at* 115°. The steroid (36·2 mg.) was dissolved in pyridine (25 c.c.) and refluxed :

Time (hr.) ...	0	0·5	1	2	3	4	5	6	7	8	24	30	48
ε at 325 mμ	200	1700	1930	2470	3050	3660	4180	4780	5470	6100	9000	9400	10,900

These results fit the following modified first-order kinetic equation $kt/a = \log_e [a/(a - x)] - x/a$ (where k is a constant, a is the initial concentration of steroid toluenesulphonate, and x is the concentration of triene after t min.).

(d) *In pyridine at* 115°, *with added toluene*-p-*sulphonic acid.* The steroid (23·1 mg.), anhydrous toluene-*p*-sulphonic acid (21·5 mg.), and pyridine (25 c.c.) were refluxed :

Time (hr.)	1	2	3	4	6	8	24	29	48	55	72
ε at 325 mμ ...	805	1200	1560	2040	2930	3820	5750	5980	6800	6900	7600

(e) *In pyridine at* 115°, *with added sodium acetate.* The steroid (17·7 mg.), powdered fused sodium acetate (68·3 mg.), and pyridine (25 c.c.) were refluxed :

Time (hr.)	1	2	5	11	24	48
ε at 325 mμ	170	120	140	235	405	770

5α-*Acetoxy*-9α : 11α-*epoxyergosta*-7 : 22-*dien*-3β-*ol* (IV; R = H, R′ = Ac).—The 5-acetoxy-7 : 9 : 22-triene (485 mg.) was treated with 1·2 equivs. of monoperphthalic acid in ether (56 c.c.) (the per-acid solution was made by the procedure of Bohme, *Org. Synth.*, 1940, **20**, 70). After 20 hr. at 28°, the solution was washed with aqueous sodium hydrogen carbonate, dried, and evaporated. The resulting syrup, dissolved in benzene (30 c.c.), was chromatographed on alumina (50 g.; 2 × 20 cm.). A benzene–ether (1 : 1) eluate (490 mg.) was rechromatographed and crystallised from methanol, to afford the *epoxide* (40%), m. p. 163—164°, $[\alpha]_D$ +48°, $\lambda_{max.}$ 206 mμ (ε 6500) (Found : C, 76·7; H, 10·1. $C_{30}H_{46}O_4$ requires C, 76·6; H, 9·8%).

9α : 11α-*Epoxyergosta*-7 : 22-*diene*-3β : 5α-*diol* (IV; R = R′ = H).—The triene diol (430 mg.) was treated with 1·2 mols. of perbenzoic acid in benzene (56 c.c.) (the per-acid solution was prepared by the method of Kolthoff *et al.*, *loc. cit.*). After 6 hr. at 28°, the steroids were isolated as in the previous example and chromatographed. Elution with ether–ethanol (9 : 1) gave the *epoxide* (79%), needles (from methanol), m. p. 214—217°, $[\alpha]_D$ −4°, $\lambda_{max.}$ 207 mμ (ε 6600) (Found : C, 78·5; H, 10·3. $C_{28}H_{44}O_3$ requires C, 78·5; H, 10·3%). The epoxide and acetic anhydride–pyridine at 30° gave the 3-acetate (see below).

Other Acetates of 9α : 11α-*Epoxyergosta*-7 : 22-*diene*-3β : 5α-*diol.*—The epoxide 3 : 5-diacetate (70%), m. p. 128°, $[\alpha]_D$ +50°, $\lambda_{max.}$ 205 mμ (ε 6800), was obtained by using perbenzoic acid in benzene (Jones *et al.* give m. p. 125—127°, $[\alpha]_D$ +51·5°). Hydrolysis with potassium hydroxide in aqueous methanol gave a difficultly separable mixture of the diol and the 5-acetate (see above). The epoxide 3-acetate (60%, together with 35% of unchanged material), m. p. 237—238°, $[\alpha]_D$ +4°, $\lambda_{max.}$ 206 mμ (ε 7100), was obtained from the 3-acetoxy-5-hydroxy-triene and monoperphthalic acid in ether (Jones *et al.* give m p. 229—237°, $[\alpha]_D$ +2°). In another experiment, the 3-acetoxy-5-hydroxy-triene (5·3 g.) in benzene (50 c.c.) was treated with 1·3 mols. of monoperphthalic acid in ether (72 c.c.) at 20° for 48 hr. The solution was washed with aqueous sodium hydrogen carbonate, and the product recrystallised from methanol–benzene, giving the epoxide 3-acetate (3 g.), m. p. 234—236°. The mother-liquors were evaporated and the residue chromatographed in benzene (50 c.c.) on alumina (50 g.; 2 × 20 cm.). The benzene eluate (700 mg.; m. p. 206—208°) was again chromatographed; elution with benzene–ether (9 : 1) gave successively 3β-*acetoxy*-7ξ : 8ξ-9α : 11α-*diepoxyergost*-22-*en*-5α-*ol* (V;

R = Ac, R′ = H) (3%), platelets (from methanol–benzene), m. p. 234—235°, $[\alpha]_D$ −10°, $\lambda_{max.}$ 203 mμ (ε 1020) (Found: C, 74·25; H, 10·0. $C_{30}H_{46}O_5$ requires C, 74·1; H, 9·5%), and 3β-*acetoxy*-5α-*hydroxy*-8β-*ergosta*-9 : 22-*dien*-7-*one* (XI*B*; R = Ac, R′ = H) (3%), m. p. 206—208°, $[\alpha]_D$ −40°, $\lambda_{max.}$ 206 mμ (ε 3050) (Found: C, 76·25; H, 10·0. $C_{30}H_{46}O_4$ requires C, 76·6; H, 9·8%). The 7-ketone gave a yellow 2 : 4-dinitrophenylhydrazone. The diepoxide with potassium hydroxide in aqueous methanol or with lithium aluminium hydride in ether–dioxan gave the 3β : 5α-*dihydroxydiepoxide* (V; R = R′ = H) (95%) which crystallised from methanol–benzene as plates, m. p. 251—252°, $[\alpha]_D$ −18°, $\lambda_{max.}$ 206 mμ (ε 1200) (Found: C, 74·15; H, 9·9. $C_{28}H_{44}O_4$,0·5CH_3·OH requires C, 74·3; H, 10·0%), and was reconverted by acetic anhydride–pyridine into the 3-acetate. From another experiment with the 3-acetoxy-5-hydroxy-triene (4 g.) and 1·3 mols. of monoperphthalic acid in chloroform–ether (1 : 1; 135 c.c.) at 0° for 24 hr., then at 25° for 24 hr., and chromatography on alumina (300 g.; 5 × 60 cm.), the following were the main products: unchanged triene (15%); 3β-*acetoxy*-5α-*hydroxy*-8α-*ergosta*-9 : 22-*dien*-7-*one* (XI*A*; R = Ac, R′ = H) (8%), needles (from methanol), m. p. 143—144°, $[\alpha]_D$ +17°, $\lambda_{max.}$ 205 mμ (ε 3500) (Found: C, 76·95; H, 9·5. $C_{30}H_{46}O_4$ requires C, 76·6; H, 9·8%) (slowly formed a 2 : 4-dinitrophenylhydrazone), 3β-acetoxy-7ξ : 8ξ-9α : 11α-diepoxyergost-22-en-5α-ol (15%), m. p. 226—228°, $[\alpha]_D$ −7°, $\lambda_{max.}$ 204 mμ (ε 900), and 3β-*acetoxy*-5α-*hydroxyergosta*-8(9) : 22-*dien*-7-*one* (XII; R = Ac, R′ = H), m. p. 237—238°, $[\alpha]_D$ −83°, $\lambda_{max.}$ 256 mμ (ε 9300) (Found: C, 76·3; H, 9·6. $C_{30}H_{46}O_4$ requires C, 76·6; H, 9·8%) (slowly formed a crimson 2 : 4-dinitrophenylhydrazone).

3β-*Acetoxy*-5α-*hydroxy*-9β-*ergosta*-7 : 22-*dien*-11-*one* (VI; R = Ac).—The 3β-acetoxy-5α-hydroxy-epoxide was treated with boron trifluoride–ether complex in benzene as described by Jones *et al.* but for 72 hr. The product was chromatographed on alumina; elution with light petroleum–benzene (1 : 1; 50 c.c.) gave 3β-*acetoxyergosta*-5 : 8(9) : 22-*trien*-11-*one* (VII) (13%), needles (from methanol), m. p. 128°, $[\alpha]_D$ −34°, $\lambda_{max.}$ 249 mμ (ε 10,800) (Found: C, 79·9; H, 9·9. $C_{30}H_{44}O_3$ requires C, 79·7; H, 9·7%); this was hydrolysed by alkali to the *sterol*, m. p. 125—126°, $[\alpha]_D$ −33°, $\lambda_{max.}$ 249 mμ (ε 11,600) (Found: C, 82·2; H, 11·5. $C_{28}H_{42}O_2$ requires C, 81·95; H, 10·25%). Further elution, finally with benzene, gave 3β-acetoxy-5α-hydroxy-9β-ergosta-7 : 22-dien-11-one (53%), m. p. 189°, $[\alpha]_D$ −122°, $\lambda_{max.}$ 207 (ε 4000) and 292 mμ (ε 180) which appeared to react slowly with 2 : 4-dinitrophenylhydrazine {Jones *et al.*, give m. p. 181—187°, $[\alpha]_D$ −135°, $\lambda_{max.}$ 293 mμ (ε 190)}. Further elution with benzene–ether (9 : 1) gave 15% of mixed dien-11-ones. Reduction of the time of the reaction to 7 hr. improved the yield of 7 : 22-dien-11-one to 75%; in this case, the crude product was crystallised from methanol–benzene, without chromatography.

Base-catalysed Rearrangement of 3β-*Acetoxy*-5α-*hydroxy*-9β-*ergosta*-7 : 22-*dien*-11-*one*.—(*a*) The ketone was unaltered by filtration of a benzene solution through a column of untreated alumina.

(*b*) The ketone (620 mg.), 10% aqueous potassium hydroxide (5 c.c.), and methanol (70 c.c.) were refluxed for 2½ hr. The steroids were dissolved in benzene (50 c.c.) and chromatographed on alumina (50 g.; 2 × 20 cm.). Elution with benzene–ether (1 : 1) and crystallisation from methanol afforded a *compound* (58%), as needles, m. p. 184—186°, $[\alpha]_D$ +19°, $\lambda_{max.}$ 243 mμ (ε 7500) (Found: C, 78·5; H, 10·7. $C_{28}H_{44}O_3$ requires C, 78·5; H, 10·3%). Further elution with ether–ethanol (9 : 1) gave 3β : 5α-*dihydroxyergosta*-8(9) : 22-*dien*-11-*one* (IX; R = R′ = H) as needles, m. p. 223—224°, $[\alpha]_D$ +75°, $\lambda_{max.}$ 256 mμ (ε 6400) (Found: C, 78·2; H, 10·25. $C_{28}H_{44}O_3$ requires C, 78·5; H, 10·3%).

(*c*) The ketone (158 mg.), Amberlite resin " IRA 400-OH " (0·5 g.), and methanol (40 c.c.) were refluxed for 16 hr. The steroid product was boiled for 30 min. with acetic anhydride (5 c.c.), and the acetic anhydride removed. The residue was chromatographed in light petroleum–benzene (1 : 1; 40 c.c.) on alumina (15 g.; 1 × 15 cm.); elution with light petroleum–benzene (1 : 1) and crystallisation from methanol gave a *compound* (37%), m. p. 177—179°, $[\alpha]_D$ +33°, $\lambda_{max.}$ 243 mμ (ε 10,950) (Found: C, 75·4; H, 10·15. $C_{32}H_{48}O_5$ requires C, 75·0; H, 9·4%). After the benzene eluates which followed had been discarded, elution with benzene–ether (9 : 1) and then crystallisation from methanol afforded 3β-*acetoxy*-5α-*hydroxy*-*ergosta*-8(9) : 22-*dien*-11-*one* (IX; R = Ac, R′ = H) (26%), m. p. 191—193°, $[\alpha]_D$ +74°, $\lambda_{max.}$ 256 mμ (ε 8400) (Found: C, 77·0; H, 10·0. $C_{30}H_{46}O_4$ requires C, 76·6; H, 9·8%), which does not form a 2 : 4-dinitrophenylhydrazone [Jones *et al.* give m. p. 192—197°, $[\alpha]_D$ +81°, $\lambda_{max.}$ 257 mμ (ε 9100)]. The same acetate was obtained from the corresponding 3 : 5-diol (above) and acetic anhydride–pyridine at 25°.

Acid-catalysed Rearrangement of 3β-*Acetoxy*-5α-*hydroxy*-9β-7 : 22-*dien*-11-*one*.—The ketone (673 mg.), N-sulphuric acid (30 c.c.), and dioxan (50 c.c.) were refluxed for 90 min. The crude steroid product was refluxed for 30 min. with acetic anhydride (30 c.c.), then chromatographed in

light petroleum–benzene (1 : 1; 30 c.c.) on alumina (50 g., 2 × 20 cm.). Later fractions eluted by light petroleum–benzene were crystallised from methanol, to give 3β : 5α-diacetoxyergosta-8(9) : 22-dien-11-one (3%), m. p. 150—152°, $[\alpha]_D$ +93°, $\lambda_{max.}$ 254 mμ (ε 6500) (Found: C, 74·5; H, 9·45. Calc. for $C_{32}H_{48}O_5$: C, 75·0; H, 9·4%) [Jones *et al.* give m. p. 150—153°, $[\alpha]_D$ +121°, $\lambda_{max.}$ 254 mμ (ε 9000)]. From further light petroleum–benzene (1 : 1) eluates, a steroid *acetate* (13%), m. p. 199—202°, $[\alpha]_D$ −25°, $\lambda_{max.}$ 243 mμ (ε 11,000) (Found: C, 76·7; H, 10·1. $C_{30}H_{46}O_4$ requires C, 76·6; H, 9·8%), was obtained; the same acetate was made from the compound $C_{28}H_{44}O_3$, m. p. 184—186° (above), and acetic anhydride–pyridine at 25°, or acetic anhydride at 115°. Continued elution, with benzene–ether (9 : 1), gave 3β-acetoxy-5α-hydroxyergosta-8(9) : 22-dien-11-one (43%), m. p. 196—197°, $[\alpha]_D$ +66°, $\lambda_{max.}$ 256 mμ (ε 6600).

3β-*Acetoxy*-5α-*hydroxyergost*-22-*en*-11-*one* (VIII).—3β-Acetoxy-5α-hydroxyergosta-8(9) : 22-dien-11-one (95 mg.) in dry ether (12 c.c.) was added to anhydrous liquid ammonia (150 c.c.). Lithium (25 mg.) was added and the solution stirred for 30 min. A trace of ferric nitrate was added to the (blue) solution to destroy the remaining lithium, and the ammonia was removed in a vacuum. The steroids were isolated and left at 25° for 16 hr. with acetic anhydride (1 c.c.) and pyridine (10 c.c.). The product was chromatographed in light petroleum–benzene (1 : 1; 20 c.c.) on alumina (10 g., 1 × 10 cm.). Benzene eluates were crystallised from aqueous methanol, to afford the 22-*en*-11-*one* (55%) as needles, m. p. 221—222°, $[\alpha]_D$ 0, $\lambda_{max.}$ 205 mμ (ε 2500) (Found: C, 73·85; H, 9·7. $C_{30}H_{48}O_4,CH_3{\cdot}OH$ requires C, 73·8; H, 10·3%) [Jones *et al.* (personal communication) have made this compound independently and find m. p. 210—220°, $[\alpha]_D$ 0].

Acid Treatment of 3β : 5α-*Diacetoxy*-9α : 11α-*epoxyergosta*-7 : 22-*diene*.—(*a*) The epoxide (620 mg.), 2N-sulphuric acid (20 c.c.), and dioxan (100 c.c.) were shaken at 25° for 30 min. The steroid product was chromatographed in light petroleum–benzene (1 : 1, 20 c.c.) on alumina (50 g.; 2 × 20 cm.). Elution with benzene–ether (1 : 1) and crystallisation from methanol gave needles of 3β : 5α-*diacetoxy*-7ξ : 11α-*dihydroxyergosta*-8(9) : 22-*diene* (X; R = R′ = Ac) (12%), m. p. 152—153°, $[\alpha]_D$ +41°, $\lambda_{max.}$ 207 mμ (ε 7000) (Found: C, 72·4; H, 9·3. $C_{32}H_{50}O_6$ requires C, 72·5; H, 9·4%); unchanged epoxide (67%) was also obtained.

(*b*) The epoxide (504 mg.), 5N-sulphuric acid (15 c.c.), and dioxan (100 c.c.) were shaken at 25° for 4 hr., and the product was chromatographed. The light petroleum–benzene (1 : 1) elutates (350 mg.) were crystallised from methanol, to give 3β-*acetoxyergosta*-5 : 9 : 22-*trien*-7-*one* (XIII; R = Ac) (20%), m. p. 171—172°, $[\alpha]_D$ −112°, $\lambda_{max.}$ 235 mμ (ε 13,300) (Found: C, 79·9; H, 9·6. $C_{30}H_{44}O_3$ requires C, 79·7; H, 9·7%). Infra-red bands: 7126 cm.$^{-1}$ (acetoxy-group); doublet at 1668 and 1600 cm.$^{-1}$ (αβ-unsaturated ketone system). The Tortelli–Jaffé test was positive and the compound slowly formed a crimson 2 : 4-dinitrophenylhydrazone. The 7-ketone (110 mg.), refluxed for 1 hr. with N-potassium hydroxide (5 c.c.) in methanol (30 c.c.), afforded the 3β-*hydroxy*-5 : 8(9) : 22-*trien*-7-*one* (XIV; R = H), m. p. 166—168°, $[\alpha]_D$ −12°, $\lambda_{max.}$ 246 mμ (ε 11,000) (Found: C, 81·7; H, 10·5. $C_{28}H_{42}O_2$ requires C, 81·9; H, 10·2%). This with cold acetic anhydride–pyridine (48 hr.) gave the 3-*acetate*, m. p. 193—194°, $[\alpha]_D$ −21°, λ_{max} 245 mμ (ε 11,300) (Found: C, 79·2; H, 10·0. $C_{30}H_{44}O_3$ requires C, 79·7; H, 9·7%), which slowly formed a crimson 2 : 4-dinitrophenylhydrazone.

Acid Treatment of 3β-*Acetoxy*-9α : 11α-*epoxyergosta*-7 : 22-*dien*-5α-*ol*.—(*a*) The epoxide (407 mg.), 4N-sulphuric acid (28 c.c.), and dioxan (100 c.c.) were shaken together for 30 min. The isolated steroids were dissolved in benzene (30 c.c.) and chromatographed on alumina (50 g.; 2 × 20 cm.). A solid (355 mg.) from benzene–ether eluates was not resolved. Further elution with ether–ethanol (9 : 1), and crystallisation from methanol, afforded *ergosta*-8(9) : 22-*diene*-3β : 5α : 7ξ : 11α-*tetrol* (X; R = R′ = H) (7%), m. p. 188—189°, $[\alpha]_D$ −15°, $\lambda_{max.}$ 208 mμ (ε 4900) (Found: C, 75·05; H, 9·95. $C_{28}H_{46}O_5$ requires C, 75·35; H, 10·3%).

(*b*) The epoxide (600 mg.), 4N-sulphuric acid (28 c.c.), and dioxan (100 c.c.) were left at 25° for 3 days. The crude steroid product was chromatographed; elution with benzene–ether (1 : 1; 600 c.c.) and crystallisation from methanol yielded 3β-hydroxyergosta-5 : 8(9) : 22-trien-7-one (XIV; R = H) (38%), m. p. and mixed m. p. 166—170°, $[\alpha]_D$ −17°, $\lambda_{max.}$ 245 mμ (ε 12,050). Continued elution with benzene–ether (1 : 1; 500 c.c.) gave 3β : 5α-*dihydroxy-ergosta*-9 : 22-*dien*-7-*one* (XI*B*; R = R′ = H) (20%), needles, m. p. 212—214°, $[\alpha]_D$ −61°, $\lambda_{max.}$ 204 (ε 3900) and 320 mμ (ε 93) (Found: C, 78·7; H, 10. $C_{28}H_{44}O_3$ requires C, 78·5; H, 10·3%). Further elution with ether–ethanol (9 : 1) gave 3β : 5α-*dihydroxyergosta*-8(9) : 22-*diene*-7-*one* (XII; R = R′ = H) (43%), m. p. 240—242°, $[\alpha]_D$ −68°, λ_{max} 257 (ε 7000) and 315 mμ (ε 225) (Found: C, 78·5; H, 10·0. $C_{28}H_{44}O_3$ requires C, 78·5; H, 10·3%), converted by acetic anhydride–pyridine at 25° into the 3-acetate, m. p. 225—228°, $[\alpha]_D$ −81°, λ_{max} 257 mμ

(ε 9200). In an experiment similar to (*b*), the dihydroxy-epoxide (IV; R = R′ = H) gave the same three products in 29, 24, and 28% yield respectively.

(*c*) In one experiment, the epoxide (372 mg.) was dissolved in hot methanol–chloroform. As no crystals separated on cooling, the solution was evaporated and chromatographed, affording unchanged epoxide (35%) and 3β-acetoxy-5α-hydroxy-8α-ergosta-9 : 22-dien-7-one (XI*A*; R = Ac, R′ = H) (35%), m. p. and mixed m. p. 138—139°, $[\alpha]_D$ +14° (no significant ultraviolet absorption).

Acid Treatment of 3β-*Acetoxy*-5α-*hydroxyergosta*-9 : 22-*dien*-7-*one*.—The ketone (XI*B*; R = Ac, R′ = H) (195 mg.) was refluxed in dioxan (20 c.c.) and N-sulphuric acid (10 c.c.) for 90 min. The steroid product was treated with acetic anhydride (0·5 c.c.) and pyridine (10 c.c.) at 25° for 16 hr., then chromatographed in light petroleum–benzene (1 : 1; 30 c.c.) on alumina (50 g.; 2 × 20 cm.). Benzene eluates were crystallised from methanol, giving 3β-acetoxyergosta-5 : 8(9) : 22-trien-7-one (33%), m. p. 186—187°, $[\alpha]_D$ −9°, $\lambda_{max.}$ 244 mμ (ε 10,600). Finally, benzene–ether (1 : 1) eluted 3β-acetoxy-5α-hydroxyergosta-8(9) : 22-dien-7-one (36%), m. p. 234—235°, $[\alpha]_D$ −93°, $\lambda_{max.}$ 256 mμ (ε 8900).

Alkali Treatment of 3β-*Acetoxy*-5α-*hydroxyergostadien*-7-*ones*.—(*a*) The ketone (XII; R = Ac, R′ = H) (40 mg.), methanol (30 c.c.), and aqueous 10% potassium hydroxide (5 c.c.) were refluxed for 1 hr. Crystallisation from methanol afforded 3β-hydroxyergosta-5 : 8(9) : 22-trien-7-one (XIV; R = H), m. p. 160—166°, $[\alpha]_D$ −13°, $\lambda_{max.}$ 247 mμ (ε 10,000).

(*b*) The same product (92%), m. p. 163—164°, $[\alpha]_D$ −13°, $\lambda_{max.}$ 246 mμ (ε 10,200), was obtained similarly from 3β-acetoxy-5α-hydroxyergosta-9 : 22-dien-7-one (XI*B*; R = Ac, R′ = H), and from the 3β : 5α-dihydroxy-9 : 22-dien-7-one.

The authors are indebted to Professors M. Stacey, F.R.S., and E. R. H. Jones, F.R.S., for arranging for this investigation to be undertaken. They also thank Dr. J. C. Robb for discussions on kinetics, Dr. D. H. Whiffen for infra-red absorption data, and Messrs. Glaxo Laboratories Ltd. for financial assistance.

CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM 15.

[*Received, June 15th,* 1953.]