306. *Preparation of Cortisol Acetate and 21-Acetoxy-17α-hydroxypregna-4 : 9-diene-3 : 20-dione from 5α-Steroids.*

By R. M. Evans, G. F. H. Green, J. S. Hunt, A. G. Long, B. Mooney, and G. H. Phillipps.

4 : 5α-Dihydrocortisone (XII; R = R′ = O; R″ = H) has been reduced to 4 : 5α-dihydrocortisol (XII; R = O; R′ = H, β-OH; R″ = H), the 3- and the 20-keto-group being protected by ketalisation. In the conditions needed for ketalising the 20-keto-group a non-hydroxylic by-product, not hydrolysed to a 20-ketone by acid, is formed.

Acid-catalysed bromination in acetic acid of 4 : 5α-dihydrocortisol 21-acetate or 11β-hydroxyergostan-3-one (II; R = H) yielded 2 : 4-dibromo-Δ^9-compounds, from which ergosta-4 : 9-dien-3-one (XI) and 21-acetoxy-17α-hydroxypregna-4 : 9-diene-3 : 20-dione (XVII) were made. Various esters (II) were tried in attempts to prevent elimination of the 11-hydroxy-group during the halogenation. In ethereal solvents, particularly dioxan, this elimination is prevented, and the 2 : 4-dibromo-compounds can then be converted into cortisol acetate (XIII; R = H, β-OH; R′ = Ac) and 11β-hydroxyergost-4-en-3-one (VIII) respectively.

A practicable conversion of 4 : 5α-dihydrocortisone acetate into cortisone acetate has been described in an earlier publication.[1] Attempts to apply such methods to the manufacture of cortisol acetate from 5α-steroids showed that the 11β-hydroxy-group in the intermediate 4 : 5α-dihydrocortisol acetate caused difficulties in the acid-catalysed bromination, as it was readily eliminated with the formation of a Δ^9-steroid. A similar but probably less ready elimination occurs in the Δ^4- and 5β-3-oxo-steroids,[2] and oxidation of the 11β-hydroxy-group has been mentioned as a further undesirable adjunct to the bromination of a 3-oxo-5β-steroid.[3]

In view of the lack of information on the stability of the 11β-hydroxy-3-oxo-5α-steroids in such conditions, we have studied the properties of simple ergostane derivatives obtained from compounds described in an earlier part of our work.[4]

11β-Hydroxy-compounds of this type were converted in acetic acid containing hydrogen bromide into Δ^9-steroids; these products were stable, so that bromination of 11β-hydroxyergostan-3-one (II; R = H), as well as of the Δ^9-ketone (X; X = H), generated 2α : 4α-dibromoergost-9-en-3-one (X; X = Br), which with sodium iodide in acetone and subsequent dehalogenation gave ergosta-4 : 9-dien-3-one (XI). The double bond in ring C is given the 9 : 11-position on the basis of earlier workers' results,[2,5] and the properties

[1] Evans, Hamlet, Hunt, Jones, Long, Oughton, Stephenson, Walker, and Wilson, *J.*, 1956, 4356.
[2] Graber, Haven, and Wendler, *J. Amer. Chem. Soc.*, 1953, **75**, 4722.
[3] Oliveto, Gerold, Weber, Jorgensen, Rausser, and Hershberg, *ibid.*, p. 5486.
[4] Bladon, Henbest, Jones, Lovell, Wood, Woods, Elks, Evans, Hathway, Oughton, and Thomas, *J.*, 1953, 2921.
[5] *E.g.*, Shoppee and Reichstein, *Helv. Chim. Acta*, 1943, **26**, 1316, and earlier papers; Heymann and Fieser, *J. Amer. Chem. Soc.*, 1952, **74**, 5938; Bernstein, Lenhard, and Williams, *J. Org. Chem.*, 1954 **19**, 41; Heyl and Herr, *J. Amer. Chem. Soc.*, 1955, **77**, 488.

of our products support this interpretation. Dehalogenation of the dibromo-compound (X; X = Br) gave ergost-9-en-3-one (X; X = H).

Recent studies with 11β-hydroxy-steroids have shown the unexpected ease with which esters can be made and also that such esters may be more stable in acidic solutions than the free 11β-alcohols. Adapting published methods we have made mono- and di-formates,[6] -acetates,[7] and -trifluoroacetates [8] of ergostane-3β : 11β-diol (I; R = R′ = H), selective esterification and, in the diesters, saponification at the 3-position being possible; however, reaction of ethyl chloroformate [9] with the 11β-hydroxy-group could not be achieved. Selective hydrolysis of the diesters and subsequent oxidation yielded the esters of 11β-hydroxyergostan-3-one (II; R = H); this ketol was also available from the 3β : 11β-diol (I; R = R′ = H) by Oppenauer oxidation.[10a] Except for the acetates, the 11β-esters were not difficult to hydrolyse in conditions that the cortical side-chain might be expected to survive.[11] Although they resemble in this respect the corresponding compounds in the 5β-series, they appear less stable to acidic conditions: for instance, the 11β-formates, although more stable than the 11β-alcohols, are still readily converted into Δ^9-compounds by hydrogen bromide in solvents such as acetic acid and methylene dichloride. Polarimetric evidence suggested that in acetic acid containing hydrogen bromide, or in acetic anhydride and chloroform containing perchloric acid, the 11β-hydroxy-5α-steroids were converted first into 11β-acetates, which then lost the elements of acetic acid.

This inability to exploit esters for our purposes led us to devise conditions for bromination that would curb protonation of the 11β-substituent and so be to the disadvantage of elimination.[12] The desired halogenation (with rearrangement) in ring A is a thermodynamically controlled process in which protons are presumably needed only to unite with the carbonyl group.[13] Directing our efforts at sparing the 11β-hydroxyl group on the basis of such premises, we sought a Lewis base as solvent or additive [14] that would not hinder the halogenation and would not give rise to complications with hydrogen bromide or bromine. In practice ethers,[15] particularly dioxan or diethyl ether, had the desired properties; diphenyl ether was inactive, since resonance detracts from the basic nature of the oxygen atom.[16]

In dioxan 11β-hydroxyergostan-3-one (II; R = H) was brominated to the 2α : 4α-dibromo-ketol (III; X = Br), which gave the 11β-hydroxyergost-4-en-3-one (VIII) by treatment with sodium iodide in acetone and subsequent dehalogenation, or by dehalogenation to the 4-bromo-compound (IV) with subsequent dehydrobromination by means of semicarbazide.[1] Oxidation of the ketol (VIII) gave the unsaturated dione (VII), also derived from ergostane-3 : 11-dione (VI; X = Y = H) by bromination, partial dehydrobromination, and final dehalogenation. Spectroscopic and polarimetric evidence suggests that the bromine atoms at the 2- and the 4-position are equatorially disposed to ring A in the bromo-ketones made in this investigation.[1]

[6] (*a*) Lardon and Reichstein, *Helv. Chim. Acta*, 1954, **37**, 443; (*b*) Oliveto, Gerold, Rausser, and Hershberg, *J. Amer. Chem. Soc.*, 1955, **77**, 3564.

[7] (*a*) Steiger and Reichstein, *Helv. Chim. Acta*, 1937, **20**, 817; (*b*) ref. 3; (*c*) Crawshaw, Henbest, and Jones, *J.*, 1954, 731; (*d*) Kemp, Kappas, Salamon, Herling, and Gallagher, *J. Biol. Chem.*, 1954, **210**, 123.

[8] Cf. Lardon and Reichstein, *Helv. Chim. Acta*, 1954, **37**, 388.

[9] Fieser, Herz, Klohs, Romero, and Utne, *J. Amer. Chem. Soc.*, 1952, **74**, 3309.

[10] (*a*) Brooks, Hunt, Long, and Mooney, *J.*, 1957, 1175; (*b*) cf. Rothman and Wall, *J. Amer. Chem. Soc.*, 1957, **79**, 3228.

[11] Callow and James, *J.*, 1956, 4739; ref. 10.

[12] Cf. Dhar, Hughes, Ingold, Mandour, Maw, and Woolf, *J.*, 1948, 2093.

[13] Crowne, Evans, Green, and Long, *J.*, 1956, 4351.

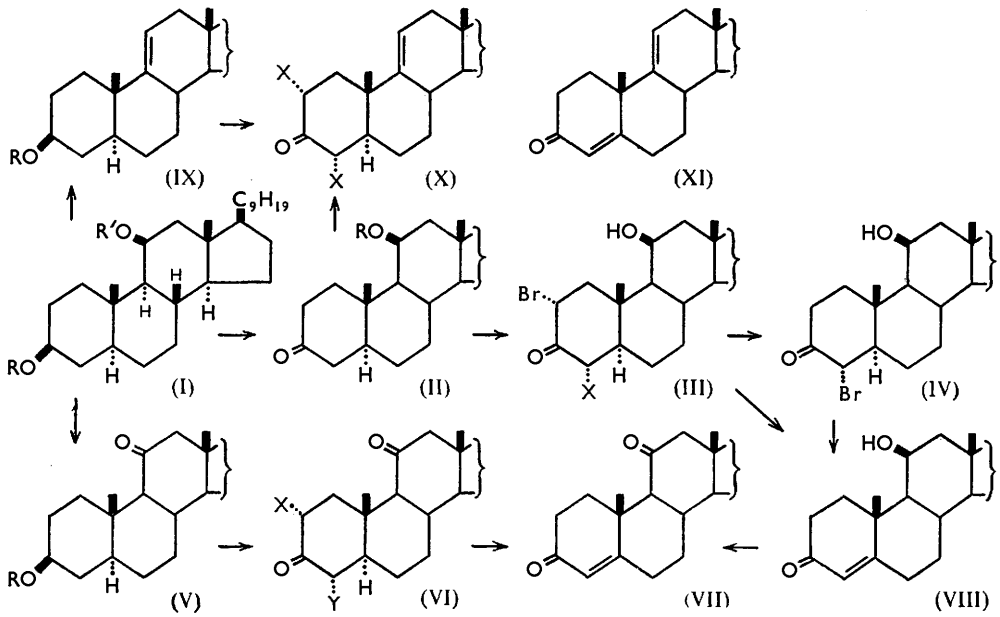
[14] Bell, "Acids and Bases," Methuen and Co. Ltd., London, 1952, p. 30; cf. Glasstone, *Trans. Faraday Soc.*, 1937, **33**, 200; Zellhoeffer, Copley, and Marvel, *J. Amer. Chem. Soc.*, 1938, **60**, 1337.

[15] (*a*) Meerwein and van Emster, *Ber.*, 1922, **55**, 2500; Young, Caserio, and Brandon, *Science*, 1953, **117**, 473; Kosower and Winstein, *J. Amer. Chem. Soc.*, 1956, **78**, 4354; (*b*) cf. Hirschmann, Miller, Wood, and Jones, *ibid.*, p. 4956.

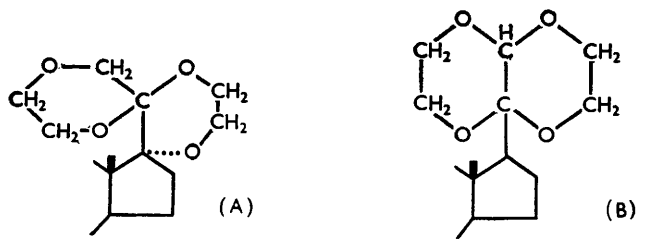
[16] Cf. Greenwood and Martin, *Quart. Rev.*, 1954, **8**, 1; Burwell, *Chem. Rev.*, 1954, **54**, 619; Lappert, *ibid.*, 1956, **56**, 1017; Edwards, Gerrard, and Lappert, *J.*, 1957, 348.

These conversions of Δ^9- and 11β-hydroxy-3-oxo-5α-steroids into Δ^4-3-ketones indicate not only the possibility of new methods for making steroids such as cortisol and the 9-halogeno-corticoids,[17] but also means of avoiding undesirable reactions (particularly halogenation in ring c) that may occur when the 4 : 5-double bond is introduced into 3 : 11 dioxo-steroids. Therefore we continued our studies with these ends in view.

Using dihydrocortisone acetate (XII; R = R′ = O; R″ = Ac) as source, we aimed at making dihydrocortisol acetate (XII; R = O; R′ = H, β-OH; R″ = Ac) by reducing



the 11-oxo-group after protecting the 3- and the 20-keto-group by ketalisation with ethylene glycol.[18] The 3-oxo-group is the more readily ketalised, the 20-oxo-group being affected only after prior hydrolysis of the 21-ester, and then more slowly. Formation of the 20-ketal is accompanied by the generation of a non-hydroxylic compound, whose side-chain is resistant to sodium borohydride and from which the 20-ketone group cannot be



regenerated by mild acid-catalysed hydrolysis.[19] Its stability to acid likens it to the oxetones,[20] sapogenins,[21] and certain sugar anhydrides [22] and distinguishes its behaviour

[17] Ref. 15*b*; Fried and Sabo, *J. Amer. Chem. Soc.*, 1957, **79**, 1130; cf. Barkley, Farrar, Knowles, and Raffelson, *ibid.*, 1954, **76**, 5017; Graber, Snoddy, and Wendler, *Chem. and Ind.*, 1956, 57.

[18] Bernstein, Littell, *et al.*, *J. Org. Chem.*, 1953, **18**, 70; *J. Amer. Chem. Soc.*, 1954, **76**, 6116.

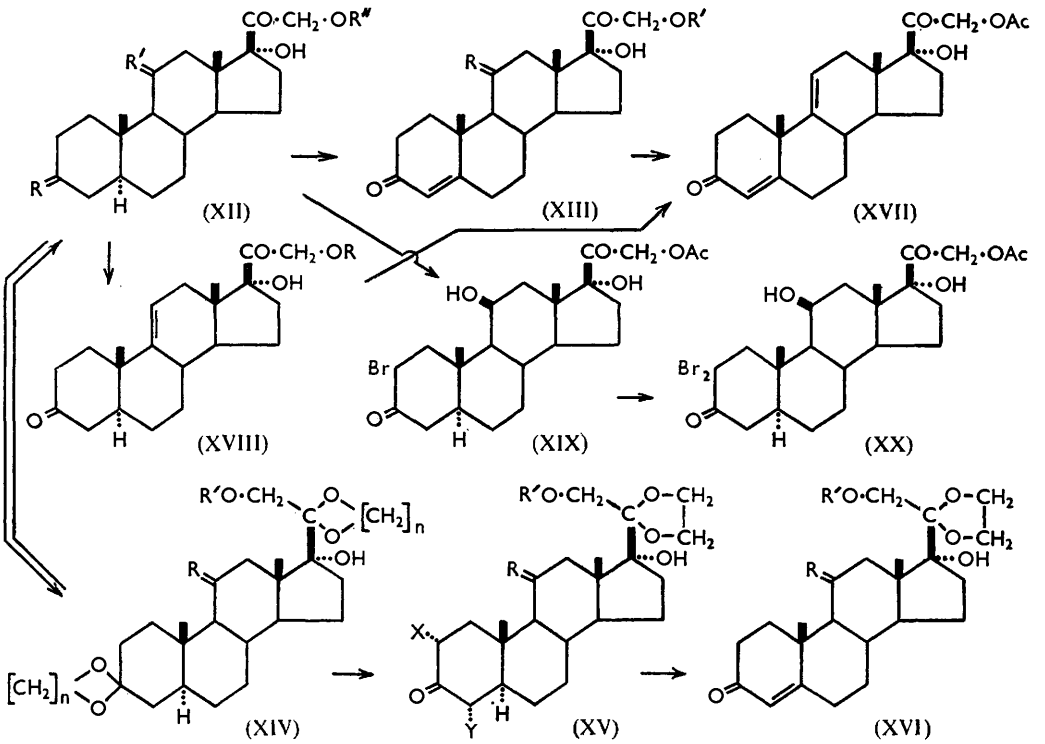
[19] Cf. Levin, Magerlein, McIntosh, Hanze, Fonken, Thompson, Searcy, Scheri, and Gutsell, *ibid.*, p. 546.

[20] Farlow, Burdick, and Adkins, *ibid.*, 1934, **56**, 2498.

[21] Fieser and Fieser, " Natural Products related to Phenanthrene," Reinhold Publ. Corp., New York, 1949, p. 585.

[22] Cf. Haworth and Streight, *Helv. Chim. Acta*, 1932, **15**, 693; Schlubach and Behre, *Annalen*, 1934, **508**, 16; McDonald, *Adv. Carbohydrate Chem.*, 1946, **2**, 253.

from that expected of the ketals of the pregnane-20 : 21-diones;[23] we therefore suppose that it is a spiroketal, *e.g.*, with the system (A), or a tetraoxadecalin[24] derivative (B). However, it did not give acetaldehyde when treated with sulphuric acid and so differs in one respect from many derivatives of dioxan.[25] Unfortunately the generation of such by-products thwarted efficient ketalisation of dihydrocortisone (XII; R = R′ = O; R″ = H), and it could not be improved by the use of trimethylene glycol instead of ethylene glycol. We found that the 3-oxo-group in 4 : 5α-dihydrocortisol and its 21-acetate (XII; R = O;



(XII; R = R′ = O; R″ = H) = 4: 5α-Dihydrocortisone.
(XII; R = O; R′ = H, β-OH; R″ = H) = 4: 5α-Dihydrocortisol.
(XIII; R = O; R′ = H) = Cortisone.
(XIII; R = H, β-OH; R′ = H) = Cortisol.

R′ = H, β–OH; R″ = H and Ac) and in cholestan-3-one could be ketalised by means of refluxing methanol without an intentionally added catalyst.[26]

Mild conditions suffice for hydrolysis of the 3 : 3-ethylenedioxy-group, but the 20-ketals survive the conditions[1,18] used in this work for dehydrogenating ring A. Accordingly we have been able to convert the 4-bromo-3-oxo-20-ketal (XV; X = R′ = H; Y = Br; R = O), made by acid-catalysed 2 : 4-dibromination of the 20-ketal (XV; X = Y = R′ = H; R = O) with subsequent partial dehalogenation, into the Δ^4-semicarbazone; reduction of this compound, with subsequent removal of the semicarbazone

[23] Mattox, *J. Amer. Chem. Soc.*, 1952, **74**, 4340; Taub, Pettebone, Wendler, and Tishler, *ibid.*, 1954, **76**, 4094; Mancera, Rosenkranz, and Sondheimer, *ibid.*, 1955, **77**, 5669.
[24] Baker *et al.*, *J.*, 1932, 86; 1933, 1598; Böeseken *et al.*, *Rec. Trav. chim.*, 1935, **54**, 733; 1938, **37**, 133; Jaeger and Smith, *J.*, 1955, 160.
[25] Brown, Calderbank, Johnson, Joshi, Quayle, and Todd, *J.*, 1955, 959.
[26] Cf. Oliveto, Gerold, and Hershberg, *J. Amer. Chem. Soc.*, 1954, **76**, 6113.

group and acetylation, afforded the 20-ketal (XV; X = Y = H; R = H, β-OH; R′ = Ac) of cortisol acetate, albeit in low yield.

Reduction of the bis-ketal (XIV; $n = 2$; R = O; R′ = H) with sodium borohydride and hydrolysis of the product gave 4 : 5α-dihydrocortisol. Its acetate (XII; R = O; R′ = H, β-OH; R″ = Ac) was as unstable in acetic acid containing hydrogen bromide as the behaviour of the simple 11β-hydroxy-5α-steroids foreshadowed, and excellent yields of the Δ^9-steroid (XVIII; R = Ac) resulted. However, the 11β-alcohol was more stable in dioxan containing hydrogen bromide, and bromination in this solvent yielded crystallisable 2-bromo- (XIX) and 2 : 2-dibromo-compounds (XX), but not a pure 2 : 4-dibromo-compound. Nevertheless, treatment of suitable crude dibromo-products with sodium iodide in refluxing acetone and subsequent dehalogenation gave cortisol acetate, but in disappointing yield. Bromination of 4 : 5α-dihydrocortisol acetate (XII; R = O; R′ = H, β-OH; R″ = Ac) or of the 2-bromo-compound (XIX) in *tert.*-butyl alcohol or with basic catalysis was accompanied by oxidation of the 11-hydroxy-group to 11-ketone.[3]

Dehydrogenation of ring A in the Δ^9-compound (XVIII; R = Ac) by bromination and dehydrobromination was more successful. The resulting $\Delta^{4:9}$-diene (XVII) is a useful source for biologically active 9-halogeno-compounds.[17]

Experimental

Unless other methods are mentioned, m. p.s were measured with a Kofler block; optical rotations and ultraviolet and infrared absorption pertain to solutions in $CHCl_3$, EtOH, and CS_2 (Nujol for the 5α-pregnane derivatives) respectively, unless otherwise stated. The acid-washed alumina has been described before; [27] other grades were bought from P. Spence and Sons Ltd., Widnes, Lancs. The methods used for infrared spectroscopy have already been described and interpretations of these and the ultraviolet spectra are based on recent compilations.[1,28] Much information on the infrared absorption of the ergostane derivatives and some of the ketals has been given already; [29] for the rest, the assignments that hold good with an error of only a few cm.$^{-1}$ are C–O in 3β-alcohols (equatorial), 1040 cm.$^{-1}$; in 11β-alcohols (axial), 1030 cm.$^{-1}$ (weaker than the foregoing absorption); in formates, 1180, and in acetates, 1230 cm.$^{-1}$; in ethers (ketals in the pregnane series), 1000—1100 cm.$^{-1}$; C–F, in trifluoroacetates, 1155, 770, and 730 cm.$^{-1}$; C=C, in Δ^9-steroids, 820 cm.$^{-1}$, and in Δ^4-3-ketones, 865 cm.$^{-1}$. Weak maxima at 970 and 920 cm.$^{-1}$ may be shown by the formates.[30]

Molecular-rotation Differences.—Consistent changes agreeing with expectation have been noted, except for the conversion of 11β-alcohols into the corresponding Δ^9-steroids: in two examples, (I; R = R′ = H, β-OH) and (II; R′ = H, β–OH), in the ergostane series the ΔM_D for this change is −16° (±8°), and for the conversion of 4 : 5α-dihydrocortisol acetate (XII; R = O; R′ = H, β–OH; R″ = Ac) $\Delta M_D = -75°$ (and for 11β-hydroxytigogenin and its 3-acetate, $\Delta M_D = -6°$ and −54°, respectively). In the 5β-series the changes are larger, *e.g.*, for 4 : 5β-dihydrocortisol acetate $\Delta M_D = -153°$, as they are for Δ^4-3-ketones, *e.g.*, for cortisol acetate (XIII; R = H, β-OH; R′ = Ac) −164°, corticosterone acetate −144° (acetone), and 11β-hydroxyergost-4-en-3-one (VIII) −166°.

Using our values for the rotations [see comments after the description herein of ergost-9-en-3β-ol (IX; R = H)], we have corrected the ΔE values given by Crawshaw *et al.*[7c] for the introduction of unsaturation between positions 9 and 11, as follows (the figures being given for the 3-alcohol and its acetate respectively): ergostan-3β-ol +20°, +48°; tigogenin +30°, +79°; cholest-9-en-3β-ol +16°, +37°. Acetylation at the 3-position in the Δ^9-compounds corresponding to the above 5α-steroids is exceptional (but consistent) in giving values of −9°, −6°, and −8° respectively, such esterification usually being accompanied [31] by ΔM_D −34° ± 11°. The 11α-acetoxy-group also conduces to an anomalous change.[10]

[27] Elks, Evans, Long, and Thomas, *J.*, 1954, 451.
[28] Page, *Chem. and Ind.*, 1957, 58.
[29] Page, *J.*, 1955, 2017; Cummins and Page, *J.*, 1957, 3847.
[30] Archer, Lewis, Martini, and Jackman, *J. Amer. Chem. Soc.*, 1954, **76**, 4915.
[31] Ref. 21, p. 208.

Ergostane derivatives.

3β-*Hydroxyergostan*-11-*one* (V; R = H).—The 3β-acetate [30] (V; R = Ac) (7·4 g.) was refluxed for 2·5 hr. with N-potassium hydroxide in methanol (1 l.). The *ketol* (V; R = H) (6·3 g., 93%) separated from hexane as needles, m. p. 161—164°, $[\alpha]_D^{23}$ +43° (c 1·37) (Found: C, 81·0; H, 11·4. $C_{28}H_{48}O_2$ requires C, 80·7; H, 11·6%).

Ergostane-3β : 11β-*diol* (I; R = R′ = H).—3β-Hydroxyergostan-11-one (V; R = H) (12·2 g.) was reduced in 2 hr. in refluxing ethanol (300 ml.) and water (40 ml.) containing sodium borohydride (5·0 g.). Isolation with chloroform afforded the diol named above (10·3 g., 84%), irregular plates (from methanol), m. p. 173—175°, $[\alpha]_D^{20}$ +29°. A recrystallised specimen had m. p. 176—177°, $[\alpha]_D^{25}$ +28° (*c* 1·93) (this compound loses methanol of solvation only slowly) {lit.,[32] m. p. 175—176°, $[\alpha]_D^{20}$ +28°}. Residues from the early crystallisations could be oxidised, giving ergostane-3 : 11-dione (VI; X = Y = H) (1·1 g.).

With acetic anhydride and pyridine the 3β : 11β-diol gave the 3β-acetate (I; R = Ac; R′ = H), rectangular plates (from aqueous acetone), m. p. 131—133°, $[\alpha]_D^{26}$ +20° (*c* 1·52) (Found: C, 78·1; H, 11·2. Calc. for $C_{30}H_{52}O_3$: C, 78·2; H, 11·4%) {lit.,[7c] m. p. 134—135°, $[\alpha]_D^{20}$ +25°}. The 3β-*formate* (I; R = CHO; R′ = H) was made by formylation [6] of the diol (I; R = R′ = H) (1·0 g.) either with acetic–formic anhydride [acetic anhydride (1·35 ml.), 98% formic acid (0·45 ml.), at 0° for 2 hr.] in chloroform (10 ml.) and pyridine (1·8 ml.) for 20 hr., or with 98% formic acid (5 ml.) in pure benzene or ethyl formate (75 ml.), refluxed for 24 hr.; it crystallised from hexane as rods, m. p. 125—128°, $[\alpha]_D^{25}$ +20° (*c* 1·1) [Found: C, 77·7; H, 11·2; CHO, 7·1 (by saponification). $C_{29}H_{50}O_3$ requires C, 78·0; H, 11·3; CHO, 6·5%]. This ester was hydrolysed in 2 days at 20° in methanol (80 ml.) and water (10 ml.) containing potassium hydrogen carbonate (2 g.).

The 3β-acetate was also made as follows. The ketol acetate [4] (V; R = Ac) (1·0 g.) was reduced in refluxing tetrahydrofuran (100 ml.) and ethyl acetate (10 ml.) in 3·5 hr. with lithium borohydride (1·0 g.). Careful neutralisation and isolation gave the ester (I; R = Ac; R′ = H) in 86% yield.

11β-*Hydroxyergostan*-3-*one* (II; R = H).—(i) A solution of ergostane-3β : 11β-diol (I; R = R′ = H) (20 g.) in toluene (830 ml.) and *cyclo*hexanone (156 ml.) was distilled to dehydrate it. Aluminium *iso*propoxide (10·4 g.) in anhydrous toluene (104 ml.) was added and the Oppenauer oxidation carried out for 1 hr. in the usual way.[10] The isolated steroid was triturated with light petroleum (b. p. 40—60°; 50 ml.), and the solid *ketol* (II; R = H) (15·2 g., 77%), m. p. 168—174°, $[\alpha]_D^{24}$ +40° (*c* 0·9), filtered off. Crystallisation from methanol gave needles, m. p. 172—174°, $[\alpha]_D^{23}$ +39° (*c* 1·14), giving a precipitate with Brady's reagent (Found: C, 80·9; H, 11·5. $C_{28}H_{48}O_2$ requires C, 80·7; H, 11·6%).

(ii) To a suspension of Raney nickel (20 g.) in sulphur-free toluene (270 ml.) and *cyclo*hexanone (60 ml.) previously refluxed over Raney nickel [33–35] was added the 3 : 11-diol (I; R = R′ = H) (10 g.). The mixture was refluxed for 48 hr. in an anhydrous atmosphere. The steroid obtained after filtration (to remove the nickel) was chromatographed on alumina (Grade H). Light petroleum–ether eluted the ketol (II; R = H), which crystallised from methanol as needles (5 g., 51%), m. p. 171—173°, $[\alpha]_D^{23}$ +40° (*c* 0·7). From ether–chloroform eluates some diol (I; R = R′ = H) (1·98 g.) was recovered.

A solution of the ketol in 0·125N-ethereal hydrogen bromide was stable for at least 0·25 hr.; the ketol could then be recovered efficiently.

3β : 11β-*Diacetoxyergostane* (I; R = R′ = Ac).—The diol (I; R = R′ = H) (5·0 g.) was esterified under nitrogen by acetyl chloride (10 ml.) and *NN*-dimethylaniline (25 ml.) in refluxing benzene (80 ml.) and toluene (40 ml.).[10] The diacetate (I; R = R′ = Ac) (5·33 g., 89%) separated as rods (from methanol), m. p. 117—119°, $[\alpha]_D^{21}$ +30° (*c* 1·06), similar in properties to a specimen described in the literature.[7c] Complete hydrolysis of this diacetate (0·50 g.) occurred in 24 hr. in refluxing 2N-ethanolic potassium hydroxide (50 ml.); with methanolic alkali the conversion was slower.

11β-*Acetoxyergostan*-3β-*ol* (I; R = H; R′ = Ac).—The diacetate (I; R = R′ = Ac) (0·50 g.)

[32] Crawshaw, Henbest, Jones, and Wagland, *J.*, 1955, 3420.
[33] Cf. Kleiderer and Kornfeld, *J. Org. Chem.*, 1948, **13**, 455; Mosettig and Scheer, *ibid.*, 1952, **17**, 764.
[34] Pietro and Traverso, *Gazzetta*, 1952, **82**, 540.
[35] *Org. Synth.*, 1941, **21**, 15.

was hydrolysed for 65 min. in 0·5N-methanolic potassium hydroxide (30 ml.). Two crystallisations of the isolated steroid from methanol yielded the hydroxy-ester (I; R = H; R′ = Ac) (0·18 g.) as needles, m. p. 136—138°, $[\alpha]_D^{24}$ +38° (*c* 0·99) (Found: C, 78·5; H, 11·6. Calc. for $C_{30}H_{52}O_3$: C, 78·2; H, 11·4%). {Crawshaw *et al.*[32] give m. p. 140—141°, $[\alpha]_D^{20}$ +50°, for this compound.}

3β : 11β-*Diformyloxyergostane* (I; R = R′ = CHO).—Chloroform (10 ml.) containing acetic anhydride (5 ml.) was cooled to 0° and " AnalaR " 98—100% formic acid (1·82 ml.) added. The solution was kept at 0° for 2 hr.; the diol (I; R = R′ = H) (0·50 g.) in chloroform (15 ml.) was added, the solution refluxed for 20 hr., and the steroid isolated. The *formate* (I; R = R′ = CHO) (0·30 g.), m. p. 100—101°, $[\alpha]_D^{26}$ +35° (*c* 1·0), crystallised as needles from acetonitrile (Found: C, 76·1; H, 10·6. $C_{30}H_{50}O_4$ requires C, 75·9; H, 10·6%). In refluxing methylene dichloride, ether, ethyl bromide, and methyl formate only mono-esterification occurred in the foregoing conditions. An attempt at formylating the diol by means of formic acid and trifluoroacetic anhydride [36] gave a mixture of esters.

The above diformate (0·50 g.) was hydrolysed completely within 2 hr. at 20° in methanol (45 ml.) and water (5 ml.) containing potassium hydroxide (1·4 g.).

11β-*Formyloxyergostan*-3β-*ol* (I; R = H; R′ = CHO).—The diol (I; R = R′ = H) (1·0 g.) was formylated as described above, and the crude product refluxed for 20 hr. in anhydrous methanol (150 ml.). Evaporation of the alcohol and crystallisation of the residue from hexane–acetonitrile and finally aqueous acetone gave the 11-*formate* (I; R = H; R′ = CHO) (0·19 g.) as needles, m. p. 94—100°, 120—131° (capillary tube), $[\alpha]_D^{22}$ +36° (*c* 0·87) (Found: C, 77·7; H, 11·4. $C_{29}H_{50}O_3$ requires C, 78·0; H, 11·3%).

Alternatively the 3β : 11β-diformate (I; R = R′ = CHO) (0·5 g.) was hydrolysed in 2 days at 20° to the 11-formate in methanol (150 ml.) and water (20 ml.) containing potassium hydrogen carbonate (2 g.).

3β-*Formyloxyergost*-9-*ene* (IX; R = CHO).—The diol (I; R = R′ = H) (0·5 g.) in 98—100% formic acid (12·5 ml.) and chloroform (5 ml.) was treated at 0° with N-perchloric acid in anhydrous acetic acid (1 ml.). Then acetic anhydride (2 ml.) in chloroform (5 ml.) was added in 0·5 hr. Slight bubbling (probably carbon monoxide) was visible. The solution was left at 0° for 5 hr., then at 20° overnight. The solution was next treated with aqueous sodium acetate, and the steroid crystallised as leaflets (0·37 g.), m. p. 108—110°, from aqueous acetone. The pure specimen of this formate (IX; R = CHO) had m. p. 110—111°, $[\alpha]_D^{22}$ +16° (*c* 1·01), $\lambda_{max.}$ 206 mμ (ε 2910). Yields nearly as good were achieved when perchloric acid was not used in the above type of experiment (cf. ref. 6) (Found: C, 81·1; H, 11·2. $C_{29}H_{48}O_2$ requires C, 81·25; H, 11·3%).

The foregoing ester (0·27 g.) was completely hydrolysed in 24 hr. at 20° with potassium hydrogen carbonate (1 g.) in water (5 ml.) and methanol (100 ml.).

11β-*Formyloxyergostan*-3-*one* (II; R = CHO).—Chloroform (20 ml.), acetic anhydride (10 ml.) and 98% formic acid (3·65 ml.) were kept at 0° for 2 hr. The ketol (II; R = H) (0·50 g.) in chloroform (30 ml.) was added and the mixture refluxed for 20 hr. The isolated steroid, crystallised twice from aqueous acetone, occurred as prisms (0·443 g., 83%), m. p. 143—148°. A pure specimen of the 11-*formate* (II; R = CHO), crystallised from acetonitrile, had m. p. 147—150°, $[\alpha]_D^{22}$ +50° (*c* 1·4) (Found: C, 79·0; H, 11·0. $C_{29}H_{48}O_3$ requires C, 78·3; H, 10·9%).

3β : 11β-*Bistrifluoroacetoxyergostane* (I; R = R′ = CF_3·CO).—The 3 : 11-diol (I; R = R′ = H) (1·0 g.) in pyridine (15 ml.) and chloroform (15 ml.) at −40° was treated with trifluoroacetic anhydride (6 ml.) in chloroform (15 ml.). The solution was set aside for 3 hr. at 20°. The steroidal product crystallised from acetonitrile as prisms (1·18 g., 81%), m. p. 120—123°, $[\alpha]_D^{26}$ +30°, of the *diester* (I; R = R′ = CF_3·CO). The specimen recrystallised for analysis had m. p. 121—123°, $[\alpha]_D^{28}$ +32° (*c* 0·81) (Found: C, 63·1; H, 8·0; F, 18·1. $C_{32}H_{48}O_4F_6$ requires C, 62·9; H, 7·9; F, 18·65%). This ester (1·0 g.) was hydrolysed completely in 3·5 hr. in 0·7N-methanolic sodium hydroxide (40 ml.).

11β-*Trifluoroacetoxyergostan*-3β-*ol* (I; R = H; R′ = CF_3·CO).—The above diester (1·0 g.) in methanol (100 ml.) was stirred during the addition in 12 min. of 0·05N-methanolic sodium hydroxide (35·0 ml., 1·05 equiv.), and then for 15 min. more. The steroid was isolated as a colourless gum (0·79 g.), giving from slightly aqueous acetonitrile crystalline 11-*ester* (I; R = H; R′ = CF_3·CO) (0·28 g.), m. p. 72—82°, 81—93° (capillary tube), $[\alpha]_D^{22}$ +41° (*c* 1·0) (Found: C, 70·1; H, 9·9. $C_{30}H_{49}O_3F_3$ requires C, 70·0; H, 9·6%).

[36] Cf. Bourne, Stacey, Tatlow, *et al.*, *J.*, 1949, 2976; 1954, 2006; *Nature*, 1951, **168**, 942.

3β-*Trifluoroacetoxyergost-9-ene* (IX; R = CF_3·CO).—The 3 : 11-diol (I; R = R′ = H) (1·0 g.) was kept [8] at 20° in trifluoroacetic anhydride (6 ml.) for 2·5 hr. Crystals began to separate after about 0·5 hr. Extraction with ether and crystallisation from acetonitrile, then aqueous acetone, gave rods of the Δ^9-*ester* (IX; R = CF_3·CO) (0·64 g., 54%), m. p. 99—101°, $[\alpha]_D^{30}$ +14° (*c* 0·88), $\lambda_{max.}$ 206 mμ (ε 4190) (Found: C, 72·4; H, 9·7. $C_{30}H_{47}O_2F_3$ requires C, 72·5; H, 9·5%). This ester (0·26 g.) was completely hydrolysed in 17·5 hr. in refluxing 0·7N-methanolic sodium hydroxide (40 ml.).

Ethyl 11β-*Hydroxyergostan*-3β-*yl Carbonate* (I; R = CO_2Et; R′ = H).—To the 3 : 11-diol (I; R = R′ = H) (1·0 g.) in pyridine (15 ml.) ethyl chloroformate (3·0 ml.) was added [9] in 2 min. The temperature rose to 55°; the solution was then heated at 80° for 1·5 hr. Crystallisation from aqueous acetone of the water-precipitated steroid gave the *ester* named above (1·1 g., 95%), m. p. 131—134°. Recrystallisation from acetone afforded laminæ (0·73 g.), m. p. 135—137°, $[\alpha]_D^{26}$ +22° (*c* 1·4), ν 1736, 1260, and 1250 cm.$^{-1}$ (Found: C, 75·9; H, 11·0. $C_{31}H_{54}O_4$ requires C, 75·9; H, 11·1%).

Ergostane-3 : 11-*dione* (VI; X = Y = H).—3β-Hydroxyergostan-11-one (V; R = H) (5·0 g.) in *tert.*-butyl alcohol (100 ml.), water (6 ml.), and pure pyridine (6 ml.) was treated with *N*-bromoacetamide (3 equiv.), the solution being left for 20 hr. under nitrogen at 20°. The isolated *dione* (VI; X = Y = H) (3·5 g., 70%) crystallised from hexane as prisms, m. p. 155—158°, $[\alpha]_D^{25}$ +61° (*c* 1·03) (Found: C, 80·7; H, 11·0. $C_{28}H_{46}O_2$ requires C, 81·1; H, 11·2%). The 3-(2 : 4-*dinitrophenylhydrazone*) formed orange plates (from ethyl acetate), m. p. 249—251° (decomp.), $[\alpha]_D^{20}$ −20° (*c* 0·16), $\lambda_{max.}$ (in $CHCl_3$) 368 mμ (ε 26,500), ν (in Nujol) 1700 cm.$^{-1}$ (Found: N, 9·2. $C_{34}H_{50}O_5N_4$ requires N, 9·4%).

2α-*Bromoergostane*-3 : 11-*dione* (VI; X = Br; Y = H).—The dione (VI; X = Y = H) (1 g.) was dissolved in glacial acetic acid (20 ml.), to which 7N-hydrogen bromide in acetic acid (0·4 ml.) was added. Bromine (0·212 g., 1·1 mol.) in glacial acetic acid was run in as the solution was swirled. The crystals (0·305 g.), m. p. 208—215°, that separated were collected and washed with water and after crystallisation from *cyclo*hexane (yield, 0·178 g.) had m. p. 215—218°, $[\alpha]_D^{20}$ +67° (*c* 1·2) (Found: C, 68·4; H, 9·0; Br, 16·6. $C_{28}H_{45}O_2Br$ requires C, 68·2; H, 9·2; Br, 16·2%). We thank Mr. R. F. K. Meredith for making this bromo-dione.

2α : 4α-*Dibromoergostane*-3 : 11-*dione* (VI; X = Y = Br).—Ergostane-3 : 11-dione (VI; X = Y = H) (2 g.) in anhydrous acetic acid (100 ml.) was treated with 7N-hydrogen bromide in acetic acid (1·5 ml.), then 0·943M-bromine in acetic acid (11·3 ml., 2·2 equiv.) was run in within 2 min., the solution being stirred. Dilution of the solution with water after 35 min. and crystallisation of the precipitate from hexane afforded rods of the 2 : 4-*dibromo-ketone* (1·57 g.; 57%), m. p. 153—156° (decomp.), $[\alpha]_D^{23}$ +38° (*c* 1·62) (Found: Br, 28·0. $C_{28}H_{44}O_2Br_2$ requires Br, 27·9%).

Ergost-4-*ene*-3 : 11-*dione* (VII).—(i) The 2 : 4-dibromo-ketone (VI; X = Y = Br) (10·0 g.) was treated with sodium iodide (5 g.) and bromoacetone in acetone (200 ml.) as described earlier.[1] The product, after dehalogenation, was chromatographed on alumina (Grade O); the benzene eluates crystallised from slightly aqueous acetonitrile, giving plates of the *ene-dione* (VII) (3·1 g., 43%), m. p. 119—122°, $[\alpha]_D^{22}$ +166°, $\lambda_{max.}$ 237·5 mμ (ε 15,400). The purest sample, plates from methanol or acetonitrile, had m. p. 120—124°, $[\alpha]_D^{26}$ +165° (*c* 1·05), $\lambda_{max.}$ 238 mμ (ε 15,400) (Found: C, 81·4; H, 10·95. $C_{28}H_{44}O_2$ requires C, 81·5; H, 10·8%). The 3-(2 : 4-*dinitrophenylhydrazone*), yellow needles, had m. p. 234—237°, $[\alpha]_D^{20}$ +400° (*c* 0·4), $\lambda_{max.}$ 389 mμ (ε 30,240), ν (in Nujol) 1703 cm.$^{-1}$ (Found: C, 69·2; H, 7·9; N, 9·5. $C_{34}H_{48}O_5N_4$ requires C, 68·9; H, 8·2; N, 9·5%).

(ii) 11β-Hydroxyergost-4-en-3-one (VIII) (0·48 g.) in "AnalaR" acetone (50 ml.) was oxidised [10,37] in 1 min. with 1·33N-potassium dichromate in 5N-sulphuric acid (2·30 ml.). The crude product (0·46 g.), m. p. 105—112°, was purified as described above, to give the pure dione (VII) (0·23 g., 49%).

2α-*Bromo*-11β-*hydroxyergostan*-3-*one* (III; X = H).—The ketol (II; R = H) (3 g.) in pure dioxan (125 ml.) was treated at 20° with bromine (1·24 g., 1·08 equiv.) in 1 min. The solution was kept for another 0·5 min., then diluted with aqueous sodium hydrogen carbonate. Rapid crystallisation of the precipitate from hexane gave plates of the 2α-*bromo-ketone* (III; X = H) (2·54 g., 71%), m. p. 140—151°, slow crystallisation of which gave needles (2·24 g., 63%), m. p. 174—177°, $[\alpha]_D^{22}$ +48° (*c* 1·0) (Found: C, 68·0; H, 9·4; Br, 15·7. $C_{28}H_{47}O_2Br$ requires

[37] Djerassi, Engle, and Bowers, *J. Org. Chem.*, 1956, **21**, 1547.

C, 67·9; H, 9·6; Br, 16·1%). Spectra of the higher-melting form showed evidence of hydrogen-bonding in Nujol mulls. Rapid crystallisation converted it into the plates.

2α : 4α-*Dibromo*-11β-*hydroxyergostan*-3-*one* (III; X = Br).—The ketol (II; R = H) (5 g.) in pure dioxan (197 ml.) at 12° was treated with a drop of 4N-hydrogen bromide in dioxan, and then bromine (3·93 g., 2·05 mol.) was added in 2 min. The solution was kept at 20° for 80 min. (by which time the rotation had stopped decreasing). The isolated steroid crystallised from ethanol, giving the 2α : 4α-*dibromo-ketone* (III; X = Br) (3·82 g., 56%), m. p. 192—200° (decomp.). Recrystallisation afforded needles (2·11 g., 33%), m. p. 213—214° (decomp.), $[\alpha]_D^{23}$ +12°. The analytical specimen had m. p. 210—212° (decomp.), $[\alpha]_D^{22}$ +10° (*c* 0·4) (Found: C, 58·5; H, 8·1; Br, 26·7. $C_{28}H_{46}O_2Br_2$ requires C, 58·6; H, 8·1; Br, 27·8%).

4α-*Bromo*-11β-*hydroxyergostan*-3-*one* (IV).—The crude 2 : 4-dibromo-compound (III; X = Br) (3·01 g.) in acetic acid (70 ml.) and methylene dichloride (25 ml.) was stirred vigorously and treated at 20° under carbon dioxide with 1·64N-chromous chloride (5·76 ml.) through a capillary jet during 1·6 hr.[1] Isolation of the steroid with methylene chloride afforded a residue (2·43 g.), $[\alpha]_D^{20}$ +21° (*c* 1·0) (Found: Br, 16·0%); trituration with acetone and filtration afforded the 4α-*bromo-ketone* (IV) (0·48 g., 14%), m. p. 173—177°, $[\alpha]_D^{21}$ +2°. Recrystallisation from methanol–ether gave the pure compound as plates (0·39 g., 11%), m. p. 170—173°, $[\alpha]_D^{25}$ −2° (*c* 1·0) (Found: C, 68·0; H, 9·7; Br, 15·65. $C_{28}H_{47}O_2Br$ requires C, 67·9; H, 9·6; Br, 16·1%).

11β-*Hydroxyergost*-4-*en*-3-*one* (VIII).—(i) The 2 : 4-dibromo-ketone (III; X = Br) (2·31 g.) was treated with sodium iodide (11·6 g.) in acetone (70 ml.) containing bromoacetone, as described earlier.[1] Dehalogenation (with chromous chloride) of the product and isolation gave the crude steroid (1·80 g.), $[\alpha]_D^{20}$ +85°. Four crystallisations from acetone gave rhombs of product (VIII) (0·75 g., 49%), m. p. 169—173°, $[\alpha]_D^{20}$ +106° (*c* 0·9), $\lambda_{max.}$ 241 mμ (ε 15,100) (Found: C, 81·3; H, 11·1. $C_{28}H_{46}O_2$ requires C, 81·1; H, 11·2%).

(ii) The 4-bromo-ketone (IV) (0·25 g.) was dehydrobrominated with semicarbazide.[1] The crude product (VIII) (0·195 g., 93%), m. p. 167—172°, obtained by decomposition of the semicarbazone, crystallised from acetone, giving the pure compound (0·175 g., 84%).

2α : 4α-*Dibromoergost*-9-*en*-3-*one* (X; X = Br).—(i) The ketol (II; R = H) (1 g.) in pure dioxan (20 ml.) at 10° was treated with 5·3N-hydrogen bromide in dioxan (3·56 ml.) and then with bromine (0·272 ml., 2·2 mole) dropwise with stirring. The solution (N with respect to hydrogen bromide) was kept at 20° for 18 min., diluted with sodium acetate solution, and extracted with ether. The isolated steroid (1·6 g.) was crystallised four times from ethanol, giving needles of the pure Δ⁹-*ketone* (X; X = Br) (0·20 g., 14%), m. p. 220—220·5° (decomp.), $[\alpha]_D^{25}$ +2° (*c* 0·92) (Found: C, 60·6; H, 8·0; Br, 27·7. $C_{28}H_{44}OBr_2$ requires C, 60·4; H, 8·0; Br, 28·7%).

(ii) The enone (X; X = H) (1 g.), stirred in acetic acid (50 ml.) to which 5·6N-hydrogen bromide in acetic acid had been added, was brominated with 0·90M-bromine in acetic acid (9·8 ml., 2·2 equiv.). A pale yellow colour remained after 3 min. and crystallisation began. The mixture was stirred for 75 min. in all, and the crystals (1·12 g., 80%), m. p. 203° (decomp.; capillary tube), were then collected and washed. Crystallisation from ethyl acetate gave needles of the pure ketone (X; X = Br) (0·82 g.), m. p. 216° (decomp.; capillary tube), with a second crop (0·22 g., total 75%), m. p. 212° (decomp.; capillary tube). A recrystallised specimen for analysis had m. p. 222° (decomp.), $[\alpha]_D^{24}$ +2° (*c* 1·6), $\lambda_{max.}$ 210 (ε 3500) and 206 mμ (ε 3360) (Found: C, 60·3; H, 8·0; Br, 28·5%).

The above dibromo-compound (472 mg.) in chloroform (20 ml.) and acetic acid (10 ml.) was stirred under nitrogen at 20° for 1 hr. with acid-washed zinc dust (2 g.). Filtration, isolation of the steroid from the filtrate, and crystallisation afforded ergost-9-en-3-one (X; X = H) (237 mg., 70%).

Ease of Conversion of Ergostane-3β : 11β-*diol and its Acetates into* Δ⁹-*Steroids*.—The diol (I; R = R′ = H), diacetate (I; R = R′ = Ac), and 3-acetate (I; R = Ac; R′ = H) were dissolved severally (100 mg. each) in chloroform (12 ml.) containing acetic anhydride (2·4 ml.). 60% Perchloric acid (0·5 ml.) was added to acetic anhydride (10 ml.) with cooling, and part (1·6 ml.) of the solution was added to each of the steroid solutions. The rotation of the diol increased just perceptibly for 2 min., then fell to $[\alpha]_D$ +11° in 35 min., darkening the while; with the diacetate the rotation fell evenly from $[\alpha]_D$ +29° to a steady +12° in 60 min., and the solution darkened; with the 3-acetate $[\alpha]_D$ +20° ⟶ 31° in 1·5 min., then reached constant $[\alpha]_D$ +16° in 24 min. (In each case the rotations were calculated from the weight of starting

material.) Each experiment afforded 3β-acetoxyergost-9-ene (IX; R = Ac) in 70% yield after addition of potassium acetate and isolation and crystallisation of the steroid.

An attempt at isolating the diacetate after 1·5 minutes' treatment of the 3-acetate gave a mixture containing (by infrared and polarimetric analysis) about 80% of the former and 20% of the Δ^9-ester (IX; R = Ac).

Ergost-9-en-3β-ol (IX; R = H).—The 3 : 11-diol (I; R = R′ = H) (10·0 g.) in chloroform (150 ml.) and acetic anhydride (30 ml.) was treated with acetic anhydride (20 ml.) to which " AnalaR " 60% w/w perchloric acid (1·0 ml.) had been added. The solution became warm and darkened. After 45 min. it was diluted with aqueous potassium acetate, and the steroid isolated and hydrolysed in 1 hr. with potassium hydroxide (24 g.) in ethanol (600 ml.). The water-precipitated product (8·0 g., 84%), m. p. 147—150°, crystallised from methanol as rhombs of the enol (IX; R = H), m. p. 148—149°, $[\alpha]_D^{23}$ +21° (*c* 0·93), $\lambda_{max.}$ 205 mμ (ε 3600) (Found: C, 83·8; H, 12·1. Calc. for $C_{28}H_{48}O$: C, 83·9; H, 12·1%). Crawshaw *et al.*[7c] give m. p. 147·5—149°, $[\alpha]_D$ +29°, for this compound, but in a letter to us Dr. Henbest writes that their pure material has m. p. 152—153°, $[\alpha]_D$ +19°. The 3β-acetate (IX; R = Ac), crystallised from methanol and aqueous acetone, had m. p. 127—129°, $[\alpha]_D^{27}$ +17° (*c* 1·76), $\lambda_{max.}$ 203 mμ (ε 4290) (Found: C, 81·5; H, 11·5. Calc. for $C_{30}H_{50}O_2$: C, 81·4; H, 11·4% {lit.,[7c,32] m. p. 128—132°, $[\alpha]_D$ +17°}.

Ergost-9-en-3-one (X; X = H).—(i) The enol (IX; R = H) (8·0 g.) in refluxing " AnalaR " acetone (400 ml.) was oxidised with 0·33M-potassium dichromate in 4N-sulphuric acid (26 ml.) added quickly;[10,37] after the solution had been stirred for another 2·5 min., the excessive oxidant was destroyed with sodium pyrosulphite. The water-precipitated *enone* (X; X = H) crystallised from aqueous acetone (charcoal) as hexagonal plates (6·75 g.; 85%), m. p. 151—153°. Recrystallised material had m. p. 153—155°, $[\alpha]_D^{25}$ +39° (*c* 1·24), $\lambda_{max.}$ 204 mμ (ε 4550) (Found: C, 84·2; H, 11·5. $C_{28}H_{46}O$ requires C, 84·4; H, 11·6%).

(ii) A solution of 11β-hydroxyergostan-3-one (II; R = H) (2 g.) in pure acetic acid (45 ml.) was treated with 6·5N-hydrogen bromide in acetic acid (8 ml.). After 15 min. aqueous sodium acetate was added and the precipitated steroid crystallised twice (from acetone and hexane), to give the enone (X; X = H) (0·05 g.), m. p. 150—152°.

Stability of the 3 : 11-*Diesters in Solvents containing Hydrogen Bromide.*—In 0·65N-hydrogen bromide in acetic acid the formate (I; R = R′ = CHO) and acetate (I; R = R′ = Ac) decomposed within a few min., the rotation tending negativewards. Pure products could not be isolated. The trifluoroacetate (I; R = R′ = CF_3·CO) was stable and recovered in 63% yield after 3 hours' treatment. All the esters withstood 0·65N-hydrogen bromide in dioxan more effectively and were recoverable in >40% yield after 0·5 hr. The diacetate was stable in 2% (v/v) ethanolic methylene dichloride made 0·13N in hydrogen bromide, from which it could be recovered in 54% yield. See method (ii) for making ergost-9-en-3-one (X; X = H).

Ergosta-4 : 9-dien-3-one (XI).—2α : 4α-Dibromoergost-9-en-3-one (X; X = Br) (210 mg.) was treated with sodium iodide (1·06 g.) in acetone (31 ml.), as previously described.[1] Dehalogenation and extraction with methylene dichloride gave a gum (160 mg.), crystallising satisfactorily after elution with ether from alumina. This solid (146 mg.) had $\lambda_{max.}$ 238 mμ ($E_{1\,cm.}^{1\%}$ 374). Two further crystallisations from acetonitrile yielded laminæ of the *dienone* (XI) (74 mg., 49%), m. p. 107—109°, $[\alpha]_D^{24}$ +69° (*c* 0·8), $\lambda_{max.}$ 239 mμ (ε 15,600) (Found: C, 85·0; H, 11·2. $C_{28}H_{44}O$ requires C, 84·8; H, 11·2%).

5α-*Pregnane derivatives*

4 : 5α-*Dihydrocortisone* (XII; R = R′ = O; R″ = H).—The 21-acetate (XII; R = R′ = O; R″ = Ac) (50 g.), suspended in refluxing methanol (1 l.), was stirred while M-potassium hydrogen carbonate (136 ml., 1·1 equiv.) was added[38] during 1·5 min. Heating and stirring were continued for another 15·5 min., and the solution cooled and neutralised cautiously with glacial acetic acid. Concentration afforded a slurry, from which the *alcohol* (XII; R = R′ = O; R″ = H) (45·3 g.) was obtained by extraction with methylene dichloride. This material, m. p. 196—205°, $[\alpha]_D^{22}$ +74°, was good enough for most purposes; successive crystallisations from methanol and acetone afforded the pure compound as needles, m. p. 217—221° (decomp.), $[\alpha]_D^{22}$ +78° (*c* 0·4), +78° (*c* 0·5 in acetone), +81° (*c* 1·0 in dioxan), +90° (*c* 1·0 in EtOH or MeOH), ν 1706 $cm.^{-1}$ (Found: C, 69·4; H, 8·3. $C_{21}H_{30}O_5$ requires C, 69·6; H, 8·3%).

[38] Cf. Reichstein and von Euw, *Helv. Chim. Acta*, 1938, **21**, 1181.

A sample of this compound described [39] with m. p. 229—233°, $[\alpha]_D^{24}$ +100°, may be the 21-acetate. Sondheimer, Batres, and Rosenkranz [39a] give m. p. 208—210°, $[\alpha]_D$ +78°, for the 21-alcohol.

Acid-catalysed hydrolysis was less efficient.[40]

17α : 21-*Dihydroxy*-3 : 3-*dimethoxy*-5α-*pregnane*-11 : 20-*dione* [XII; R = $(OMe)_2$; R′ = O; R″ = H].—4 : 5α-Dihydrocortisone (XII; R = R′ = O; R″ = H) (18·2 g.) dissolved in refluxing anhydrous methanol and yielded, on cooling, the 3 : 3-*dimethoxy-compound* (14·4 g., 64%), m. p. 172—175°, $[\alpha]_D^{22}$ +53°. The recrystallised ketal separated as needles (8·6 g., 38%), m. p. 177—181°, $[\alpha]_D^{22}$ +52° (*c* 1·1), ν 1701 and 1101 cm.$^{-1}$ (Found: C, 67·9; H, 8·9. $C_{23}H_{36}O_6$ requires C, 67·6; H, 8·9%). The 21-*acetate* [XII; R = $(OMe)_2$; R′ = O; R″ = Ac], made with acetic anhydride and pyridine or from 4 : 5α-dihydrocortisone acetate (XII; R = R′ = O; R″ = Ac) by ketalisation in the above manner, crystallised from methanol containing a trace of pyridine as plates, m. p. 205—212°, $[\alpha]_D^{22}$ +87° (*c* 0·6), ν (in $CHCl_3$) 1748, 1728, and 1708, and 1100 cm.$^{-1}$ (the spectrum of a Nujol mull gave anomalous bands in the 1725—1740 cm.$^{-1}$ region) (Found: C, 67·0; H, 8·5. $C_{25}H_{38}O_7$ requires C, 66·65; H, 8·5%).

The 3 : 3-dimethoxy-21-alcohol [XII; R = $(OMe)_2$; R′ = O; R″ = H] (1 g.) gave the 3-ketone (XII; R = R′ = O; R″ = H) (0·55 g.) by hydrolysis with acetone (45 ml.), water (5 ml.) and 2N-hydrochloric acid for 1·5 hr. at room temperature.[18]

Cholestan-3-one also formed a ketal in the foregoing conditions. However it was best made by the following method.

3 : 3-*Dimethoxycholestane*.—Cholestan-3-one (0·50 g.) was refluxed in anhydrous methanol (50 ml.) with anhydrous oxalic acid (10 mg.) for 3 hr.; the solution was then evaporated under reduced pressure to small bulk. A solid (0·53 g.), m. p. 77—79°, crystallised slowly. It was recrystallised from methanol with methylene dichloride or *tert.*-butyl alcohol (with a trace of pyridine) as a mixture of blades and needles of 3 : 3-*dimethoxycholestane*, m. p. 79—80°, $[\alpha]_D^{24}$ +23° (*c* 0·84 in 99 : 1 $CHCl_3$–pyridine) (Found: C, 80·65; H, 12·0. $C_{29}H_{52}O_2$ requires C, 80·5; H, 12·1%).

3 : 3-*Ethylenedioxy*-17α : 21-*dihydroxy*-5α-*pregnane*-11 : 20-*dione* (XII; R = O·CH_2·CH_2·O; R′ = O; R″ = H) *and the Formation of a Non-hydroxylic Ketal*.—4 : 5α-Dihydrocortisone (XII; R = R′ = O; R″ = H) (17·9 g.) was heated for 5 hr. in refluxing benzene (650 ml.) and ethylene glycol (140 ml.) containing toluene-*p*-sulphonic acid monohydrate (0·54 g.), the evolved water being separated from the azeotrope.[18] The steroidal product was separated into benzene-soluble and -insoluble fractions, the latter crystallising from acetone as rhombs of the 3-ketal (XII; R = O·CH_2·CH_2·O; R′ = O; R″ = H) (0·42 g.), m. p. 208—213°, $[\alpha]_D^{20}$ +53° (*c* 1·1), ν 1720, 1705, 1100, and 1060 cm.$^{-1}$ (Found: C, 68·1; H, 8·45. $C_{23}H_{34}O_6$ requires C, 67·95; H, 8·4%). The 21-*acetate* (XII; R = O·CH_2·CH_2·O; R′ = O; R″ = Ac), made from the above (0·2 g.) with pyridine (5 ml.) and acetic anhydride (2·5 ml.), crystallised from acetone as rods (0·19 g.), m. p. 280—281°, $[\alpha]_D^{20}$ +82° (*c* 0·85), ν 1752, 1232, 1728, 1708, 1105, and 1062 cm.$^{-1}$ (Found: C, 67·1; H, 7·9. $C_{25}H_{36}O_7$ requires C, 66·9; H, 8·1%).

The benzene-soluble fraction from the ketalisation was isolated as a gum, part of which crystallised from acetone–hexane and then from acetone as the bisketal (XIV; n = 2; R = O; R′ = H) (3·13 g.), m. p. 184—186°, $[\alpha]_D^{20}$ +36° (see below). Concentration of the mother-liquors afforded a non-hydroxylic 3-*ketal* (1·0 g.), m. p. 219—221° (from acetone), $[\alpha]_D^{20}$ +25°. Recrystallisation afforded this compound, m. p. 223—225°, $[\alpha]_D^{20}$ +29° (*c* 1·0), ν (in CS_2) 1710 and 1100 cm.$^{-1}$ but no hydroxyl bands (Found: C, 68·3; H, 8·3. $C_{27}H_{40}O_7$ requires C, 68·0; H, 8·5%).

Properties of the foregoing ketal $C_{27}H_{40}O_7$. The compound (0·5 g.) was treated [18] for 27 hr. at room temperature with acetone (40 ml.), water (4·5 ml.), and 2N-hydrochloric acid (0·375 ml.). The filtered solution was diluted with water, and the precipitate (0·48 g.), m. p. 260—266° (decomp.), crystallised from methanol as plates of a non-hydroxylic 3 : 11-*dioxo-compound* (0·33 g.), m. p. 263—268° (decomp.), $[\alpha]_D^{22}$ +47° (*c* 0·9), ν (in CS_2) 1710, 1118, and 1102 cm.$^{-1}$ (Found: C, 69·6; H, 8·4. $C_{25}H_{36}O_6$ requires C, 69·4; H, 8·4%).

Attempted hydrolysis with 8·5% aqueous sulphuric acid in methanol [18] gave no recognisable product.

The ketal (1 g.) was reduced in 2 hr. in refluxing ethanol (90 ml.) and water (15 ml.) containing

[39] Chemerda, Chamberlin, Wilson, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 4052.
[39a] Sondheimer, Batres, and Rosenkranz, *J. Org. Chem.*, 1957, **22**, 1090.
[40] Mattox and Kendall, *J. Biol. Chem.*, 1951, **188**, 287; cf. Edwards and Kellie, *Biochem. J.*, 1954, **56**, 207.

sodium borohydride (1 g.). Addition of water precipitated an 11β-*hydroxy-compound* (0·86 g.), m. p. 262—264°, $[\alpha]_D^{22}$ +29° (*c* 1·1), ν 1095 cm.$^{-1}$ (Found: C, 67·8; H, 9·2. $C_{27}H_{42}O_7$ requires C, 67·75; H, 8·85%).

None of the compounds mentioned in this section gave a colour with alkaline triphenyltetrazolium solutions.[41]

3 : 3-20 : 20-*Bisethylenedioxy*-17α : 21-*dihydroxy*-5α-*pregnan*-11-*one* (XIV; n = 2; R = O; R′ = H).—A suspension of 4 : 5α-dihydrocortisone (XII; R = R′ = O; R″ = H) (45·3 g.) in ethylene glycol (550 ml.) containing toluene-*p*-sulphonic acid hydrate (0·192 g.) was refluxed at 100—110°/16—20 mm. with an air-condenser and nitrogen leak [18] for 4·5 hr. The product was poured into water (3 l.) containing a little sodium hydrogen carbonate, and the steroid extracted with methylene dichloride. Crystallisation from ether gave the 3 : 3-20 : 20-*bis-ketal* (XIV; n = 2; R = O; R′ = H) (36 g., 64%), m. p. 176—182°, $[\alpha]_D^{22}$ +34°. The analytical specimen crystallised from acetone as needles, m. p. 184—186°, $[\alpha]_D^{20}$ +36° (*c* 1·0), ν 1680, 1052, and 1100 cm.$^{-1}$ (Found: C, 66·7; H, 8·4. $C_{25}H_{38}O_7$ requires C, 66·6; H, 8·5%). The yields were always lower when the two-phase benzene–ethylene glycol ketalisations [18] were tried. The 21-*acetate* (XIV; n = 2; R = O; R′ = Ac), made from the foregoing bisketal (0·5 g.) in pyridine (3 ml.) and acetic anhydride (1·5 ml.) overnight at room temperature, occurred as flat needles (from acetone–hexane), m. p. 197—200°, $[\alpha]_D^{23}$ +35° (*c* 1·0), ν 1750, 1230, 1690, 1186, 1095, and 1044 cm.$^{-1}$ (Found: C, 65·75; H, 8·1. $C_{27}H_{40}O_8$ requires C, 65·8; H, 8·2%).

17α : 21-*Dihydroxy*-3 : 3-20 : 20-*bis*(*trimethylenedioxy*)-5α-*pregnan*-11-*one* (XIV; n = 3; R = O; R′ = H).—4 : 5α-Dihydrocortisone (XII; R = R′ = O; R″ = H) (1 g.), benzene (36 ml.), redistilled trimethylenediol (10 ml.), and toluene-*p*-sulphonic acid (11 mg.) were heated under reflux for 20 hr. with azeotropic removal of water. Dilution with sodium hydrogen carbonate solution and extraction with methylene dichloride, and crystallisation of the product from ether and twice from acetone, gave the 3 : 3-20 : 20-*bisketal* (0·45 g., 27%), m. p. 215—219°, $[\alpha]_D^{19}$ +47° (*c* 1·0), ν 1708 and 1102 cm.$^{-1}$ (Found: C, 67·7; H, 8·6. $C_{27}H_{42}O_7$ requires C, 67·75; H, 8·85%).

20 : 20-*Ethylenedioxy*-17α : 21-*dihydroxy*-5α-*pregnane*-3 : 11-*dione* (XV; R = O; R′ = X = Y = H).—A solution of the bisketal (XIV; n = 2; R = O; R′ = H) (0·5 g.) in acetone (20 ml.) and water (3 ml.) was treated [18] with 2N-hydrochloric acid (0·25 ml.). The optical rotation of the solution was constant within 21 hr., and extraction of the steroid with methylene dichloride afforded the 3-*oxo-ketal* named above, crystallising from acetone as rods (0·31 g., 70%), m. p. 223—226°, $[\alpha]_D^{23}$ +57° (*c* 1·0), ν 1710 and 1684 cm.$^{-1}$ (Found: C, 68·15; H, 8·5. $C_{23}H_{34}O_6$ requires C, 67·95; H, 8·4%). Its 21-*acetate*, made in the usual manner, crystallised from acetone as plates, m. p. 246—250°, $[\alpha]_D^{23}$ +54° (*c* 0·8), ν 1744, 1234, and 1708 cm.$^{-1}$ (Found: C, 67·2; H, 8·0. $C_{25}H_{36}O_7$ requires C, 66·9; H, 8·1%). Hydrolysis [18] of the 3-ketal group in the bisketal was achieved in 75% yield in 50% (v/v) aqueous acetic acid at 70° for 0·5 hr.

The above 20-ketals gave no colour with alkaline triphenyltetrazolium solutions.[41] Although the rotations of their solutions in acetic acid or chloroform containing hydrogen bromide hardly changed, no pure steroid could be recovered therefrom.

3 : 3-20 : 20-*Bisethylenedioxy*-5α-*pregnane*-11β : 17α : 21-*triol* (XIV; n = 2; R = H, β-OH; R′ = H).—Sodium borohydride (1·2 g.) was added to a solution of the 11-oxo-bisketal (XIV; n = 2; R = O; R′ = H) (1·5 g.) in methanol (26 ml.) and water (5 ml.), which was then refluxed for 6 hr. Crystallisation from acetone of the steroid extracted with methylene dichloride gave the 11β-*hydroxy-bisketal* (1·0 g., 67%) as rods, m. p. 228—231°, $[\alpha]_D^{21}$ +19° (*c* 1·0), ν 1185 and 1100 cm.$^{-1}$ (Found: C, 66·6; H, 9·2. $C_{25}H_{40}O_7$ requires C, 66·35; H, 8·9%). Its 21-*acetate* was eluted from alumina (Grade H) with ether and crystallised from acetone–*cyclo*hexane as rhombs, m. p. 152—155°, $[\alpha]_D^{24}$ +18° (*c* 1·3), ν 1740, 1232, and 1095 cm.$^{-1}$ (Found: C, 65·8; H, 8·75. $C_{27}H_{42}O_8$ requires C, 65·6; H, 8·6%). (Some 11β-esterification may have accompanied the desired acetylation [7]; see below.)

11β-*Acetoxy*-3 : 3-20 : 20-*bisethylenedioxy*-5α-*pregnane*-17 : 21-*diol* (XIV; n = 2; R = H, β-OAc; R′ = H).—Toluene (8 ml.), *NN*-dimethylaniline (10 ml.), and acetyl chloride (2 ml.) were added to a solution of the bisketal (XIV; n = 2; R = H, β-OH; R′ = H) (1 g.) in benzene (16 ml.). The mixture was refluxed under nitrogen [7, 10] for 20 hr., then cooled; the steroid (1·17 g.), isolated with ether, was hydrolysed at the 21-position in 50 min. in refluxing methanol (15 ml.) and water (10 ml.) containing potassium hydrogen carbonate (0·7 g.).[38] Precipitation and crystallisation from methanol gave the 11β-*acetate* (0·77 g., 71%) as plates,

[41] Zaffaroni, *Recent Progr. Hormone Res.*, 1953, **8**, 77.

m. p. 160—163°, $[\alpha]_D^{20}$ +32° (*c* 0·84), ν 1734, 1250, and 1098 cm.$^{-1}$ (Found: C, 65·5; H, 8·3. $C_{27}H_{42}O_8$ requires C, 65·6; H, 8·6%).

The 11β : 21-*diacetate* (XIV; n = 2; R = H, β-OAc; R′ = Ac), made by simple acetylation of the above, formed solvated plates (from hexane), m. p. 115—120° (after losing solvent at 95—105°). Recrystallisation from carbon tetrachloride, then from light petroleum, and finally heating the crystals at 80°/0·1 mm. for 3 hr. gave the pure ester, m. p. 115—120°, $[\alpha]_D^{22}$ +31° (*c* 1·0), ν (in CS_2) 1750 and 1240 (21-acetate), 1730 and 1240 (11-acetate), and 1095 cm.$^{-1}$ (Found: C, 64·9; H, 8·3. $C_{29}H_{44}O_9$ requires C, 64·9; H, 8·3%).

20 : 20-*Ethylenedioxy*-11β : 17α : 21-*trihydroxy*-5α-*pregnan*-3-*one* (XV; R = H, β-OH; R′ = X = Y = H).—The bisketal (XIV; n = 2; R = H, β-OH; R′ = H) (0·58 g.) was hydrolysed at the 3-position with acetone (24 ml.), water (3·5 ml.), and 2N-hydrochloric acid (0·29 ml.) as described [18] for this purpose. The 20-*ketal* (XV; R = H, β-OH; R′ = X = Y = H) (0·25 g., 48%) crystallised from acetone as needles, m. p. 225—226°; recrystallised material had m. p. 228—230°, $[\alpha]_D^{21}$ +29° (*c* 0·85), ν 1708 and 1072 cm.$^{-1}$ (Found: C, 67·6; H, 9·0. $C_{23}H_{36}O_6$ requires C, 67·6; H, 8·9%). Its 21-*acetate* formed rhombs (from methanol), m. p. 245—251°, $[\alpha]_D^{20}$ +24° (*c* 0·7), ν 1735 and 1255, and 1708 cm.$^{-1}$ (Found: C, 66·45; H, 8·5. $C_{25}H_{38}O_7$ requires C, 66·6; H, 8·5%).

4 : 5α-*Dihydrocortisol* (XII; R = O; R′ = H, β-OH; R″ = H).—A solution of the bisketal (XIV; R = H, β-OH; R′ = H) (27 g.) in methanol (500 ml.) and 8·5% (v/v) sulphuric acid (50 ml.) was refluxed [18] for 1 hr. Isolation of the steroid with ethyl acetate and crystallisation therefrom yielded the *ketol* (XII; R = O; R′ = H, β-OH; R″ = H) (16·03 g., 74%), m. p. 234—240° (decomp.), $[\alpha]_D^{24}$ +67° (in dioxan); recrystallisation from acetone gave a specimen, m. p. 230—240° (decomp.), $[\alpha]_D^{21}$ +66° (*c* 1·1; dioxan), ν 1703 and 1692 cm.$^{-1}$ (Found: C, 69·5; H, 9·0. $C_{21}H_{32}O_5$ requires C, 69·2; H, 8·85%). Acetylation afforded the 21-acetate, m. p. 222—226°, $[\alpha]_D^{26}$ +78°, in 81% yield. Crystallisation from chloroform gave a specimen, m. p. 222—226°, $[\alpha]_D^{21}$ +81° (*c* 0·5), +80° (*c* 1·0 in dioxan), ν 1745, 1230, 1725, and 1700 cm.$^{-1}$ (Found: C, 68·1; H, 8·7. Calc. for $C_{23}H_{34}O_6$: C, 67·95; H, 8·4%). Pataki *et al.*[42] give m. p. 210—212°, $[\alpha]_D^{20}$ +69°, for this compound.

11β-*Acetoxy*-17α : 21-*dihydroxy*-5α-*pregnane*-3 : 20-*dione* (XII; R = O; R′ = H, β-OAc; R″ = H).—The 11β-acetoxy-bisketal (XIV; n = 2; R = H, β-OAc; R″ = H) (1 g.) was hydrolysed with methanolic sulphuric acid.[18] The *dione* named above was obtained from ether (as needles, 0·51 g., 62%) and then from acetone–hexane, m. p. 205—209°, $[\alpha]_D^{23}$ +60° (*c* 0·84), ν 1710, 1265, and 1700 cm.$^{-1}$ (Found: C, 68·1; H, 8·5. $C_{23}H_{34}O_6$ requires C, 67·95; H, 8·4%). The 11 : 21-*diacetate* formed solvated needles, m. p. 210—215° (after loss of solvent at 100—105°). The solvent-free compound, obtained at 100°/0·1 mm. in 2 hr., had m. p. 210—215°, $[\alpha]_D^{24}$ +85° (*c* 0·54), ν 1752 and 1225 (21-acetate), 1728 and 1245 (11β-acetate), and 1728 and 1692 cm.$^{-1}$ (Found: C, 66·8; H, 8·05. $C_{25}H_{36}O_7$ requires C, 66·9; H, 8·1%).

11β : 21-*Diacetoxy*-20 : 20-*ethylenedioxy*-17α-*hydroxy*-5α-*pregnan*-3-*one* (XV; R = H, β-OAc; R′ = Ac; X = Y = H).—This compound was made by selective hydrolysis of the bisketal (XIV; R = H, β-OAc; R′ = H) (0·63 g.) with acetone (20 ml.), water (3 ml.) and 2N-hydrochloric acid (0·25 ml.), as described before.[18] Isolation by means of methylene dichloride gave a gel which was acetylated by the usual method; the product was crystallised thrice from aqueous methanol and twice from hexane, giving needles of the 11 : 21-*diacetate* (XV; R = H, β-OAc; R′ = Ac; X = Y = H) (0·20 g., 32%), m. p. 164—166°, $[\alpha]_D^{22}$ +40° (*c* 0·6), ν (in CS_2) 1750 and 1240 (21-acetate), 1732 and 1240 (11β-acetate), 1716 and 1100 cm.$^{-1}$ (Found: C, 66·0; H, 8·4. $C_{27}H_{40}O_8$ requires C, 65·8; H, 8·2%).

21-*Acetoxy*-17α-*hydroxy*-5α-*pregn*-9-*ene*-3 : 20-*dione* (XVIII; R = Ac).—A solution of 4 : 5α-dihydrocortisol acetate (XII; R = O; R′ = H, β-OH; R″ = Ac) (1 g.) in glacial acetic acid (40 ml.) was treated under nitrogen with 5·5N-hydrogen bromide in acetic acid (8 ml.). Crystals began to separate almost at once; after 20 min. the mixture was poured into sodium acetate solution and filtered, giving the Δ^9-*compound* (XVIII; R = Ac) (0·955 g.), m. p. 240—245° (capillary; decomp.). Recrystallisation from ethyl acetate gave plates (0·88 g., 92%), m. p. 244—253° (decomp.), $[\alpha]_D^{21}$ +62° (*c* 0·5), ν 1735, 1240, 1725, 1705, 1640, and 812 cm.$^{-1}$ (Found: C, 71·2; H, 8·2. $C_{23}H_{32}O_5$ requires C, 71·1; H, 8·3%). The same conversion took place within 0·5 hr. in solution in chloroform, but the yield of the Δ^9-compound was not so good (see below). The compound (XVIII; R = Ac) consumed 1 equiv. of permonophthalic acid within a few hr.

[42] Pataki, Rosenkranz, and Djerassi, *J. Biol. Chem.*, 1952, **195**, 751.

Action of Hydrogen Bromide on Solutions of 4 : 5α-*Dihydrocortisol Acetate* (XII; R = O; R′ = H, β-OH; R″ = Ac).—The change reported above pertains to chloroform solutions made 0·082N in hydrogen bromide; in 0·03N-solutions no change occurred. With 0·125N-hydrogen bromide in methylene dichloride as solvent the elimination was studied polarimetrically: such solutions, made 0·25M in methanol, ethanol, benzyl alcohol, ethyl acetate, or ether showed diminishing rotations in <15 min.; with alcohols this trend was reversed subsequently.[43] Addition of 10% (v/v) ether prolonged the duration of change to *ca.* 32 min. Diphenyl ether had no effect. In pure acetic acid made 0·37N in hydrogen bromide the elimination finished (with crystallisation) in <20 min. In 0·125N-hydrogen bromide in dioxan as sole solvent no change occurred during 3 hr., and the 11β-alcohol (XII; R = O; R′ = H, β-OH; R′ = Ac) was recovered almost quantitatively.

21-*Acetoxy*-2α-*bromo*-20 : 20-*ethylenedioxy*-17α-*hydroxy*-5α-*pregnane*-3 : 11-*dione* (XV; R = O; R′ = Ac; X = Br; Y = H).—A solution of the 20-ketal (XV; R = O; R′ = Ac; X = Y = H) (1 g.) in pure methylene chloride (15 ml.) was brominated in 0·5 min. with bromine (0·404 g., 1·15 mol.) in the same solvent (5 ml.). The isolated *bromo-ketone* (1·12 g.) crystallised from ethyl acetate as plates (0·87 g., 81%), m. p. 238—239° (decomp.), $[\alpha]_D^{22}$ +68° (*c* 1·0), ν (in $CHBr_3$) 1735, 1230, 1725, 1698, 1100, and 819 cm.$^{-1}$ (Found: C, 56·8; H, 6·5; Br, 15·3. $C_{25}H_{35}O_7Br$ requires C, 56·9; H, 6·7; Br, 15·15%).

21-*Acetoxy*-4α-*bromo*-20 : 20-*ethylenedioxy*-17α-*hydroxy*-5α-*pregnane*-3 : 11-*dione* (XV; R = O; R′ = Ac; X = H; Y = Br).—The crude 2 : 4-dibromo-compound (XV; R = O; R′ = Ac; X = Y = Br) was made by treating the ketal (XV; R = O; R′ = Ac; X = Y = H) (5 g.) in pure methylene dichloride (75 ml.) and ether (15 ml.) at 20° with bromine (4·04 g., 2·3 mol.) in methylene chloride (45 ml.) during 17 min. (a drop of hydrogen bromide in methylene chloride was used to initiate the halogenation). The solution was then neutralised and the steroid extracted and washed (7·7 g.). This dibromo-substance (which could not be purified) was partially dehalogenated [1] in acetic acid (150 ml.), chloroform (40 ml.), and methylene dichloride (25 ml.) at −5° under carbon dioxide with 1·15N-chromous chloride (22·8 ml., 1·2 equiv.), with stirring during 15 min. The solution was kept for another 15 min., then poured into water. The extracted steroid (5·85 g.), m. p. 190—208°, $[\alpha]_D^{22}$ +35° (Found: Br, 16·2%), was fractionally crystallised from ethyl acetate, then from chloroform, giving the 4-bromo-ketal (XV; R = O; R′ = Ac; X = H; Y = Br) (0·61 g., 12%), m. p. 240—241°, $[\alpha]_D^{22}$ +24°. Other crops contained 1·73 g. (32%), m. p. >236°, $[\alpha]_D$ <+30°. (All these fractions melted with decomp.)

A specimen, recrystallised from ethyl acetate, had m. p. 240—244° (decomp.), $[\alpha]_D^{22}$ +24° (*c* 0·55), ν 1744, 1226, 1726, and 1696 cm.$^{-1}$ (Found: C, 57·1; H, 6·65; Br, 15·15. $C_{25}H_{35}O_7Br$ requires C, 56·9; H, 6·7; Br, 15·15%).

The foregoing 4-bromo-ketal (100 mg.) was converted into 21-acetoxy-20 : 20-ethylenedioxy-17α-hydroxypregn-4-ene-3 : 11-dione (XVI; R = O; R′ = Ac) (50 mg., 59%), m. p. 203—206°, *via* the semicarbazone of the latter, by the method given in a preceding paper.[1] Crystallisation from acetone–ether gave the pure product, m. p. 204—209°, $[\alpha]_D^{24}$ +152° (*c* 0·9), $\lambda_{max.}$ 237·5 mμ (ε 15,300), ν 1742, 1230, 1696, 1665, and 1616 cm.$^{-1}$ {lit.,[18] m. p. 212—215°, $[\alpha]_D^{29}$ +153°, $\lambda_{max.}$ 237—238 (ε 16,700)}.

20 : 20-*Ethylenedioxy*-11β : 17α : 21-*trihydroxypregn*-4-*en*-3-*one* (XVI; R = H, β-OH; R′ = H).—The 4-bromo-ketal (XV; R = O; R′ = Ac; X = H; Y = Br) (1·2 g.) was converted into its 3-semicarbazone; [1] without purification this was reduced in 1 hr. in refluxing ethanol (25 ml.) and water (5 ml.) containing potassium hydrogen carbonate (0·45 g.) and sodium borohydride (0·6 g.). The steroid was isolated from the neutralised product and dissolved in acetic acid (7 ml.), water (2·5 ml.) and " 50—60% " pyruvic acid (2 ml.). The solution was kept for 17·5 hr. The extracted steroid (0·28 g.) crystallised from acetone as needles (45 mg., 5%) of the *trihydroxy-ketal* (XVI; R = H, β-OH; R′ = H), m. p. 219—221°, $[\alpha]_D^{26}$ +109° (*c* 0·5), $\lambda_{max.}$ 241·5 mμ (ε 15,400), ν 1670, 1618, 865, and 1105 cm.$^{-1}$ (Found: C, 67·5; H, 8·4. $C_{23}H_{34}O_6$ requires C, 68·0; H, 8·4%).

2-*Bromo*-4 : 5α-*dihydrocortisol Acetate* (XIX).—Dihydrocortisol acetate (XII; R = O; R′ = H, β-OH; R″ = Ac) (20 g.) was dissolved in warm dioxan (200 ml.) and cooled to 23°. Bromine (2·8 ml.) was added in 20 sec., and after 1½ min. the pale yellow solution was poured into aqueous sodium hydrogen carbonate. The dry precipitate gave crystals (14·9 g., 62%), m. p. 182° (decomp.), from aqueous acetic acid. Further crystallisation from this solvent and

[43] Cf. Mattox, *J. Amer. Chem. Soc.*, 1952, **74**, 4340; Taub, Pettebone, Wendler, and Tishler, *ibid.*, 1954, **76**, 4094; Mancera, Rosenkranz, and Sondheimer, *ibid.*, 1955, **77**, 5669.

from ethyl acetate–hexane gave the pure 2-*bromo-ketone* (XIX), m. p. 185—186° (decomp.), $[\alpha]_D^{20}$ +97° (*c* 0·7), ν 1714 and 1250 cm.$^{-1}$ (Found: C, 56·4; H, 6·8; Br, 16·0. $C_{23}H_{33}O_6Br$ requires C, 56·9; H, 6·8; Br, 16·4%).

Debromination with zinc and acetic acid of the mother-liquors [1] and crystallisation of the product yielded 4 : 5α-dihydrocortisol acetate (3·42 g.). Debromination likewise of the pure bromo-compound (XIX) gave pure dihydrocortisol acetate in 72% yield.

2 : 2-*Dibromo*-4 : 5α-*dihydrocortisol Acetate* (XX).—A solution of the 2-bromo-compound (XIX) (2 g.) in dioxan (86 ml.) was treated with bromine (0·24 ml.) and 6N-hydrogen bromide in acetic acid (2 drops). The rotation reached a maximum in 15 min., and the solution was then poured into aqueous sodium hydrogen carbonate. The dried precipitate (2·18 g.), m. p. 125° (decomp.), $[\alpha]_D$ +111° (Found: Br, 26·6%), crystallised with difficulty from ethyl acetate–hexane and methylene dichloride, to give the 2 : 2-*dibromo-ketone* (XX), m. p. 155° (decomp.), $[\alpha]_D^{20}$ +161° (*c* 0·53), ν (in $CHBr_3$) 1742, 1240, and 1726 cm.$^{-1}$ (Found: C, 48·2; H, 5·7; Br, 28·7. $C_{23}H_{32}O_6Br_2$ requires C, 49·0; H, 5·7; Br, 28·3%). Crystallisation from benzene yielded a *solvate*, m. p. 139—142° (decomp.), $[\alpha]_D^{20}$ +134° (*c* 1·0), with the foregoing bands in the infrared spectrum and an additional peak at 1485 cm.$^{-1}$ (benzene) (Found: Br, 24·0. $C_{23}H_{32}O_6Br_2,C_6H_6$ requires Br, 25·0%). Debromination with zinc and acetic acid gave pure 4 : 5α-dihydrocortisol acetate in 89% yield.

Bromination of the ketone (XIX) in methylene dichloride and *tert.*-butyl alcohol (3 : 1) for 3 hr. yielded 2-bromo-4 : 5α-dihydrocortisone acetate, debromination of which gave 4 : 5α-dihydrocortisone acetate.[1] Attempts at base-catalysed bromination [1] gave similar results.

Cortisol Acetate (XIII; R = H, β-OH; R′ = Ac).—4 : 5α-Dihydrocortisol acetate (XII; R = O; R′ = H, β-OH; R″ = Ac) (1 g.) in dioxan (43 ml.) was treated with 4N-hydrogen bromide in dioxan (1 drop) and bromine (0·863 g.) in 45 sec. The pale yellow solution was kept at 20° for 50 min. and neutralised with sodium hydrogen carbonate in much water. The precipitated dibromo-compound (1·145 g.), $[\alpha]_D^{18}$ +47° (Found: Br, 28·5%), was treated with sodium iodide (3·6 g.) in acetone (60 ml.) containing bromoacetone, as described previously.[1] Segregation of the αβ-unsaturated ketone in the product by means of its Girard derivative and crystallisation from ethyl acetate, then from acetone, gave rhombs (0·10 g., 10%) of cortisol acetate, m. p. 215—221°, $[\alpha]_D^{24}$ +158° (*c* 0·6 in dioxan), $\lambda_{max.}$ 242 mμ (ε 15,200), ν (in $CHCl_3$) 1745, 1726, 1664, and 1618 cm.$^{-1}$ (Found: C, 68·5; H, 7·95. Calc. for $C_{23}H_{32}O_6$: C, 68·3; H, 8·0%) {lit.,[44] m. p. 218—221·5°, $[\alpha]_D^{25}$ +158° (in dioxan), $\lambda_{max.}$ (in MeOH) 242 mμ (ε 15,350)}.

21-*Acetoxy*-17α-*hydroxypregna*-4 : 9-*diene*-3 : 20-*dione* (XVII).—The Δ^9-steroid (XVIII; R = Ac) (1·2 g.) in suspension in anhydrous methylene dichloride (27 ml.) and ether (6 ml.) was treated with bromine (0·349 ml., 2·2 mol.) in methylene chloride (2 ml.). The first mol. of halogen was consumed within 4 min., during which most of the steroid dissolved and was reprecipitated. Consumption of the second mol. took another 7·5 min., and resulted in a pale yellow solution, which was kept for another 6 min. before being washed with sodium hydrogen carbonate and water. The extracted steroid was treated with sodium iodide (2·5 g.) and acetone (25 ml.) containing bromoacetone, as previously described.[1] Subsequent dehalogenation and purification of the product (1·2 g.) by means of Girard derivatives afforded material (0·5 g.) of low ultraviolet absorption, probably being mainly the starting material (XVIII; R = Ac) (see below). The more stable Girard reagent yielded material (0·54 g.) crystallising from acetone (charcoal) as flat rods (0·37 g.) of the solvated *diene-dione* (XVII), m. p. 231—234° (slight decomp.), with loss of solvent at 110—120°. Drying at 140°/0·1 mm. furnished the solvent-free compound (0·315 g., 26%), $[\alpha]_D^{21}$ +124° (*c* 0·87), $\lambda_{max.}$ 239 mμ (ε 16,400), ν 1745, 1240, 1723, 1655, and 1618 cm.$^{-1}$. Graber *et al.*[2] give m. p. 231·5—234·5°, $[\alpha]_D^{22}$ +124°, $\lambda_{max.}$ (in MeOH) 240 mμ (ε 15,800), and Bernstein *et al.*[45] m. p. 239·5—241°, $\lambda_{max.}$ 238·5—240 mμ (ε 16,600), ν 1775, 1730, 1660, and 1620 cm.$^{-1}$

During the isolation of the Girard derivatives above, insoluble material, $\lambda_{max.}$ 267 mμ ($E_{1\,cm.}^{1\%}$ 228), was precipitated. Treatment with acid generated the 4 : 5-dihydro-compound (XVIII; R = Ac), which was combined with material got from the Girard derivative that had stayed in solution. It seemed possible that the use of the Girard derivatives was unnecessary, the separation being achieved by crystallisation.

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[44] Wendler, Graber, Jones, and Tishler, *J. Amer. Chem. Soc.*, 1952, **74**, 3630.
[45] Bernstein, Littell, and Williams, *ibid.*, 1953, **75**, 4830.