807. *The Preparation of 9α-Fluoro-analogues of Cortisol Acetate and Prednisolone Acetate from 11 : 20-Diketones of the 5α-Series.**

By J. Elks, G. H. Phillipps, and W. F. Wall.

3β : 17-Dihydroxy-5α-pregnane-11 : 20-dione and 3β-acetoxy-5α-pregn-16-ene-11 : 20-dione have been converted *via* 20-ethylene ketals into 3β : 11β : 17-trihydroxy-5α-pregnan-20-one. Dehydration to the $\Delta^{9:11}$-compound, acetoxylation at $C_{(21)}$, and oxidation gave 21-acetoxy-17-hydroxy-5α-pregn-9(11)-ene-3 : 20-dione. Formation of the 9β : 11β-epoxide and reaction with hydrogen fluoride then gave the 9α-fluoro-4 : 5α-dihydro-derivative of cortisol acetate, which was converted into the 9α-fluoro-analogues of cortisol acetate and of prednisolone acetate.

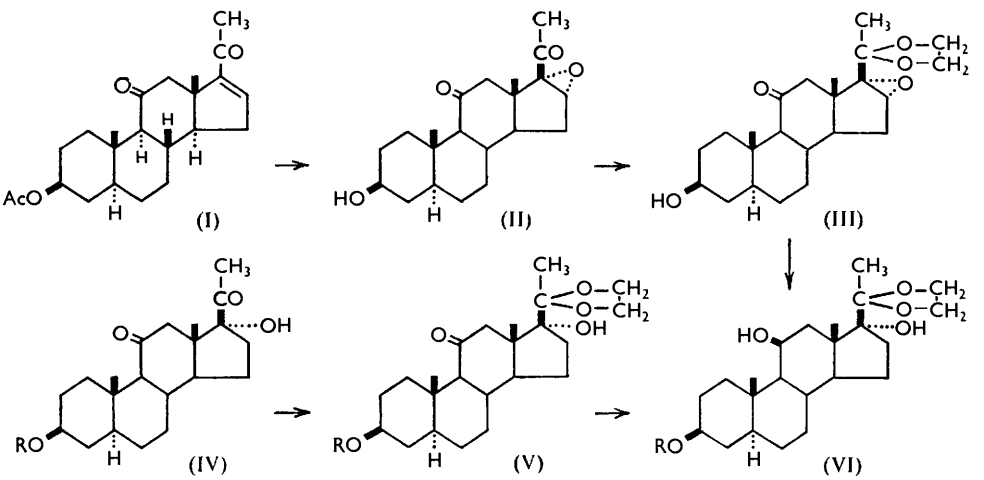
The high glucocorticoid activity of the 9α-fluoro-analogues of cortisol (11β : 17 : 21-trihydroxypregn-4-ene-3 : 20-dione) [1] and prednisolone (11β : 17 : 21-trihydroxypregna-1 : 4-diene-3 : 20-dione) [1b, 2] led us to examine their preparation from compounds of the 5α-series,

* In this paper acceptance of recent I.U.P.A.C. recommendations is anticipated: the name 5α-pregnane is used in place of *allo*pregnane (see *J.*, 1951, 3527).

[1] (*a*) Fried and Sabo, *J. Amer. Chem. Soc.*, 1954, **76**, 1455; 1957, **79**, 1130; (*b*) Hirschmann, Miller, Wood, and Jones, *ibid.*, 1956, **78**, 4956.

[2] (*a*) Hirschmann, Miller, Beyler, Sarett, and Tishler, *ibid.*, 1955, **77**, 3166; (*b*) Fried, Florey, Sabo, Herz, Restivo, Borman, and Singer, *ibid.*, p. 4181; (*c*) Hogg, Lincoln, Nathan, Hanze, Schneider, Beal, and Korman, *ibid.*, p. 4438; (*d*) Vischer, Meystre, and Wettstein, *Helv. Chim. Acta*, 1955, **38**, 1502; (*e*) Meystre, Frey, Voser, and Wettstein, *ibid.*, 1956, **39**, 734.

intermediate in the synthesis of cortisone from hecogenin. 3β : 17-Dihydroxy-5α-pregnane-11 : 20-dione [3] (IV; R = H) was a convenient starting material, since the formation from it of the 20-ketal [4] (V; R = H) was much more efficient than the ketalisation of 17 : 21-dihydroxy-20-oxo-steroids.[5] Reduction of the 20-ketal (V; R = H) with sodium borohydride gave an excellent yield of the 11β-alcohol (VI; R = H) with no significant quantity of the 11α-epimer.[5,6]

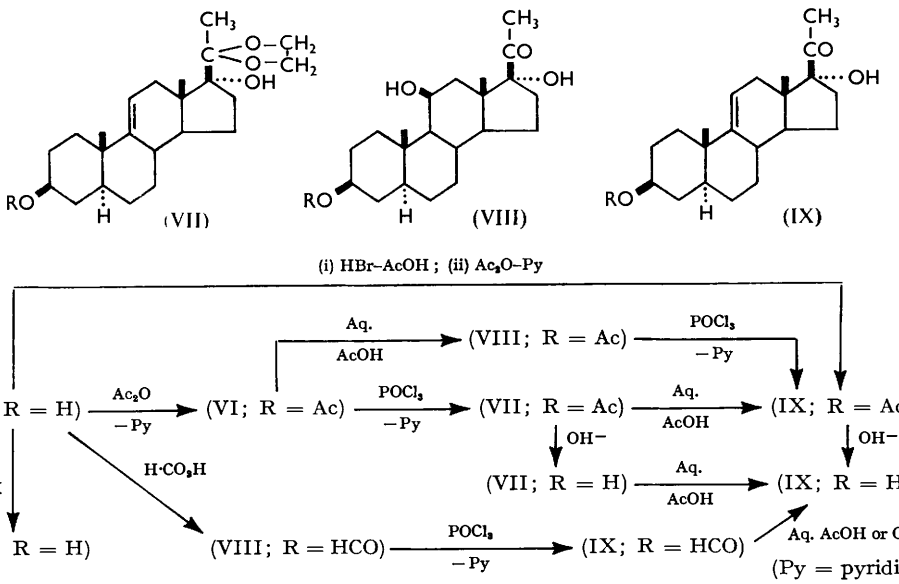


A shorter but lower-yielding route to the 11β-alcohol (VI; R = H) began with 3β-acetoxy-5α-pregn-16-ene-11 : 20 dione (I).[7] Reaction of this compound with alkaline hydrogen peroxide [3b] gave the 16α : 17-epoxide (II) which was in turn converted into its 20-ethylene ketal (III).[8] Reversal of the order of these reactions was not satisfactory, ketalisation of the 16-en-20-one [8] giving only a poor yield. Lithium aluminium hydride reduced both the 11-oxo- and the 16α : 17-epoxy-group of the 20-ketal (III) and gave the 11β : 17-diol (VI; R = H). Sodium borohydride, on the other hand, reduced only the 11-oxo-group, with formation of the 20-ethylene ketal of 16α : 17-epoxy-3β : 11β-dihydroxy-5α-pregnan-20 one.

Since an 11β-hydroxy-group may undergo oxidation [5c,9] or elimination [5c] during acid-catalysed bromination (such as is required at $C_{(21)}$ during some stage of the synthesis), the triol (VI; R = H) was next converted into the $\Delta^{9(11)}$-20-ketone (IX; R = H). Of the several routes examined, and shown in the chart (p. 4003), we preferred the one involving protection of the 3β-hydroxyl of (VI; R = H) as acetate, dehydration with phosphorus oxychloride in pyridine to the $\Delta^{9(11)}$-compound (VII; R = Ac), deketalisation with aqueous acetic acid to the 20-ketone (IX; R = Ac) and alkaline hydrolysis to the required 3β : 17-dihydroxy-5α-pregn-9(11)-en-20-one (IX; R = H). In the dehydration stage, low yields resulted from the use of pure dry reagents; however, addition of water [10] or phosphoric acid (but not of pyridine hydrochloride) allowed dehydration to proceed satisfactorily.

[3] (*a*) Barton, Evans, Hamlet, Jones, and Walker, *J.*, 1954, 747; (*b*) Pataki, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1952, **74**, 5615.
[4] Djerassi, Batres, Romo, and Rosenkranz, *ibid.*, p. 3634; U.S.P. 2,702,291.
[5] (*a*) Antonucci, Bernstein, Heller, Lenhard, Littell, and Williams, *J. Org. Chem.*, 1953, **18**, 70; (*b*) Levin, Magerlein, McIntosh, Hanze, Fonken, Thompson, Searcy, Scheri, and Gutsell, *J. Amer. Chem. Soc.*, 1954, **76**, 546; (*c*) Evans, Green, Hunt, Long, Mooney, and Phillipps, *J.*, 1958, 1529.
[6] Oliveto, Clayton, and Hershberg, *J. Amer. Chem. Soc.*, 1953, **75**, 486; Magerlein and Levin, *ibid.*, p. 3654; Allen, Bernstein, and Littell, *ibid.*, 1954, **76**, 6116.
[7] Cameron, Evans, Hamlet, Hunt, Jones, and Long, *J.*, 1955, 2807.
[8] Cf. Bernstein, Heller, and Stolar, *J. Amer. Chem. Soc.*, 1954, **76**, 5674.
[9] Oliveto, Gerold, Weber, Jorgensen, Rausser, and Hershberg, *ibid.*, 1953, **75**, 5486.
[10] Graber, Haven, and Wendler, *ibid.*, p. 4722; Kemp, Kappas, Salamon, Herling, and Gallagher, *J. Biol. Chem.*, 1954, **210**, 123.

By avoiding purification of the intermediates, it was possible to obtain the pure $\Delta^{9(11)}$-compound (IX; R = Ac) in 74% yield from the 3β : 11β : 17-triol (VI; R = H).



The action of hydrogen bromide on the 3β : 11β : 17-triol (VI; R = H) caused elimination of the 11β-hydroxyl group [5c] and concurrent hydrolysis of the 20-ketal, but this route to the acetate (IX; R = Ac), although short, gave a low yield.

The product was identical with a sample prepared from hecogenin by a different route [11] and kindly supplied by Dr. R. K. Callow.

The 9 : 11-double bond of the 20-ketone (IX; R = H) did not seriously interfere with the bromination to the 21-bromo-20-ketone (X; R = H), provided this was done in chloroform containing alcohol and saturated with hydrochloric acid.[12] The crude bromo-compound with potassium acetate in acetone gave the 21-acetoxy-compound (XI; R = H), which was separated from unchanged 20-ketone (IX; R = H) and other reactive ketones by making use of its unreactivity to Girard reagent P.[13] Oxidation of the 3β-hydroxy-group of the monoacetate (XI; R = H) by chromic acid in acetone [14] gave 21-acetoxy-17-hydroxy-5α-pregn-9(11)-ene-3 : 20-dione (XII), identical with a specimen prepared from the 4 : 5α-dihydro-derivative of cortisone acetate.[5c]

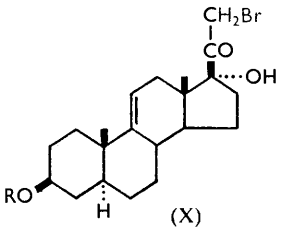
The 3β-hydroxy-20-ketone (IX; R = H) was very sparingly soluble in most solvents, and we examined the bromination and acetolysis of two of its more soluble derivatives. The 3-acetate (IX; R = Ac) was satisfactorily converted into the 3 : 21-diacetate (XI; R = Ac), but this was not taken further, since its conversion into the required 3-oxo-compound (XII) promised to be difficult. Bromination of the formate (IX; R = HCO) in methylene chloride containing ether, and subsequent addition of methanol to the acid solution, gave the 21-bromo-3β-alcohol (X; R = H), which was then converted into the 21-acetate (XI; R = H), but the overall yield was lower than that obtained by bromination of the 3β-hydroxy-compound (IX; R = H).

The introduction of a 4 : 5-double bond into $\Delta^{9(11)}$-3-ketones of the 5α-series is described elsewhere.[5c] We hoped that some of the difficulties of the reaction could be lessened if

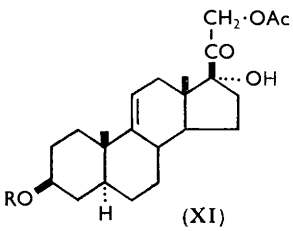
[11] Callow and James, *J.*, 1956, 4739.
[12] B.P. 761,009.
[13] B.P. 762,716; 757,803.
[14] Brooks, Hunt, Long, and Mooney, *J.*, 1957, 1175.

ring c contained a less reactive grouping than a double bond, and we therefore next investigated the conversion of the $\Delta^{9(11)}$-3-ketone (XII) into the fluorohydrin (XX).

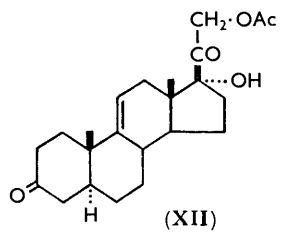
The 9 : 11-double bond of the compound (XII) reacted with *N*-bromoacetamide in aqueous dioxan, with perchloric acid as catalyst, but, unlike the bromohydrins from



(X)

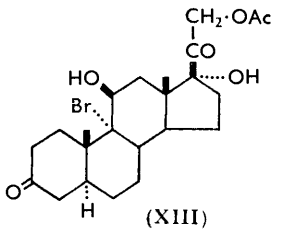


(XI)



(XII)

$\Delta^{4:9(11)}$-3-ketones [1a] and $\Delta^{1:4:9(11)}$-3-ketones [2b, 2c] described in the literature, the bromohydrin (XIII) lost bromine on attempted isolation. The crude products showed excess carbonyl absorption in the infrared region, possibly owing to formation of an 11-oxo-group



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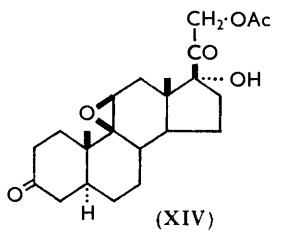
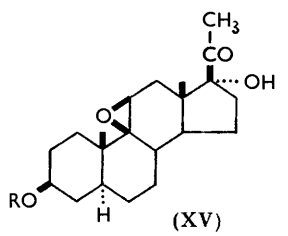
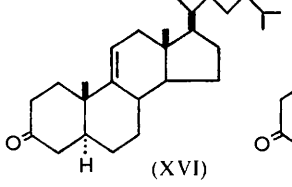


(XIV)

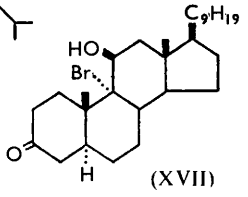


(XV)

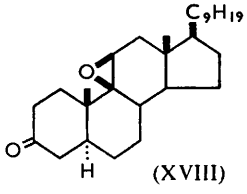
(see below). The 9β : 11β-epoxide (XIV) was, however, obtained by ring closure of the unisolated bromohydrin with alkali and subsequent re-acetylation. Reaction of the epoxide with hydrogen bromide would be expected to regenerate the bromohydrin (XIII),[1a] but this product also was too unstable to be isolated. The bromohydrin derived from the simpler $\Delta^{9:11}$-compound (IX; R = H) was also found to be unstable (cf. ref. 11), but again the epoxide (XV; R = H) could be formed with alkali *in situ*.



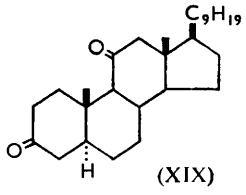
(XVI)



(XVII)



(XVIII)



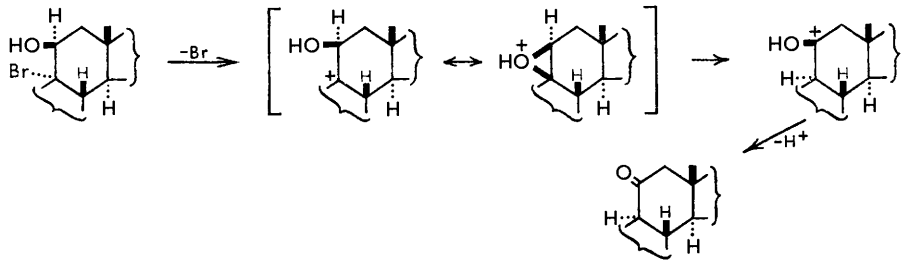
(XIX)

In model experiments ergost-9(11)-en-3-one (XVI) [5c] reacted with *N*-bromoacetamide to give crystallisable 9α-bromo-11β-hydroxyergostan-3-one [15] (XVII), which on treatment with potassium acetate in boiling ethanol [1] or when boiled in ethanol alone yielded mixtures of the 9β : 11β-epoxide (XVIII) and ergostane-3 : 11-dione (XIX). The formation of the latter compound recalls the acid isomerisation in the cholanic acid series of a 9α : 11β-diol to the corresponding 11-ketone; [16] the unusual *cis*-elimination was attributed to the intermediate formation of a 9-carbonium ion; a similar mechanism may operate in the formation of our ketone (XIX).

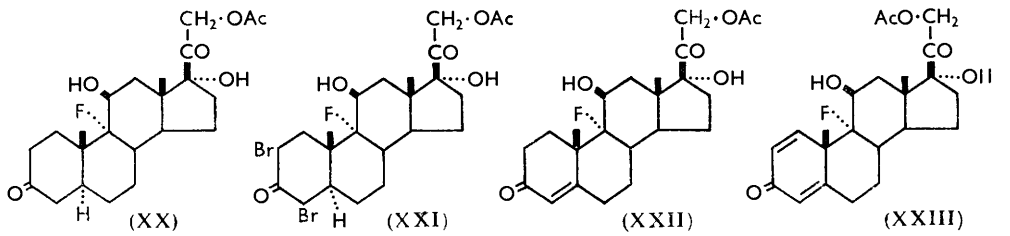
Ring closure of the bromohydrin (XVII) to the 9β : 11β-epoxide (XVIII) was achieved in good yield by the use of potassium *tert.*-butoxide in *tert.*-butyl alcohol at room temperature.[15]

[15] Cf. Henbest, Jones, Wagland, and Wrigley, *J.*, 1955, 2477.
[16] Heyman and Fieser, *J. Amer. Chem. Soc.*, 1951, **73**, 5252.

Reaction of the 9β : 11β-epoxide (XIV) with hydrogen fluoride in chloroform [1] gave the 9α-fluoro-11β-alcohol (XX), whose physical properties agreed with those reported [2a, b] for



material prepared by hydrogenation of the 9α-fluoro-derivative (XXII) of cortisol acetate. Dibromination in acetic acid and acid-catalysed rearrangement then gave the crude 2 : 4-dibromo-3-ketone (XXI), which was used without purification. Treatment with sodium iodide in acetone containing bromoacetone [17] and subsequent deiodination with chromous chloride gave a crude product containing both the saturated 3-ketone (XX) and



the Δ^4-3-ketone (XXII). Separation with Girard reagent P and chromatography gave a low yield of the 9α-fluoro-derivative (XXII) of cortisol acetate.

The crude dibromo-3-ketone (XXI) was also dehydrobrominated by means of semicarbazide, as described elsewhere for an analogue.[18] Separation with Girard reagent P [19] and chromatography of the unreactive ketones gave a very low yield of the 9α-fluoro-derivative (XXIII) of prednisolone acetate which was identified by infrared spectroscopy and, as expected, had powerful liver glycogen activity.

Experimental

Rotations were determined on *ca.* 1% solutions in $CHCl_3$, and ultraviolet spectra in ethanol, unless otherwise stated. M. p.s were taken on a Kofler block. A Perkin–Elmer model 21 double-beam spectrophotometer equipped with rock-salt optics was used for the determination of infrared spectra.

3β : 17-*Dihydroxy*-5α-*pregnane*-11 : 20-*dione* 20-*Ethylene Ketal* (V; R = H).—3β : 17-Dihydroxy-5α-pregnane-11 : 20-dione (IV; R = H) (20 g.) and toluene-*p*-sulphonic acid (0·3 g.) were refluxed for 2½ hr. (air condenser) in dry ethylene glycol (1 l.) at 100°/20 mm., with a nitrogen leak. The steroid dissolved in about 20 min. and the ketal then began to crystallise. The cooled suspension was poured into water (*ca.* 10 l.) containing an excess of sodium hydrogen carbonate, and after 1 hr. the precipitate was collected, washed with water, and dried at 90°/20 mm. The product (21·48 g., 95·5%) had m. p. 252—255°, $[\alpha]_D$ +31°, and on crystallisation from aqueous methanol containing a drop of pyridine it gave the 20-*ketal*, m. p. 254—257°, $[\alpha]_D$ +30·6° (Found: C, 70·5; H, 9·0. $C_{23}H_{36}O_5$ requires C, 70·4; H, 9·2%), $\nu_{max.}$ (in Nujol) 3450 (OH), 1692 (ketone), and 1082 and 1044 $cm.^{-1}$ (ketal).

The diol was acetylated with pyridine and acetic anhydride overnight at room temperature. The 3-*monoacetate* (V; R = Ac) separated from methanol with a drop of pyridine as needles,

[17] Evans, Hamlet, Hunt, Jones, Long, Oughton, Stephenson, Walker, and Wilson, *J.*, 1956, 4356.
[18] B.P. 788,306.
[19] B.P. 788,307.

m. p. 197—199°, $[\alpha]_D$ +17° (Found: C, 69·1; H, 8·8. $C_{25}H_{38}O_6$ requires C, 69·1; H, 8·8%), $\nu_{max.}$ (in CS_2) 3620 (OH), 1734 and 1240 (OAc), 1706 (ketone), and 1080 and 1044 cm.$^{-1}$ (ketal).

3β-*Hydroxy*-5α-*pregn*-16-*ene*-11 : 20-*dione* 20-*Ethylene Ketal*.—3β-Acetoxy-5α-pregn-16-ene-11 : 20-dione (I) (5·0 g.) was treated as above for 4 hr. at 95°/15 mm. with toluene-*p*-sulphonic acid (150 mg.) and dry ethylene glycol (125 ml.). The pink solution was cooled and poured into water (800 ml.) containing an excess of sodium hydrogen carbonate, and the product was extracted into ether. Removal of the solvent from the washed and dried extract left a froth, which was boiled under reflux for 30 min. in methanol (100 ml.) and aqueous 2N-sodium hydroxide (25 ml.). Addition of water to the cooled solution precipitated a gummy solid (3·3 g.) which, after two crystallisations from aqueous methanol containing a drop of pyridine, gave the 20-*ketal* as a solvate, m. p. 112—115°. After desolvation at 110°/0·1 mm. it had m. p. 150—155° (Found: C, 73·9; H, 9·0. $C_{23}H_{34}O_4$ requires C, 73·8; H, 9·15%), $\nu_{max.}$ (in Nujol) 3550 and 3300 (OH), 1698 (ketone), and 1190 cm.$^{-1}$ (ketal).

16α : 17-*Epoxy*-3β-*hydroxy*-5α-*pregnane*-11 : 20-*dione* (II).—3β-Acetoxy-5α-pregn-16-ene-11 : 20-dione (I) (1·0 g.) in methanol (50 ml.) was treated at room temperature with aqueous 4N-sodium hydroxide (2·0 ml.) and hydrogen peroxide (100-vol.; 4·0 ml.) and then kept at 0—5° for 16 hr. Dilution of the suspension with water and filtration gave a crystalline product (0·76 g.), m. p. 170—173° which, on recrystallisation from aqueous methanol, yielded the *epoxide* as plates, m. p. 173—175°, $[\alpha]_D$ +90° (Found: C, 72·7; H, 8·3. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%), $\nu_{max.}$ (in Nujol) 3520 (OH), 1708 and 1695 (ketones), and 994 and 852 cm.$^{-1}$ (epoxide): it had only general absorption in the ultraviolet region.

16α : 17-*Epoxy*-3β-*hydroxy*-5α-*pregnane*-11 : 20-*dione* 20-*Ethylene Ketal* (III).—The foregoing epoxide (1·0 g.) was treated in the usual way for 2½ hr. at 95°/13 mm. with toluene-*p*-sulphonic acid (20 mg.) and dry ethylene glycol (50 ml.). The pink solution was poured into water (300 ml.) containing an excess of sodium hydrogen carbonate, and the product was isolated with chloroform. Crystallisation from methanol gave plates (480 mg., 43%), m. p. 164—167°. After further crystallisation, the 20-*ketal* had m. p. 177—179° (after a change of crystal form at 170—173°) and $[\alpha]_D$ +67° (Found: C, 70·9; H, 8·8. $C_{23}H_{34}O_5$ requires C, 70·7; H, 8·8%), $\nu_{max.}$ (in Nujol) 1704 (ketone) and 1194 cm.$^{-1}$ (ketal).

16α : 17-*Epoxy*-3β : 11β-*dihydroxy*-5α-*pregnan*-20-*one* 20-*Ethylene Ketal*.—16α : 17-Epoxy-3β-hydroxy-5α-pregnane-11 : 20-dione 20-ethylene ketal (100 mg.) and sodium borohydride (100 mg.) were boiled together under reflux for 3 hr. in ethanol (10 ml.) and water (2 ml.). The solution was diluted with water and concentrated *in vacuo* to yield crystals (95 mg.), m. p. 168—172°. Further crystallisation from aqueous methanol gave 16α : 17-*epoxy*-3β : 11β-*dihydroxy*-5α-*pregnan*-20-*one* 20-*ethylene ketal* as needles, m. p. 169·5—173°, $[\alpha]_D$ +43° (Found: C, 70·2; H, 9·1. $C_{23}H_{36}O_5$ requires C, 70·4; H, 9·2%), $\nu_{max.}$ (in Nujol) 3500 (OH) and 1180 cm.$^{-1}$ (ketal).

3β : 11β : 17-*Trihydroxy*-5α-*pregnan*-20-*one* 20-*Ethylene Ketal* (VI; R = H).—(a) *From* 3β : 17-*dihydroxy*-5α-*pregnane*-11 : 20-*dione* 20-*ethylene ketal* (V; R = H). The 11-ketone (21·25 g.) and sodium borohydride (5·3 g.) were boiled under reflux for 2 hr. in ethanol (320 ml.) and water (32 ml.). The solution was diluted with water (160 ml.) and concentrated, finally *in vacuo*, to give a suspension of the crystalline product (21·25 g., 99·7%), m. p. 191—194°, $[\alpha]_D$ +7·3°, which was filtered off after addition of more water. Crystallisation from aqueous methanol containing a drop of pyridine gave the *triol* as glistening plates of a solvate, m. p. 150° then 192—196°, which, after desolvation, had only the higher m. p. and $[\alpha]_D$ +8° (Found: C, 69·7; H, 9·6. $C_{23}H_{38}O_5$ requires C, 70·0; H, 9·7%), $\nu_{max.}$ (in Nujol) 3600—3400 (OH) and 1076 and 1040 cm.$^{-1}$ (ketal). On one occasion material of the same m. p. was obtained, which differed from the usual material in its infrared spectrum in Nujol, but not in chloroform.

Acetylation of the triol with acetic anhydride and pyridine at room temperature and crystallisation from methanol gave the 3-*monoacetate* (VI; R = Ac) as prisms, m. p. 242—245°, $[\alpha]_D$ +1·3° (Found: C, 68·5; H, 9·25. $C_{25}H_{40}O_6$ requires C, 68·8; H, 9·25%), $\nu_{max.}$ (in Nujol) 3600 and 3480 (OH), 1722 and 1245 (OAc), and 1080 and 1042 cm.$^{-1}$ (ketal).

Hydrolysis of the 3-monoacetate with potassium hydrogen carbonate in boiling aqueous methanol regenerated the triol (VI; R = H).

(b) *From* 16α : 17-*epoxy*-3β-*hydroxy*-5α-*pregnane*-11 : 20-*dione* 20-*ethylene ketal* (III). The epoxide (100 mg.) in dry tetrahydrofuran (20 ml.) was treated with lithium aluminium hydride in ether (6·5% solution; 5 ml.), and the mixture was then boiled under reflux for 5 hr. The excess of reagent was destroyed by addition of ethyl acetate, and the suspension was diluted

with ether (80 ml.) and shaken with dilute sodium hydroxide solution. The ether layer was washed twice with water, dried, and evaporated to dryness. The residue crystallised from aqueous methanol, to give the triol (VI; R = H) as plates (68 mg., 67%), m. p. 189—194°, $[\alpha]_D$ +8°.

3β-*Acetoxy*-17-*hydroxy*-5α-*pregn*-9(11)-*en*-20-*one* 20-*Ethylene Ketal* (VII; R = Ac).—3β-Acetoxy-11β : 17-dihydroxy-5α-pregnan-20-one 20-ethylene ketal (3·0 g.) in dry pyridine (24 ml.) was added at room temperature to a mixture of phosphoric acid (0·5 ml.) and phosphorus oxychloride (6 ml.) in pyridine (24 ml.). After 24 hr. the suspension was poured into ice and water (500 ml.). The precipitated product (2·84 g., 100%), m. p. 198—203°, $[\alpha]_D$ −9°, was crystallised from methanol to give the $\Delta^{9(11)}$-*compound* as plates, m. p. 201—203°, $[\alpha]_D$ −8·8° (Found: C, 71·6; H, 9·1. $C_{25}H_{38}O_5$ requires C, 71·7; H, 9·1%), $\nu_{max.}$ (in CS_2) 3620 (OH), 1733 and 1240 (OAc), and 1092 cm.$^{-1}$ (ketal).

Treatment of the acetate with boiling methanolic sodium hydroxide for 1 hr. and crystallisation from methanol gave hexagonal plates of 3β : 17-*dihydroxy*-5α-*pregn*-9(11)-*en*-20-*one* 20-*ethylene ketal* (VII; R = H) as a methanol solvate, m. p. 224—227°, $[\alpha]_D$ −8° (Found: C, 70·6; H, 9·7. $C_{23}H_{36}O_4,CH_3{\cdot}OH$ requires C, 70·6; H, 9·9%), $\nu_{max.}$ (in Nujol) 3550 and 3350 (OH), 1092 (ketal), and 1645 and 812 cm.$^{-1}$ (trisubstituted ethylene).

3β-*Acetoxy*-17-*hydroxy*-5α-*pregn*-9(11)-*en*-20-*one* (IX; R = Ac).—(a) *From* 3β-*acetoxy*-17-*hydroxy*-5α-*pregn*-9(11)-*en*-20-*one* 20-*ethylene ketal* (VII; R = Ac). The ketal (2·63 g.) was heated at 100° for 30 min. in 50% aqueous acetic acid (150 ml.). Addition of water to the cooled solution gave a precipitate (2·36 g.), m. p. 195—199°, $[\alpha]_D$ −12°, which, on crystallisation from methanol, gave the 20-ketone (IX; R = Ac), m. p. 202—205°, $[\alpha]_D$ −14° (Found: C, 74·1; H, 9·2. Calc. for $C_{23}H_{34}O_4$: C, 73·8; H, 9·15%), $\nu_{max.}$ (in Nujol) 3470 (OH), 1712 and 1258 (OAc), 1712 (ketone), 1350 ($COCH_3$), and 818 cm.$^{-1}$ (trisubstituted ethylene). Callow and James [11] give m. p. 198·5—200·5°, $[\alpha]_D$ −15°; a mixed m. p. with a sample kindly supplied by Dr. R. K. Callow was undepressed.

(b) *From* 3β : 11β : 17-*trihydroxy*-5α-*pregnan*-20-*one* 20-*ethylene ketal* (VI; R = H). The triol (10·85 g.) in glacial acetic acid (310 ml.) was treated with 5·5N-hydrogen bromide in acetic acid (30 ml.). The optical rotation of the solution rose rapidly during the first minute, and then began to fall at about the same rate. The rate of change of rotation had become slow and steady after 30 min. and the yellow solution was then poured into water (3 l.), and the product isolated with methylene chloride. Treatment of the residue with aqueous-methanolic sodium hydroxide gave crude 3β : 17-dihydroxy-5α-pregn-9(11)-en-20-one (IX; R = H), which could not readily be purified by crystallisation. With acetic anhydride in pyridine and crystallisation it gave the 3-monoacetate (IX; R = Ac) (35%), m. p. 197—201° (from methanol), $[\alpha]_D$ −10·3°.

(c) *From* 3β-*acetoxy*-11β : 17-*dihydroxy*-5α-*pregnan*-20-*one* (VIII; R = Ac). The 11β : 17-diol (see below) (500 mg.) in dry pyridine (4 ml.) was added to a solution of phosphorus oxychloride (0·3 ml.) in pyridine (4 ml.) and after 22 hr. at room temperature the suspension was poured into ice and water (150 ml.). The precipitated product, on crystallisation from methanol, gave the $\Delta^{9:11}$-compound (IX; R = Ac) (280 mg., 59%), m. p. 201·5—204°, $[\alpha]_D$ −14°.

3β : 17-*Dihydroxy*-5α-*pregn*-9(11)-*en*-20-*one* (IX; R = H).—(a) *From* 3β-*acetoxy*-17-*hydroxy*-5α-*pregn*-9(11)-*en*-20-*one* (IX; R = Ac). The 3-acetate (136 g.) and potassium hydrogen carbonate (45·2 g.) were boiled under reflux for 2½ hr. in methanol (4500 ml.) and water (1120 ml.). The acetate gradually dissolved during the first hour, and the product then began to separate. Most of the solvent was removed *in vacuo*, and water was added to precipitate the product (118·5 g., 98·5%), m. p. 235—240°, $[\alpha]_D$ −18°. Crystallisation from methanol gave the *diol* with m. p. 236—242°, $[\alpha]_D$ −15° (*c* 0·35) (Found: C, 76·0; H, 9·6. $C_{21}H_{32}O_3$ requires C, 75·9; H, 9·7%), $\nu_{max.}$ (in Nujol) 3550 and 3350 (OH), 1692 (ketone), 1350 ($CO{\cdot}CH_3$), and 820 cm.$^{-1}$ (trisubstituted ethylene).

The diol with acetic anhydride and pyridine re-formed the 3-monoacetate, m. p. 198—202°, $[\alpha]_D$ −14°.

(b) *From* 3β : 17-*dihydroxy*-5α-*pregn*-9(11)-*en*-20-*one* 20-*ethylene ketal* (VII; R = H). The methanol solvate (200 mg.) of the ketal was heated at 100° for 30 min. in acetic acid (8 ml.) and water (4 ml.). Water (100 ml.) was added to the cooled solution and the crystalline 20-ketone (IX; R = H) (167 mg., 100%), m. p. 235—240°, $[\alpha]_D$ −16° (*c* 0·3), was collected by filtration.

(c) *From* 3β-*formyloxy*-17-*hydroxy*-5α-*pregn*-9(11)-*en*-20-*one* (IX; R = HCO). The formate

(see below) (500 mg.) was heated at 100° for 40 min. in acetic acid (20 ml.) and water (10 ml.). Isolation of the product as in (b) gave the 3β-hydroxy-compound (IX; R = H) (440 mg., 96%), m. p. 228—236°, $[\alpha]_D$ −15° (*c* 0·35).

3β : 11β : 17-*Trihydroxy-5α-pregnan*-20-*one* (VIII; R = H).—3β : 11β : 17-Trihydroxy-5α-pregnan-20-one 20-ethylene ketal (VI; R = H) (500 mg.) was heated at 100° for 30 min. in 50% aqueous acetic acid (20 ml.). Addition of water to the resultant suspension gave crystals (410 mg., 92·5%), m. p. 255° then 270—275°, $[\alpha]_D$ +32° (*c* 0·43 in AcOH), which, on recrystallisation from aqueous methanol, yielded the 20-*ketone* as elongated prisms, m. p. 260° and, after resolidification, 290° (decomp.), $[\alpha]_D$ +31° (*c* 0·35 in AcOH) (Found: C, 71·55; H, 9·5. $C_{21}H_{34}O_4$ requires C, 71·95; H, 9·8%), $\nu_{max.}$ (in Nujol) 3400 (OH), 1690 (ketone), and 1350 cm.$^{-1}$ (CO·CH_3).

3β-*Acetoxy*-11β : 17-*dihydroxy-5α-pregnan*-20-*one* (VIII; R = Ac) *from* 3β-*Acetoxy*-11β : 17-*dihydroxy-5α-pregnan*-20-*one* 20-*Ethylene Ketal* (VI; R = Ac).—(a) *With aqueous acetic acid.* The 20-ketal (1·25 g.) was heated at 100° for 30 min. in 50% aqueous acetic acid (60 ml.), and water was added. The crystalline product (1·03 g., 90%), m. p. 209—213°, $[\alpha]_D$ +8°, was recrystallised from aqueous methanol. The 20-*ketone* first separated as small plates, which changed to prisms in one day. The two crystalline forms both had m. p. 213—216°, $[\alpha]_D$ +8° (Found: C, 70·5; H, 9·2. $C_{23}H_{36}O_5$ requires C, 70·4; H, 9·2%), but differed in their infrared spectra in Nujol. The plates showed $\nu_{max.}$ 3530 (OH), 1730 and 1250 (OAc), 1694 (ketone), and 1352 cm.$^{-1}$ (CO·CH_3) whereas the prisms showed $\nu_{max.}$ 3500 (OH), 1710 and 1273 weak, 1732 and 1248 (OAc), 1700 (ketone), and 1352 cm.$^{-1}$ (CO·CH_3). The two forms had identical spectra in bromoform, confirming their polymorphism.[20]

(b) *With formic acid in benzene.* The 20-ketal (5·0 g.) was boiled in benzene (250 ml.) and 98% formic acid (50 ml.) with distillation of 200 ml. in 2 hr. More benzene (200 ml.) was then added, and distilled during 1 hr. Removal of the remaining solvent *in vacuo* left crystals (4·4 g., 98%), m. p. 195—209°, which, on crystallisation from aqueous methanol, gave the 20-ketone (3·5 g., 78%), m. p. 210—213°, $[\alpha]_D$ +8°.

3β-*Formyloxy*-11β : 17-*dihydroxy-5α-pregnan*-20-*one* (VIII; R = HCO).—3β : 11β : 17-Trihydroxy-5α-pregnan-20-one 20-ethylene ketal (VI; R = H) (15 g.) in benzene (150 ml.) and 98% formic acid (37·5 ml.) were concentrated to 60 ml. during 2 hr. Benzene (120 ml.) was added, and after concentration to 40 ml. and dilution with light petroleum (400 ml.) the product (13·3 g., 97%) separated as crystals, m. p. 169—175°, $[\alpha]_D$ 0°. Crystallisation from benzene gave the *formate* with m. p. 184—186°, $[\alpha]_D$ −2° (Found: C, 70·0; H, 8·8. $C_{22}H_{34}O_5$ requires C, 69·8; H, 9·0%), $\nu_{max.}$ (in Nujol) 3550 and 3450 (OH), 1680 (ketone), and 1704 and 1175 cm.$^{-1}$ (formate).

3β-*Formyloxy*-17-*hydroxy-5α-pregn*-9(11)-*en*-20-*one* (IX; R = HCO).—(a) *From* 3β : 17-*dihydroxy-5α-pregn*-9(11)-*en*-20-*one* (IX; R = H). The diol (5·0 g.) in benzene (250 ml.) was treated as above with 98% formic acid (50 ml.). The product separated from benzene as crystals (3·95 g., 73%), m. p. 183—186°, $[\alpha]_D$ −15·5°. A second crop (0·7 g., 13%), m. p. 178—180°, $[\alpha]_D$ −18°, was obtained by addition of light petroleum to the mother-liquors. Recrystallisation from *cyclo*hexane gave the *formate* with m. p. 185—189°, $[\alpha]_D$ −16° (Found: C, 73·5; H, 9·0. $C_{22}H_{32}O_4$ requires C, 73·3; H, 9·0%), $\nu_{max.}$ (in Nujol) 3500 (OH), 1695 (ketone), 1695 and 1216 (formate), 1350 (CO·CH_3), and 818 cm.$^{-1}$ (trisubstituted ethylene).

(b) *From* 3β-*formyloxy*-11β : 17-*dihydroxy-5α-pregnan*-20-*one* (VIII; R = HCO). The diol was dehydrated with phosphorus oxychloride and phosphoric acid in pyridine, as described for the acetate (VIII; R = Ac). Crystallisation of the crude product from benzene–light petroleum (1 : 1) gave the $\Delta^{9:11}$-compound (59%), m. p. 184—186°, $[\alpha]_D$ −17°.

21-*Acetoxy*-3β : 17-*dihydroxy-5α-pregn*-9(11)-*en*-20-*one* (XI; R = H).—(a) *From* 3β : 17-*dihydroxy-5α-pregn*-9(11)-*en*-20-*one* (IX; R = H). A vigorously stirred suspension of the finely divided 20-ketone (90 g.) in chloroform (1800 ml.) containing 1% of alcohol was saturated with hydrogen chloride during 15 min., and a solution of bromine (15·0 ml.) in chloroform (500 ml.) was then added during 45 min. After a further 5 min. ether (4500 ml.) was added and after 25 min. the solid was filtered off. The filtrate was washed with water, aqueous sodium hydrogen carbonate, and water, dried, and evaporated to dryness *in vacuo*. The residual pale yellow gum was combined with filtered solid and boiled under reflux for 2 hr., with stirring, in acetone (5 l.) containing anhydrous potassium acetate (270 g.).

Removal of the acetone *in vacuo* and addition of water precipitated the crude product

[20] Dickson, Page, and Rogers, *J.*, 1955, 443.

(109 g.), which was boiled under reflux for 45 min. with Girard reagent P (51 g.) in dry methanol (2250 ml.) and acetic acid (112 ml.). The suspension was cooled to 5°, and after 18 hr. the crystalline product (76·7 g., 73%) was collected, washed with cold methanol, and dried at 90°/20 mm.; it had m. p. 235—238°, $[\alpha]_D$ +45° (*c* 0·4), and showed $\nu_{max.}$ (in Nujol) 3600—3500 (OH) and 1720 and 1240 cm.$^{-1}$ (OAc). Crystallisation from methanol gave 21-*acetoxy*-3β : 17-*dihydroxy*-5α-*pregn*-9(11)-*en*-20-*one* (XI; R = H) as a methanol solvate, m. p. 239—241°, $[\alpha]_D$ +42° (*c* 0·53). Its infrared spectrum showed $\nu_{max.}$ (in Nujol) 3600 and 3450 (OH), 1760 and 1210 (OAc), and 1724 cm.$^{-1}$ (ketone), and differed from that of the unsolvated crude material. For analysis it was desolvated at 120°/0·1 mm. (Found: C, 71·0; H, 9·0. $C_{23}H_{34}O_5$ requires C, 70·7; H, 8·8%).

The mother-liquors from the Girard purification were poured into water containing an excess of sodium hydrogen carbonate, and the rest of the unreactive material was isolated with ether as a yellow glass (11·6 g.) which did not crystallise satisfactorily. The aqueous phase from the extraction was acidified with hydrochloric acid and extracted with ether. The residue was acetylated and crystallised, to give 3β-acetoxy-17-hydroxy-5α-pregn-9(11)-en-20-one (3·5%), m. p. 199—201°, $[\alpha]_D$ −12°.

Acetylation of the 21-acetate (XI; R = H) with acetic anhydride and pyridine, and crystallisation from ethyl acetate gave the 3 : 21-diacetate (XI; R = Ac) as plates, m. p. 227—230°, $[\alpha]_D$ +40°, after drying at 100°/10 mm., identical with material prepared from 3β-acetoxy-17-hydroxy-5α-pregn-9(11)-en-20-one (IX; R = Ac) as described below.

(b) *From* 3β-*formyloxy*-17-*hydroxy*-5α-*pregn*-9(11)-*en*-20-*one* (IX; R = HCO). A solution of the formate (3·0 g.) in methylene chloride (40 ml.) and ether (10 ml.) was saturated with hydrogen chloride and then brominated as described in (a). Methanol (5 ml.) was then added, and the crude bromo-compound isolated, treated with potassium acetate, and purified as in (*a*), to give the 21-acetate (XI; R = H) (1·45 g., 45%), m. p. 232—235°, $[\alpha]_D$ +42° (*c* 0·3).

3β : 21-*Diacetoxy*-17-*hydroxy*-5α-*pregn*-9(11)-*en*-20-*one* (XI; R = Ac).—A solution of 3β-acetoxy-17-hydroxy-5α-pregn-9(11)-en-20-one (IX; R = Ac) (3·0 g.) in chloroform containing 1% of alcohol (45 ml.) was saturated with hydrogen chloride during 10 min. and a solution of bromine (1·35 g., 1·05 mol.) in chloroform (15 ml.) was then added dropwise to the stirred solution during 15 min. After a further 5 min. the pale yellow solution was washed with water, aqueous sodium hydrogen carbonate, and water, and the solvent was removed *in vacuo* from the dried solution. The crude 21-bromo-compound (4·0 g.) was treated with potassium acetate and Girard reagent as described above for the 3β-hydroxy-compound, to give the 3 : 21-*diacetate* (2·55 g., 72%), m. p. 221—225°. Further crystallisation from ethyl acetate and drying at 100°/10 mm. gave material with m. p. 225—229° and $[\alpha]_D$ +41° (Found: C, 69·2; H, 8·2. $C_{25}H_{36}O_6$ requires C, 69·4; H, 8·4%), $\nu_{max.}$ (in Nujol) 3500 (OH), 1745 and 1238 (21-OAc), 1730 (20-ketone), 1704 (ketone), and 1704 and 1262 cm.$^{-1}$ (OAc).

21-*Acetoxy*-17-*hydroxy*-5α-*pregn*-9(11)-*ene*-3 : 20-*dione* (XII).—N-Potassium dichromate in 3N-sulphuric acid (180 ml.) was added to a boiling solution of 21-acetoxy-3β : 17-dihydroxy-5α-pregn-9(11)-en-20-one (XI; R = H) (15 g.) in acetone (4500 ml.), and after 5 min. most of the acetone was removed by distillation *in vacuo*. Precipitation with water, crystallisation from ethyl acetate, and drying for 24 hr. at 100°/10 mm. gave the 3-ketone as plates (12·6 g., 84·5%), m. p. 247—249°, $[\alpha]_D$ +66° (*c* 0·3). A further 6% was obtained by oxidation of material from the mother-liquors.

The compound was identical with material prepared from 4 : 5α-dihydrocortisone acetate *via* the bis-ketal.[5c]

The finely divided 21-acetate (600 mg.) was shaken for 4 days at room temperature in suspension in 1·8% aqueous sodium hydroxide (4·5 ml.) and dioxan (17 ml.). The crystalline product (530 mg.), m. p. 235—245°, was filtered off after addition of much water, and recrystallised from aqueous dioxan to give, after drying at 120°/0·1 mm., 17 : 21-*dihydroxy*-5α-*pregn*-9(11)-*ene*-3 : 20-*dione*, m. p. 235—240°, $[\alpha]_D$ +55° (*c* 0·42 in dioxan) (Found: C, 73·0; H, 9·0. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%), $\nu_{max.}$ (in Nujol) 3550—3500 (OH), 1702 (ketone), and 814 cm.$^{-1}$ (trisubstituted ethylene).

21-*Acetoxy*-9β : 11β-*epoxy*-17-*hydroxy*-5α-*pregnane*-3 : 20-*dione* (XIV).—A hot solution of 21-acetoxy-17-hydroxy-5α-pregn-9(11)-ene-3 : 20-dione (12·12 g.) in pure dioxan (3640 ml.) and water (485 ml.) was cooled quickly to 30° under nitrogen whereupon the steroid started to separate. *N*-Bromoacetamide (12·12 g.) and then 3% aqueous perchloric acid (242 ml.) were added immediately. In 15 min. the steroid redissolved, and after a further 10 min. the excess of

N-bromoacetamide was destroyed by addition of aqueous sodium pyrosulphite until the yellow colour disappeared. Aqueous 2N-sodium hydroxide (460 ml.) was added, together with sufficient water (900 ml.) to give a single phase, and after 20 min. the pale brown solution was acidified with acetic acid (60 ml.). The dioxan was distilled from the almost decolorised solution *in vacuo*, and the aqueous residue was diluted with water and extracted with chloroform. Removal of the solvent *in vacuo* left a solid (11 g.), which was treated with acetic anhydride and pyridine at 100°. Crystallisation of the product from ethyl acetate gave the *epoxide* (6·83 g., 54·5%), m. p. 201—206°, $[\alpha]_D$ +67°. Further crystallisation gave material with m. p. 205—208° and $[\alpha]_D$ +69° (Found: C, 68·4; H, 8·2. $C_{23}H_{32}O_6$ requires C, 68·3; H, 8·0%), $\nu_{max.}$ (in Nujol) 3550 (OH), 1752 and 1224 (21-OAc), and 1720 cm.$^{-1}$ (ketone), $\nu_{max.}$ (in $CHBr_3$) 1742 and 1230 (21-OAc), 1725 (20-ketone), and 1708 cm.$^{-1}$ (ketone).

21-*Acetoxy*-9α-*fluoro*-11β : 17-*dihydroxy*-5α-*pregnane*-3 : 20-*dione* (XX).—Anhydrous hydrogen fluoride (4·0 ml.) was added at 0° to a solution of 21-acetoxy-9β : 11β-epoxy-17-hydroxy-5α-pregnane-3 : 20-dione (XIV) (3·0 g.) in dry chloroform (300 ml.). During 4 hr. at 0°, with occasional swirling, the chloroform solution became pale brown and the supernatant hydrogen fluoride dark purple. The mixture was poured into aqueous sodium hydrogen carbonate, and the pale yellow chloroform layer was washed twice with water, dried, and evaporated. The residual froth was triturated with methanol and, after separation of an unidentified by-product (100 mg.), the solvent was removed *in vacuo*. Crystallisation of the residue from benzene (25 ml.) gave the fluorohydrin (XX) as needles (0·95 g., 30%), m. p. 228—231°, $[\alpha]_D$ +63° (Found: C, 65·5; H, 8·0; F, 4·3. Calc. for $C_{23}H_{33}O_6F$: C, 65·1; H, 7·8; F, 4·5%), $\nu_{max.}$ (in Nujol) 1732 and 1240 (OAc), and 1708 cm.$^{-1}$ (ketone), $\nu_{max.}$ (in $CHCl_3$) 3550—3400 (OH), 1740 (21-OAc), 1724 (20-ketone), and 1706 cm.$^{-1}$ (ketone). Hirschmann *et al.*[2a] give m. p. 233—233·5°, $[\alpha]_D$ +65·4° (in $CHCl_3$), and Fried *et al.*[2b] give m. p. 234—235°, $[\alpha]_D$ +67° (in acetone).

21-*Acetoxy*-2 : 4-*dibromo*-9α-*fluoro*-11β : 17-*dihydroxy*-5α-*pregnane*-3 : 20-*dione* (XXI).—Bromine (2·85 g.) in acetic acid (20 ml.) was added gradually during 10 min. to a stirred solution of the fluorohydrin (XX) (3·6 g.) in 0·675N-hydrogen bromide in acetic acid (81 ml.). After a further 20 min. at room temperature the solution was poured into water (700 ml.), the precipitated product was extracted into methylene chloride, and the extract was washed with aqueous sodium hydrogen carbonate and water. Removal of the solvent *in vacuo* from the dried extract left the crude 2 : 4-dibromo-compound as a pale yellow froth (5·1 g.).

21-*Acetoxy*-9α-*fluoro*-11β : 17-*dihydroxypregn*-4-*ene*-3 : 20-*dione* (XXII).—Bromine (0·46 ml.) was added to acetone (13 ml.) and, when the solution became colourless, sodium carbonate (1·2 g.) was added with stirring. When free from hydrogen bromide (30 min.) the solution was filtered, and the filtrate was added to a boiling suspension of sodium iodide (12·6 g.) in acetone (45 ml.). After 15 min. a solution of crude 21-acetoxy-2 : 4-dibromo-9α-fluoro-11β : 17-dihydroxy-5α-pregnane-3 : 20-dione (XXI) [2·55 g.; from 1·8 g. of (XX)] in acetone (11 ml.) was added and the mixture was boiled under reflux for 2 hr. The brown suspension was cooled and solid carbon dioxide added, before addition of an excess of 2N-chromous chloride (40 ml.). The suspension was allowed to warm to room temperature during 20 min., most of the acetone was removed *in vacuo*, and after dilution with water the product was extracted into methylene chloride. Removal of the solvent from the washed and dried extract left a pale yellow froth (1·7 g.), which was treated with acetic anhydride and pyridine at room temperature, in case some hydrolysis of the 21-acetoxy-group had occurred. The crude acetylated product, isolated with methylene chloride, had $\lambda_{max.}$ 239·5 mμ ($E^{1\%}_{1\,cm.}$ 153). It was boiled under reflux for 30 min. with Girard reagent P (0·9 g.) in dry ethanol (27 ml.) and acetic acid (1·35 ml.). The solution was cooled to 20°, 40% aqueous formaldehyde (3·6 ml.) was added, and, after 25 min., the solution was poured into aqueous 4% sodium hydrogen carbonate (135 ml.). The suspension was extracted with ethyl acetate, and the extract washed with aqueous sodium hydrogen carbonate and water. Removal of solvent from the dried extract left a yellow froth (890 mg.) (Found: F, 3·9%), which had $E^{1\%}_{1\,cm.}$ 37 at 235—240 mμ. The aqueous layers from the extraction were combined and acidified to pH 1 with 2N-hydrochloric acid. After 1 hr. the cloudy solution was extracted with ethyl acetate, and the extract was washed with aqueous sodium hydrogen carbonate and water. Removal of solvent from the dried extract left the crude product (XXII) as a yellow froth (685 mg.) (Found: F, 4·3%), $\lambda_{max.}$ 238·5 mμ ($E^{1\%}_{1\,cm.}$ 270).

This product (650 mg.) in benzene containing 5% chloroform (75 ml.) was chromatographed on acid-washed alumina (20 g.; Brockmann grade II—III). Benzene and up to 20% ether in

benzene eluted mixtures (310 mg.) deficient in conjugated ketone. Elution with 1 : 4-ether–benzene and up to 1 : 1 chloroform–benzene gave crystalline fractions (180 mg. total), m. p. *ca.* 200—210° which, on crystallisation from ethyl acetate, gave the acetate (XXII) (114 mg., 6%) in two crops. Two interconvertible crystalline forms were obtained, both ethyl acetate solvates, of m. p. 205—208° and m. p. 222—227° respectively. The low-melting form had an infrared spectrum identical with that of an authentic sample with the higher melting point, $\nu_{max.}$ (in Nujol) 1750 and 1262 (21-acetate), 1718 (ketone), and 1642 and 878 cm.$^{-1}$ (conjugated ketone). Both of the forms were desolvated at 120°/0·1 mm., without change in m. p. (Found: C, 65·2; H, 7·1; F, 4·3. Calc. for $C_{23}H_{31}O_6F$: C, 65·4; H, 7·4; F, 4·5%). They had $[\alpha]_D$ +151° and $\lambda_{max.}$ 239 mμ (ε 15,900). The two desolvated forms had slightly different infrared spectra in bromoform, $\nu_{max.}$ 1740 and 1232 (21-OAc), 1722 (20-ketone), and 1658 and 1620 cm.$^{-1}$ (conjugated ketone and Δ^4), but differed considerably in Nujol. The differences in solution spectra could be accounted for by a trace of ethyl acetate in one of the samples. Fried and Sabo [1a] give m. p. 232—233° (or 205—208° then 226—228°), $[\alpha]_D$ +143°, and $\lambda_{max.}$ 238 mμ (ε 16,800).

21-*Acetoxy*-9α-*fluoro*-11β : 17-*dihydroxypregna*-1 : 4-*diene*-3 : 20-*dione* (XXIII).—Crude 21-acetoxy-2 : 4-dibromo-9α-fluoro-11β : 17-dihydroxy-5α-pregnane-3 : 20-dione (XXI) [2·55 g.; from 1·8 g. of (XX)] and semicarbazide hydrochloride (2·5 g.) were heated under nitrogen at 100° for 90 min. in dimethylformamide (37 ml.) and water (2·5 ml.). After concentration *in vacuo* to *ca.* 15 ml., acetic acid (75 ml.), water (37 ml.), and 50% pyruvic acid (18 ml.) were added, and the mixture was heated under nitrogen at 100° for 90 min. The solution was poured into water (1 l.), and the product was isolated with methylene chloride as a yellow froth (880 mg.), $\lambda_{max.}$ 239 mμ ($E^{1\%}_{1\,cm.}$ 339). It was acetylated with acetic anhydride and pyridine at room temperature, and was then boiled under reflux with Girard reagent P (0·56 g.) in ethanol (16 ml.) and acetic acid (1·6 ml.). The cooled solution was poured into aqueous 4% sodium hydrogen carbonate (120 ml.), and the unchanged material was extracted into ethyl acetate. The solvent was removed *in vacuo* from the washed and dried extract, to give a yellow froth (637 mg.), $\lambda_{max.}$ 238 mμ ($E^{1\%}_{1\,cm.}$ 343) (Found: F, 3·4%). This crude material (620 mg.), in benzene containing 4% of chloroform (75 ml.), was chromatographed on acid-washed alumina (20 g.; Brockmann grade II—III). Elution with benzene gave a yellow gum (30 mg.) and then 20—30% ether-in-benzene eluted crude 21-acetoxy-9α-fluoro-11β-hydroxy-5α-pregna-1 : 4 : 16-triene-3 : 20-dione (180 mg.). Chloroform eluted a pale yellow gum (98 mg.) which, on crystallisation from ethyl acetate (1 ml.), gave, after drying at 100°/0·1 mm., the desired acetate (XXIII) (5 mg.), m. p. 220—228°, and a second crop (6 mg.), m. p. 223—231°, $\lambda_{max.}$ (in MeOH) 238 mμ (ε 15,400), $\nu_{max.}$ (in Nujol) 3450 and 3350 (OH), 1732 and 1270 (21-OAc), 1710 (ketone), 1660, 1618, 1600, and 890 cm.$^{-1}$ ($\Delta^{1:4}$-3-ketone). The literature [2] gives a range of constants, m. p. 235—238° to 244—246°, and $\lambda_{max.}$ *ca.* 239 mμ (ε 14,500—16,300).

3β-*Acetoxy*-9β : 11β-*epoxy*-17-*hydroxy*-5α-*pregnan*-20-*one* (XV; R = Ac).—3β : 17-Dihydroxy-5α-pregn-9(11)-en-20-one (5·0 g.), in dioxan (500 ml.) and water (75 ml.), was treated with *N*-bromoacetamide (5·0 g.) and aqueous 1·38% perchloric acid (77 ml.). After 20 min. at room temperature the excess of *N*-bromoacetamide was destroyed by addition of aqueous sodium pyrosulphite until the yellow colour disappeared. After addition of 2N-sodium hydroxide (125 ml.) and sufficient water (200 ml.) to give a single phase, the clear solution was left for 30 min. under nitrogen, and acidified with acetic acid. The dioxan was distilled *in vacuo* and, after addition of more water to the aqueous residue, the solid (2·94 g.) was filtered off. This material (2·8 g.) was acetylated with pyridine and acetic anhydride at 100°, and crystallised from aqueous methanol, to give the 9β : 11β-*epoxide* (1·88 g.) (34%), m. p. 163—169°, $[\alpha]_D$ +7·3°. Further crystallisation gave material with m. p. 174—176° and $[\alpha]_D$ +5·5° (Found: C, 70·8; H, 8·7. $C_{23}H_{34}O_5$ requires C, 70·7; H, 8·8%), $\nu_{max.}$ (in Nujol) 1722 and 1242 (OAc), 1695 (ketone), and 1354 cm.$^{-1}$ (CH_3·CO).

Hydrolysis of the acetate with potassium hydrogen carbonate in boiling aqueous methanol gave a crude product (94%) as plates, m. p. 254—260°. Crystallisation from methanol gave the 3β : 17-*diol* (XV; R = H) as prisms, m. p. 230—245°, with changes in crystalline form and decomposition, $[\alpha]_D$ +6° (*c* 0·35) (Found: C, 72·4; H, 9·2. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·3%). The infrared spectrum was the same as for the plates, $\nu_{max.}$ (in Nujol) 3360—3240 (OH) and 1702 and 1678 cm.$^{-1}$ (ketone).

9α-*Bromo*-11β-*hydroxyergostan*-3-*one* (XVII) (With Mr. G. F. H. Green).—Ergost-9(11)-en-3-one (5 g.) in dioxan (205 ml.) and water (23 ml.) was treated with *N*-bromoacetamide

(7·0 g.) and 60% perchloric acid (6·25 ml.). A yellow colour developed almost at once; after 2 min. just sufficient aqueous sodium pyrosulphite was added to remove the colour and the steroid solution was poured into water. The precipitated product (5·72 g., 93%), m. p. 112—114° (decomp.) (Found: Br, 15·0%), crystallised from *cyclo*hexane to give the *bromohydrin* (60%), m. p. 127—129° (decomp.) (capillary), $[\alpha]_D$ +38° (Found: C, 67·8; H, 9·6; Br, 15·5. $C_{28}H_{47}O_2Br$ requires C, 67·8; H, 9·6; Br, 16·1%), $\nu_{max.}$ (in CS_2) 3620 (OH), 1710 (ketone), and 748 cm.$^{-1}$ (C–Br).

The crude bromohydrin (500 mg.) was boiled for 1 hr. in ethanol, and the crude product (458 mg.) (Found: Br, 3·5%) was isolated by precipitation with water. Three crystallisations from aqueous acetone gave ergostane-3 : 11-dione (XIX) (131 mg.), m. p. 152—155°, $[\alpha]_D$ +63°, which appeared from its infrared spectrum (in CS_2) to contain a little of the 9β : 11β-epoxide. A similar result was obtained by boiling in the presence of two equivalents of potassium acetate.

9β : 11β-*Epoxyergostan*-3-*one* (XVIII) (With Mr. G. F. H. Green).—A solution of the foregoing bromohydrin (340 mg.) in dry *tert.*-butyl alcohol (20 ml.) was treated at room temperature during 0·5 min. with a solution of potassium *tert.*-butoxide [prepared from potassium (42·5 mg.) and *tert.*-butyl alcohol (4·6 ml.)]. After 5 min. the pale yellow cloudy solution was poured into water containing a little magnesium sulphate, and the precipitated product (290 mg.), m. p. 139—140°, $[\alpha]_D$ +30·5°, was crystallised twice from aqueous acetone, to give the *epoxide* (124 mg., 43%), m. p. 144—146°, $[\alpha]_D$ +32° (Found: C, 81·3; H, 11·2. $C_{28}H_{46}O_2$ requires C, 81·1; H, 11·2%), $\nu_{max.}$ (in CS_2) 1714 cm.$^{-1}$ (single ketone).

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