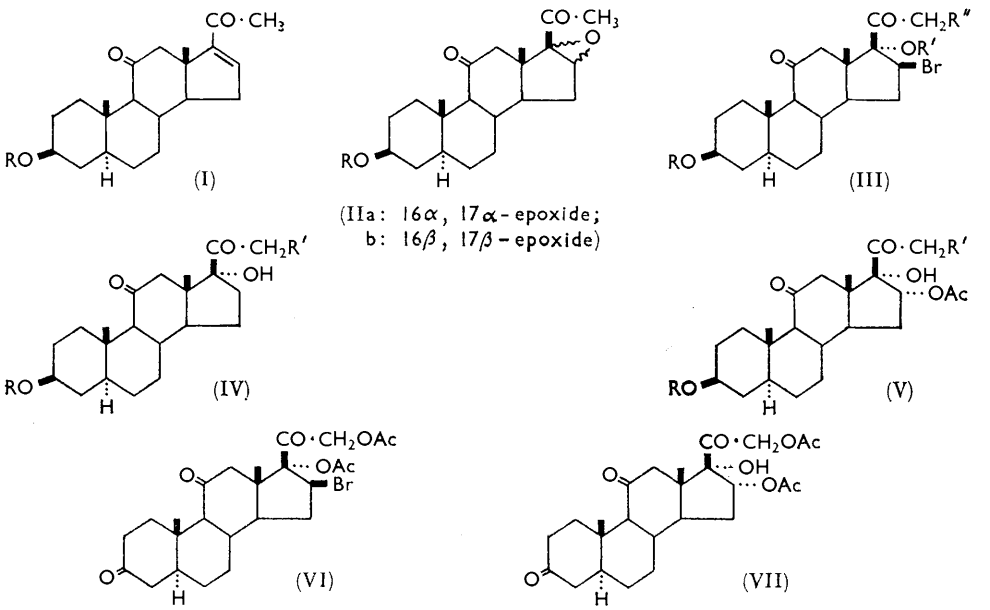
23. *Compounds Related to the Steroid Hormones. Part XII.*[1] *Improved Method for Making* 16α-*Acetoxy*-4,5α-*Dihydrocortisone* 21-*Acetate.*

By S. Eardley, W. Graham, A. G. Long, and J. F. Oughton.

Attempts at the 21-bromination of the 16,17-epoxides (II; R = H and Ac) achieved limited success, owing in part to competitive halogenation at the 9-position. Conversion of the bromohydrin (III; R = R′ = R″ = H) into its diacetate and subsequent selective hydrolysis yielded the 17-acetate (III; R = R″ = H; R′ = Ac); further hydrolysis (with efficient participation by the neighbouring group) gave the 16α-acetoxy-17α-alcohol (V; R = R′ = H), which could be brominated at the 21-position and then converted by potassium acetate into the 3-hydroxy-21-acetate (V; R = H, R′ = OAc). Oxidation of this product afforded the title compound (VII). This route is shorter than that described in the preceding Paper.

The route previously described [1] for making 16,17,21-trihydroxy-20-ketones neglects the suitability of certain manufacturing intermediates derived efficiently from hecogenin: the 11-ketone (I; R = Ac) is an example.[2] Many possibilities can be envisaged, but we considered mainly the 3-acetoxy- and 3-hydroxy-16,17-epoxides (II; R = Ac and H) derived from this 11-ketone. Practicable processes can then be divided into two categories: in the first, the 21-acetoxyl group is introduced in the next step, in the second its introduction is deferred. The scope of all these processes is delimited by the capabilities of selective methods of acylation, saponification, and oxidation, the restrictions being severer in conversions of the first category.



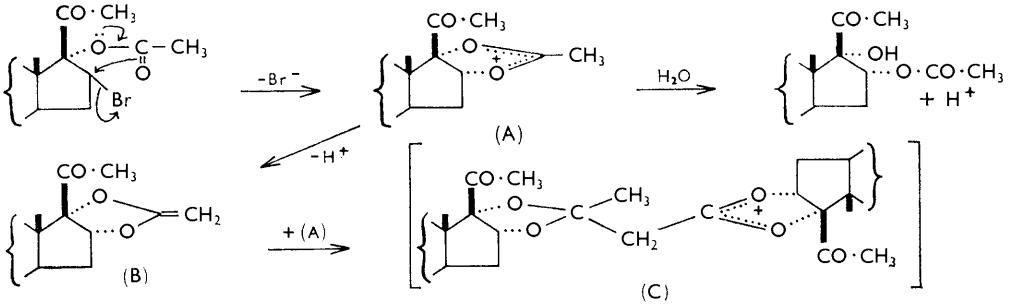
Conversion of the epoxide (IIa; R = H) into the 21-acetoxy-bromohydrin (III; R = R′ = H; R″ = OAc), with subsequent oxidation to the ketone (VI), would yield a

[1] Part XI, preceding Paper.
[2] Cameron, Evans, Hamlet, Hunt, Jones, and Long, *J.*, 1955, 2807.

compound suitable for the Romo de Vivar [3] rearrangement, by which a 16β-bromo-17α-acetoxy-compound can be converted into a 16α-acetoxy-17α-ol. We found this route wanting in the earliest stages, since acid-catalysed bromination of the epoxide (II; R = H) and subsequent treatment with potassium acetate failed to yield a pure product, ever after chromatography and attempts to remove those ketones (such as the starting material) which give water-soluble Girard derivatives.[4] (21-Acetoxy-17α-hydroxy-20-ketones do not normally react with Girard reagents.[5]) By the action of hydrogen bromide in acetic acid on the crude 21-acetoxy-16,17-epoxide the product yielded an impure specimen of the 21-acetoxy-bromohydrin (III; R = R′ = H; R″ = OAc); hydrogenation in the presence of Raney nickel then gave the ketol acetate (IV; R = OAc, R′ = H) and the methyl-ketone (IV; R = R′ = H). The major difficulties can be traced to competitive halogenation at the 9-position, which gives highly dextrorotatory by-products that yield $\Delta^{8(9)}$-11-ketones on dehydrobromination.[6] These shortcomings intrude less in similar work with 5β-steroids.[7]

Attempts at conversions in the second category showed more promise in the synthesis of 16-hydroxy-steroids. Treatment of the epoxides (IIa; R = H or Ac) with hydrogen bromide gave bromohydrins that were converted by acid-catalysed acetylation into the 3,17-diacetate (III; R = R′ = Ac; R″ = H).[8] Acid-catalysed hydrolysis of the 3-acetoxy-group with methanolic sulphuric acid [9] proceeded almost selectively, giving the 17α-acetoxy-16β-bromo-ketone (III; R = R″ = H; R′ = Ac).

Romo and Romo de Vivar [3] recommended hot collidine or solutions of metal acetates in acetic acid for converting 17α-acetoxy-16β-bromo-steroids into 17α-hydroxy-16α-acetates, the ion (A) intervening. A by-product in the selective hydrolysis mentioned above proved that the change occurred in methanolic sulphuric acid, but this conversion was incomplete. Reactions in the presence of acetic acid are unsuitable for our purposes, as concomitant esterification of the 3-hydroxy-group in the bromo-acetate (III; R = H, R′ = Ac, R″ = OAc) would nullify the advantage won in the previous stage; consequently, we tried collidine for the conversion of this compound into the ketol ester (V; R = R′ = H).



Ordinary samples of collidine and heating on a steam-bath introduce enough water to open the cyclic carbonium ion (A) and form the 16α-acetoxy-17α-alcohol and a proton. Previous users of this method describe no precautions on this account, but we found that redistilled collidine, heated electrically or in a sealed tube, gives high yields of a polymer that presumably results from thermal elimination of a proton from the ion (A), with

[3] Romo and Romo de Vivar, *J. Org. Chem.*, 1956, **21**, 902; Allen, Weiss, *et al.*, *J. Amer. Chem. Soc.*, 1959, **81**, 4968; 1960, **82**, 3696.
[4] Glaxo Laboratories Ltd., B.P. 762,716.
[5] Green and Long, *J.*, 1961, 2532.
[6] Henbest, Jones, Wagland, and Wrigley, *J.*, 1955, 2477; Jones and Wluka, *J.*, 1959, 907. Rearrangement may give rise to 17α-acetyl-16α-hydroxy-17β-methyl-11-oxo-Δ^{12}-18-nor-steroids and their derivatives (cf. Taub, Hoffsommer, Slater, and Weadler, *J. Org. Chem.*, 1961, **26**, 2852).
[7] (*a*) Julian, Meyer, Ryden, *et al.*, *J. Amer. Chem. Soc.*, 1949, **71**, 3574; 1950, **72**, 5145; 1955, **77**, 4601; (*b*) Glaxo Laboratories Ltd., B.P. 858,427.
[8] Turner, *J. Amer. Chem. Soc.*, 1953, **75**, 3489; see also refs. 3 and 11.
[9] Oliveto, Gerold, Weber, Jorgensen, Rausser, and Hershberg, *J. Amer. Chem. Soc.*, 1953, **75**, 5486; Warnant, *Bull. Soc. chim. France*, 1956, 1456.

formation [10] of the keten acetal (B) and subsequent attack on the carbonium ion (A) to give the ion (C). The outcome of this process depends on the capacity of the medium to discharge the ions and so to restrict the production of polymers. In the usual conditions there is a deficiency in water, and the yields of the required ketol acetate are low and variable; deliberate addition of an equivalent amount or an excess of water secures the desired improvement.

Bromination of the product (V; R = R′ = H) and subsequent treatment with potassium acetate in refluxing acetone [11] led to the 21-acetate (V; R = H, R′ = OAc). The yield was low for conversions of this type, and was not much augmented by recovery of the unchanged ketone (V; R = R′ = H) as its Girard derivative, since the 16α-acetoxy-group, like the 16α-methyl, hinders condensations at the 20-position.[12] Competitive substitution at the 9-position may reduce the efficiency of the halogenation.

Oxidation of the 3-hydroxy-21-acetate (V; R = H, R′ = OAc) with potassium dichromate and sulphuric acid in aqueous acetone [13] gave 16α-acetoxy-4,5α-dihydrocortisone acetate (VII), whose conversion into 16α-acetoxyprednisone has already been described.[1]

Experimental

Unless stated otherwise, m. p.s were measured on a Kofler hot-stage apparatus, and solutions for ultraviolet and infrared spectroscopy were made up with ethanol and bromoform, respectively; optical rotations were measured on 0·5—1% solutions in chloroform at 18—23°. Collidine was bought from British Drug Houses; infrared spectroscopy suggested that it was a mixture of 2,4,6- and 2,3,6-trimethylpyridine and 3,5-dimethylpyridine in the proportions 60 : 30 : 5. Florisil was bought from the Floridin Earth Co., Tallahassee, Florida, U.S.A.

Paper chromatography was carried out with solvent system L and the TSTZ spray reagent, as described before.[14] The methyl ketones (III; R = R′ = R″ = H) and (V; R = R′ = H) were detected by spraying the paper with a solution of bromine in acetic acid and leaving them to dry for ½ hr.; subsequent spraying with TSTZ then revealed the compounds (presumably because 21-bromo- and then 21-hydroxy-ketones had been formed).

16α,17-*Epoxy*-3β-*hydroxy*-5α-*pregnane*-11,20-*dione* (IIa; R = H).—(*a*) The bromohydrin (III; R = R′ = R″ = H) (8·5 g.) (see below) was suspended with anhydrous potassium acetate (4 g.) in acetone (85 ml.) and heated [15] at reflux for 1 hr. Some of the solvent was distilled off, and water added to the solution to give the *epoxide* (6·78 g., 99%), m. p. 177—179° (cap.), $[\alpha]_D$ +95° ($CHCl_3$), +81° (dioxan). A specimen gave lustrous plates, m. p. 173—175° (from aqueous methanol), $[\alpha]_D$ +90°, $\nu_{max.}$ (Nujol) 3520 (OH), and 1708 and 1695 cm.$^{-1}$ (ketones), and $\nu_{max.}$ ($CHBr_3$) 3620 (OH), 1702 (ketones), and 916 and 865 cm.$^{-1}$ (epoxide) (Found: C, 72·7; H, 8·3. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%).

(*b*) Hydrogen peroxide (100 vol.; 93 ml.) was added to 3β-hydroxy-5α-pregn-16-ene-11,20-dione (I; R = H) (33 g.) [2] in chloroform (220 ml.) and methanol (500 ml.); 5N-sodium hydroxide was then added [7a,16] over 20 min. The mixture was diluted with 10% sodium chloride (1 l.) and the steroidal product isolated with chloroform, evaporation of which gave an oil. Crystals of the oxide (II; R = H) were obtained by dissolving this oil in methanol (300 ml.), with subsequent evaporation to small bulk: first crop (9·9 g., 29%), m. p. 169—176° (cap.), $[\alpha]_D$ +95°; second crop (8·6 g., 25%), m. p. 156—162° (cap.), $[\alpha]_D$ +88°. The mother-liquors contained a saturated ketone, probably 3β-hydroxy-16α-methoxy-5α-pregnane-11,20-dione.

Attempts at Introducing Substituents at the 21-*Position in the* 16α,17-*Epoxide* (IIa; R = H).—A stirred solution of the epoxide (10 g.) in chloroform (100 ml.) (containing *ca.* 1% ethanol) was treated with bromine (5·08 g., 1·1 mol.) in chloroform (20 ml.), added dropwise at the rate

[10] Cf. Fairbourne, *J.*, 1930, 369; Winstein and Buckles, *J. Amer. Chem. Soc.*, 1942, **64**, 2787; Adams, Doyle, Hunter, and Nayler, *J.*, 1960, 2674.
[11] Glaxo Laboratories Ltd., B.P. 761,009; Evans, Hamlet, Hunt, Jones, Long, Oughton, Stephenson, Walker, and Wilson, *J.*, 1956, 4356.
[12] Ehmann, Heusler, Meystre, Wieland, Anner, Wettstein, *et al.*, *Helv. Chim. Acta*, 1959, **42**, 2043, 2548.
[13] Brooks, Hunt, Long, and Mooney, *J.*, 1957, 1175.
[14] Brooks, Evans, Green, Hunt, Long, Mooney, and Wyman, *J.*, 1958, 4614.
[15] Löken, Rosenkranz, Sondheimer, *et al.*, *J. Amer. Chem. Soc.*, 1956, **78**, 816, 1738.
[16] Kritchevsky, Garmaise, and Gallagher, *J. Amer. Chem. Soc.*, 1952, **74**, 483.

of uptake.[11] This took 70 min. A white solid began to separate. 5·3N-Hydrogen bromide in acetic acid (10 ml.) was added, and the mixture stirred for another 20 min. The solid (13·7 g.) was fully precipitated with ether; after being washed to neutrality with water, a bromo-compound could be isolated (10·8 g.), m. p. 186—187° (cap.) (decomp.), $[\alpha]_D$ +77° (*c* 0·5% in dioxan) (Found: Br, 32·7%). This material (8·0 g.) was heated with anhydrous potassium acetate (20 g.) in refluxing acetone (160 ml.) for 1 hr. Concentration of the solution and addition of water precipitated a product (6·2 g.), m. p. 96—106° (cap.), $[\alpha]_D$ +104°, that yielded no pure compounds by chromatography or by treatment [4] with Girard's reagent P. A stirred solution of the mixture (6·1 g.) in acetic acid (61 ml.) was treated at 15° with 5·3N-hydrogen bromide in acetic acid (6·1 ml.). After 30 mins., water (350 ml.) was added, and the bromohydrin extracted into methylene dichloride, in which it was washed with sodium hydrogen carbonate solution. This product, in refluxing methanol (146 ml.) and water (5·2 ml.), was stirred for 3½ hr. with W1 nickel catalyst (31 g. of a methanolic sludge).[7,17] The steroidal product was extracted into methylene dichloride, washed therein with 2N-hydrochloric acid and water, and obtained by evaporation of the solvent; it was treated [4] for 30 mins. in refluxing methanol (58 ml.) and acetic acid (1·2 ml.) with Girard's reagent P (0·9 g.), and the unreacted material was obtained as crystals and as an ethyl acetate extract, after treatment of the mother-liquors with 4% sodium hydrogen carbonate solution. Crystallisation of the combined products from methanol gave 21-acetoxy-3β,17-dihydroxy-5α-pregnane-11,20-dione (IV; R = H, R′ = OAc) (2·47 g., 29% from the oxide), m. p. 236—238°, $[\alpha]_D$ +90° (dioxan).[4,11] Acidification (to pH 1) of the water-soluble components from the Girard reaction gave the crude 17-hydroxy-dione (IV; R = R′ = H) (0·43 g.). No conditions could be found for the production of a pure bromo-epoxide; the description above indicates that simultaneous halogenation at the 9- and 21-positions occurs, substitution in ring c giving rise to the high dextrorotation of such dibromo-compounds. Bromination of the bromohydrins (III; R = H and Ac; R′ = R″ = H) also gave impure products.

3β-Acetoxy-16β-bromo-17-hydroxy-5α-pregnane-11,20-dione (III; R = Ac, R′ = R″ = H).—3β-Acetoxy-5α-pregn-16-ene-11,20-dione (I; R = Ac) (37·2 g.) [2] in solution in chloroform (170 ml.) was treated with hydrogen peroxide (93 ml.) in methanol (430 ml.), the solution being cooled to 5°. 5N-Sodium hydroxide (56 ml.) was added [17,18] dropwise over 25 min. at 5—10° and the mixture set aside for 2 hr. at room temperature. The steroid was extracted with chloroform. The residue after evaporation of the extract was heated for 1 hr. on a steam-bath with acetic anhydride (70 ml.) and pyridine (130 ml.). Water (750 ml.) was added to the cooled solution and the resulting precipitate refluxed for a few minutes with methanol. The cooled suspension yielded the epoxide (IIa; R = Ac) (36·6 g., 94%), m. p. 233—237° (cap.), $[\alpha]_D$ +72°. This procedure shows an improvement over the method due to Pataki *et al.*,[7,17] who cite m. p. 236—238°, $[\alpha]_D$ +72°, for this compound.

Traces of the starting material (I; R = Ac) could be removed as a water-soluble sulphonate.[5] The mother-liquors contained other compounds, possibly a 16-methoxy-20-ketone and a 16β,17β-epoxy-20-ketone. Reduction of the mother-liquors with chromous chloride,[15] with subsequent hydrolysis and acetylation, converted most of the steroids therein into the Δ^{16}-20-ketone, which could be recovered.

Recrystallisation from ethanol of one of the above fractions gave the *16β,17β-oxide* (IIb; R = Ac), m. p. 196—198° (cap.), $[\alpha]_D$ −13°, $\nu_{max.}$ 1720 and 1248 (acetate), 1705 (ketones), and 900 and 860 cm.$^{-1}$ (epoxide) (Found: C, 70·9; H, 8·2. $C_{23}H_{32}O_5$ requires C, 71·1; H, 8·3%).

The above-mentioned epoxide (IIa; R = Ac) (45·4 g.) was almost completely dissolved in methylene dichloride (162·5 ml.), acetic acid (290 ml.), and water (9 ml.) at 16°; 5·1N-hydrogen bromide in acetic acid (60·5 ml.) was added quickly with stirring, the temperature being kept below 22°. After 35 min. water (225 ml.) was added to the reddish solution, and the steroid extracted into methylene dichloride, from which it was obtained by evaporation. Traces of this solvent were removed by evaporation of a methanolic solution (250 ml.) of the residue, the solid being filtered from a thick suspension in methanol. This was the *bromohydrin* (III; R = Ac, R′ = R″ = H), (52·1 g., 95%), used for succeeding experiments. A specimen, crystallised from ethanol and dried *in vacuo* at 110°, had m. p. 222—224° (cap.; corr.) (decomp.), $[\alpha]_D$ +38°, $\nu_{max.}$ 1722 and 1255 (acetate), and 1712 cm.$^{-1}$ (ketones) (Found: C, 58·9; H, 7·25;

[17] Pataki, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1952, **74**, 5615; cf. Syhora, *Coll. Czech. Chem. Comm.*, 1961, **26**, 1026.

[18] Julian, Karpel, *et al.*, *J. Amer. Chem. Soc.*, 1949, **71**, 3574; 1956, **78**, 3153.

Br, 16·7. $C_{23}H_{33}BrO_5$ requires C, 58·9; H, 7·1; Br, 17·0%). Traces of the Δ^{16}-20-one (I; R= Ac) in the epoxide (IIa; R = Ac) may give rise to 3β-*acetoxy*-16α-*bromo*-5α-*pregnane*-11,20-*dione* in the above procedure. This compound has been made by addition of hydrogen bromide (in acetic acid) to the unsaturated ketone; crystals from methanol had m. p. 128—132° (cap.) (decomp.), $[\alpha]_D$ +72°. A specimen crystallised from aqueous acetic acid as rhombs, m. p. 184° (after a change to blades at >136°; some decomp.), $[\alpha]_D$ +67°, $\nu_{max.}$ (CS_2) 1730 and 1245 (acetate), and 1710 cm.$^{-1}$ (ketones) (Found: C, 60·6; H, 7·2; Br, 18·0. $C_{23}H_{33}BrO_4$ requires C, 61·0; H, 7·3; Br, 17·7%).

Treatment of the bromohydrin (III; R = Ac, R′ = R″ = H) with zinc in alcohol gave the unsaturated ketone (I; R = Ac), m. p. 162—167°, $[\alpha]_D$ +63°; reduction [7,17] with Raney nickel, or palladium–charcoal or –calcium carbonate gave the 17-hydroxy-compound (IV; R = Ac, R′ = H). With sodium hydrogen sulphite in refluxing aqueous ethanol, the bromohydrin yielded the oxide (IIa; R = Ac), and on hydrolysis with aqueous methanolic sulphuric or perchloric acid (see below) it gave, in yields over 90%, the 3,17-*diol* (III; R = R′ = R″ = H), m. p. 226—227° (cap.), $[\alpha]_D$ +71° (*c* 0·1% in dioxan), $\nu_{max.}$ (Nujol) 3390 and 3320 (OH), 1712 and 1690 (ketones), and 1352 cm.$^{-1}$ (CO·Me) (Found: C, 58·9; H, 7·2; Br, 18·6. $C_{21}H_{31}BrO_4$ requires C, 59·0; H, 7·3; Br, 18·7%).

3β,17-*Diacetoxy*-16β-*bromo*-5α-*pregnane*-11,20-*dione* (III; R = R′ = Ac, R″ = H).—(*a*) The bromohydrin (III; R = Ac, R′ = R″ = H) (1·0 g.) was stirred overnight [8] with acetic anhydride (25 ml.) containing toluene-*p*-sulphonic acid (0·5 g.). The resulting solution was diluted with water (75 ml.) to give a white solid, which crystallised from aqueous methanol as fine needles of the *diacetate* (0·63 g.), m. p. 159—160° (cap.), $[\alpha]_D$ +30°, $\nu_{max.}$ 1740 and 1240 (17-OAc), 1725 and 1248 (3β-OAc), and 1710 to 1720 cm.$^{-1}$ (11- and 20-oxo-groups) (Found: C, 58·4; H, 6·7; Br, 15·5. $C_{25}H_{35}BrO_6$ requires C, 58·7; H, 6·9; Br, 15·6%).

(*b*) A swirled suspension of the bromohydrin (III; R = Ac, R′ = R″ = H) (110 g.) in carbon tetrachloride (2·2 l.) was kept at 0° while a solution of perchloric acid (3 ml.; *d* 1·54) in acetic anhydride (140 ml.) [8] was run in. The solid dissolved within 5 min. and the solution was kept for 18 hr. at 0°. White needles separated out as a thick mass. The mixture was extracted with chloroform and the extract washed with sodium hydrogen carbonate solution. Evaporation to dryness (with further evaporation of a methanolic solution to remove all the chloroform) left white crystals, which were recrystallised from aqueous methanol as needles of the diacetate (III; R = R′ = Ac, R″ = H) (100 g., 84%), m. p. 164—167° (cap.), $[\alpha]_D$+31°. The mother-liquors contained some of the 16-acetate (V; R = Ac, R′ = H), the formation of which is discussed below. We thank Mr. W. Wall for details of this experiment. Benzene could be used as solvent for the reaction instead of carbon tetrachloride.

17-*Acetoxy*-16β-*bromo*-3β-*hydroxy*-5α-*pregnane*-11,20-*dione* (III; R = R″ = H, R′ = Ac).—A solution of the diacetate (III; R = R′ = Ac, R″ = H) (38 g.) in methylene dichloride (500 ml.) was treated [8] with a cold solution of 1 : 1-aqueous sulphuric acid (184 ml.) in methanol (710 ml.), added with swirling. The solution was kept overnight at room temperature, then extracted with water (500 ml.), 4% sodium hydrogen carbonate in water (500 ml.), and water (2 × 500 ml.), the washings being back-extracted with methylene dichloride (150 ml.). The combined extracts were distilled to dryness, methanol (100 ml.) was added, and the solution again evaporated. The residue, a yellowish solid, was dissolved in methanol (380 ml.); water (150 ml.) was added, and the solution kept overnight at 0°. The first crop of crystals consisted of the *monoacetate* (15·6 g., 45%), R_F 0·81. A specimen recrystallised several times had m. p. 152—154° (cap.), $[\alpha]_D$ +42°, $\nu_{max.}$ 3600 (OH), 1740 and 1240 (17-OAc), 1724 (20-ketone) and 1704 cm.$^{-1}$ (11-ketone) (Found: C, 59·2; H, 7·0; Br, 16·4. $C_{23}H_{33}BrO_5$ requires C, 58·8; H, 7·1; Br, 17·0%).

The second crop (12·8 g.), m. p. 200—208° (decomp.) $[\alpha]_D$ +34°, R_F 0·34 and 0·71 (Found: Br, 8·1%) was a mixture of the 17-acetate (III; R = R″ = H, R′ = Ac) and the 16-acetate (V; R = R′ = H), the latter arising by a reaction of the type described below. Consequently, this material gave, with collidine, excellent conversions into pure specimens of the 16-acetate.

16α-*Acetoxy*-3β,17-*dihydroxy*-5α-*pregnane*-11,20-*dione* (V; R = R′ = H).—The dione (III; R = R″ = H, R′ = Ac) (5·0 g.) in collidine (50 ml.) and water (25 ml.) was stirred [3] in an atmosphere of nitrogen on a steam-bath (95°) for 3 hr. The cooled product was diluted with ethyl acetate and shaken with 2N-sulphuric acid (3 × 50 ml.), then water (2 × 20 ml.). Most of the brown colour was removed from the organic phase by the washing. The washings were extracted with ethyl acetate, and the combined organic layers were dried. Evaporation to

small bulk gave the 16α-*acetoxy*-3β,17-*diol* (3·49 g.) as birefringent rectangular prisms, m. p. 250–251°, $[\alpha]_D^{24}$ +28°, R_F 0·30. Second (0·22 g.) and third crops (0·28 g.), m. p.s 247—249° and 245—249°, respectively, brought the yield to 90%. A sample, crystallised for analysis, separated as fine needles, m. p. 247—248·5° (from aqueous methanol), $[\alpha]_D$ +28°, $\nu_{max.}$ 1734 and 1230 (acetate), and 1704 cm.$^{-1}$ (ketones) (Found: C, 67·5; H, 8·4. $C_{23}H_{34}O_6$ requires C, 67·95; H, 8·4%).

Prior experiments established that purified collidine contained insufficient water (measured by the Karl Fischer reagent) to satisfy the stoicheiometry of the reaction, although reactions on a steam-bath were subject to a beneficial but variable ingress of water. Experiments with sealed tubes provided reliable evidence that a large excess of water promoted the most efficient reactions, so that adoption of the conditions described above improved an inconsistent and inefficient method giving polymers (see below) as well as the required ketol acetate (V; R = R′ = H), into a consistently high-yielding process for making the latter. Heating the bromo-acetate (III; R = R″ = H, R′ = Ac) (0·30 g.) in refluxing collidine (5 ml.) for 45 min. gave a precipitate; this was filtered off, washed with ether, and triturated with water. The resulting solid (0·23 g.), m. p. >300°, $\nu_{max.}$ 3600 (OH) and 1712 cm.$^{-1}$ (ketone) (Found: Br, 0·5%), was insoluble in all the common organic solvents and in molten camphor. This represents a 93% yield if the process is of the type depicted in (A) ⟶ (C) (see text).

3β,16α-*Diacetoxy*-17-*hydroxy*-5α-*pregnane*-11,20-*dione* (V; R = Ac, R′ = H).—The bromohydrin monoacetate (III; R = R″ = H, R′ = Ac) (1·0 g.) and sodium acetate (2·5 g.) in acetic acid (50 ml.) were heated [3] at reflux for 3 hr. and poured into water (200 ml.). The diacetate separated as needles (0·66 g.), m. p. 191—192° (cap.). Recrystallisation from methanol of this material or of the product from a similar experiment on the 3,17-diacetoxy-bromohydrin (III; R = R′ = Ac, R″ = H) gave the 3,16-*diacetate*, m. p. 198·5—200° (cap.), $[\alpha]_D$ +13°, $\nu_{max.}$ 1724 and 1245 (acetates), and 1708 cm.$^{-1}$ (ketones) (Found: C, 66·9; H, 8·2. $C_{25}H_{36}O_7$ requires C, 66·7; H, 8·1%).

16α-*Acetoxy*-21-*bromo*-3β,17-*dihydroxy*-5α-*pregnane*-11,20-*dione* (V; R = H, R′ = Br).—A solution of 16α-acetoxy-3β,17-dihydroxy-5α-pregnane-11,20-dione (V; R = R′ = H) (1·0 g.) in chloroform (20 ml.) was saturated [11] with dry hydrogen chloride; 1·1N-bromine in chloroform (4·92 ml., 1·1 mol.) was run in during 15 min., the solution being stirred during this time and for 10 min. more. The colourless solution was washed with saturated sodium acetate (20 ml.) and sodium hydrogen carbonate solutions (20 ml.), then with water, and finally dried. Evaporation left a solid (1·31 g.) that yielded the 21-*bromo-compound*, from benzene–ether containing a few drops of methanol, as solvated prisms (1·01 g., 76%), m. p. 138—148° (decomp.), $\nu_{max.}$ 1742 and 1230 (acetate), 1708 (ketones), and 1480 cm.$^{-1}$ (benzene) (Found: C, 60·6; H, 7·1; Br, 15·25. $3C_{23}H_{33}BrO_6,2C_6H_6$ requires C, 60·3; H, 6·9; Br, 14·9%). Two more crystallisations from the same solvent mixture gave material, m. p. 145—147° (isolated crystals had m. p. 188—190°), $[\alpha]_D^{25}$ +37°, R_F 0·46. Isolation of this compound was not necessary in the manufacture of the 21-acetate (V; R = H, R′ = OAc) (see below).

16α,21-*Diacetoxy*-3β,17-*dihydroxy*-5α-*pregnane*-11,20-*dione* (V; R = H, R′ = OAc).—(*a*) A mixture of the foregoing bromo-compound (0·726 g.) and fused potassium acetate (1·05 g.) in acetone (30 ml.) was refluxed [11] for 75 min., filtered, and the insoluble material washed with hot acetone (10 ml.). Water (50 ml.) was added to the filtrate, which was extracted with chloroform (8 × 30 ml.) until the extracts no longer removed material reducing TSTZ. The combined extracts were washed with water (2 × 20 ml.) and dried. A solid (0·824 g.) was obtained by evaporation; crystallisation from benzene–hexane containing a few drops of methanol afforded clumps (0·452 g.), m. p. 225—227°, $[\alpha]_D^{27}$ +30°, and recrystallisation from ethyl acetate gave the 16,21-*diacetate* as birefringent prisms, m. p. 247—249°, $[\alpha]_D^{27}$ +34·5°, R_F 0·28, $\nu_{max.}$ 1752—1736 and 1232 (acetates), and 1708 cm.$^{-1}$ (ketone) (Found: 65·1; H, 8·1. $C_{25}H_{36}O_8$ requires C, 64·6; H, 7·8%).

(*b*) A solution of the dione (V; R = R′ = H) (5·40 g.) in chloroform (110 ml.) was saturated with hydrogen chloride; 1·37N-bromine in chloroform (19·8 ml., 1 mol.) was added in 20 min., the solution being stirred for this time and for 10 min. more. The colourless solution was treated as described above to yield the crude 21-bromo-compound (V; R = H, R′ = Br) (7·6 g.), which was dissolved without purification in AnalaR acetone (150 ml.) to which anhydrous potassium acetate (9·7 g.) had been added. The mixture was stirred and refluxed for 75 min. The 16α,21-diacetate (6·94 g.) was isolated in a crude state as described in (*a*) above; crystallisation from ethyl acetate furnished a purer specimen (3·28 g., 53%), m. p. 238—239°, R_F 0·03

(very weak) and 0·28. The residues from the crystallisation gave several spots on a paper chromatogram; they were heated for 0·5 hr. with Girard's reagent P (0·55 g.) in refluxing absolute ethanol (30 ml.) containing acetic acid (0·6 ml.).[4] The cooled solution was poured into an excess of saturated sodium hydrogen carbonate solution, and the unchanged steroid extracted into chloroform giving, after crystallisation, the 16α,21-diacetate (0·12 g.) in a crude state. Chromatography on Florisil and paper chromatography of the fractions showed that the other components of the mixture could not be readily separated.

The aqueous phase from the Girard reaction was brought to pH 1 with concentrated hydrochloric acid. Isolation of the steroid with chloroform, and crystallisation of the product from methanol gave the 20-ketone (V; R = R′ = H) (0·08 g.), m. p. 237—239°.

16α-*Acetoxy*-4,5α-*dihydrocortisone Acetate* (VII).—A solution of the dione (V; R = H, R″ = OAc) (0·132 g.) in AnalaR acetone (25 ml.) was gently refluxed while 0·33M-potassium dichromate in 4N-sulphuric acid (0·43 ml., 1·5 mol.) was added,[13] and for 2 min. more. Sodium pyrosulphite was introduced to reduce the remaining oxidant, then the mixture was poured into water (50 ml.). Isolation with chloroform and crystallisation of the crude product from ethyl acetate gave the 3-ketone as blades (0·043 g.), m. p. 260—262°, $[\alpha]_D^{29}$ +47°, R_F 0·70, identified with a specimen made by another method.[1] Second and third crops totalling 0·061 g. raised the yield to 78%. A yield of 85% was achieved on a 3 g. scale.

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