12-*Oxygenated Pregnane Derivatives. Part I.* (a) 21-*Acetoxy*-12α : 17α-*dihydroxypregn*-4-*ene*-3 : 20-*dione ;* (b) 12α : 21-*Diacetoxy*-17α-*hydroxypregn*-4-*ene*-3 : 20-*dione ;* (c) 3α : 12α : 21-*Triacetoxy*-17α-*hydroxypregnan*-20-*one ; and* (d) *Miscellaneous Observations.*

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Degradation of deoxycholic acid to 3α : 12α-diacetoxypregnan-20-one (I) and conversion of the latter into the compounds named in the title are described. Some miscellaneous observations pertaining to the chemistry of these transformations are included.

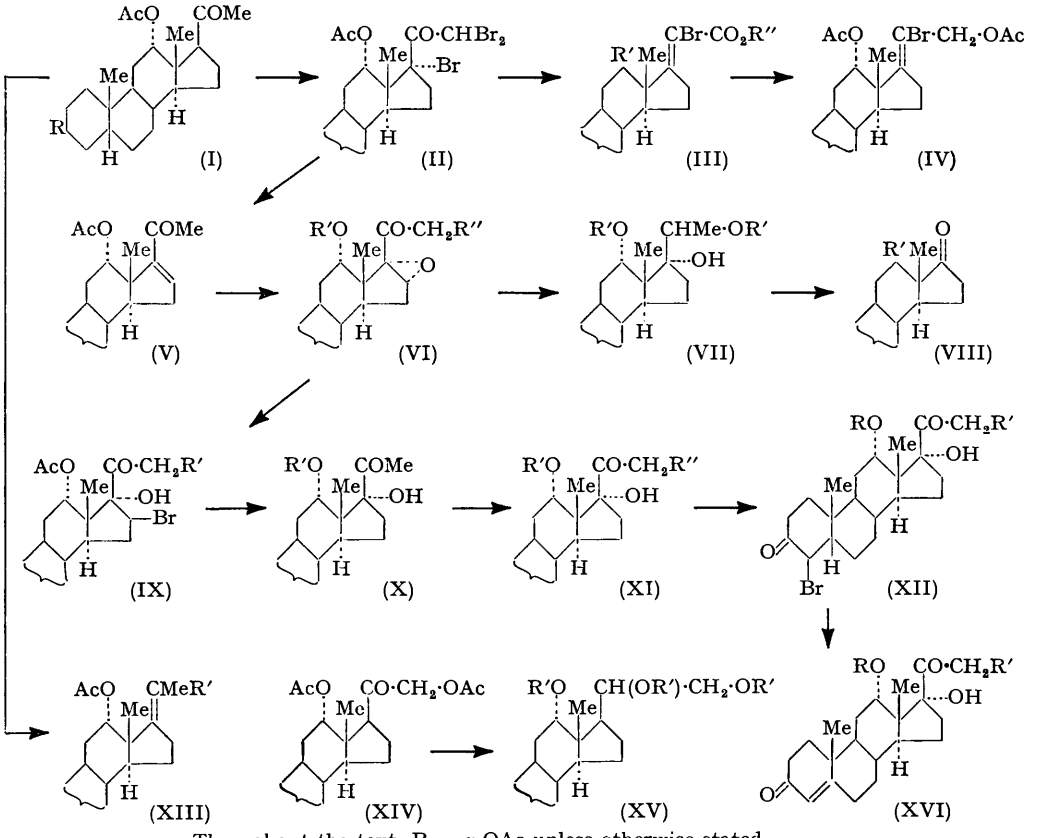
The preparation of 12α : 17α : 21-trihydroxypregn-4-ene-3 : 20-dione (XVI; R = H, R′ = OH) has been undertaken, as this isomer of hydrocortisone is worthy of biological study.

Conversion of deoxycholic acid into 3α : 12α-diacetoxypregnan-20-one (I) was effected by adaptation of standard methods (Meystre, Frey, Wettstein, and Miescher, *Helv. Chim. Acta*, 1944, **27**, 1815; Meystre, Ehrmann, Neher, and Miescher, *ibid.*, 1945, **28**, 1252; Kendall, U.S.P. 2,541,074).

The preparation of 3α : 12α-diacetoxypregn-16-en-20-one (V) from (I) by allylic bromination of 3α : 12α : 20-triacetoxypregn-17-ene (XIII; R′ = OAc) (Marshall, Kritchevsky, Lieberman, and Gallagher, *J. Amer. Chem. Soc.*, 1948, **70**, 1837) as described by Djerassi and Scholz (*J. Org. Chem.*, 1949, **14**, 660) was uneconomic as only 20—25% overall yields were obtained. A more satisfactory procedure was bromination of (I) to the 17 : 21 : 21-tribromo-derivative (II), followed by reaction with sodium iodide in acetic acid. The high

overall yields referred to by Julian (118th Meeting Amer. Chem. Soc., Sept. 3—8, 1950, p. 19c) were, however, reached only with 25-g. batches, falling to *ca.* 50% with larger quantities.

(a) *Preparation of* 21-*Acetoxy*-12α : 17α-*dihydroxypregn*-4-*ene*-3 : 20-*dione* (XVI; R = H, R′ = OAc).—Epoxidation of (V) with alkaline hydrogen peroxide (Julian, Meyer, Karpel, and Waller, *J. Amer. Chem. Soc.*, 1950, **72**, 5154) furnished the 16α : 17α-epoxide (VI; R′ = Ac, R″ = H) in good yield, the constitution of which was confirmed by reduction with lithium aluminium hydride or sodium borohydride to a tetraol formulated as (VII; R = α-OH, R′ = H) on the basis of molecular rotations [see (d) (viii)]. The compound gave the 3α : 12α : 20β-triacetate (VII; R′ = Ac) on acetylation and testane-3 : 12 : 17-trione (VIII; R = R′ = :O) on cautious oxidation with chromic acid.



Throughout the text, R = α-OAc unless otherwise stated.

No difficulty was experienced in cleaving the epoxide ring with hydrogen bromide, to give 3α : 12α-diacetoxy-16β-bromo-17α-hydroxypregnan-20-one (IX; R′ = H) which was also prepared from (V) in one operation by reaction with *N*-bromoacetamide in aqueous acidic *tert.*-butanol (cf. Sarett, *J. Biol. Chem.*, 1946, **162**, 628). Debromination of (IX) by Raney nickel in ethanol, as recommended by Julian *et al.* (*loc. cit.*), gave erratic yields, but by using hydrogen and 2% palladium–calcium carbonate (Busch and Stove, *Ber.*, 1916, **49**, 1063), consistent yields of (X; R′ = Ac) exceeding 90% were readily obtained [cf. (d) (v)].

The 3α : 12α-diacetoxy-17α-hydroxypregnan-20-one prepared in this way formed needles which usually melted at 74—77° and occasionally at 104—105°. In addition to this unexpectedly low melting point, the infra-red spectrum of the material * showed

* Kindly determined by Dr. A. E. Kellie, Courtauld Institute of Biochemistry, who will report elsewhere results on this and other compounds herein described.

certain unusual features. We studied its reactions in some detail in order to establish its structure. The compound was largely unchanged on attempted acetylation, although small quantities of a new product which was probably 3α : 12α : 17α-triacetoxypregnan-20-one were also formed. It was unaffected by *N*-bromosuccinimide, lead tetra-acetate, and hydrogen bromide. Careful oxidation with chromium trioxide at room temperature led to 3α : 12α-diacetoxytestan-17-one (VIII; R′ = α-OAc) (Reich, *Helv. Chim. Acta*, 1945, **28**, 863) and a second product which was not identified. Reduction with lithium aluminium hydride, followed by acetylation, furnished 3α : 12α : 20β-triacetoxypregnan-17α-ol (VII; R′ = Ac) and a small quantity of an isomer. Finally, dehydration with thionyl chloride–pyridine gave 3α : 12α-diacetoxypregn-16-en-20-one (V) (Djerassi and Scholz, *loc. cit.*). The formulation (X; R′ = Ac) is thus proved beyond reasonable doubt.

Hydrolysis of the compound (X; R′ = Ac) with methanolic potassium carbonate furnished the triol (X; R = α-OH, R′ = H) in 84% yield, the structure of this compound following from its reconversion into the diacetate and formation of a di-*p*-nitrobenzoate. In addition, ethyl chloroformate gave 3α-ethoxycarbonyloxy-12α : 17α-dihydroxypregnan-20-one (X; R = α-$EtO_2C{\cdot}O{\cdot}$, R′ = H) (cf. Fieser and Rajagopalan, *J. Amer. Chem. Soc.*, 1950, **72**, 5530) which passed into 12α-acetoxy-3α-ethoxycarbonyloxy-17α-hydroxypregnan-20-one (X; R = α-$EtO_2C{\cdot}O{\cdot}$, R′ = Ac) on acetylation. Chromic acid oxidation, however, gave a complex ketonic mixture from which testane-3 : 12 : 17-trione (VIII; R = R′ = :O) could not be isolated [cf. (X; R′ = Ac) ⟶ (VIII); also (d) (vii)].

With 1 mol. of bromine 3α : 12α : 17α-trihydroxypregnan-20-one (X; R = α-OH, R′ = H) furnished the unstable bromo-derivative (XI; R = α-OH, R′ = H, R″ = Br) and thence the 21-iodide and 21-acetate (XI; R = α-OH, R′ = H, R″ = Ac). Oxidation of the last compound with *N*-bromoacetamide in aqueous *tert.*-butanol (Reich and Reichstein, *Helv. Chim. Acta*, 1943, **26**, 562) gave 21-acetoxy-12α : 17α-dihydroxypregnane-3 : 20-dione [XI; R = :O, R′ = H, R″ = OAc; see (d) vii) for evidence regarding preferential oxidation of the 3-hydroxyl group in 3α : 12α : 17α-trihydroxypregnan-20-ones], which was characterised by acetylation to the 12α : 21-diacetate (XI; R = :O, R′ = Ac, R″ = OAc), also formed as described under (*b*) below. Careful bromination of the monoacetoxy-ketone gave exclusively the 4β-bromo-derivative (XII; R = H, R′ = OAc; cf. Fieser and Ettore, *J. Amer. Chem. Soc.*, 1953, **75**, 1700, p. 1700). The last stage of the partial synthesis was accomplished by dehydrobromination of the last by Kendall's method (Mattox and Kendall, *J. Biol. Chem.*, 1951, **188**, 287) as modified by Kritchevsky, Garmaise, and Gallagher (*J. Amer. Chem. Soc.*, 1952, **74**, 483) to give the required 21-acetoxy-12α : 17α-dihydroxypregn-4-ene-3 : 20-dione (XVI; R = H, R′ = OAc) in satisfactory yield

(b) *Preparation of* 12α : 21-*Diacetoxy*-17α-*hydroxypregn*-4-*ene*-3 : 20-*dione* (XVI; R = Ac, R′ = OAc).—Partial hydrolysis of 3α : 12α-diacetoxypregn-16-en-20-one (V) furnished the 12α-acetoxy-3α-hydroxy-compound, reconverted into (V) by acetylation and characterised as the 3-*p*-nitrobenzoate. Epoxidation gave 12α-acetoxy-16α : 17α-epoxy-3α-hydroxypregnan-20-one (VI; R = α-OH, R′ = Ac, R″ = H) which formed a 3-*p*-nitrobenzoate. Treatment of this oxide with hydrobromic acid–acetic acid at −18° for 20 hours led to the formation of 12α-acetoxy-16β-bromo-3α : 17α-dihydroxypregnan-20-one in moderate yield. Reductive removal of the the 16β-bromine atom gave 12α-acetoxy-3α : 17α-dihydroxypregnan-20-one (X; R = α-OH, R′ = Ac) and thence 3α : 12α-diacetoxy-17α-hydroxypregnan-20-one (X; R′ = Ac) identical with material described under (*a*). With one equivalent of bromine, (X; R = α-OH, R′ = Ac) furnished the unstable 21-bromide (XI; R = α-OH, R′ = Ac, R″ = Br) which decomposed on attempted purification [cf. (*d*) (vi) for observations regarding the lability of the 12α-acetyl group in 12α-acetoxy-17α-hydroxypregnan-20-ones)]. It was therefore converted *via* the iodide into 12α : 21-diacetoxy-3α : 17α-dihydroxypregnan-20-one (XI; R = α-OH, R′ = Ac, R″ = OAc) and the constitution of this was confirmed by acetylation to (XI; R′ = Ac, R″ = OAc), also formed as described in (*c*) below. Oxidation of the diacetate (XI; R = α-OH, R′ = Ac, R″ = OAc with *N*-bromoacetamide in aqueous *tert.*-butanol gave the 3 : 20-dione (XI; R = :O, R′ = Ac, R″ = OAc) described in (*a*) above. Bromination at $C_{(4)}$, followed by dehydrobromination, led to 12α : 21-diacetoxy-17α-hydroxypregn-4-ene-3 : 20-dione (XVI; R = Ac, R′ = OAc), identical with material prepared by route (*a*).

(c) *Preparation of* 3α : 12α : 21-*Triacetoxy*-17α-*hydroxypregnan*-20-*one* (XI; R′ = Ac, R″ = OAc).—Alternative routes to this compound were developed in order to compare the product thus obtained with material prepared as in (*b*).

(i) Monobromination of 3α : 12α-diacetoxy-17α-hydroxypregnan-20-one (X; R′ = Ac) gave a sticky bromo-compound which was converted into the 21-iodide and thence in low yield into 3α : 12α : 21-triacetoxy-17α-hydroxypregnan-20-one (XI; R′ = Ac, R″ = OAc).

(ii) 3α : 12α-Diacetoxy-16α : 17α-epoxypregnan-20-one (VI; R′ = Ac, R″ = H) (see above) and hydrogen bromide in acetic acid at room temperature gave the 16β-bromide (IX; R′ = H) [cf. (*a*)], which was treated *in situ* with one mol. of bromine, yielding the 16β : 21-dibromo-compound (IX; R′ = Br). Replacement of the 21-bromine atom by acetoxyl in the last compound was effected by means of potassium acetate in hot acetone and was accompanied by regeneration of the epoxide ring with formation of 3α : 12α : 21-triacetoxy-16α : 17α-epoxypregnan-20-one (VI; R′ = Ac, R″ = OAc) (cf. Julian *et al.*, *loc. cit.*). Reaction with hydrogen bromide cleaved the epoxide ring with formation of the bromohydrin (IX; R′ = OAc), which passed into 3α : 12α : 21-triacetoxy-17α-hydroxypregnan-20-one (XI; R′ = Ac, R″ = OAc) when heated with Raney nickel in ethanol.

(d) *Miscellaneous.*—(i) Attempts to employ Wagner and Moore's method for building up the cortical side chain (*ibid.*, 1949, **71**, 4160) were not successful. Reaction of (I) with 3 mols. of bromine gave the tribromide (II) [see (*a*)], which passed into 20-bromo-3α : 12α-dihydroxypregn-17-en-21-oic acid (III; R = R′ = α-OH, R″ = H) on Favorski rearrangement. Esterification with diazomethane gave the methyl ester which was characterised by conversion into the diacetate (III; R′ = α-OAc, R″ = Me), and by oxidation to methyl 20-bromo-12α-hydroxy-3-oxopregn-17-en-21-oate (III; R = :O, R′ = α-OH, R″ = Me) with aluminium *tert.*-butoxide in *cyclo*hexanone–toluene and to methyl 20-bromo-3 : 12-dioxopregn-17-en-21-oate (III; R = R′ = :O, R″ = Me) with chromic–acetic acid. Reduction with lithium aluminium hydride gave 20-bromo-3α : 12α : 21-trihydroxypregn-17-ene. The triacetate (IV) of this compound, however, was recovered unchanged after treatment with osmium tetroxide or with hydrogen peroxide–osmium tetroxide (Miescher and Schmidlin, *Helv. Chim. Acta*, 1950, **33**, 1840).

(ii) Sarett's cyanohydrin procedure (*J. Amer. Chem. Soc.*, 1948, **70**, 1454) for introducing the 17α-hydroxyl group into pregnan-20-ones gave discouraging results. Conversion of diacetoxypregnan-20-one (I) into the cyanohydrin by reaction with potassium cyanide in ethanolic acetic acid did not proceed as readily as in the pregnane-11 : 20-dione series, the desired compound being obtained in only 25% yield (allowing for recovery of unchanged material). Its dehydration with phosphorus oxychloride was also difficult, 3α : 12α-diacetoxy-20-cyanopregn-17-ene (XIII; R′ = CN) being obtained in too low a yield to warrant a further study. Even less satisfactory results attended the use of 3α : 12α : 21-triacetoxypregnan-20-one (XIV) (Meystre and Wettstein, *Helv. Chim. Acta*, 1947, **30**, 1037) as starting material : the yield of cyanohydrin could not be raised above *ca.* 12% (allowing for recovered starting material), and dehydration failed to give a product with a satisfactory analysis.

(iii) Gallagher's enol acetate method (*J. Amer. Chem. Soc.*, 1949, **71**, 3262) for preparing 17α-hydroxy-pregnan-20-ones could not be applied to 12α-acetoxypregnan-20-ones : 3α : 12α : 20-triacetoxypregn-17-ene (XIII; R′ = OAc) failed to react with perbenzoic acid, perphthalic acid, or hydrogen peroxide–osmium tetroxide (Miescher and Schmidlin, *loc. cit.*). Performic acid, in contrast, proved too vigorous, degrading the compound to 3α : 12α-diacetoxytestan-17-one (VIII; R′ = α-OAc), which was hydrolysed to 3α : 12α-dihydroxytestan-17-one (VIII; R = R′ = α-OH) and then converted into testane-3 : 12 : 17-trione (VIII; R = R′ = :O).

Hirschmann, Brown, and Wendler (*ibid.*, 1951, **73**, 5373) had previously shown that the 12-oxo-group fails to undergo enol-acetylation. So we studied 3-ethoxycarbonyloxy- and 3α-acetoxy-pregnane-12 : 20-dione in which the 12α-acetoxy-residue is replaced by the smaller keto-group. In this way we hoped to avoid the steric hindrance effects presumably exercised by the 12α-acetoxyl group on the epoxidation of (XIII; R′ = OAc).

3α : 12α-Dihydroxypregnan-20-one gave an excellent yield (cf. Fieser, Herz, Klohs, Romero, and Utne, *ibid.*, 1952, **74**, 3309) of the 3α-ethoxycarbonyloxy-derivative, smoothly

oxidised by *N*-bromosuccinimide in *tert.*-butanol to the 12 : 20-dione. Enol-acetylation with acetic anhydride–toluene-*p*-sulphonic acid, followed by reaction of the total product with perbenzoic acid and subsequent hydrolysis, failed to yield the desired 17α-hydroxy-derivative, although reaction with the peracid undoubtedly occurred. Similar results were obtained with 3α-acetoxypregnane-12 : 20-dione, which was conveniently prepared by partial oxidation of 3α : 12α-dihydroxypregnan-20-one with potassium chromate–acetic acid to the 12-keto-derivative, followed by acetylation.

(iv) Conversion of (I) into the $C_{(20)}$-enol ether (XIII; R′ = OEt) was examined as it was hoped that this compound would undergo epoxidation with formation of (X; R′ = Ac). By reaction with ethyl orthoformate in the presence of sulphuric or toluene-*p*-sulphonic acid 3α : 12α-diacetoxy-20-ethoxypregn-17(or 20)-ene (XIII; R′ = OEt) was obtained in *ca.* 12% yield. Treatment with perbenzoic acid failed to give the 17α-hydroxy-derivative, vigorous reaction accompanied by side-chain degradation taking place. Belleau and Gallagher (*J. Amer. Chem. Soc.*, 1952, **74**, 2816) have since described the conversion of (11-oxo) pregnanolone into a mixture of the Δ^{17}- and Δ^{20}-enol ethers, which were severally degraded to the (11-oxo) 17-keto-steroid and ethyl ester of etianic acid by perbenzoic acid.

(v) Julian *et al.* (*loc. cit.*) converted 21-acetoxy-16β-bromo-17α-hydroxypregn-4-ene-3 : 20-dione into compound S acetate by Raney nickel in hot ethanol. By this reaction, (IX; R′ = H) gave yields varying from 3% to 70%. We consequently studied the conversion of (IX; R′ = H) into (X; R′ = Ac) in some detail.

Chemical methods of reduction failed to effect the required change. Zinc dust or activated zinc in boiling ethanol led to (V). No reaction occurred with zinc dust, chromous chloride, or Raney nickel at room temperature, or with sodium iodide in boiling acetone. Silver nitrate–pyridine had no effect at room temperature, but produced the epoxide (VI; R′ = Ac, R″ = H) after brief heating at 100°. Attempts to cleave the epoxide ring with thiourea–toluene-*p*-sulphonic acid (King and Campbell, *ibid.*, 1949, **71**, 3556) gave a sulphur-free product which failed to crystallise. Thiolacetic acid and pyridine hydrobromide (cf. Mancera, Rosenkranz, and Djerassi, footnote p. 1280 to Djerassi, Martinez, and Rosenkranz, *J. Org. Chem.*, 1951, **16**, 1278) were without effect, as was hydrogen iodide under the conditions employed by Barton, Miller, and Young (*J.*, 1951, 2598). The method finally adopted for preparing 17α-hydroxypregnan-20-ones (X) from the epoxides (VI; R″ = H) lay in conversion into the bromohydrins (IX; R′ = H) followed by reductive removal of the 16β-bromine atom by catalytic hydrogenation over 2% palladium–calcium carbonate [cf. (*a*) above].

(vi) Partial hydrolysis of (X; R′ = Ac) would give 12α-acetoxy-3α : 17α-dihydroxy-pregnan-20-one (X; R = α-OH, R′ = Ac). With the 12α-OH group thus protected, the way would have been open to the introduction of the 21-acetoxyl group, etc. 0·3N-Sodium hydroxide (1 hour) or methanolic potassium carbonate (1 equiv. for 12 hours) at room temperature and methanolic hydrochloric acid (1 hour) under reflux, which convert (I) into the 12α-acetoxy-3α-hydroxy-derivative, gave the fully hydrolysed product (X; R = α-OH, R′ = H). This atypical behaviour probably arises from the close proximity of the 17α-hydroxy-group to the 12α-acetoxy-group with consequent hydrogen bonding and lability (cf. Petrow, Rosenheim, and Starling, *J.*, 1943, 135).

(vii) We had previously found that *N*-bromoacetamide in aqueous *tert.*-butanol (Reich and Reichstein, *Helv. Chim. Acta*, 1943, **26**, 562) effects smooth conversion of 3α : 12α-dihydroxypregnan-20-one into pregnane-3 : 12 : 20-trione. We applied this reaction to 3α : 12α : 17α-trihydroxypregnan-20-one (X; R = α-OH; R′ = H) as attempts to confirm its structure by chromic acid oxidation to testane-3 : 12 : 17-trione had failed [see (*a*)]. The product, however, was clearly not the expected 17α-hydroxypregnane-3 : 12 : 20-trione, as it gave a monoacetate smoothly and quantitatively; as it did not give an ethoxycarbonyloxy-derivative it was formulated as 12α : 17α-dihydroxypregnane-3 : 20-dione (X; R = :O, R′ = H). In support of this structure we found that monobromination gave an excellent yield of 4β-bromo-12α : 17α-dihydroxypregnane-3 : 20-dione (XII; R = R′ = H), which passed into the αβ-unsaturated ketone 12α : 17α-dihydroxypregn-4-ene-3 : 20-dione (XVI; R = R′ = H), characterised as the monoacetate.

(viii) Reduction of (XIV) with lithium aluminium hydride followed by acetylation of the

total product and chromatography gave 3α : 12α : 20ξ : 21-tetra-acetoxypregnane (XV; R′ = Ac), readily hydrolysed to a pregnane-3α : 12α : 20ξ : 21-tetraol (XV; R = α-OH, R′ = H). Molecular-rotational data appeared to indicate an α-configuration at $C_{(20)}$. This conclusion, however, makes no allowance for the strong vicinal effect, clearly revealed by infra-red studies, which the 12α-acetoxyl group exerts on the polar residues in the side chain.

(ix) Reduction of the epoxide (VI; R′ = Ac, R″ = OAc) with lithium aluminium hydride furnished pregnane-3α : 12α : 17α : 20ξ : 21-pentaol in unsatisfactory yield. The compound was characterised as a tetra-acetate, but its conversion into (XI; R′ = Ac, R″ = OAc) [cf. (*c*)] was not proceeded with in view of results described above.

Experimental

Optical rotations were measured in chloroform solution in a 1-dm. tube unless otherwise stated. Ultra-violet absorption spectra (in *iso*propanol) were kindly determined by Dr. R. E. Stuckey and Mr. P. Stross, B.Sc. Alumina, B.D.H., chromatography grade, was used.

3α : 12α-*Diacetoxy*-17 : 21 : 21-*tribromopregn*-20-*one* (II).—Diacetoxypregnanone (I) (12·5 g.) in glacial acetic acid (400 ml.) containing hydrogen bromide in acetic acid (2 ml. of 50% w/v) was treated at 40° with stirring with a molar solution of bromine in acetic acid (60 ml.) at such a rate that the bromine colour did not persist. The temperature was then raised to 70° and a further quantity of bromine solution (30 ml.) added, stirring with temperature control being maintained for a further 30 min. The mixture was then poured into water and the precipitated solids were collected, washed, dried, and purified from aqueous acetone. 3α : 12α-*Diacetoxy*-17 : 21 : 21-*tribromopregnan*-20-*one* had m. p. 174—175° (decomp.), $[\alpha]_D^{23}$ +74° (*c*, 0·102) (Found : C, 45·9; H, 5·2; Br, 36·0. $C_{25}H_{35}O_5Br_3$ requires C, 45·8; H, 5·3; Br, 36·6%).

3α : 12α-*Diacetoxypregn*-16-*en*-20-*one* (V).—The foregoing compound (15 g.) in acetic acid (200 ml.) was warmed on a steam-bath with sodium iodide (30 g.) for 30 min. The product precipitated in water was extracted with ether, which was washed successively with water, 20% potassium metabisulphite solution, 20% sodium thiosulphate solution, water, sodium hydrogen carbonate solution, and water. After being dried, the ethereal solution was evaporated to small bulk and *n*-hexane was added; 3α : 12α-*diacetoxypregn*-16-*en*-20-*one* crystallised, having m. p. 190—192° (Found : C, 72·0; H, 8·9. Calc. for $C_{25}H_{36}O_5$: C, 72·1; H, 8·7%). The crude bromo-compound was used for preparation of (V) in quantity.

3α : 12α-*Diacetoxy*-16α : 17α-*epoxypregnan*-20-*one* (VI; R′ = Ac, R″ = H).—3α : 12α-Diacetoxypregn-16-en-20-one (10 g.) in methanol (400 ml.) was treated at 0° with 4N-sodium hydroxide (20 ml.) and hydrogen peroxide (40 ml. of 30%). After 24 hr. at room temperature the solution was diluted with a large volume of water, neutralised with acetic acid, and extracted with ether. The extract was washed with sodium iodide solution, sodium thiosulphate solution, and water, dried, and evaporated. The residue was purified from *n*-hexane. 3α : 12α-*Diacetoxy*-16α : 17α-*epoxypregnan*-20-*one* formed prisms, m. p. 119—121°, $(\alpha]_D^{30}$ +92° (*c*, 2·324 in EtOH) (Found : C, 69·1; H, 8·4. $C_{25}H_{36}O_6$ requires C, 69·4; H, 8·4%).

Pregnane-3α : 12α : 17α : 20β-*tetraol* (VII; R = α-OH).—3α : 12α-Diacetoxy-16α : 17α-epoxypregnan-20-one (850 mg.) in dry ether (40 ml.) was added dropwise with stirring during 15 min. to lithium aluminium hydride (600 mg.) in ether (60 ml.). After 30 minutes' heating under reflux the mixture was decomposed with ice-water and acidified with 10% aqueous sulphuric acid, and the product extracted with ether–chloroform. Purification from aqueous methanol gave *pregnane*-3α : 12α : 17α : 20β-*tetraol*, needles, m. p. 262—264°, $[\alpha]_D^{23}$ +30° (*c*, 0·672 in EtOH) (Found : C, 71·5; H, 10·3. $C_{21}H_{36}O_4$ requires C, 71·6; H, 10·2%).

The triacetate formed needles, m. p. 191—192°, $[\alpha]_D^{23}$ +133° (*c*, 0·302), from aqueous methanol. It was also obtained by treating (VI; R′ = Ac, R″ = H) (500 mg.) in ethanol (5 ml.) and 0·2N-sodium hydroxide (6 ml.) at 0° with sodium borohydride (100 mg.). After 18 hr. at 5°, the mixture was diluted with water, and the product extracted with chloroform, giving an oil (500 mg.). This was acetylated and purified by chromatography on alumina (15 g.) from which the triacetate was obtained by elution with benzene and benzene–ether.

3α : 12α-*Diacetoxy*-16β-*bromo*-17α-*hydroxypregnan*-20-*one* (IX; R′ = H).—3α : 12α-Diacetoxy-16α : 17α-epoxypregnan-20-one (10 g.) in glacial acetic acid (55 ml.) was treated with hydrogen bromide in acetic acid (6 ml. of 50%) for 30 min. at room temperature; the mixture was then diluted with water, and the precipitated solids were collected, washed, and dried *in vacuo* over potassium hydroxide. Crystallisation from acetone–hexane gave 3α : 12α-*diacetoxy*-16β-

bromo-17α-hydroxypregnan-20-one, needles, m. p. 166—168°, $[\alpha]_D^{23}$ +193° (*c*, 1·506) (Found: C, 58·9; H, 7·4; Br, 15·3. $C_{25}H_{37}O_6Br$ requires C, 58·5; H, 7·3; Br, 15·6%).

3α : 12α-*Diacetoxy-17α-hydroxypregnan-20-one* (X; R′ = Ac).—(i) The foregoing compound (5 g.) in 95% ethanol (200 ml.) was stirred with Raney nickel (25 g., prepared as described in Adkins's "Reactions of Hydrogen," University of Wisconsin Press, Wisconsin, 1937) on a steam-bath for 5 hr. The hot solution was filtered (Hyflo), the residue thoroughly washed with ethanol, and the filtrate taken to dryness under reduced pressure. The residue was chromatographed in benzene on alumina (100 g.). Elution with benzene and benzene–ether furnished 3α : 12α-*diacetoxy-17α-hydroxypregnan-20-one*, needles, m. p. 74—77° or 104—105°, $[\alpha]_D^{22}$ +128° (*c*, 0·496) (Found: C, 69·4; H, 9·0. $C_{25}H_{38}O_6$ requires C, 69·1; H, 8·8%).

(ii) The bromohydrin (5 g.) in 90% methanol (250 ml.) was catalytically hydrogenated over 2% palladium–calcium carbonate (10 g.). After removal of the catalyst, the solution was partially evaporated, and the residue extracted with ether. Crystallisation from hexane gave (X; R′ = Ac).

Acetylation of the foregoing compound (1 g.) in pyridine (15 ml.) and acetic anhydride (10 ml.) under reflux for 2 hr., followed by chromatography in benzene (10 ml.) on alumina (30 g.) and elution with ether–benzene (10 ⟶ 40%) gave unchanged starting material. From 50% ether–benzene to acetone eluates a small quantity of crystals, m. p. 203°, was obtained. A further amount was isolated by rechromatography of the mother-liquors from the first fractions. The compound, crystallised from acetone–hexane, had m. p. 203° (Found: C, 67·7; H, 8·5. 3α : 12α : 17α-*Triacetoxypregnan-20-one*, $C_{27}H_{40}O_7$, requires C, 68·1; N, 8·4%).

Oxidation of 3α : 12α-*Diacetoxy-17α-hydroxypregn-20-one*.—The compound (500 mg.) in glacial acetic acid (7·75 ml.) was treated with chromic acid (10·1 ml. of 2% solution in 90% acetic acid) for 5 hr. at room temperature. The neutral fraction of the oxidation product (520 mg.) failed to crystallise. It was chromatographed in benzene on alumina (15 g.). From 30% to 50% ether–benzene eluates 3α : 12α-diacetoxytestan-17-one (*ca.* 100 mg.) was obtained, having m. p. 156—157°, $[\alpha]_D^{19}$ +181° (*c*, 0·432 in acetone) (Found: C, 71·1; H, 8·8. Calc. for $C_{23}H_{34}O_5$: C, 70·8; H, 8·7%), not depressed on admixture with an authentic specimen (Reich, *loc. cit.*). By rechromatography of the first fractions a further quantity was obtained from 30% to 50% ether–benzene eluates. Benzene to ether–benzene (10% to 30%) eluates gave a product (*ca.* 100 mg.), needles or plates, m. p. 158—159°, $[\alpha]_D^{19}$ +90° (*c*, 0·376 in acetone) (Found: C, 69·1; H, 8·4%).

Hydrolysis of 3α : 12α-diacetoxytestan-17-one with methanolic sodium hydroxide furnished 3α : 12α-dihydroxytestan-17-one, m. p. 144° and 163—164° (Found: C, 74·5; H, 9·8. Calc. for $C_{19}H_{30}O_3$: C, 74·5; H, 9·8%).

Testane-3 : 12 : 17-trione (VIII; R = R′ = :O).—3α : 12α-Dihydroxytestan-17-one (100 mg.) in acetic acid (3·6 ml.) was stirred at room temperature for 25 hr., chromic acid (3·6 ml. of 2% solution in acetic acid) being added at the start of the reaction and after 4, 8, and 23 hr. The mixture was then poured into water, and the product isolated with ether and crystallised from benzene–light petroleum. Testane-3 : 12 : 17-trione formed crystals, m. p. 268—270°, not depressed on admixture with an authentic specimen (Reich, *loc. cit.*).

Reduction of 3α : 12α-*Diacetoxy-17α-hydroxypregnan-20-one*.—3α : 12α-Diacetoxy-17α-hydroxypregnan-20-one (200 mg). in ether (20 ml.) was added to a boiling suspension of lithium aluminium hydride (150 mg.) in ether (25 ml.). After a further 30 min., the mixture was decomposed with ice-water, acidified to Congo-red with dilute sulphuric acid, and extracted with chloroform (3 × 80 ml.). The solids obtained therefrom were acetylated with acetic anhydride (2·5 ml.)–pyridine (2·5 ml.) and chromatographed in benzene on alumina (3 g.). Early ether–benzene eluates gave 3α : 12α : 20β-triacetoxypregnan-17α-ol, m. p. 191—192°, alone or on admixture with a sample prepared as above. From later acetone–ether and acetone eluates a substance was obtained, m. p. 268—273°, identical with that prepared by the reduction of 3α : 12α-diacetoxy-16β-bromo-17α-hydroxypregnan-20-one with a very active Raney nickel catalyst and tentatively formulated as 3α : 12α-diacetoxy-17α : 20α-dihydroxypregnane.

Dehydration of 3α : 12α-*Diacetoxy-17α-hydroxypregnan-20-one*.—The compound (100 mg.) in dry pyridine (1 ml.) was treated with thionyl chloride (0·03—0·05 ml.) at room temperature for 5 min., after which it was poured into water. Crystallisation of the precipitated solids from acetone–hexane furnished 3α : 12α-diacetoxypregn-16-en-20-one, needles, m.p. and mixed m. p. 190—191°, $\lambda_{max.}$ 237 mμ (log ε 4·0).

3α : 12α : 17a-*Trihydroxypregnan-20-one* (X; R = α-OH, R′ = H).—(i) 3α : 12α-Diacetoxy-17α-hydroxypregnan-20-one (8·13 g.) in methanol (320 ml.) was treated with potassium carbonate (1·5 g., 1·15 equiv.) in water (15 ml.) for 12 hr. at room temperature. After precipitation

with water the product was collected and purified from aqueous methanol. 3α : 12α : 17α-*Trihydroxypregnan*-20-*one* formed needles, m. p. 193—194°, $[\alpha]_D^{24}$ +81° (*c*, 0·422) (Found : C, 71·9; H, 10·0. $C_{21}H_{34}O_4$ requires C, 72·0; H, 9·7%).

(ii) The same product was obtained by treating the diacetate (2 g.) in ethanol (500 ml.) with 0·6N-aqueous sodium hydroxide (500 ml.) for 1 hr. at room temperature.

(iii) 3α : 12α : 17α-Trihydroxypregnan-20-one was also obtained by heating the diacetate (200 mg.) in methanol (5 ml.) with concentrated hydrochloric acid (0·15 ml.) for 1 hr. under reflux.

The *di*-p-*nitrobenzoate* formed needles, m. p. 208—210° (Found : C, 65·0; H, 7·1; N, 4·4. $C_{35}H_{40}O_{10}N_2$ requires C, 64·8; H, 6·2; N, 4·3%).

3α-*Ethoxycarbonyloxy*-12α : 17α-*dihydroxypregnan*-20-*one* (X; R = α-$EtO_2C{\cdot}O{\cdot}$, R′ = H), prepared by treatment of 3α : 12α : 17α-trihydroxypregnan-20-one (500 mg.) in pyridine (3 ml.) with ethyl chloroformate (0·5 g.) with cooling, followed by reaction at room temperature overnight, formed needles, m. p. 216—217°, $[\alpha]_D^{23}$ +82° (*c*, 0·0586) (Found : C, 68·0; H, 8·9. $C_{24}H_{38}O_6$ requires C, 68·2; H, 9·0%), after crystallisation from aqueous methanol. Its *acetate*, after purification from acetone–hexane, formed crystals, m. p. 119—120°, $[\alpha]_D^{22}$ +119° (*c*, 0·428) (Found : C, 67·1; H, 8·6. $C_{26}H_{40}O_7$ requires C, 67·2; H, 8·6%).

21-*Bromo*-3α : 12α : 17α-*trihydroxypregnan*-20-*one* (XI; R = α-OH, R′ = H, R″ = Br).—3α : 12α : 17α-Trihydroxypregnan-20-one (2 g.) in chloroform (60 ml.) at 40° was treated with stirring with a solution of bromine in chloroform (32 ml. of 0·138M) added dropwise during 20 min. Stirring was continued without external heating for a further 15 min. The solution was diluted with chloroform to 250 ml., washed with water, sodium hydroxide solution (5%), and water, dried, and evaporated. The residue was crystallised once from chloroform with as little heating as possible and the bromo-compound, needles, m. p. 113—115°, 169—172°, was used directly for the next stage of the partial synthesis.

21-*Acetoxy*-3α : 12α : 17α-*trihydroxypregnan*-20-*one* (XI; R = α-OH, R′ = H, R″ = OAc).—The foregoing compound (1·51 g.) in dry acetone (100 ml.) was heated with sodium iodide (900 mg.) for 15 min. After filtration from sodium bromide the solution was heated with potassium hydrogen carbonate (7·6 g.) and acetic acid (4·36 ml.) under reflux for 12 hr. The mixture was then diluted with water, and the product isolated with ether. Crystallisation from acetone–hexane gave 21-*acetoxy*-3α : 12α : 17α-*trihydroxypregnan*-20-*one*, needles, m. p. 218—220°, $[\alpha]_D^{24}$ +72° (*c*, 0·402) (Found : C, 67·8; H, 8·8. $C_{23}H_{36}O_6$ requires C, 67·7; H, 8·8%).

21-*Acetoxy*-12α : 17α-*dihydroxypregnane*-3 : 20-*dione* (XI; R = :O, R′ = H, R″ = OAc).—The foregoing compound (500 mg.) and *N*-bromoacetamide (550 mg.) in *tert.*-butanol (10 ml.), pyridine (0·2 ml.), and water (0·2 ml.) were left at room temperature for 7 hr. After precipitation with water, the product was collected and purified from acetone–hexane. 21-*Acetoxy*-12α : 17α-*dihydroxypregnane*-3 : 20-*dione* formed needles, m. p. 221°, $[\alpha]_D^{24}$ +80° (*c*, 0·424) (Found : C, 67·9; H, 8·5. $C_{23}H_{34}O_6$ requires C, 68·0; H, 8·4%).

12α : 21-*Diacetoxy*-17α-*hydroxypregnane*-3 : 20-*dione* (XI; R = :O, R′ = Ac, R″ = OAc), prepared by acetylation of the foregoing compound, formed plates, m. p. 198°, $[\alpha]_D^{26}$ +122° (*c*, 0·430) (Found : C, 66·7; H, 7·9. $C_{25}H_{36}O_7$ requires C, 66·9; H, 8·0%), from acetone–hexane.

21-*Acetoxy*-4-*bromo*-12α : 17α-*dihydroxypregnane*-3 : 20-*dione* (XII; R = H, R′ = OAc).—(i) 21-Acetoxy-12α : 17α-dihydroxypregnane-3 : 20-dione (270 mg.) in acetic acid (10 ml.) was treated with hydrogen bromide (1 drop of 50% solution in acetic acid) and bromine (0·68 ml.; 0·984M-solution in acetic acid). Rapid absorption of bromine occurred. After 15 min. the mixture was precipitated with water, and the bromo-compound isolated with ether. The bromo-compound formed needles, m. p. 188—189° (decomp.), on crystallisation from acetone–hexane with as little heating as possible. It was used immediately.

(ii) 21-Acetoxy-12α : 17α-dihydroxypregnane-3 : 20-dione (3 g.) in acetic acid (75 ml.) was treated with stirring at room temperature with bromine in acetic acid (0·6 ml.; 0·98M) and hydrogen bromide in acetic acid (1 drop of 50% solution). When decolorisation was complete a mixture of bromine in acetic acid (6·99 ml.; 0·98M) and anhydrous sodium acetate in acetic acid (7·38 ml.; 0·92N) was added at such a rate that the solution remained colourless (*ca.* 5 min.). After dilution with water the mixture was extracted with ether, which was washed with water, aqueous sodium carbonate, and water, and dried. Evaporation gave the bromo-derivative which was too unstable for analysis.

21-*Acetoxy*-12α : 17α-*dihydroxypregn*-4-*ene*-3 : 20-*dione* (XVI; R = H, R′ = OAc).—The foregoing bromo-derivative (160 mg.) in acetic acid (30 ml. of 98%) was heated with semicarbazide hydrochloride (110 mg.) and anhydrous sodium acetate (110 mg.) at 70° for 2 hr. in an atmosphere of nitrogen. Pyruvic acid (1·62 ml.) in water (3·25 ml.) was then added and the temperature kept at 70° for a further 2 hr. After dilution with water the product was isolated

with ether and purified from acetone–hexane. 21-*Acetoxy*-12α : 17α-*dihydroxypregn*-4-*ene*-3 : 20-*dione* formed needles, m. p. 195—197°, $[\alpha]_D^{24}$ +146° (*c*, 0·422), $\lambda_{max.}$ 240 mμ (log ε 4·21) (Found : C, 68·3; H, 8·0. $C_{23}H_{32}O_6$ requires C, 68·3; H, 7·9%).

Acetylation gave 12α : 21-*diacetoxy*-17α-*hydroxypregn*-4-*ene*-3 : 20-*dione*, plates, m. p. 179°, $[\alpha]_D^{26}$ +192° (*c*, 0·428) (Found : C, 66·7; H, 7·5. $C_{25}H_{34}O_7$ requires C, 67·2; H, 7·6%), after crystallisation from acetone–hexane.

12α-*Acetoxy*-3α-*hydroxypregn*-16-*en*-20-*one* (V; R = α-OH), prepared by heating 3α : 12α-diacetoxypregn-16-en-20-one (1·5 g.) in methanol (50 ml.) with potassium carbonate (300 mg.) in water (5 ml.) for 1 hr. under reflux under nitrogen, formed needles, m. p. 195—197°, $[\alpha]_D^{25}$ +117° (*c*, 0·94) (Found : C, 73·8; H, 9·1. $C_{23}H_{34}O_4$ requires C, 73·7; H, 9·2%), from acetone–hexane. The 3-p-*nitrobenzoate* (from methanol) had m. p. 237—239° (Found : C, 68·4; H, 7·1; N, 2·1. $C_{30}H_{37}O_7N$ requires C, 68·8; H, 7·1; N, 2·7%).

12α-*Acetoxy*-16α : 17α-*epoxy*-3α-*hydroxypregnan*-20-*one* (VI; R = α-OH, R″ = H; R′ = Ac), prepared by treating 12α-acetoxy-3α-hydroxypregn-16-en-20-one (7 g.) in methanol (900 ml.) and water (105 ml.) at 0° with cooled 30% hydrogen peroxide (87 ml.) and 5% sodium carbonate solution (14 ml.) for 16 hr. at 0°, had m. p. 97—103° (Found : C, 71·5; H, 8·5. $C_{23}H_{34}O_5$ requires C, 70·8; H, 8·7%), after crystallisation from benzene–hexane. The 3-p-*nitrobenzoate* separated from benzene–hexane in needles, m. p. 223—225° (Found : C, 66·1; H, 6·6; N, 2·0. $C_{30}H_{37}O_8N$ requires C, 66·8; H, 6·9; N, 2·6%).

12α-*Acetoxy*-16β-*bromo*-3α : 17α-*dihydroxypregnan*-20-*one*, prepared by treatment of 12α-acetoxy-16α : 17α-epoxy-3α-hydroxypregnan-20-one (1 g.) in chloroform (22 ml.) with hydrobromic acid in acetic acid (2·5 ml. of saturated solution + 7·5 ml. of acetic acid) at −18° for 20 hr., had m. p. 165—166° or 172—173°, $[\alpha]_D^{22}$ +109° (*c*, 0·39) (Found : C, 58·1; H, 7·5; Br, 17·8. $C_{23}H_{35}O_5Br$ requires C, 58·6; H, 7·4; Br, 17·0%) after crystallisation from acetone–hexane.

12α-*Acetoxy*-3α : 17α-*dihydroxypregnan*-20-*one* (X; R = α-OH, R′ = Ac) was prepared from the foregoing compound by catalytic hydrogenation in aqueous methanol (10% of H_2O) with 2% palladium–calcium carbonate. Crystallisation from acetone–hexane gave needles, m. p. 167—169°, $[\alpha]_D^{22}$ +116° (*c*, 0·438) (Found : C, 67·6; H, 9·4. $C_{23}H_{36}O_5,H_2O$ requires C, 67·3; H, 9·0%). The 3-p-*nitrobenzoate* formed needles, m. p. 216—218° (Found : C, 66·6; H, 7·3; N, 2·2. $C_{30}H_{39}O_8N$ requires C, 66·6; H, 7·2; N, 2·5%).

12α-*Acetoxy*-21-*bromo*-3α : 17α-*dihydroxypregnan*-20-*one* (XI; R = α-OH, R′ = Ac, R″ = Br).—A solution of bromine in acetic acid (15·75 ml.; 0·195M) was added to one of 12α-acetoxy-3α : 17α-dihydroxypregnan-20-one (1·236 g.) containing 2 drops of hydrogen bromide in acetic acid, stirred at 30°, at such a rate that each drop was immediately decolorised. Stirring was continued for a further 30 min., after which the mixture was poured into water and the bromo-compound isolated with ether and used without further purification.

12α : 21-*Diacetoxy*-3α : 17α-*dihydroxypregnan*-20-*one* (XI; R = α-OH, R′ = Ac, R″ = OAc).—The foregoing crude bromo-compound was heated under reflux for 15 min. with sodium iodide (1·5 g.) in acetone (42 ml.). The cooled solution was filtered, the residue was washed with acetone (10 ml.), and the combined acetone filtrates were heated with potassium hydrogen carbonate (6·2 g.) and acetic acid (4 ml.) under reflux overnight. 12α : 21-*Diacetoxy*-3α : 17α-*dihydroxypregnan*-20-*one*, isolated with ether, formed needles, m. p. 236—238°, $[\alpha]_D^{23}$ +119° (*c*, 0·51) (Found : C, 66·8; H, 8·6. $C_{25}H_{38}O_7$ requires C, 66·7; H, 8·5%), on crystallisation from ethyl acetate and finally from chloroform–ether.

Oxidation with *N*-bromoacetamide gave (XI; R = :O, R′ = Ac, R″ = OAc).

12α : 21-*Diacetoxy*-17α-*hydroxypregn*-4-*ene*-3 : 20-*dione* (XVI; R = Ac, R′ = OAc).—12α : 21-Diacetoxy-17α-hydroxypregnane-3 : 20-dione was brominated with 1 mol. of bromine in acetic acid, to give 12α : 21-diacetoxy-4-bromo-17α-hydroxypregnane-3 : 20-dione, m. p. 112°, 151—153° (decomp.), after crystallisation from ether. The bromo-compound was not sufficiently stable for analysis and was used immediately. It was dehydrobrominated in the usual way, giving 12α : 21-diacetoxy-17α-hydroxypregn-4-ene-3 : 20-dione, m. p. 175° not depressed on admixture with a sample prepared as described above.

3α : 12α : 21-*Triacetoxy*-17α-*hydroxypregnan*-20-*one* (XI; R′ = Ac, R″ = OAc).—3α : 12α-Diacetoxy-17α-hydroxypregnan-20-one (1 g.) in acetic acid (10 ml.) was treated with 50% hydrogen bromide in acetic acid (1 ml.), followed by 0·97M-bromine–acetic acid (2·6 ml.) at room temperature. Crystalline material separated. The mixture was kept at 40° for 30 min., then poured into water, and the bromo-compound isolated with ether. The resulting crude material was heated in dry acetone (75 ml.) with freshly fused potassium acetate (7·5 g.) for 5 hr. The product, isolated with ether, was chromatographed in benzene on alumina (25 g.). From 30% to 50% ether–benzene eluates, 3α : 12α : 21-*triacetoxy*-17α-*hydroxypregnan*-20-*one* was obtained,

having m. p. 140—141°, $[\alpha]_D^{22\cdot6}$ +138° (*c*, 0·458) (Found : C, 65·6; H, 7·9. $C_{27}H_{40}O_8$ requires C, 65·8; H, 8·1%).

3α : 12α-*Diacetoxy*-16β : 21-*dibromo*-17α-*hydroxypregnan*-20-*one* (IX; R′ = Br).—3α : 12α-Diacetoxy-16α : 17α-epoxypregnan-20-one (6·4 g.) in acetic acid (32 ml.) was left at room temperature for 20 min. with 50% w/v hydrobromic acid–acetic acid (4·3 ml.). 0·97M-Bromine–acetic acid (17 ml.) was then added during 15 min. at 40°. Temperature control was maintained for a further hour, then the mixture was poured into water. The precipitated solids, on purification from aqueous acetone, yielded 3α : 12α-*diacetoxy*-16β : 21-*dibromo*-17α-*hydroxypregnan*-20-*one*, needles, m. p. 192—194°, $[\alpha]_D^{20}$ +85° (*c*, 0·572) (Found : C, 50·1; H, 6·3; Br, 26·6. $C_{25}H_{36}O_6Br_2$ requires C, 50·7; H, 6·1; Br, 27·0%).

3α : 12α : 21-*Triacetoxy*-16α : 17α-*epoxypregnan*-20-*one* (VI; R′ = Ac, R″ = OAc).—The foregoing compound (4 g.) was heated with fused potassium acetate (22 g.) in dry acetone (200 ml.) under reflux for 4½ hr. The product, isolated with ether, was purified from acetone–hexane to give 3α : 12α : 21-*triacetoxy*-16α : 17α-*epoxypregnan*-20-*one*, m. p. 154—155°, $[\alpha]_D^{20}$ +85° (*c*, 0·564) (Found : C, 66·0; H, 7·9. $C_{27}H_{38}O_8$ requires C, 66·1; H, 7·8%).

3α : 12α : 21-*Triacetoxy*-16β-*bromo*-17α-*hydroxypregnan*-20-*one* (IX; R′ = OAc).—3α : 12α : 21-Triacetoxy-16α : 17α-epoxypregnan-20-one (550 mg.) in glacial acetic acid (3 ml.) was treated with 30% w/v hydrogen bromide–acetic acid (1 ml.) at room temperature for 30 min. The mixture was poured into water, and the precipitated solids were collected, washed, dried, and purified from aqueous methanol. 3α : 12α : 21-*Triacetoxy*-16β-*bromo*-17α-*hydroxypregnan*-20-*one* had m. p. 93° and 167—168°, $[\alpha]_D^{20}$ +119° (*c*, 0·456) (Found : C, 56·2; H, 6·6; Br, 13·5. $C_{27}H_{39}O_8Br$ requires C, 56·7; H, 6·8; Br, 14·0%).

3α : 12α : 21-*Triacetoxy*-17α-*hydroxypregnan*-20-*one* (XI; R′ = Ac, R″ = OAc).—The foregoing compound (460 mg.) in 95% ethanol (15 ml.) was heated with Raney nickel (2 g.) with stirring under reflux for 5 hr. The mixture was filtered hot through Hyflo, which was thoroughly washed with ethanol. The filtrate and washings were evaporated to dryness and the resulting oil was chromatographed in benzene on alumina (10 g.). Benzene–ether eluates furnished 3α : 12α : 21-triacetoxy-17α-hydroxypregnan-20-one, m. p. 141°, $[\alpha]_D^{22}$ +137° (*c*, 0·478) (Found : C, 65·3; H, 7·7. Calc. for $C_{27}H_{40}O_8$: C, 65·8; H, 8·1%), not depressed on admixutre with a specimen prepared as above.

20-*Bromo*-3α : 12α-*dihydroxypregn*-17-*en*-21-*oic acid* (III; R = R′ = α-OH, R″ = H).—Finely powdered 3α : 12α-diacetoxy-17 : 21 : 21-tribromopregnan-20-one (22·7 g.) in ethanol (360 ml.) was shaken with 10% potassium hydroxide solution (280 ml.) for 18 hr. at room temperature. The filtered solution was concentrated *in vacuo*, water added, and the solution acidified with dilute sulphuric acid to Congo-red. The precipitated solids were collected, washed with water, and dried, and a portion crystallised from methanol–ether. 20-*Bromo*-3α : 12α-*dihydroxypregn*-17-*en*-21-*oic acid* formed plates, m. p. 249—251° (Found : C, 59·0; H, 7·5; Br, 18·8. $C_{21}H_{31}O_4Br$ requires C, 59·0; H, 7·3; Br, 18·7%).

Methyl 20-*bromo*-3α : 12α-*dihydroxypregn*-17-*en*-21-*oate* (III; R = R′ = α-OH; R″ = Me), prepared from the crude acid (9·5 g.) in ether (150 ml.) and excess of diazomethane at room temperature (24 hr.), formed needles, m. p. 192—193°, $[\alpha]_D^{28}$ +84° (*c*, 0·998) (Found : C, 59·8; H, 7·5; Br, 18·4. $C_{22}H_{33}O_4Br$ requires C, 59·8; H, 7·5; Br, 18·1%), from aqueous methanol.

Methyl 20-*Bromo*-12α-*hydroxy*-3-*oxopregn*-17-*en*-21-*oate* (III; R = :O, R′ = α-OH, R″ = Me).—Methyl 20-bromo-3α : 12α-dihydroxypregn-17-en-21-oate (850 mg.) was dissoved in a solution of aluminium *tert.*-butoxide in benzene (9 ml. of 20%) and the benzene removed by distillation. Toluene (7 ml.) and *cyclo*hexanone (6 ml.) were added and the mixture was heated under reflux for 20 min. After acidification with dilute sulphuric acid, the organic solvents were removed in steam during 3 hr. The residue, isolated with ether, was purified from chloroform–hexane. Methyl 20-bromo-12α-hydroxy-3-oxopregn-17-en-21-oate formed crystals, m. p. 196—199°, $[\alpha]_D^{23}$ +94° (*c*, 1·35).

Methyl 20-*Bromo*-3 : 12-*dioxopregn*-17-*en*-21-*oate* (III; R = R′ = :O; R″ = Me).—The dihydroxy-compound (1·3 g.) in glacial acetic acid (25 ml.) was treated with cooling at 10—15° with chromic acid (800 mg.) in acetic acid (16 ml.) and water (2 ml.), and the whole kept at room temperature for 1 hr., then poured into sulphite solution and extracted with ether. The neutral fraction, purified from benzene–hexane, gave *methyl* 20-*bromo*-3 : 12-*dioxopregn*-17-*en*-21-*oate*, m. p. 212—214°, $[\alpha]_D^{22}$ +243° (*c*, 1·15) (Found : C, 60·6; H, 6·6; Br, 18·0. $C_{22}H_{29}O_4Br$ requires C, 60·4; H, 6·6; Br, 18·3%).

20-*Bromopregn*-17-*ene*-3α : 12α : 21-*triol*, prepared by treating (III; R = R′ = α-OH, R″ = Me) (1·147 g.) in ether with excess of lithium aluminium hydride at room temperature for 2 hr., had m. p. 149—151°, $[\alpha]_D^{21}$ +56° (*c*, 0·3) (Found : C, 58·7; H, 8·4. $C_{21}H_{33}O_3Br,H_2O$

requires C, 58·5; H, 8·1%). Its *triacetate* (IV) had m. p. 146—147°, $[\alpha]_D^{21}$ +120° (*c*, 0·48) (Found: C, 60·2; H, 7·3; Br, 14·1. $C_{27}H_{39}O_6Br$ requires C, 60·4; H, 7·2; Br, 14·7%). It failed to react with osmic acid in ethereal solution.

3α : 12α-*Diacetoxypregnan*-20-*one Cyanohydrin*.—3α : 12α-Diacetoxypregnan-20-one (1·88 g.) in ethanol (17 ml.) and acetic acid (6·4 ml.) was treated with potassium cyanide (6 g.) added portionwise with stirring at 0°. After a further ½ hr. at 0°, stirring was continued at room temperature for 2 hr., the mixture was poured into water, and the product extracted with ethyl acetate. Crystallisation from benzene–light petroleum gave the *cyanohydrin* (270 mg.), m. p. 190—191°, $[\alpha]_D^{23}$ +105° (*c*, 1·916) (Found: C, 69·4; H, 8·8; N, 3·2. $C_{26}H_{39}O_5N$ requires C, 7·01; H, 8·8; N, 3·2%). Chromatography of the residues led to recovery of 40% of (I).

3α : 12α-*Diacetoxy*-20-*cyanopregn*-17-*ene* (XIII; R′ = CN).—The foregoing cynaohydrin (200 mg.) in pyridine (3 ml.) was treated with phosphorus oxychloride (0·2 ml.). After being kept overnight the mixture was poured into water (60 ml.) and extracted with benzene (60 ml.). The benzene solution was washed successively with water, dilute acid, and water, and dried, and the solvent was removed. The residual oil (185 mg.) in benzene (2 ml.) was chromatographed on alumina (4 g.). The first benzene eluates gave 3α : 12α-*diacetoxy*-20-*cyanopregn*-17-*ene*, m. p. 188—191°, $[\alpha]_D^{25}$ +184° (*c*, 0·09) (Found: C, 73·2; H, 8·6; N, 3·3. $C_{26}H_{37}O_4N$ requires C, 73·1; H, 8·6; N, 3·3%), after crystallisation from aqueous methanol.

3α : 12α : 21-*Triacetoxypregnan*-20-*one cyanohydrin*, prepared as above from the appropriate ketone, had m. p. 176—178°, $[\alpha]_D^{20}$ +99° (*c*, 0·3772) (Found: C, 67·1; H, 8·1; N, 3·1. $C_{28}H_{41}O_7N$ requires C, 66·8; H, 8·2; N, 2·8%), after purification from benzene–light petroleum. Dehydration gave a *product*, m. p. 152—153° (Found: C, 68·3; H, 8·5; N, 1·2. $C_{28}H_{39}O_6N$ requires C, 69·3; H, 8·0; N, 2·9%).

3α : 12α-*Diacetoxytestan*-17-*one* (VIII; R′ = α-OAc).—3α : 12α : 20-Triacetoxypregn-17-ene (2·19 g.) was treated with perhydrol (2·2 ml.) and formic acid (21·9 ml.) for 44 hr. at room temperature, then with hot water. The precipitated solids were collected, dried, and purified from aqueous methanol, giving 3α : 12α-diacetoxytestan-17-one, m. p. and mixed m. p. 154—155°, $[\alpha]_D^{19}$ +171° (*c*, 0·838) (Found: C, 70·3; H, 8·7. Calc. for $C_{23}H_{34}O_5$: C, 70·8; H, 8·7%). The same compound was prepared from pregnane-3α : 12α : 17α : 20β-tetraol by oxidation with sodium bismuthate (Norymberski, *Biochem. J.*, 1953, **55**, 371), followed by acetylation.

3α-*Ethoxycarbonyloxy*-12α-*hydroxypregnan*-20-*one* had m. p. 144° (from aqueous methanol), $[\alpha]_D^{25}$ +115° (*c*, 0·414) (Found: C, 70·9; H, 9·4. $C_{24}H_{38}O_5$ requires C, 70·9; H, 9·4%). The 12 : 20-*dione*, prepared from this (870 mg.; crude) in *tert.*-butanol (20 ml.) and water (4 ml.) with *N*-bromosuccinimide (600 mg.) overnight at room temperature, had m. p. 135°, $[\alpha]_D^{22\cdot8}$ +183° (*c*, 1·058) (Found: C, 71·8; H, 9·0. $C_{24}H_{36}O_5$ requires C, 71·3; H, 8·9%), after crystallisation from aqueous methanol.

3α-*Hydroxypregnane*-12 : 20-*dione*, prepared by treatment of 3α : 12α-dihydroxypregnan-20-one (1·66 g.) in acetic acid (45 ml.) with potassium chromate (1·74 g.) in water (4 ml.) at room temperature for 20 hr., had m. p. 149—151°, $[\alpha]_D^{23}$ +188° (*c*, 0·796) (Found: C, 76·0; H, 9·6. $C_{21}H_{32}O_3$ requires C, 75·9; H, 9·6%), after purification from acetone–hexane. The *acetate* had m. p. 159—161°, $[\alpha]_D^{23}$ +193° (*c*, 0·564) (Found: C, 73·8; H, 9·0. $C_{23}H_{34}O_4$ requires C, 73·8; H, 9·1%).

3α : 12α-*Diacetoxy*-20-*ethoxypregn*-17-*ene* (XIII; R′ = OEt).—(i) (I) (1·7 g.) in ethanol (2·5 ml.) and ethyl orthoformate (1 ml.) containing concentrated sulphuric acid (1 drop) was heated under reflux for 30 min. Methanol (10 ml.) containing pyridine (1 drop) was added and the mixture left overnight at 0°. The separated solids were collected, washed with ice-cold methanol (yield 270 mg.; 15%), and purified from acetone–methanol. 3α : 12α-*Diacetoxy*-20-*ethoxypregn*-17-*ene* formed needles, m. p. 200—211°, $[\alpha]_D^{19}$ +140·8°, falling to +132·6° in 3½ hr. (*c*, 0·692) (Found: C, 73·0; H, 9·3. $C_{27}H_{42}O_5$ requires C, 72·6; H, 9·4%).

(ii) (I) (1 g.) in ethyl orthoformate (6 ml.) containing toluene-*p*-sulphonic acid (100 mg.) was heated under reflux for 1 hr., and the enol ether isolated as before (m. p. 190—194°; 120 mg., 11·4%).

12α : 17α-*Dihydroxypregnan*-3 : 20-*dione* (X; R = :O, R′ = H).—(i) 3α : 12α : 17α-Trihydroxypregnan-20-one (530 mg.) in *tert.*-butanol (10 ml.), pyridine (0·4 ml.), and water (0·4 ml.) was oxidised with *N*-bromoacetamide (370 mg., 1·75 mols.) at room temperature for 7 hr., giving 12α : 17α-*dihydroxypregnane*-3 : 20-*dione*, needles, m. p. 210—212°, $[\alpha]_D^{27}$ +71° (*c*, 0·404) (Found: C, 72·3; H, 9·3. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·2%), after purification from acetone–hexane.

(ii) Trihydroxypregnanone (50 mg.) in *tert.*-butanol (4 ml.) and water (0·4 ml.) was oxidised with *N*-bromosuccinimide (56 mg.) at room temperature for 2 hr., giving the same dione.

The 12α-*acetate*, m. p. 105°, $[\alpha]_D^{27}$ +113° (*c*, 0·456) (Found: C, 70·4; H, 8·7. $C_{23}H_{34}O_5$ requires C, 70·8; H, 8·7%), crystallised from acetone–hexane.

4β-*Bromo*-12α : 17α-*dihydroxypregnane*-3 : 20-*dione* (XII; R = R′ = H) was prepared by treatment of 12α : 17α-dihydroxypregnane-3 : 20-dione (340 mg.) in acetic acid (10 ml.) and hydrogen bromide (1 drop of 50% solution in acetic acid) with 0·985M-bromine–acetic acid (1·01 ml.) for 15 min. at room temperature. After crystallisation from acetone–hexane, it formed needles, m. p. 170—171° (decomp.), $[\alpha]_D^{23}$ +86° (*c*, 0·422) (Found: C, 61·0; H, 7·3; Br, 16·1. $C_{21}H_{31}O_4Br$ requires C, 59·0; H, 7·3; Br, 18·7%).

12α : 17α-*Dihydroxypregn*-4-*ene*-3 : 20-*dione* (XVI; R = R′ = H), prepared from the foregoing compound by dehydrobromination (with semicarbazide), formed needles, m. p. 224—226°, $[\alpha]_D^{22}$ +92° (*c*, 0·408), $\lambda_{max.}$ 240 mμ (log ε 4·28) (Found: C, 72·7; H, 8·7. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%), from acetone–hexane. The acetate separated from acetone–hexane in plates, m. p. 149°.

3α : 12α : 20ξ : 21-*Tetra-acetoxypregnane* (XV; R′ = Ac).—3α : 12α : 21-Triacetoxypregnan-20-one (1·5 g.) in ether (150 ml.) was added to lithium aluminium hydride (1·5 g.) in ether (100 ml.) which had been heated under reflux for 15 min. Heating was continued for 30 min. and the product, isolated with ethyl acetate, acetylated (acetic anhydride–pyridine, 15 : 20 ml., for 1 hr. at 100°) and chromatographed in benzene on alumina (40 g.). From the benzene to benzene–ether (70 : 30) eluates, 3α : 12α : 20ξ : 21-*tetra-acetoxypregnane* (30% yield) was obtained, forming needles, m. p. 131°, $[\alpha]_D^{20}$ +109° (*c*, 0·496) (Found: C, 66·7; H, 8·5. $C_{29}H_{44}O_8$ requires C, 66·9; H, 8·5%), from acetone–hexane.

Pregnane-3α : 12α : 20ξ : 21-*tetraol* (XV; R = α-OH, R′ = H), prepared by hydrolysis of the foregoing compound with methanolic sodium hydroxide, formed needles, m. p. 209—211°, $[\alpha]_D^{22}$ +101° (*c*, 0·442) (Found: C, 68·1; H, 10·4. $C_{21}H_{36}O_4,H_2O$ requires C, 68·1; H, 10·3%), from aqueous methanol.

Pregnane-3α : 12α : 17α : 20ξ : 21-*pentaol*, prepared by reduction of 3α : 12α : 21-triacetoxy-16α : 17α-epoxypregnan-20-one (1·6 g.) in ether (100 ml.) with lithium aluminium hydride (1·8 g.) in ether (180 ml.) for 2 hr. under reflux, formed needles, m. p. 262—263° (Found: C, 68·9; H, 9·7. $C_{21}H_{36}O_5$ requires C, 68·5; H, 9·8%), from methanol–ethyl acetate.

The *tetra-acetate* separated from acetone–hexane in crystals, m. p. 167—168° (Found: C, 64·9; H, 7·9. $C_{29}H_{44}O_9$ requires C, 64·9% H, 8·2%).

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