12-*Oxygenated Pregnane Derivatives. Part V.** 12β : 21-*Diacetoxy*-17α-*hydroxypregn*-4-*ene*-3 : 20-*dione.*

By (Mrs.) W. J. Adams, D. N. Kirk, D. K. Patel, V. Petrow, and (Mrs.) I. A. Stuart-Webb.

[Reprint Order No. 5879.]

Conversion of hecogenin into 12β : 21-diacetoxy-17α-hydroxypregn-4-ene-3 : 20-dione (XI) is described.

Deoxycholic acid proved unsatisfactory for the preparation of the dione (XI) as conversion into 3α : 12β-dihydroxycholanic acid could not be achieved in adequate yield (cf. Koechlin and Reichstein, *Helv. Chim. Acta*, 1942, **25**, 918). Better results followed the use of hecogenin (I; R = :O, R′ = H).

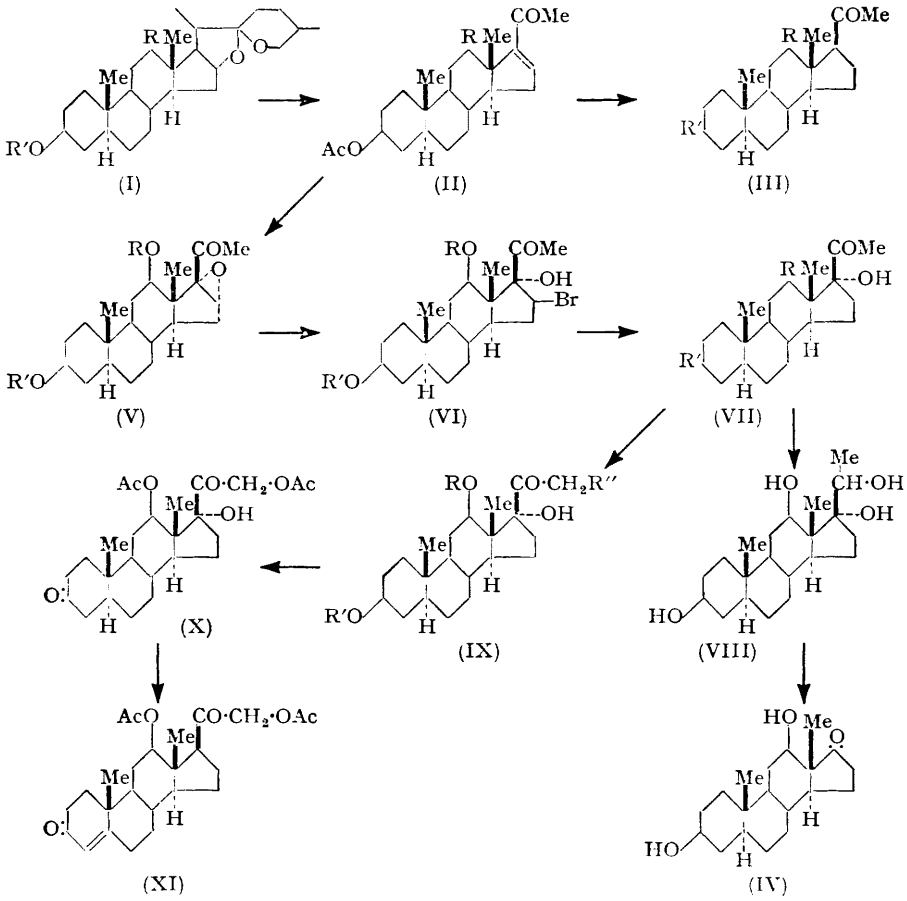
Reduction of hecogenin to 5α : 22a-spirostan-3β : 12β-diol (rockogenin) (I; R = β-OH, R′ = H) has previously been effected by hydrogen and Adams catalyst, with sodium in ethanol, or with lithium aluminium hydride (Marker, Wagner, Ulshafer, Wittbecker, Goldsmith, and Ruof, *J. Amer. Chem. Soc.*, 1947, **69**, 2167; Hirschmann, Snoddy, and Wendler, *ibid.*, 1952, **74**, 2693; Rothman, Wall, and Eddy, *ibid.*, p. 4013). We now find that sodium borohydride is preferable for this purpose. Acetylation of the product, followed by separation of the 12α- and the 12β-isomer and degradation, furnished 3β : 12β-diacetoxy*allo*pregn-16-en-20-one (II; R = β-OAc) (cf. U.S.P. 2,408,828), the structure of which was confirmed by hydrogenation, hydrolysis, and oxidation to *allo*-pregnane-3 : 12 : 20-trione.

An alternative route to the compound (II; R = β-OAc) was also examined. Hecogenin acetate was degraded to 3β-acetoxy*allo*pregn-16-ene-12 : 20-dione (II; R = :O) (cf. Part II, *J.*, 1954, 2209). Reduction with lithium aluminium hydride gave a mixture of *allo*pregn-16-ene-3β : 12β : 20-triols which was directly oxidised with manganese dioxide in benzene, a specific oxidant for allylic alcohols (cf. Sondheimer, Amendolla, and Rosenkrantz, *J. Amer. Chem. Soc.*, 1953, **75**, 5930). Acetylation of the product, however, furnished 3β-acetoxy-12β-hydroxy*allo*pregn-16-en-20-one (II; R = β-OH) in place of the expected acetate (II; R = β-OAc). The structure of this product followed from its catalytic hydrogenation to 3β-acetoxy-12β-hydroxy*allo*pregnan-20-one (III; R = β-OH, R′ = β-OAc) which passed into (i) the known 3β-acetoxy*allo*pregnane-12 : 20-dione (III; R = :O, R = β-OH) on oxidation and (ii) the known *allo*pregnane-3 : 12 : 20-trione (III; R = R′ = :O) on hydrolysis and oxidation. Attempts to convert the monoacetate (II; R = β-OH) into the foregoing diacetate (II; R = β-OAc), however, proved unsuccessful. This surprising result is only partially explained by the known difficulty in acylating 12β-hydroxy-steroids (Marker *et al.*, *loc. cit.*; Pataki, Meyer, and Reichstein, *Helv. Chim. Acta*, 1953, **36**, 1295) as the 17α-hydroxy-derivatives described below passed easily into the 12β-acetates.

* Part IV, *J.*, 1954, 4688.

Conversion of the diacetate (II; R = β-OAc) into 3β : 12β-diacetoxy-17α-hydroxy*allo*-pregnan-20-one (VII; R = R′ = β-OAc) followed the general methods described in Parts I (*J.*, 1954, 1825) and II (*loc. cit.*). The former compound was treated with alkaline hydrogen peroxide to give 3β : 12β-diacetoxy-16α : 17α-epoxy*allo*pregnan-20-one (V; R = R′ = Ac), which passed into 3β : 12β-diacetoxy-16β-bromo-17α-hydroxy*allo*pregnan-20-one (VI; R = R′ = Ac) on reaction with hydrogen bromide. Reductive removal of the bromine atom furnished the required (VII; R = R′ = β-OAc).

The constitution assigned to the last compound was established (i) by its dehydration with phosphorus oxychloride in pyridine to 3β : 12β-diacetyoxy*allo*pregn-16-en-20-one (II; R = β-OAc), (ii) by its hydrolysis with 2 molar equivalents of alkali to 3β : 12β : 17α-trihydroxy*allo*pregnan-20-one (VII; R = R′ = β-OH), also prepared from (II; R = β-OH) by the foregoing reaction sequence and converted into (VII; R = R′ = β-OAc) by acetic anhydride–pyridine at room temperature, and (iii) by its reduction [or that of (VII; R = R′ = β-OH)] with sodium borohydride in the presence of excess of sodium hydrogen



carbonate to *allo*pregnane-3β : 12β : 17α : 20ξ-tetrol (VIII), which was oxidised with sodium bismuthate in acetic acid to a product formulated as 3β : 12β-dihydroxyandrostan-17-one (IV) and different from the isomeric 3β : 12α-dihydroxyandrostan-17-one described in Part II (*loc. cit.*).

Conversion of the diacetate (VII; R = R′ = β-OAc) into 12β-acetoxy-3β : 17α-dihydroxy*allo*pregnan-20-one (VII; R = β-OAc, R′ = β-OH) could not be effected by methanolic sodium hydrogen carbonate at room temperature or by 1 equivalent of sodium

carbonate in methanol, complete hydrolysis to the triol (VII; R = R′ = β-OH) taking place (cf. the behaviour of 3α : 12α-diacetoxy-17α-hydroxypregnan-20-one described in Part I, *loc. cit.*). Hydrolysis with catalytic quantities of hydrochloric acid in methanolic solution for 3 hours on the steam-bath, however, furnished the diol (VII; R = β-OAc, R′ = β-OH). The last compound was additionally prepared from 3β : 12β-diacetoxy-16α : 17α-epoxy*allo*pregnan-20-one (V; R = R′ = Ac). Partial hydrolysis with 1 equivalent of methanolic potassium carbonate at room temperature gave 12β-acetoxy-16α : 17α-epoxy-3β-hydroxy*allo*pregnan-20-one (V; R = Ac, R′ = H) [cf. the behaviour of (VII; R = R′ = β-OAc), above], which was converted into the bromohydrin (VI; R = Ac, R′ = H) by hydrogen bromide in chloroform solution. Use of acetic acid as solvent led to reacetylation of the 3β-hydroxyl group. Debromination with hydrogen and palladium–calcium carbonate gave the diol (VII; R = β-OAc, R′ = β-OH).

Before proceeding to the introduction of the 21-acetoxyl group into the last compound, the conversion of the 3β-hydroxyl group into carbonyl was examined. Oxidation of the diol (VII; R = β-OAc, R′ = β-OH) with *N*-bromoacetamide gave the expected 12β-acetoxy-17α-hydroxy*allo*pregnane-3 : 20-dione (VII; R = β-OAc, R′ = :O). Alternatively, 3β : 12β : 17α-trihydroxy*allo*pregnan-20-one (VII; R = R′ = β-OH) was converted by excess of *N*-bromoacetamide in pyridine into 12β : 17α-dihydroxy*allo*pregnane-3 : 20-dione (VII; R = β-OH, R′ = :O) which gave the acetoxy-ketone (VII; R = β-OAc, R′ = :O) on acetylation.

Bromination of 12β-acetoxy-3β : 17α-dihydroxy*allo*pregnan-20-one (VII; R = β-OAc, R′ = β-OH) in chloroform gave the corresponding 21-bromo-compound (IX; R = Ac, R′ = H, R″ = Br) which was treated with sodium iodide and subsequently with potassium acetate to give 12β : 21-diacetoxy-3β : 17α-dihydroxy*allo*pregnan-20-one (IX; R = Ac, R′ = H, R″ = OAc). The constitution assigned to this compound was supported by its acetylation to 3β : 12β : 21-triacetoxy-17α-hydroxy*allo*pregnan-20-one (IX; R = R′ = Ac, R″ = OAc), separately prepared from 3β : 12β-diacetoxy-17α-hydroxy*allo*pregnan-20-one (VII; R = R′ = β-OAc) by the same reaction sequence. Bromination of the 3β : 12β-dihydroxy-compound (VII; R = R′ = β-OH), however, though apparently yielding a homogeneous monobromo-derivative, gave a mixture of products (mixture *A*, see below) when converted into the 21-acetate (and debrominated). After unsuccessful attempts at resolution, the mixture was acetylated and submitted to chromatography on alumina, the diacetate (VII; R = R′ = β-OAc) and the triacetate (IX; R = R′ = Ac, R″ = OAc) being obtained.

Conversion of 12β : 21-diacetoxy-3β : 17α-dihydroxy*allo*pregnan-20-one (IX; R = Ac, R′ = H, R″ = OAc) into the corresponding 3-ketone (X) was achieved by oxidation with *N*-bromoacetamide in aqueous *tert.*-butanol. Alternatively, mixture *A* was oxidised with *N*-bromoacetamide in aqueous pyridine, and the product acetylated and chromatographed to give the foregoing monoketone and the diketone (VII; R = β-OAc, R′ = :O).

Dibromination of 12β : 21-diacetoxy-17α-hydroxy*allo*pregnane-3 : 20-dione (X) followed the hoped-for pattern, no evidence for halogenation in the cortical side chain being obtained (cf. Part II, *loc. cit.*; see also Fleisher and Kendall, *J. Org. Chem.*, 1951, **16**, 572). Polarimetric study of the reaction revealed behaviour typical of 2 : 2-dibromination followed by rearrangement to the 2 : 4-dibromo-derivative of (X). The last compound was not isolated, but was treated directly with sodium iodide in acetone (Rosenkranz, Mancera, Gatica, and Djerassi, *J. Amer. Chem. Soc.*, 1950, **72**, 4077) and then briefly with zinc in acetic acid, to give 12β : 21-diacetoxy-17α-hydroxypregn-4-ene-3 : 20-dione (XI).

Experimental

Optical rotations were measured in chloroform solution in a 1-dm. tube unless otherwise stated. Aluminium oxide (from B.D.H.; chromatography grade) was used.

3β : 12β-*Diacetoxy*-5α : 22α-*spirostan* (I; R = β-OAc, R′ = Ac).—Hecogenin acetate (50 g.) in methanol (1 l.) was heated with sodium hydroxide (25 g.) and water (40 ml.) under reflux for 1 hr. Sodium borohydride (3·0 g.) in methanol (120 ml. of 90%) containing sodium hydroxide (1 g.) was added dropwise during 2 hr., heating being maintained for a further 2 hr.

The product, isolated with chloroform, was acetylated under reflux with pyridine (20 ml.) and acetic anhydride (150 ml.) for 2 hr., percolated in benzene solution through alumina (50 g.) and crystallised from methylene chloride–methanol. It had m. p. 200—202°, $[\alpha]_D^{23}$ −64°, (*c* 0·552 in acetone). Hirschmann, Snoddy, and Wendler (*J. Amer. Chem. Soc.*, 1952, **74**, 2693) give m. p. 202—206·5°, $[\alpha]_D^{23}$ −65° (in acetone).

3β : 12β-*Diacetoxy*allo*pregn*-16-*en*-20-*one* (II; R = β-OAc), prepared from the foregoing compound by Marker and Rohmann's method (*ibid.*, 1940, **62**, 518; see also Wagner, Moore, and Forker, *ibid.*, 1950, **72**, 1856), formed crystals, m. p. 134—135°, $[\alpha]_D^{22\cdot5}$ +18° (*c*, 0·434), $\lambda_{max.}$ 233, 310 mμ (3·96, 1·91) (in *iso*propanol) (Found: C, 72·0; H, 8·9. $C_{25}H_{36}O_5$ requires C, 72·1; H, 8·9%).

Hydrogenation of the foregoing compound (100 mg.) in methanol (35 ml.) over 2% palladium–calcium carbonate (500 mg.), followed by hydrolysis and oxidation with chromium trioxide, furnished *allo*pregnane-3 : 12 : 20-trione, m. p. 206—211°. The m. p. was not depressed on admixture with an authentic specimen prepared as described by Wagner *et al.* (*loc. cit.*).

3β-*Acetoxy*-12β-*hydroxy*allo*pregn*-16-*en*-20-*one* (II; R = β-OH).—3β-Acetoxy*allo*pregn-16-ene-12 : 20-dione (22·5 g.) in ether (1 l.) was heated with lithium aluminium hydride (4 g.) in ether (300 ml.) under reflux for 2 hr.; excess of hydride was decomposed with moist ethyl acetate. The ethereal solution was removed, washed, dried, and evaporated. The residue in benzene (1100 ml.) was dried by distillation (*ca.* 100 ml. removed) and heated with manganese dioxide (30 g.) under reflux for 3 hr. The cooled, filtered solution was taken to dryness and the residue acetylated with acetic anhydride–pyridine overnight in the cold. Crystallisation from methanol furnished 3β-*acetoxy*-12β-*hydroxy*allo*pregn*-16-*en*-20-*one*, m. p. 222—224°, $[\alpha]_D^{25}$ −30° (*c* 0·42) (Found: C, 73·8; H, 9·5. $C_{23}H_{34}O_4$ requires C, 73·8; H, 9·1%).

3β-*Acetoxy*-12β-*hydroxy*allo*pregnan*-20-*one* (III; R = β-OH, R′ = β-OAc), prepared by hydrogenation of the foregoing compound (1·0 g.) in methanol (20 ml.) over 2% palladium–calcium carbonate, formed prisms, m. p. 150—151°, $[\alpha]_D^{28}$ −14° (*c*, 0·396) (Found: C, 73·5; H, 9·9. $C_{23}H_{36}O_4$ requires C, 73·4; H, 9·6%), after crystallisation from acetone–hexane. Attempted acetylation in the presence of perchloric acid (Reichstein, *Helv. Chim. Acta*, 1953, **36**, 1305) gave an oil from which crystalline material could not be obtained.

Oxidation of the foregoing compound (500 mg.) in acetic acid (20 ml.) with potassium dichromate (480 mg.) in water (4 ml.) at room temperature for 56 hr. furnished 3β-acetoxy*allo*pregnane-12 : 20-dione, m. p. and mixed m. p. 189—192°.

The hydroxy-acetate (III; R = β-OH, R′ = β-OAc) (900 mg.) in methanol (45 ml.) was heated under reflux under nitrogen with aqueous sodium hydroxide (7 ml. of N) for 1 hr. Titration showed that 1 acetyl group had been removed. The crude dihydroxy-compound was oxidised with chromium trioxide (400 mg.) in acetic acid (11 ml.) for 24 hr. at room temperature to give *allo*pregnane-3 : 12 : 20-trione, m. p. and mixed m. p. 206—209°.

3β : 12β-*Diacetoxy*-16α : 17α-*epoxy*allo*pregnan*-20-*one* (V; R = R′ = Ac).—The diacetate (II; R = β-OAc) (10 g.), dissolved in methanol (750 ml.) and water (100 ml.), was treated at 0° with hydrogen peroxide (100 ml. of 30%) and aqueous sodium carbonate (40 ml. of 5%). After 48 hr. the solution was diluted with water and set aside, and the precipitated solids were collected and purified from aqueous methanol. 3β : 12β-*Diacetoxy*-16α : 17α-*epoxy*allo*pregnan*-20-*one* formed needles, m. p. 169—171°, $[\alpha]_D^{23}$ +61° (*c*, 0·462) (Found: C, 69·2; H, 8·3. $C_{25}H_{36}O_6$ requires C, 69·4; H, 8·4%).

3β : 12β-*Diacetoxy*-16β-*bromo*-17α-*hydroxy*allo*pregnan*-20-*one* (VI; R = R′ = Ac).—The foregoing compound (5·28 g.) in acetic acid (30 ml.) was treated with hydrogen bromide in acetic acid (3·2 ml. of 50%) for 30 min. at room temperature, after which the mixture was diluted with water and the precipitated solids were purified from methanol. 3β : 12β-*Diacetoxy*-16β-*bromo*-17α-*hydroxy*allo*pregnan*-20-*one* formed needles, m. p. 153—154°, $[\alpha]_D^{20}$ +56° (*c*, 0·4386) (Found: C, 57·9; H, 7·3; Br, 15·9. $C_{25}H_{37}O_6Br$ requires C, 58·4; H, 7·2; Br, 15·6%).

3β : 12β-*Diacetoxy*-17α-*hydroxy*allo*pregnan*-20-*one* (VII; R = R′ = β-OAc).—3β : 12β-Diacetoxy-16β-bromo-17α-hydroxy*allo*pregnan-20-one (5 g.) in aqueous methanol (250 ml. of 90%) was hydrogenated over 2% palladium–calcium carbonate (10 g.) at room temperature and atmospheric pressure. Crystallisation of the product from ether–hexane furnished 3β : 12β-*diacetoxy*-17α-*hydroxy*allo*pregnan*-20-*one*, needles, m. p. 125—127° or 143—144°, $[\alpha]_D^{22}$ +7° (*c*, 0·326) (Found: C, 69·1; H, 8·8. $C_{25}H_{38}O_6$ requires C, 69·1; H, 8·8%).

Dehydration of 3β : 12β-*Diacetoxy*-17α-*hydroxy*allo*pregnan*-20-*one*.—(*a*) The diacetate (VII; R = R′ = β-OAc) (200 mg.) in pyridine (2 ml.) was treated at 0° with thionyl chloride (0·06 ml.) added dropwise during 5 min.; then the mixture was poured into water. Crystallisation of the

product from acetone–hexane gave the 17-*sulphite*, m. p. 164—165° (Found : C, 61·1; H, 7·5; S, 7·5. $C_{25}H_{38}O_8S$ requires C, 60·2; H, 7·7; S, 6·4%).

(*b*) The diacetate (VII; R = R′ = β-OAc) (200 mg.) was heated under reflux with phosphorus oxychloride (0·2 ml.) in pyridine (4 ml.) for 30 min. The product, in benzene, was percolated through alumina (6 g.) and then crystallised from hexane, to give 3β : 12β-diacetoxy-*allo*pregn-16-en-20-one, m. p. 136—137° (Found: C, 72·5; H, 8·7. Calc. for $C_{25}H_{36}O_5$: C, 72·1; H, 8·7%), not depressed on admixture with an authentic specimen (above).

3β : 12β : 17α-*Trihydroxy*allo*pregnan*-20-*one* (VII; R = R′ = β-OH), prisms, m. p. 241—242° (variable), $[\alpha]_D^{19}$ +23° (*c*, 0·218 in EtOH) (Found : C, 71·9; H, 9·8. $C_{21}H_{34}O_4$ requires C, 72·0; H, 9·7%), after crystallisation from methanol, was prepared by hydrolysis of the diacetate (VII; R = R′ = β-OAc) (510 mg.) in methanol (35 ml.) with aqueous sodium hydroxide (10 ml. of 0·5N) for 12 hr. at room temperature.

3β-*Acetoxy*-16α : 17α-*epoxy*-12β-*hydroxy*allo*pregnan*-20-one (V; R = H, R′ = Ac), plates (from acetone), m. p. 233—236°, $[\alpha]_D^{25}$ +38° (*c*, 0·430) (Found : C, 70·5; H, 8·6. $C_{23}H_{34}O_5$ requires C, 70·8; H, 8·7%), was prepared by treating 3β-acetoxy-12β-hydroxy*allo*pregn-16-en-20-one (1·9 g.) in methanol (240 ml.) and water (30 ml.) with hydrogen peroxide (24 ml. of 30%) and aqueous sodium carbonate (4 ml. of 5%) at 0° for 16 hr.

3β-*Acetoxy*-16β-*bromo*-12β : 17α-*dihydroxy*allo*pregnan*-20-*one* (VI; R = H, R′ = Ac), shimmering leaflets (from ether–chloroform), m. p. 197—198°, $[\alpha]_D^{25}$ +46° (*c*, 0·440) (Found: C, 58·7; H, 7·1; Br, 17·4. $C_{23}H_{35}O_5Br$ requires C, 58·6; H, 7·4; Br, 17·0%), was prepared by treating the foregoing compound (800 mg.) in chloroform (16 ml.) and acetic acid (6 ml.) with hydrogen bromide (1·9 ml. of saturated solution in acetic acid) at −30° to −7° for 12 hr.

3β : 12β : 17α-*Trihydroxy*allo*pregnan*-20-*one* (VII; R = R′ = β-OH).—The foregoing compound (750 mg.) in aqueous methanol (70 ml. of 90%) was hydrogenated over 2% palladium–calcium carbonate. The product was chromatographed in benzene on alumina (20 g.). The 1 : 1 ether–benzene eluates yielded a substance (260 mg.; m. p. 84—110°) which was hydrolysed by heating it with potassium carbonate (150 mg.) in methanol (25 ml.) and water (5 ml.) under nitrogen for 1 hr. Crystallisation of the product from methanol yielded the triol (VII; R = R′ = β-OH), m. p. 233—235° (variable), alone or on admixture with a sample prepared as above. Acetylation gave the diacetate (VII; R = R′ = β-OAc).

allo*Pregnane*-3β : 12β : 17α : 20ξ-*tetrol* (VIII).—3β : 12β-Diacetoxy-17α-hydroxy*allo*pregnan-20-one (2 g.) in methanol (300 ml.) and aqueous sodium hydrogen carbonate (2 g. in 100 ml.) was treated with sodium borohydride (1 g.). After 16 hr. at room temperature the product was isolated with chloroform and crystallised from aqueous methanol, yielding allo*pregnane*-3β : 12β : 17α : 20ξ-*tetrol*, m. p. 247—249° (Found : C, 71·1; H, 10·4. $C_{21}H_{36}O_4$ requires C, 71·6; H, 10·3%), similarly obtained from the triol (VII; R = R′ = β-OH).

3β : 12β-*Dihydroxyandrostan*-17-*one* (IV), m. p. 179—180° (from acetone–hexane), $[\alpha]_D^{23}$ +62° (*c* 0·3) (Found : C, 74·1; H, 10·2. $C_{19}H_{30}O_3$ requires C, 74·5; H, 9·9%), was prepared by oxidising the foregoing compound (200 mg.) with sodium bismuthate (4 g.) in aqueous acetic acid (40 ml. of 50%) for 12 hr. with vigorous stirring at room temperature.

12β-*Acetoxy*-3β : 17α-*dihydroxy*allo*pregnan*-20-*one* (VII; R = β OAc, R′ = β OH).—3β : 12β-Diacetoxy-17α-hydroxy*allo*pregnan-20-one (3·2 g.) in methanol (160 ml.) was heated under reflux for 3 hr. with methanolic hydrochloric acid (2·08 ml. of a solution prepared from 0·6 ml. of concentrated hydrochloric acid made up to 5 ml. with methanol). The product was isolated with ether and crystallised from acetone–hexane, to give 12β-*acetoxy*-3β : 17α-*dihydroxy*allo*pregnan*-20-*one*, needles, m. p. 147° or 163—164°, $[\alpha]_D^{24}$ −6° (*c*, 0·362) (Found: C, 70·5; H, 9·2. $C_{23}H_{36}O_5$ requires C, 70·4; H, 9·3%).

12β-*Acetoxy*-16α : 17α-*epoxy*-3β-*hydroxy*allo*pregnan*-20-*one* (V; R = Ac, R′ = H).—3β : 12β-Diacetoxy-16α : 17α-epoxy*allo*pregnan-20-one (1 g.) dissolved in methanol (30 ml.) was treated with potassium carbonate (175 mg.) in water (5 ml.) for 15 hr. at room temperature. After precipitation with water the solids were collected and crystallised from aqueous methanol. 12β-*Acetoxy*-16α : 17α-*epoxy*-3β-*hydroxy*allo*pregnan*-20-*one* formed plates, m. p. 203—204°, $[\alpha]_D^{25}$ +64° (*c*, 0·530) (Found : C, 70·7; H, 8·8. $C_{23}H_{34}O_5$ requires C, 70·8; H, 8·7%).

12β-*Acetoxy*-16β-*bromo*-3β : 17α-*dihydroxy*allo*pregnan*-20-*one* (VI; R = Ac, R′ = H), needles (from ether–hexane), m. p. 180—182° (decomp.), $[\alpha]_D^{23}$ +62° (*c*, 0·440) (Found : C, 58·9; H, 7·6; Br, 16·6. $C_{23}H_{35}O_5Br$ requires C, 58·6; H, 7·4; Br, 17·0%), was prepared by treating the foregoing compound (500 mg.) in chloroform (25 ml.) with hydrogen bromide (0·5 ml. of 50% in acetic acid) at room temperature for 16 hr.

12β-*Acetoxy*-3β : 17α-*dihydroxy*allo*pregnan*-20-*one* (VII; R = β-OAc, R′ = β-OH), m. p. 162°, not depressed on admixture with a sample prepared as above, was obtained when the

foregoing compound (570 mg.) in aqueous methanol (30 ml. of 90%) was hydrogenated over 2% palladium-calcium carbonate.

12β-*Acetoxy*-17α-*hydroxy*allo*pregnane*-3 : 20-*dione* (VII; R = β-OAc, R′ = :O).—The foregoing compound (110 mg.) in *tert.*-butanol (5 ml.), water (0·2 ml.), and pyridine (0·2 ml.) was treated with *N*-bromoacetamide (110 mg.) for 16 hr. at room temperature. After dilution with water the product was extracted with ether, debrominated by treatment for 10 min. with zinc dust in acetic acid on the steam-bath, and crystallised from acetone–hexane. 12β-*Acetoxy*-17α-*hydroxy*allo*pregnane*-3 : 20-*dione* was obtained having m. p. 140·5—141°, $[\alpha]_D^{25}$ +35° (*c*, 0·3352) (Found: C, 70·8; H, 8·7. $C_{23}H_{34}O_5$ requires C, 70·8; H, 8·7%).

12β : 17α-*Dihydroxy*allo*pregnane*-3 : 20-*dione* (VII; R = β-OH, R′ = :O), prepared by oxidising 3β : 12β : 17α-trihydroxy*allo*pregnan-20-one (200 mg.) in pyridine (6 ml.) and water (0·4 ml.) with *N*-bromoacetamide (300 mg., 3 mols.) for 24 hr. at room temperature, followed by brief debromination with zinc and acetic acid at 100°, formed needles, m. p. 220—221°, $[\alpha]_D^{23}$ −8° (*c*, 0·438) (Found: C, 72·0; H, 9·2. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·2%), from aqueous methanol. Acetylation gave the 12-acetate, m. p. 140—141° (Found: C, 70·5; H, 8·9. Calc. for $C_{23}H_{34}O_5$: C, 70·8; H, 8·7%), not depressed on admixture with the product described above.

12β : 21-*Diacetoxy*-3β : 17α-*dihydroxy*allo*pregnan*-20-*one* (IX; R = Ac, R′ = H, R″ = OAc).—A stirred solution of 12β-acetoxy-3β : 17α-dihydroxy*allo*pregnan-20-one (2·6 g.) in chloroform (75 ml.) at 40° was treated dropwise with bromine (18 ml. of 0·375M-solution in chloroform). When decolorisation was complete the solution was washed, dried, and evaporated and the residue treated with ether–hexane, to give the crude 21-bromo-derivative (800 mg.; m. p. 121—125°).

The last compound in acetone (30 ml.) was heated with sodium iodide (480 mg.) under reflux for 25 min., the cooled solution was filtered, and potassium hydrogen carbonate (4 g.) and acetic acid (2·4 ml.) were added. After 18 hr. under reflux the mixture was poured into water, and the product isolated with ether and crystallised from acetone–hexane. 12β : 21-*Diacetoxy*-3β : 17α-*dihydroxy*allo*pregnan*-20-*one* formed crystals, m. p. 189—190°, $[\alpha]_D^{24}$ +37° (*c* 0·618) (Found: C, 66·7; H, 8·5. $C_{25}H_{38}O_7$ requires C, 66·7; H, 8·5%).

21-*Bromo*-3β : 12β : 17α-*trihydroxy*allo*pregnan*-20-*one* (IX; R = R′ = H, R″ = Br).—3β : 12β : 17α-Trihydroxy*allo*pregnan-20-one (280 mg.) in acetic acid–chloroform (30 ml. of 1 : 1) was stirred at 40° whilst a solution of bromine in chloroform (2·94 ml. of 0·272M) was added dropwise. After decolorisation, the solution was diluted with chloroform and washed with water, dilute sodium carbonate solution, and water, after which it was dried and evaporated under reduced pressure. A portion was triturated with aqueous methanol, to give 21-bromo-3β : 12β : 17α-*trihydroxy*allo*pregnan*-20-*one*, m. p. 205—210° (decomp.), $[\alpha]_D^{25}$ +33° (*c*, 0·418 in EtOH) (Found: C, 61·5; H, 8·2; Br, 15·0. $C_{21}H_{33}O_4Br$ requires C, 58·7; H, 7·7; Br, 18·7%). Recrystallisation led to further loss of bromine.

3β : 12β : 21-*Triacetoxy*-17α-*hydroxy*allo*pregnan*-20-*one* (IX; R = R′ = Ac, R″ = OAc).—(*a*) 3β : 12β-Diacetoxy-17α-hydroxy*allo*pregnan-20-one (500 mg.) in chloroform (20 ml.) was brominated at 40° with bromine (4·7 ml. of 0·272M-solution in chloroform). After 40 min. the product was isolated, crystallised from ether–hexane (yield 370 mg.; m. p. 144—145°) and heated in acetone (70 ml.) with sodium iodide (220 mg.) for 30 min. After filtration, potassium hydrogen carbonate (1·85 g.) and acetic acid (1·1 ml.) were added, the mixture was heated under reflux for 20 hr., and the product isolated with ether. After dehalogenation by brief treatment with zinc and acetic acid at 100° and crystallisation from acetone–hexane, 3β : 12β : 21-*triacetoxy*-17α-*hydroxy*allo*pregnan*-20-*one* was obtained as needles, m. p. 199—200°, $[\alpha]_D^{20}$ +26° (*c*, 0·397) (Found: C, 66·1; H, 8·2. $C_{27}H_{40}O_8$ requires C, 65·9; H, 8·1).

(*b*) Crude 21-bromo-3β : 12β : 17α-trihydroxy*allo*pregnan-20-one was converted into the 21-acetoxy-derivative as in (*a*). Acetylation of the product was followed by chromatography in benzene on alumina (10 g.). Elution with benzene–ether furnished 3β : 12β-diacetoxy-17α-hydroxy*allo*pregnan-20-one, m. p. 123—125° alone or on admixture with an authentic specimen (see above). Elution with ether–acetone gave 3β : 12β : 21-triacetoxy-17α-hydroxy*allo*pregnan-20-one, m. p. 197—198° (Found: C, 65·9; H, 8·1%), not depressed on admixture with a sample prepared as above.

(*c*) The same product was obtained by acetylation of 12β : 21-diacetoxy-3β : 17α-dihydroxy-*allo*pregnan-20-one.

12β : 21-*Diacetoxy*-17α-*hydroxy*allo*pregnane*-3 : 20-*dione* (X).—(*a*) 12β : 21-Diacetoxy-3β : 17α-dihydroxy*allo*pregnan-20-one (700 mg.) in *tert.*-butanol (30 ml.), water (1 ml.), and pyridine (1 ml.) was treated with *N*-bromoacetamide (800 mg.) for 20 hr. at room temperature. After

debromination (zinc dust in acetic acid for 10 min. at 100°), the product was crystallised from acetone–hexane, to give 12β : 21-*diacetoxy*-17α-*hydroxy*allo*pregnane*-3 : 20-*dione*, m. p. 195—196°, $[\alpha]_D^{24}$ +60° (*c*, 0·432) (Found : C, 66·7; H, 8·0. $C_{25}H_{36}O_7$ requires C, 67·0; H, 8·0%).

(*b*) Crude 21-bromo-3β : 12β : 17α-trihydroxy*allo*pregnan-20-one (700 mg.) was acetoxylated as before. The product in pyridine (24 ml.) and water (1·6 ml.) was oxidised with *N*-bromoacetamide (1·2 g.), briefly debrominated, treated with acetic anhydride (5 ml.) and pyridine (5 ml.) for 1 hr. at 100°, and chromatographed in benzene solution on alumina (20 g.). Elution with benzene–ether (1 : 4) yielded the diacetate (VII; R = R′ = β-OAc). Elution with ether–acetone gave the triacetate (X), m. p. 191—192° (Found : C, 67·7; H, 8·1%).

12β : 21-*Diacetoxy*-17α-*hydroxypregn*-4-*ene*-3 : 20-*dione* (XI).—The foregoing compound (1·28 g.) in acetic acid (130 ml.) was treated dropwise with bromine (27·5 ml. of 0·208M-solution in acetic acid) during 20 min. Hydrogen bromide (2 ml. of 50% w/v solution in acetic acid) was added and after 20 hr. the 2 : 4-dibromide was isolated by means of ether and treated under nitrogen in boiling acetone (80 ml.) with sodium iodide (8 g.) for 22 hr. The mixture was poured into sodium hydrogen sulphite solution and the product was isolated with ether, debrominated (5 g. of zinc dust in 20 ml. of acetic acid for 15 min. at 40°) and crystallised from acetone–hexane, then from aqueous methanol. 12β : 21-*Diacetoxy*-17α-*hydroxypregn*-4-*ene*-3 : 20-*dione* formed needles, m. p. 153—154°, $[\alpha]_D^{24}$ +103° (*c*, 0·388), $\lambda_{max.}$ 239 mμ (4·19) (in *iso*propanol) (Found : C, 66·7; H, 7·8. $C_{25}H_{34}O_7$ requires C, 67·2; H, 7·7%).

The authors thank the Directors of The British Drug Houses Ltd. for permission to publish this work.

CHEMICAL RESEARCH LABORATORIES,
THE BRITISH DRUG HOUSES LTD., LONDON, N.1. [*Received, November 15th*, 1954.]