*Hydroxylation of Pregn-16-en-20-ones. Part II.** D-*Homo-derivatives derived from* 16α : 17α-*Dihydroxypregnan-20-ones.*

By GEORGE COOLEY, BERNARD ELLIS, FRANK HARTLEY, and VLADIMIR PETROW.

[Reprint Order No. 6503.]

3β-Acetoxypregna-5 : 16-dien-20-one (I) adds osmic acid in the presence of pyridine to give a complex (II), which may be converted into the dihydroxy-ketones (IV; R = H), (V; R = R′ = H), and (III; R = H). The last two compounds are transformed by methanolic potassium hydroxide into 3β : 17-dihydroxy-17*a*-methyl-D-homoandrosta-5 : 17-dien-16-one (VI; R = H), which forms a quinoxaline derivative and yields the dicarboxylic acid (IX) on oxidation with alkaline hydrogen peroxide.

Pregna-4 : 16-diene-3 : 20-dione (XI) may similarly be converted into the compounds (XII), (X) and (XIII).

ADDITION of osmium tetroxide to 3β-acetoxypregna-5 : 16-dien-20-one (I) in ether containing a small proportion of pyridine was followed by rapid separation of a light-brown crystalline steroid–osmium tetroxide–pyridine complex. The normal 16α : 17α-cyclic osmate structure (II) is assigned to this compound on the basis of its conversion in low yield into 3β : 16α-diacetoxy-17α-hydroxypregn-5-en-20-one (IV; R = Ac) by very brief treatment with aqueous-alkaline mannitol, followed by acetylation of the product. Reductive hydrolysis of the osmate (II) with aqueous-ethanolic sodium sulphite led to a compound *A*, $C_{23}H_{34}O_5$, and a deacetylated compound *B*, $C_{21}H_{32}O_4$.

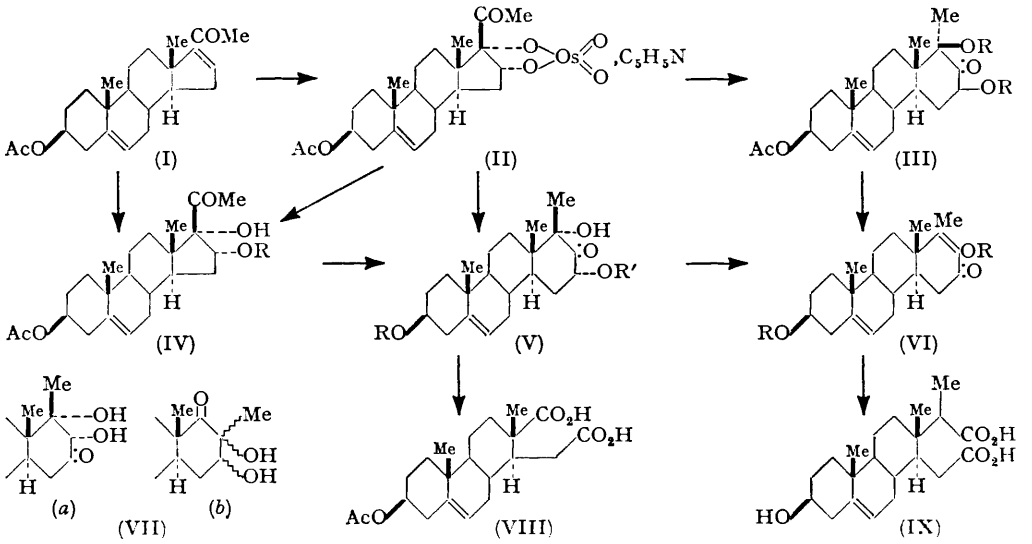
Structure of Compound A.—The first formulation, 3β-acetoxy-16α : 17α-dihydroxypregn-5-en-20-one (IV; R = H), for this product was discarded when the material proved to be different from authentic (IV) prepared as described in Part I (preceding paper). We therefore assumed that reaction of the osmate (II) with hot aqueous-ethanolic sodium sulphite had led to a labile intermediate such as (IV), which then underwent alkali-promoted rearrangement to structures of the D-homo-type (cf. Turner, *J. Amer. Chem. Soc.*, 1953, **75**, 3484). Both 17*a*-hydroxy-17*a*-methyl-D-homo- (VII*a*) and 17-hydroxy-17-methyl-D-homo- (VII*b*) structures were possible from theoretical considerations. Both were, however, excluded by the alkaline dehydrations (see below) leading to compounds (VI) and thence (IX).

Acetylation of compound *A* with acetic anhydride in pyridine at *room* temperature gave unexpectedly a triacetate, indicating (i) the presence of a less hindered, equatorial (β) 17*a*-hydroxyl group and (ii) a system of the type ·CMe(OH)·CO·C(OH)< in which acetylation of the tertiary hydroxyl group would be facilitated by a mechanism involving acyl migration. Examination of models showed that such a situation exists only in that structure in which the 16- and the 17*a*-hydroxyl group are both equatorial (β) and hence in the same plane as the 17-keto-group. The constitution 3β-acetoxy-16β : 17*a*β-dihydroxy-17*a*α-methyl-D-homoandrost-5-en-17-one (III; R = H) is consequently assigned to compound *A*. In support we find that the material (i) shows infrared absorption (kindly determined by Dr. L. J. Bellamy) consistent with a structure in which a carbonyl group in a six-membered ring is doubly bonded to hydrogen atoms furnished by two adjacent

* Part I, preceding paper.

hydroxyl groups, (ii) does not form an *iso*propylidene derivative, and (iii) does not show ultraviolet absorption characteristic of αβ-unsaturated ketones.

Heusler and Wettstein (*Chem. Ber.*, 1954, **87**, 1301) recently described a high-melting triolone prepared by reaction between 3β : 16β-diacetoxy-17α-hydroxypregn-5-en-20-one and potassium hydroxide, potassium carbonate, or alcoholic hydrochloric acid. They



recognised the product as a D-homo-steroid but did not assign a precise constitution to it. Acetylation with hot acetic anhydride gave a diacetate, whilst pyridine–acetic anhydride at 80° furnished a triacetate. Comparison of the physical constants reported for the triester with those of our 3β : 16β-17*a*β-triacetoxy-17*a*α-methyl-D-homoandrost-5-en-17-one (III; R = Ac) leaves little doubt that the two compounds are identical. The parent triolone must therefore be regarded as 3β : 16β : 17*a*β-trihydroxy-17*a*α-methyl-D-homoandrost-5-en-17-one and the diacetate derived from it as the 3β : 16β-diester.

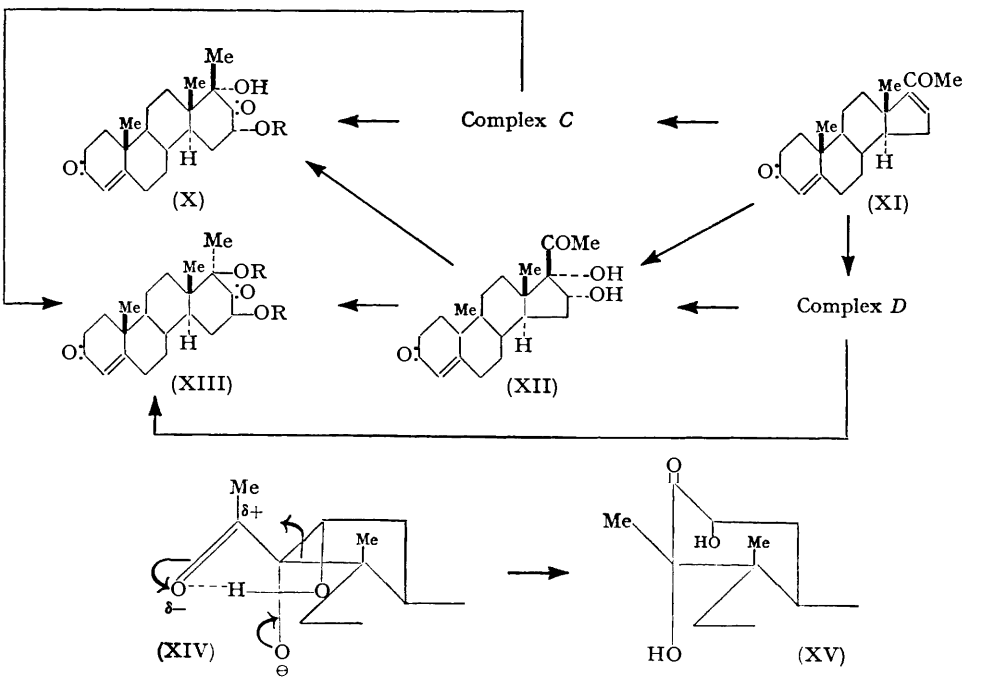
Structure of Compound B.—In contrast to compound *A*, acetylation of this triolone gave only a diacetate which differed, moreover, from the compound (IV; R = Ac). The parent compound is therefore isomeric with (III) and (IV) (free alcohols). Its constitution follows from the following evidence.

17β-Hydroxy-20-oxopregnane derivatives are known to undergo D-homo-annulation when chromatographed on to alumina showing basic, neutral, or acidic reactions, whereas 17α-hydroxy-20-oxopregnanes do not rearrange under these conditions and are also more resistant to isomerisation by alkali than are the corresponding 17β-hydroxy-epimers (cf. Turner, *loc. cit.*). In contrast, we now find that 3β-acetoxy-16α : 17α-dihydroxypregn-5-en-20-one (IV; R = H) is smoothly converted by chromatography on basic alumina into an isomeric monoacetate, which forms an *iso*propylidene derivative and passes into compound *B* diacetate an acetylation. The constitution of 3β : 16α : 17*a*α-trihydroxy-17*a*β-methyl-D-homoandrost-5-en-17-one (V; R = R′ = H) is consequently assigned to compound *B*, (i) on the reasonable assumption that the isomeric change produced by chromatography of (IV; R = H) involves normal D-homo-annulation and (ii) on the evidence of *iso*propylidene formation, which establishes the axial orientation of the *cis*-1 : 3-glycol system (cf. Sneedon and Turner, *J. Amer. Chem. Soc.*, 1953, **75**, 3500; Angyal and Macdonald, *J.*, 1952, 686). Its alternative formulation on the basis of (VII*a*) is considered less likely as (i) hot aqueous sulphite is presumably a more drastic isomerising agent than basic alumina, (ii) reductive hydrolysis and D-homo-annulation of (II) by hot sulphite gives the diolone (III; R = H) in addition to compound *B*, (iii) the compound (III) is not of type (VII*a*), but as a 16β-hydroxy-D-homo-steroid is regarded as derived from an initially formed 16α-hydroxy-D-homo-precursor by a secondary change involving an alkali-catalysed

isomerisation of a 16α(axial)-hydroxyl group to the more stable 16β(equatorial)-configuration, (iv) isomerisation of the diol (IV; R = H) by basic alumina would hardly be expected to proceed beyond the stage reached under the more drastic conditions obtaining with hot sulphite, and (v) further isomerisation of the triolone (V; R = R′ = H) would presumably lead, from analogy with (II) ⟶ (III; R = H), to the 16β(equatorial)-hydroxy-isomer and not to (VII*a*), which would represent yet a further stage in the series of changes promoted by alkali and lead ultimately to (VI; R = H) (see below). Some additional evidence bearing on this problem is presented in Part III (following paper).

Whilst the above experiments were in progress, Inhoffen, Blomeyer, and Brückner (*Chem. Ber.*, 1954, **87**, 593) reported the preparation of an osmic ester from 3β-acetoxy-5 : 6-dibromopregn-16-en-20-one, converted by hot aqueous-ethanolic sodium sulphite and zinc dust into a single, high-melting triolone considered to be 3β : 16α : 17α-trihydroxypregn-5-en-20-one (cf. IV). Acetylation gave a diacetate regarded as (IV; R = Ac). We have since repeated and confirmed these experimental findings, but are unable to accept Inhoffen, Blomeyer, and Brückner's formulations as the materials in question are identical with our D-homo-steroids (V; R = R′ = H) and (V; R = R′ = Ac).

In an attempt to confirm, by degradation, the D-homo-structure (V), the 5 : 6-dibromide of the diolone (V; R = Ac, R′ = H) was oxidised with chromium trioxide with the object of converting it, by rupture of ring D, into a keto-dicarboxylic acid (cf. Ruzicka, Gätzi, and Reichstein, *Helv. Chim. Acta*, 1939, **22**, 626; Shoppee and Prins, *ibid.*, 1943, **26**,



201). Unfortunately, oxidation proceeded beyond the required stage to give, after debromination, the dicarboxylic acid (VIII) (Kuwada, *J. Pharm. Soc. Japan*, 1936, **56**, 75).

Inhoffen, Blomeyer, and Brückner (*loc. cit.*) have previously reported that their 3β : 16α : 17α-trihydroxypregn-5-en-20-one [herein formulated as (V; R = R′ = H)] undergoes dehydration with boiling methanolic potassium hydroxide to give an enolic form of 3β-hydroxypregn-5-ene-16 : 20-dione. This interpretation of the dehydration is untenable on mechanistic grounds. In addition, it is rendered unlikely by the observation that pregnane-16 : 20-diones undergo ready alkaline hydrolysis to androstan-16-ones (Marshall and Gallagher, *J. Amer. Chem. Soc.*, 1949, **71**, 2325). We have since confirmed Inhoffen, Blomeyer, and Brückner's experimental findings and additionally obtained the

same enolic diketone from the stereoisomers (III) and (V). We assign to it the constitution 3β : 17-dihydroxy-17*a*-methyl-D-homoandrosta-5 : 17-dien-16-one (VI; R = H) on the basis of the following evidence : (*a*) its ultraviolet absorption (max. at 277 mμ), (*b*) its conversion into a diacetate (VI; R = Ac) with an absorption maximum at 245 mμ (see Dorfman, *Chem. Rev.*, 1953, **53**, 80), (*c*) its reaction with *o*-phenylenediamine to give a quinoxaline derivative, and (*d*) its oxidation with alkaline hydrogen peroxide to a dicarboxylic acid (IX) containing the same number of carbon atoms. Its formation from both (III) and (V) presumably involves alkali-catalysed rearrangement to a 17*a*-epimeric structure of type (VII*a*), followed by dehydration to the enolic diketone (VI; R = H).

Turner (*loc. cit.*) has pointed out that the rearrangement of 17-hydroxypregnan-20-ones into ketols of the D-homo-series is highly stereospecific. Thus whereas basic catalysts (aluminium *tert.*-butoxide or alumina) convert 17α- and 17β-hydroxypregnan-20-ones into 17*a*β- and 17*a*α-D-homo-ketols, respectively, Lewis acids give rise to the epimeric 17*a*α- and 17*a*β-D-homo-ketols. The results described herein are at variance with these generalisations in that D-homo-annulation of the 17α-hydroxy-compound (IV; R = H) with alumina leads stereospecifically to the 17*a*α-hydroxy(axial-OH)-steroid (V; R = Ac; R′ = H). They may, nevertheless, be reconciled with Turner's conclusions by making the legitimate assumption that orientation of the 20-carbonyl group in the transition state is governed by hydrogen bonding with the adjacent 16α-hydroxyl group. Alumina-catalysed removal of a proton from the 17-hydroxyl group of diolone (IV) and conferment of a full negative charge on oxygen will consequently lead to the transition state indicated in (XIV) and rearrangement to (XV). D-Homo-annulation of the ester (II) with hot aqueous-alcoholic sulphite, however, leads to both epimers (III) and (V) as hydrogen bonding is weakened by the competing tendency of the 16α-hydroxy-group to release protons to the surrounding medium.

Treatment of 3β-acetoxy*allo*pregn-16-en-20-one with osmic acid in the presence of pyridine led to a crystalline complex from which, by careful treatment with mannitol in aqueous potassium hydroxide, 3β-acetoxy-16α : 17α-dihydroxy*allo*pregnan-20-one was obtained, identified as the 3β : 16α-diacetate (Part I). Reductive cleavage of the complex with aqueous-ethanolic sodium sulphite, in contrast, furnished only one isolatable product, 3β : 16β : 17*a*β-trihydroxy-17*a*α-methyl-D-homoandrostan-17-one, converted into the 3β : 16β : 17*a*β-triacetate by acetic anhydride–pyridine.

Similar oxidation of pregna-4 : 16-diene-3 : 20-dione (XI) gave a crystalline complex *C*. Cleavage of this with mannitol and aqueous alkali gave 16α : 17α-dihydroxypregn-4-ene-3 : 20-dione (XII) (Part I), and heating with aqueous-ethanolic sodium sulphite provided a single product, 16β : 17*a*β-dihydroxy-17*a*α-methyl-D-homoandrost-4-ene-3 : 17-dione (XIII; R = H), also obtained directly from (XII) by D-homo-annulation under similar conditions. The diol (XIII; R = H) passed into a diacetate (XIII; R = Ac) on acetylation in pyridine and failed to form an *iso*propylidene derivative.

Inhoffen *et al.* (*loc. cit.*) describe a complex (herein referred to as complex *D*) prepared by treating the dione (XI) with osmium tetroxide in the absence of pyridine. Reduction with sodium sulphite gave a diol to which the constitution 16α : 17α-dihydroxypregn-4-ene-3 : 20-dione was assigned. We have since repeated this work and have established that the product so obtained differs from authentic (XII), but is identical with our D-homo-steroid (XIII; R = H). Reaction of complex *C* with aqueous-ethanolic sodium sulphite could be modified by the addition of zinc bromide and zinc dust : there were then formed the dihydroxy-diketone (XIII; R = H) and an isomer, the latter being also obtained directly from (XII) by alumina-promoted rearrangement. Acetylation of the new isomer gave a monoacetate, and treatment with acetone–hydrochloric acid furnished an *iso*propylidene derivative. The compound is therefore formulated as 16α : 17*a*α-dihydroxy-17*a*β-methyl-D-homoandost-4-ene-3 : 17-dione (X; R = H).

Experimental

*3β-Acetoxy-16β : 17aβ-dihydroxy-17aα-methyl-*D- (III; R = H) *and* 3β : 16α : 17*aα-trihydroxy-17aβ-methyl-*D*-homoandrost-5-en-17-one* (V; R = R′ = H).—3β-Acetoxypregna-5 : 16-dien-20-one (4 g.) in dry ether (240 ml.) containing redistilled pyridine (3·5 ml.) was treated with a

solution of osmium tetroxide (3 g.) in ether (50 ml.). Separation of light brown crystals began after 1—2 min., and was complete after 1 hr. The product was washed well with ether, giving 6·4 g. of complex. A test for nitrogen was positive.

A mixture of the foregoing complex (6·4 g.), sodium sulphite (15 g.), ethanol (110 ml.), and water (80 ml.) was refluxed for 45 min., then filtered hot, and the residue thrice washed with small portions of boiling 80% ethanol. After dilution with water, the combined filtrate and washings were extracted four times with methylene dichloride. The combined extracts were washed until neutral, dried, and concentrated to *ca.* 50 ml., whereupon crystals (810 mg.; m. p. 245—247°) separated. Purified from aqueous ethanol, 3β-*acetoxy*-16β : 17*a*β-*dihydroxy*-17a*α*-*methyl*-D-*homoandrost*-5-*en*-17-*one* formed plates, m. p. 250°, $[\alpha]_D^{20}$ −56° (*c*, 0·57 in pyridine) (Found : C, 70·4, 70·4; H, 9·3, 9·1. $C_{22}H_{34}O_5$ requires C, 70·7; H, 8·8%).

Further concentration of the methylene dichloride mother-liquor gave a product (920 mg.; m. p. 235—245°), which, purified from aqueous ethanol, gave 3β : 16α : 17*aα*-*trihydroxy*-17a*β*-*methyl*-D-*homoandrost*-5-*en*-17-*one*, needles, m. p. 255—256°, $[\alpha]_D^{20}$ −84° (*c*, 0·43) (Found : C, 72·0; H, 9·5. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·25%), not depressed on admixture with a specimen prepared by the method of Inhoffen *et al.* (*loc. cit.*).

Acetylation of the former product in pyridine for 24 hr. at room temperature gave the 3β : 16β : 17a*β*-*triacetate*, needles (from aqueous ethanol), m. p. 160—161°, $[\alpha]_D^{19}$ −29° (*c*, 0·92) (Found : C, 68·5; H, 8·1. Calc. for $C_{27}H_{38}O_7$: C, 68·3; H, 8·1%) (Heusler and Wettstein, *loc. cit.*, give m. p. 157—158°, $[\alpha]_D^{22}$ −28° ± 4°).

Acetylation of the triol (V; R = R′ = H) in pyridine for 30 min. at 100° gave the 3β : 16α-*diacetate*, flat needles (from aqueous ethanol), m. p. 176—177°, $[\alpha]_D^{19}$ −99° (*c*, 0·93) (Found : C, 69·7; H, 8·4. Calc. for $C_{25}H_{36}O_6$: C, 69·4; H, 8·4%) (Inhoffen *et al.*, *loc. cit.*, give m. p. 170—171°, $[\alpha]_D^{22}$ −98·8° ± 1°).

3β : 16α-*Diacetoxy*-17α-*hydroxypregn*-5-*en*-20-*one* (IV; R = Ac).—The foregoing complex (1·1 g.), suspended in a solution of mannitol (2·0 g.) and potassium hydroxide (0·5 g.) in water (50 ml.), was heated at 100° for 10 min. The solids obtained on filtration were washed, air-dried, and acetylated in pyridine. Two crystallisations of the product from aqueous methanol gave 3β : 16α-diacetoxy-17α-hydroxypregn-5-en-20-one (50 mg.), silky needles, m. p. 214—215° not depressed on admixture with an authentic specimen (Part I, *loc. cit.*).

3β-*Acetoxy*-16α : 17a*α*-*dihydroxy*-17a*β*-*methyl*-D-*homoandrost*-5-*en*-17-*one* (V; R = Ac, R′ = H).—A solution of 3β-acetoxy-16α : 17α-dihydroxypregn-5-en-20-one (2·6 g.) in benzene–ether (150 ml.; 1 : 1) was passed slowly through a column (12 × 1·8 cm.) of alkaline alumina. The product (2·4 g.; m. p. 185—190°) obtained on evaporation of the percolate was crystallised from ethanol to give the D-*homo-steroid*, flat needles, m. p. 200—201°, $[\alpha]_D^{22}$ −76° (*c*, 1·43) (Found : C, 70·4; H, 8·7. $C_{23}H_{34}O_5$ requires C, 70·7; H, 8·8%). Acetylation in pyridine gave the 3β : 16α-diacetoxy-compound, m. p. 176°, not depressed on admixture with a specimen prepared as described above. The iso*propylidene derivative* (70%), prepared by treating the diol (V; R = Ac; R′ = H) (350 mg.) in hot acetone (20 ml.) with two drops of concentrated hydrochloric acid and setting the mixture aside overnight, formed dense prisms (from *n*-hexane), m. p. 183—184°, $[\alpha]_D^{21}$ −85° (*c*, 0·87) (Found : C, 72·3; H, 9·0. $C_{26}H_{38}O_5$ requires C, 72·5; H, 8·9%).

Oxidation of the Diolone (V; R = Ac, R′ = H).—Bromine (600 mg.) in chloroform (20 ml.) was added dropwise during 45 min. to a stirred solution of the dihydroxy-ketone (1·5 g.) in chloroform (20 ml.) at −60°. After removal of the solvent *in vacuo* at ⩾30°, the residue in acetic acid (30 ml.) was treated with chromium trioxide (1 g.) in 80% acetic acid (10 ml.), and the mixture kept overnight. Zinc dust (6 g.) was then added, and the mixture stirred for 10 min., then heated for 10 min. at 100°. The product obtained on dilution with water was extracted with ether. The acidic fraction (0·66 g.; m. p. *ca.* 230°) was purified from aqueous ethanol to give 3β-acetoxy-16 : 17-*seco*androst-5-ene-16 : 17-dioic acid, plates, m. p. and mixed m. p. 258—260°, $[\alpha]_D^{20}$ −97° (*c*, 1·33) (Found : C, 66·7; H, 8·1. Calc. for $C_{21}H_{30}O_6$: C, 66·6; H, 8·0%).

3β : 17-*Dihydroxy*-17*a*-*methyl*-D-*homoandrosta*-5 : 17-*dien*-16-*one* (VI; R = H).—A solution of the diolone (V; R = Ac; R′ = H) (2·3 g.) in methanolic potassium hydroxide (50 ml. of 10%) was refluxed for 2 hr., a yellow insoluble potassium salt separating after the first hour. The product obtained on dilution and acidification to Congo-red was crystallised from aqueous methanol. The diosphenol (1·1 g.) formed fine hair-like needles, m. p. 196°, $[\alpha]_D^{22}$ −67° (*c*, 0·84) (Found : C, 76·3; H, 9·2. Calc. for $C_{21}H_{30}O_3$: C, 76·3; H, 9·2%). Light absorption : $\lambda_{max.}$ 277 mμ (ε 8000) [Inhoffen *et al.*, *loc. cit.*, give m. p. 186—187°, $\lambda_{max.}$ 277 mμ (ε 9120)]. The 3β : 17-diacetate, prepared by acetylation in pyridine for 30 min. at 100°, crystallised from aqueous methanol in prisms, m. p. 209—210°, $[\alpha]_D^{20}$ −66° (*c*, 1·26) (Found : C, 72·5; H, 8·2.

Calc. for $C_{25}H_{34}O_5$: C, 72·45; H, 8·25%). Light absorption : $\lambda_{max.}$ 245 mμ (ε 11,830) [Inhoffen *et al., loc. cit.*, give m. p. 197—198°, $[\alpha]_D^{19}$ −68·4°, $\lambda_{max.}$ 244 mμ (ε 11,230)]. The *quinoxaline* derivative, prepared by heating the diosphenol (200 mg.) and *o*-phenylenediamine (200 mg.) in absolute ethanol (4 ml.) under reflux for 3 hr., formed almost colourless needles (from aqueous methanol), m. p. 254° (Found : C, 80·7; H, 8·7; N, 6·7. $C_{37}H_{34}ON_2$ requires C, 80·55; H, 8·5; N, 6·95%).

The diosphenol (VI; R = H) was also obtained by similar treatment of the diolone (III; R = H) with methanolic potassium hydroxide.

3β-*Hydroxy*-17*a*-*methyl*-16 : 17-seco-D-*homoandrost*-5-*ene*-16 : 17-*dioic acid* (IX).—The foregoing diosphenol (1 g.) in ethanol (100 ml.) was treated with hydrogen peroxide (2·5 ml.; " 130 vol."), followed by 10% aqueous potassium hydroxide (8 ml.). After 18 hr. at room temperature the mixture was diluted with water and extracted twice with ether, and the aqueous phase acidified with hydrochloric acid. The solids (350 mg.; m. p. 135—140°) which slowly separated were crystallised from aqueous acetic acid. The *dicarboxylic acid* formed needles which melted with effervescence at 145°, resolidified, and finally melted at 258—259°, $[\alpha]_D^{20}$ −65° (*c*, 0·74 in EtOH) (Found : C, 63·0; H, 9·0; equiv., 210. $C_{21}H_{32}O_5,2H_2O$ requires C, 63·0; H, 9·05%; equiv., 200).

3β : 16α-*Diacetoxy*-17α-*hydroxy*allo*pregnan*-20-*one*.—Osmium tetroxide (5 g.) in ether (150 ml.) was added to 3β-acetoxy*allo*pregn-16-en-20-one (7 g.) in ether (300 ml.) and pyridine (4·5 ml.). After several hours, the complex (13·8 g.) was obtained as light brown needles.

The complex (1 g.), suspended in a solution of mannitol (2 g.) and potassium hydroxide (0·5 g.) in water (50 ml.), was heated at 100° for 5 min. The insoluble solids were dried and acetylated in pyridine to give a gum which crystallised from methanol. 3β : 16α-Diacetoxy-17α-hydroxy*allo*pregnan-20-one (90 mg.) formed needles, m. p. 158—160°, alone or in admixture with an authentic specimen (Part I).

3β : 16β : 17*a*β-*Trihydroxy*-17*a*α-*methyl*-D-*homoandrostan*-17-*one*.—A solution of the foregoing complex (8 g.) in ethanol (140 ml.) was added to sodium sulphite (20 g.) in water (100 ml.). The mixture was refluxed for 45 min., then filtered, and the product isolated by extraction with methylene dichloride. Concentration of the dried extract to *ca.* 50 ml. gave a crystalline solid (1·22 g.; m. p. 258—262°) which was purified from aqueous methanol. The D-*homosteroid* formed needles, m. p. 260—262°, $[\alpha]_D^{22}$ +23° (*c*, 0·73) (Found : C, 71·5; H, 9·9. $C_{21}H_{34}O_4$ requires C, 72·0; H, 9·8%). Further concentration of the methylene dichloride mother-liquor gave a gum from which crystalline material could not be isolated. Acetylation of the trihydroxy-ketone in pyridine for 1 hr. at 100° gave the 3β : 16β : 17*a*β-*triacetoxy-derivative*, leaflets (from aqueous methanol), m. p. 172—174°, $[\alpha]_D^{21}$ +35° (*c*, 0·91) (Found : C, 68·0; H, 8·4. $C_{27}H_{40}O_7$ requires C, 67·9; H, 8·45%).

16α : 17α-*Dihydroxypregn*-4-*ene*-3 : 20-*dione* (XII).—Osmium tetroxide (5 g.) in ether (150 ml.) was added to pregna-4 : 16-diene-3 : 20-dione (6 g.) in ether (800 ml.) and pyridine (4 ml.). After 1 hr. the complex (13 g.) was obtained as dense brown needles.

The complex (2 g.), suspended in a solution of mannitol (4 g.) and potassium hydroxide (1 g.) in water (50 ml.), was heated for 10 min. at 80°. The almost colourless solid (300 mg.) obtained on filtration was crystallised from ethanol to give 16α : 17α-dihydroxypregn-4-ene-3 : 20-dione, dense prisms, m. p. 225°, alone or in admixture with an authentic specimen (Part I, *loc. cit.*).

16β : 17*a*β-*Dihydroxy*-17*a*α-*methyl*-D-*homoandrost*-4-*ene*-3 : 17-*dione* (XIII; R = H).—(*a*) A mixture of the foregoing complex (8 g.), sodium sulphite (20 g.), ethanol (140 ml.), and water (100 ml.) was refluxed for 30 min. and then filtered. The product, isolated with methylene dichloride in the usul way, was crystallised from acetone–*n*-hexane to give material (1·5 g.; m. p. 190—195°). Recrystallised from ethanol–*n*-hexane, the D-homo-steroid formed needles, m. p. 223—225°, $[\alpha]_D^{20}$ +80° (*c*, 0·8) (Found : C, 72·3; H, 8·7. Calc. for $C_{21}H_{30}O_4$: C, 72·8; H, 8·7%). Light absorption : $\lambda_{max.}$ 239 mμ (ε 16,600). No depression in m. p. was obtained in admixture with a specimen prepared by the method of Inhoffen *et al., loc. cit.*

(*b*) A mixture of 16α : 17α-dihydroxypregn-4-ene-3 : 20-dione (500 mg.), sodium sulphite (1 g.), ethanol (20 ml.), and water (10 ml.) was refluxed for 1 hr., then diluted with water, and the product isolated with methylene dichloride. Crystallisation from acetone–*n*-hexane gave 16β : 17*a*β-dihydroxy-17*a*α-methyl-D-homoandrost-4-ene-3 : 17-dione (350 mg.), identified by m. p. and mixed m. p. with a specimen prepared by method (*a*).

Acetylation of this dione in pyridine for 24 hr. at room temperature gave the 16β : 17*a*β-*diacetate*, plates (from aqueous ethanol), m. p. 201—202°, $[\alpha]_D^{22}$ +91° (*c*, 0·88) (Found : C, 69·9, 69·5; H, 8·1, 8·15. $C_{25}H_{34}O_6$ requires C, 69·75; H, 8·0%).

16α : 17*aα*-*Dihydroxy*-17*aβ*-*methyl*-D-*homoandrost*-4-*ene*-3 : 17-*dione* (X; R = H).—16α : 17α-Dihydroxypregn-4-ene-3 : 20-dione (3 g.) in benzene–methylene dichloride (320 ml.; 3 : 1) was passed slowly through a column (18 × 2 cm.) of alkaline alumina. The product was crystallised from ethanol–*n*-hexane to give the D-*homo-steroid* (1·8 g.), needles, m. p. 190°, $[\alpha]_D^{21}$ +96° (*c*, 0·86) (Found: C, 72·4; H, 8·7. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%). Acetylation in pyridine gave the **16α-*acetoxy-derivative***, needles (from acetone–*n*-hexane), m. p. 202—203°, $[\alpha]_D^{20}$ +32° (*c*, 0·76) (Found: C, 71·0; H, 8·3. $C_{23}H_{32}O_5$ requires C, 71·1; H, 8·3%). The iso*propylidene derivative* (90%), prepared by keeping the diol (400 mg.) in hot acetone (20 ml.) with 2 drops of concentrated hydrochloric acid overnight, formed small rhombs (from aqueous ethanol), m. p. 231—232°, $[\alpha]_D^{22}$ +68° (*c*, 0·67) (Found: C, 74·6; H, 9·0. $C_{24}H_{34}O_4$ requires C, 74·6; H, 8·9%).

Cleavage of Inhoffen, Blomeyer, and Brückner's Complex Under Modified Conditions.—The complex was prepared by treating pregna-4 : 16-diene-3 : 20-dione (2·5 g.) in ether (350 ml.) with osmium tetroxide (2 g.) in ether (100 ml.). After 4 days, the dark brown precipitate (3·65 g.) was collected and washed with ether.

The complex (3 g.), sodium sulphite (13 g.), zinc bromide (1·5 g.), zinc dust (5 g.), ethanol (100 ml.), and water (150 ml.) were stirred and refluxed for 3 hr. After filtration, the filtrate was diluted, and the product isolated by extraction with methylene chloride. Crystallisation from acetone–*n*-hexane gave 16β : 17*aβ*-dihydroxy-17*aα*-methyl-D-homoandrost-4-ene-3 : 17-dione (350 mg.), m. p. and mixed m. p. 223—225°. The acetone–*n*-hexane mother-liquor deposited stout prisms (150 mg.) of 16α : 17*aα*-dihydroxy-17*aβ*-methyl-D-homoandrost-4-ene-3 : 17-dione, m. p. and mixed m. p. 190°.

CHEMICAL RESEARCH LABORATORIES,
THE BRITISH DRUG HOUSES LTD., LONDON, N.1.

[*Received, June 13th*, 1955.]