894. *Compounds related to the Steroid Hormones. Part V.* The Partial Synthesis of 21-Acetoxy-17-hydroxy-16β-methyl-5α-pregn-9-ene-3,20-dione.*

By J. Attenburrow, J. E. Connett, W. Graham, J. F. Oughton, A. C. Ritchie, and P. A. Wilkinson.

A ten-stage process is described for the conversion of 3β-acetoxy-5α-pregna-9,16-dien-20-one into 21-acetoxy-17-hydroxy-16β-methyl-5α-pregn-9-ene-3,20-dione. The 9(11)-unsaturated bond was protected during formation of the dihydroxyacetone side chain by use of 9α,11β-dichloro-intermediates. Isolation and characterisation of the 20-enol form of 3β-acetoxy-16β-methyl-5α-pregn-9(11)-en-20-one is described.

16α- and 16β-Methyl corticoids having greater gluco-corticoid activity than the non-methylated parents have been obtained in the past from bile acid intermediates [1] and from diosgenins.[2] This paper describes a route, with alternatives, shown in the accompanying flowsheet, to a useful † 16β-methylcorticoid precursor (XVIII), from 3β-acetoxy-5α-pregna-9,16-dien-20-one (I), which in turn may be obtained readily from hecogenin.[3]

Introduction of the methyl group in the 16-position by way of the 16,17-pyrazoline [4] presented little difficulty, and the 3β-acetoxy-16-methyl-5α-pregna-9,16-dien-20-one (III) was obtained in about 68% overall yield. Pyrolysis of 16,17-pyrazolines has been done in the past [1i,4,5] by melting the compound under reduced pressure, but we preferred to use a liquid medium for greater temperature control: diethylene glycol was found convenient, as the product could be isolated by dilution with water.

For the introduction of the 17α-hydroxyl group two routes were available. The first involved the Julian procedure [6] with selective epoxidation at the 16,17-position by means of alkaline peroxide, treatment with hydrogen bromide, and hydrogenation. The second route entailed selective hydrogenation at the 16,17-position and the Gallagher procedure.[7] As the latter route was likely to be complicated by the need either to carry out two selective reactions or to introduce protective groups, the former was examined first but the product obtained was not homogeneous and consisted largely of the 16α-methyl compound.‡ We therefore turned to the second line of approach.

Under basic conditions, with palladium–charcoal as catalyst, the 16-methyl-9,16-diene (III) was hydrogenated at the 16-position, leaving the 9(11)-position almost unattacked (>97% shown present by peracid titration and by infrared absorption at 820 cm.$^{-1}$), to

* Part IV, preceding paper.

† See Part VI, succeeding paper.

‡ Wendler and his co-workers [1i] recently reported that the perchloric acid-rearranged product from 16α,17α-epoxy-3α-hydroxy-16β-methylpregnane-11,20-dione gave, on hydrogenation in the presence of palladium–calcium carbonate, a 7 : 3 mixture of the 3α,17α-dihydroxy-16α- and -16β-methylpregnane-11,20-diones.

[1] (*a*) Arth, Johnston, Fried, Spooncer, Hoff, and Sarett, *J. Amer. Chem. Soc.*, 1958, **80**, 3160; (*b*) Arth, Fried, Johnston, Hoff, Sarett, Silber, Stoerk, and Winter, *ibid.*, p. 3161; (*c*) Oliveto, Rausser, Nussbaum, Gebert, Herschberg, Tolksdorf, Eisler, Perlman, and Pechet, *ibid.*, p. 4428; (*d*) Taub, Hoffsommer, Slates, and Wendler, *ibid.*, p. 4435; (*e*) Oliveto, Rausser, Herzog, Herschberg, Tolksdorf, Eisler, Perlman, and Pechet, *ibid.*, p. 6687; (*f*) Karady and Sletzinger, *Chem. and Ind.*, 1959, 1159; (*g*) Wendler and Taub, *ibid.*, 1958, 415; (*h*) Hoffsommer, *J. Org. Chem.*, 1959, **24**, 1617; (*i*) Taub, Hoffsommer, Slates, Kuo, and Wendler, *J. Amer. Chem. Soc.*, 1960, **82**, 4012.

[2] Oliveto, Rausser, Weber, Nussbaum, Gebert, Coniglio, Herschberg, Tolksdorf, Eisler, Perlman, and Pechet, *J. Amer. Chem. Soc.*, 1958, **80**, 4431.

[3] Djerassi, Martinez, and Rosenkranz, *J. Org. Chem.*, 1951, **16**, 1278; Callow and James, *J.*, 1956, 4739.

[4] Wettstein, *Helv. Chim. Acta*, 1944, **27**, 1803.

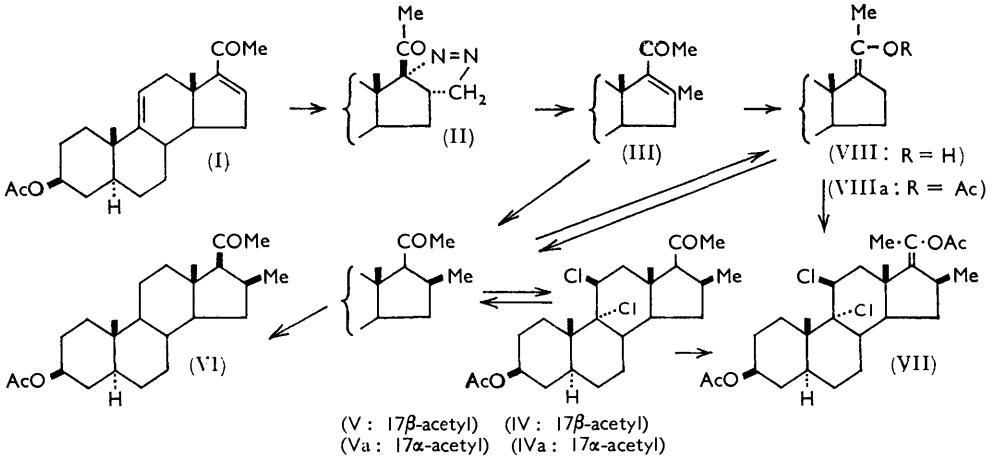
[5] Bernstein and Joseph, *J. Org. Chem.*, 1960, **25**, 1676.

[6] Julian, Meyer, Karpel, and Waller, *J. Amer. Chem. Soc.*, 1950, **72**, 5145.

[7] Kritchevsky, Garmaise, and Gallagher, *J. Amer. Chem. Soc.*, 1952, **74**, 483.

give, as expected on theoretical grounds (see also refs. 1*c*, 1*d*), the 16β-methyl compound (V). The structure of this compound was established by further hydrogenation, this time under acid conditions on palladium–charcoal, to a product whose physical constants agreed well with those described [8] for 3β-acetoxy-16β-methyl-5α-pregnan-20-one (VI).

During the experimental work in this field it was found that hydrogenation of the 16-methyl-diene (III) at room temperature as a dilute solution in a mixture of tetrahydrofuran and triethylamine led, provided that low temperatures were used in the subsequent evaporation, to a product less soluble in acetone than the normal hydrogenation product. The less soluble fraction (28%) melted some 30° the higher and its infrared spectrum in Nujol showed the presence of a hydroxyl group, with no evidence for 20-carbonyl absorption. A 17-en-20-ol structure was ascribed to this new compound for the reasons given below. Its analyses were correct for $C_{24}H_{36}O_3$ and showed an active hydrogen content of 0·21% (calc. 0·27%), whereas the ketone contained no active hydrogen. In carbon disulphide the infrared spectrum indicated a gradual change from the enol to the keto-form. The enol (VIII) changed at 100° (*in vacuo*) into a mixture of the 17α- and 17β-acetyl compounds, as shown by a drop in rotation and by infrared evidence: this heat-sensitivity could account for the indefinite melting point. The rotation of the enol in dioxan appeared to be slightly higher than that of the 17β-acetyl compound but accurate determination of this constant was impossible owing to the rearrangement that occurred in solution; for example, keeping a solution of the enol in tetrahydrofuran for 30 minutes and recovery by evaporation in the cold gave a product of decreased enol content (as estimated by infrared evidence); and if a similar solution was stirred for 30 minutes with twice its weight of active carbon, all trace of enol disappeared and only the 17β-material (V) could be recovered. No ferric chloride colour has been obtained with the enol.



Unlike the corresponding ketone, the enol was acetylated at room temperature in a mixture of acetic anhydride and pyridine, giving a diacetate (VIIIa), but also some of the 20-ketone (V), presumably arising from isomerisation of the enol before acetylation. Enols are known [9] to absorb oxygen readily in neutral solution, with the formation of hydroperoxides, and this compound (VIII) in benzene absorbed 1·75 mol., to give products of undetermined structure; when the oxygen uptake was restricted to 1 mol. the 17-hydroperoxide was isolated. Neither the 16β-methyl-20-ketone (V) nor the corresponding

[8] Romo, Lepe, and Romero, *Bol. Inst. Quim. Univ. nac. auton. México* IV, 1952, 125.
[9] Criegee, "Methoden der organischen Chemie," Georg Thieme Verlag, Stuttgart, 4th edn., Vol. VIII, p. 25.

17,20-enol acetate (VIIIa) absorbed oxygen under these conditions, which is not surprising, since it has been recently shown [10] that for 17-hydroperoxidation of steroidal 20-ketones it is necessary to form the anion of the ketone by means of potassium t-butoxide.

In tetrahydrofuran solution the introduction of dilute hydrochloric acid to bring the concentration to 0·001N converted the enol (VIII), presumably under kinetic control, into the thermodynamically unstable [4,8] β-side-chain ketone, whereas the same concentration of sodium hydroxide produced a mixture of α- and β-side-chain ketones, as shown by an almost instantaneous drop in the optical rotation of the solution. The change from enol to ketone in these solutions was confirmed by infrared examination.

Hydrogenation of conjugated ketones to enols by 1,4-addition has been discussed in the literature.[11] Presumably hydrogenation of the Δ^{16}-20-ketone (III) must occur mainly, if not completely, by this mechanism, for yields as high as 28% of the enol have been isolated despite its ready isomerisation to the ketone in solution, particularly in the presence of charcoal.

Recently, the enol of a steroid 20-ketone has been isolated [12] as a by-product of 16,17-hydrogenation of a Δ^{16}-20-oxo-21-ester in the aldosterone series. The stability of the enol isolated by the Swiss workers might be explained by hydrogen bonding between the 20-hydroxyl group and the oxygen of the 21-ester group, whereas the stability of our enol is presumably due to steric factors associated with the presence of a 16β-methyl group.

As one of the steps in the Gallagher process for the introduction of the 17α-hydroxyl group involves epoxidation of the 17,20-double bond by peracid, clearly an unprotected 9,11-double bond would also be prone to attack. To avoid this we studied the 9α,11β-dichloro-derivatives,[13] which are readily formed, reasonably stable, and yet easily converted into the parent unsaturated compounds by chromous chloride reduction. The method of preparation preferred by the American authors [13] involved the use of hydrogen chloride, which might, however, invoke in our compound undesirable chlorine substitution at $C_{(17)}$ or $C_{(21)}$, and therefore their second method of direct addition, with a solution of chlorine in an organic solvent, was investigated.

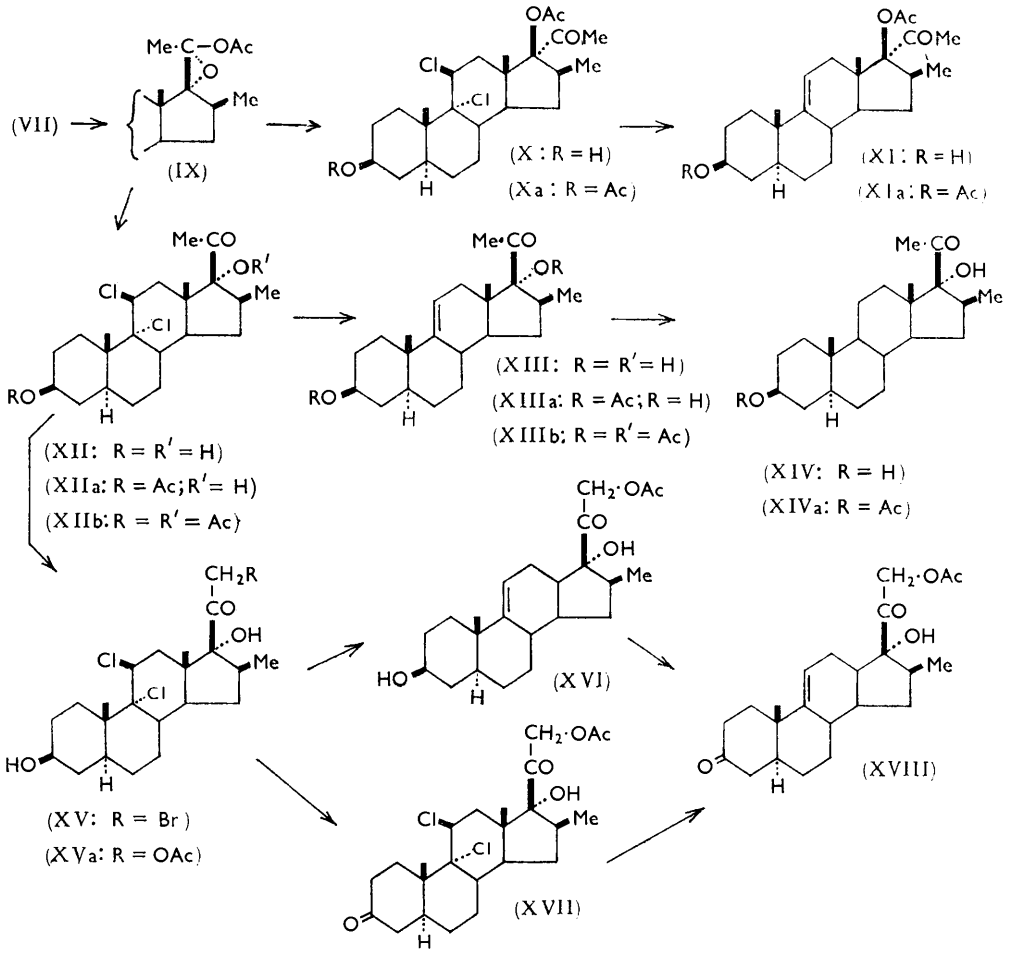
Reaction of 3β-acetoxy-16β-methyl-5α-pregn-9(11)-en-20-one (V) in carbon tetrachloride by the addition of 1·1 mol. of chlorine in the same solvent took place readily, but the product was grossly impure, and a yield of only 40% of the desired 9α,11β-dichloro-compound was obtained. Reduction of the crude product by chromous chloride gave a monochloro-compound with a specific rotation of +120°, indicating that chlorination had occurred at other reactive centres, for example, at $C_{(17)}$.

The effect of hydrogen chloride on substituents at $C_{(17)}$ was demonstrated by adding a solution of hydrogen chloride in ethanol to one of the dichloro-ketone (IV) in chloroform: the rotation changed rapidly at room temperature, and the pure 17α-side-chain isomer was isolated. Though this compound could not be identified by comparing its recorded constants,[14] it was assigned structure (IVa) on the basis of the considerable drop in molecular rotation (−238°), its infrared spectrum, and analysis. Supporting evidence was the isomerisation, under similar conditions, of the 9(11)-unsaturated 17β-compound (V) to a product formulated as the 17α-compound (Va); the molecular rotational change here was −279·5°. These values contrast with recorded molecular rotational difference of −540° between 3β-acetoxy-5α-pregnan-20-one and its 17α-isomer.[15] The ease of side-chain isomerism under alkaline conditions in 16β-methyl-20-ketones was first demonstrated

[10] Bailey, Elks, and Barton, *Proc. Chem. Soc.*, 1960, 214.
[11] Burwell, *Chem. Rev.*, 1957, **57**, 895.
[12] Heusler, Wieland, and Wettstein, *Helv. Chim. Acta*, 1959, **42**, 1586.
[13] Cf. Robinson, Finckenor, Oliveto, and Gould, *J. Amer. Chem. Soc.*, 1959, **81**, 2191; Reimann, Oliveto, Neri, Eisler, and Perlman, *ibid.*, 1960, **82**, 2308.
[14] Ryer and Gebert, *J. Amer. Chem. Soc.*, 1952, **74**, 4336; Romo, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1951, **73**, 4961; Barton and Cox, *J.*, 1948, 783.
[15] Shoppee, *J.*, 1949, 1671.

by Wettstein.[4] Romo, Lepe, and Romero [8] later found that 3β-acetoxy-16β-methylpregn-5-en-20-one gave the 17α-isomer under both acid and alkaline conditions: the latter was reduced to the saturated 17α-isomer of (VI). The $\Delta[M]_D$ in this case was −346°, which is more in keeping with our findings.

An attempt to remove hydrogen chloride from the carbon tetrachloride solution of chlorine with solid sodium hydrogen carbonate did not improve the reaction; nor did introduction of organic bases—presumably base hydrochlorides are equally effective in



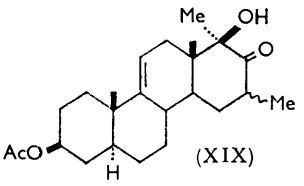
isomerisation of the side chain. Changing the solvent to methylene chloride proved beneficial, though this solvent had the disadvantage of being readily chlorinated even in diffuse daylight. It was eventually found best to use gaseous chlorine, in the absence of light, and a two-phase system comprising methylene chloride and aqueous sodium acetate: even when an excess of chlorine was used, only two atoms were taken up and the dichloro-compound (IV) was isolated in >80% yield.

Enol-acetylation of this compound to the acetate (VII) and epoxidation to the 17,20α-epoxide (IX) was done substantially by the procedure described earlier.[16] Purification of both these intermediates was complicated by the presence of two $C_{(20)}$-isomers; however, as the isomeric epoxides led, on hydrolysis, to the same 17α-hydroxy-compound (XII), highest overall yields were obtained by processing crude materials at each stage.

[16] Barton, Evans, Hamlet, Jones, and Walker, *J.*, 1954, 747.

The alternative route to the dichloro-enol acetate (VII) through the enol acetate (VIIIa) was investigated with the aim of avoiding formation of 17-chloro-compounds, but the yield of 9,11-dichloro-compound was low.

Owing to the instability of 9,11-dichloro-compounds in hot methanol, the usual method of hydrolysis of 3,20-diacetoxy-17,20-epoxides to 3,17-diols with hot methanolic alkali [16] was avoided, and hydrolysis under acid conditions was explored instead. Acetic acid containing a small quantity of aqueous sulphuric acid gave the dichloro-3β-acetoxy-17α-hydroxy-compound (XIIa), which, being more soluble than the corresponding 3,17-diol (XII), was readily purified. Dechlorination, by chromous chloride or, better, by hydrogenolysis under basic conditions with palladised charcoal, gave the 9,11-unsaturated compound (XIIIa), which was hydrogenated under acidic conditions to 3β-acetoxy-17-hydroxy-16β-methyl-5α-pregnan-20-one (XIVa). The 3-hydroxy-compound (XIV) was obtained by methanolysis at room temperature with aqueous sulphuric acid as catalyst.



(XIX)

The unsaturated diol (XIII) was obtained satisfactorily by cold acid methanolysis of the 3-acetate (XIIIa) whereas hot acid led to a product that, after acetylation, had a low rotation and an infrared spectrum typical of a D-homo-steroid. This compound, on the basis of the usual type of D-homo-rearrangement, is provisionally formulated as (XIX).

Unlike what occurs in the preparation [17] of 21-bromo-3β,17-dihydroxy-5α-pregn-9(11)-en-20-one, bromination of our 9,11-unsaturated diol (XIII) by the same method produced an unstable product containing 50% of 9,11-dibromides, as shown by reduction in the height of the Δ^9-band at 820 cm.$^{-1}$ and the continuous release of hydrogen bromide.

It thus became evident that protection of the 9,11-position by chlorine should be continued during the introduction of the 21-acetate group. First, however, a suitable medium for hydrolysis of the diacetate (IX) to the diol (XII) had to be found, particularly in view of the instability of the dichloro-compound to hot methanol and the insolubility of both (IX) and (XII) in most solvents.

Hydrolysis in methanol–methylene chloride–aqueous sulphuric acid gave the required diol in reasonable yield, but from the mother-liquors an unexpected new compound, formulated as 17β-acetoxy-9α,11β-dichloro-3β-hydroxy-16β-methyl-5α,17α-pregnan-20-one (X), was isolated in 10—15% yield. The structure assigned to this compound was based on its ultimate analysis and on infrared examination, which indicated the presence of a 9α,11β-dichloro-structure, an acetyl group, and one hydroxyl group, the latter not being in the 17-position (absorption at 1720 cm.$^{-1}$ of a non-hydrogen-bonded ketone). Acetylation of this compound produced a diacetate (Xa) with the same analysis as the diacetate (XIIb) but differing from the latter in crystalline form, optical rotation, melting point, and infrared spectrum, which for each compound showed the presence of normal non-hydrogen-bonded ketone and the absence of enol acetate structure. Hydrogenolysis of compounds (Xa) and (XIIb) gave different $\Delta^{9(11)}$-diacetates (XIa and XIIIb), indicating that the isomerism was not associated with the disposition of the chlorine atoms.

Rearrangements similar to (IX ⟶ Xa) have been reported [18] from heating 17,20-epoxide 20-acetates above their melting points or allowing them to stand in light petroleum over silica gel. Heating our epoxide (IX) to 20° above its melting point for 10 minutes gave a crude product from which the 17β-acetate (Xa) was obtained in 15% yield. The structure of the latter is further supported by its conversion [19] by zinc dust in acetic acid into 3β-acetoxy-16β-methyl-5α-pregn-9(11)-en-20-one (V).

Reducing the quantity of water in the hydrolysis medium largely avoided the formation of the 17β-acetoxy-impurity, but much better results were obtained by methanolysis at

[17] Elks, Phillipps, and Wall, *J.*, 1958, 4001.
[18] Soloway, Considine, Fukushima, and Gallagher, *J. Amer. Chem. Soc.*, 1954, **76**, 2941.
[19] Rosenfeld, *J. Amer. Chem. Soc.*, 1957, **79**, 5540.

room temperature under alkaline conditions with sufficient methylene chloride to dissolve the epoxide (IX).

In the bromination of the dichloro-diol (XII) to the 21-bromide (XV) the general method of Pataki, Rosenkranz, and Djerassi [20] with our modifications [21] for the 21-bromination of 3β,17α-dihydroxy-5α-pregnane-11,20-dione was employed. The 21-bromide was converted in good yield into the 21-acetate (XVa) by potassium acetate in refluxing acetone, provided the time of reaction was strictly limited: longer times led to dehydrochlorination, with the formation of a 7,9(11)-diene system, as shown by appearance of the ultraviolet maximum at 242 mμ. However, the 16β-methyl-21-acetate (XVa) could not be freed from unchanged dichloro-diol (XII) by the method that we [22] have previously used for 11-keto-21-acetates unsubstituted in the 16-position. Presumably the 16β-group hinders the approach of the Girard reagent to the 20-ketone in the parent 21-methyl compound. As removal of this impurity by recrystallisation was not very effective, we modified the bromination conditions and the procedure for isolation so as to obtain substantially pure 21-bromide (XV): the suspended steroid was treated with a slight excess of bromine in chloroform containing 8% of ethanol and 10 mol. of hydrogen chloride and the steroid–hydrogen chloride complex was decomposed with aqueous sodium hydrogen carbonate.

The 9,11-unsaturation was reintroduced, in good yield, by hydrogenolysis on palladium or reduction with chromous chloride or zinc dust, but oxidation of the 3-hydroxyl group in the unsaturated compound (XVI) by the standard procedure [23] (potassium dichromate–sulphuric acid in acetone) led to substantial degradation of the steroid. The 3-hydroxyl group of the dichloro-compound (XVa) was therefore oxidised, before removal of the protective chlorine atoms, with chlorine in acetic acid in the presence of a buffer. This procedure has been described [24] for selective oxidation in the 20-position of 5,6-dichloropregnane-3,20-diols, but this appears to be its first use for preparation of a 3-ketone from a 3-hydroxy-compound. Finally, 9,11-unsaturation was reintroduced, as before, by hydrogenolysis or by zinc dust and acetic acid, the latter giving a yield of 93% over both stages.

Experimental

M. p.s were determined with capillary tubes in an electrically heated block and are corrected. Optical rotations refer to *ca.* 1% chloroform solutions at 20°. Infrared spectra are for solutions in CS_2 unless otherwise stated, determined with a Perkin–Elmer model 21 double-beam spectrophotometer equipped with rock-salt optics.

3β-*Acetoxy*-16β(H)-1′-*pyrazolino*(4′,3′:16,17)-5α-*pregn*-9-*en*-20-*one* (II).—*N*-Nitrosomethylurea (80 g.) was added to a solution of 3β-acetoxy-5α-pregna-9,16-dien-20-one (104 g.) in methylene chloride (1·0 l.). A 50% aqueous solution (160 ml.) of potassium hydroxide was added at −5° during 30 min. and the reaction allowed to become complete at room temperature during 2 hr. Water (1·5 l.) was added slowly and the mixture was stirred for 15 min. in order to discharge any excess of diazomethane. The layers were separated; the aqueous phase was extracted with methylene chloride (1 × 300 ml.), and the organic phase washed with water (3 × 350 ml.), the methylene chloride extract being used as a back-wash. The residue obtained by distillation of the combined methylene chloride solutions was triturated with light petroleum (750 ml.; b. p. 100—120°). The resulting solid was dried *in vacuo* at 100° to give the *pyrazoline* (106·5 g., 92%), m. p. 158° (decomp.), $[\alpha]_D$ +72°, $\lambda_{max.}$ 229 mμ (ε 1167) (Found: C, 72·2; H, 8·9; N, 6·9. $C_{24}H_{34}N_2O_3$ requires C, 72·4; H, 8·6; N, 7·0%).

3β-*Acetoxy*-16-*methyl*-5α-*pregna*-9,16-*dien*-20-*one* (III).—The pyrazoline (II) (222 g.) was added portionwise in 25 min. with stirring to diethylene glycol (880 ml.) at 165°. When nitrogen evolution had stopped at this temperature the mixture was cooled to 100° and water (3·0 l.)

[20] Pataki, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1952, **74**, 5615.
[21] B.P. 761,009.
[22] B.P. 762,716.
[23] Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402.
[24] U.S.P. 2,811,522.

added. The crude product crystallised from ethanol to yield 3β-*acetoxy*-16-*methyl*-5α-*pregna*-9,16-*dien*-20-*one* (146 g., 71%), m. p. 139—142°, $[\alpha]_D$ +53°, $\lambda_{max.}$ 249 mμ (ε 8595), $\nu_{max.}$ 1735 and 1240 (OAc), 1658 (CO·C=C), and 820 cm.$^{-1}$ (9-C=C) (Found: C, 77·6; H, 9·3. $C_{24}H_{34}O_3$ requires C, 77·8; H, 9·2%).

3β-*Acetoxy*-16β-*methyl*-5α-*pregn*-9-*en*-20-*one* (V).—(a) *From* 3β-*acetoxy*-16-*methyl*-5α-*pregna*-9,16-*dien*-20-*one* (III). The diene (2·0 kg.) in tetrahydrofuran (12 l.) and triethylamine (2·0 l.) was hydrogenated at atmospheric pressure over 10% palladium oxide on charcoal (170 g.). When the hydrogen uptake ceased (139·8 l. in 150 min.) the catalyst and solvent were removed. The residue crystallised from methanol to give a product (1999 g.), m. p. 106—110°, $[\alpha]_D$ +30·2°. This generally contained *ca.* 3% of 9,11-saturated compound (estimated by the 820 cm.$^{-1}$ maximum and by peracid titration) which it was impossible to remove by crystallisation at this stage. The pure product was obtained by dechlorination of the corresponding 9α,11β-dichloro-compound as described in experiment (b).

(b) *From* 3β-*acetoxy*-9α,11β-*dichloro*-16β-*methyl*-5α-*pregnan*-20-*one* (IV). The dichloroketone (50 g.) in acetone (1·0 l.) and water (100 ml.) under a rigorously maintained atmosphere of carbon dioxide was treated with 2·3N-chromous chloride (300 ml.) at room temperature for 30 min. The product, isolated by dilution with water, recrystallised from methanol as plates (31·3 g., 74·5%), m. p. 113—115°, $[\alpha]_D$ +34·2°. A sample, recrystallised from methanol, gave 3β-*acetoxy*-16β-*methyl*-5α-*pregn*-9-*en*-20-*one*, m. p. 114—115°, $[\alpha]_D$ +32·7° (Found: C, 77·4; H, 9·75. $C_{24}H_{36}O_3$ requires C, 77·4; H, 9·75%), $\nu_{max.}$ 1735 and 1245 (OAc), 1708 (C=O) and 822 cm.$^{-1}$ (9-C=C) (Δ^9-bond 99·3% by peracid titration).

3β-*Acetoxy*-16β-*methyl*-5α-*pregnan*-20-*one* (VI).—3β-Acetoxy-16β-methyl-5α-pregn-9-en-20-one (V) (1·3 g.) in acetic acid (52 ml.) was hydrogenated over pre-reduced 10% palladium–charcoal (0·92 g.). Hydrogen uptake (~1 mol.) was complete in 1½ hr. Removal of the catalyst, concentration of the filtrate under reduced pressure, and precipitation of the product with water gave 3β-acetoxy-16β-methyl-5α-pregnan-20-one (1·33 g.), m. p. 148—151°, $[\alpha]_D$ +30° (cf. ref. 8 which gives m. p. 148°, $[\alpha]_D$ +29·5°).

3β-*Acetoxy*-9α,11β-*dichloro*-16β-*methyl*-5α-*pregnan*-20-*one* (IV).—A solution of 3β-acetoxy-16β-methyl-5α-pregn-9-en-20-one (V) (1·89 kg.) in methylene chloride (20·0 l.) was stirred with 10% sodium acetate solution (2 l.) and cooled in ice–salt. Chlorine was passed in during 10½ min. at 11·6 l./min. Excess of chlorine appeared in the solution at this time, and the gas flow was continued for a further 1 min. The temperature of the mixture rose from 5·5° to 18·5°. Sodium hydrogen carbonate (500 g.) in water (5·0 l.) was added and the mixture stirred until the excess of chlorine had disappeared. The organic layer was washed with water and evaporated to dryness at room temperature. The crystalline residue recrystallised from boiling acetone (10·0 l.) to which water (3·0 l. at 55°) was added, to give the crude product (1·965 kg., 83·3%), m. p. 164—165°, $[\alpha]_D$ +46·4°. Recrystallisation from ethyl acetate gave the 9α,11β-*dichloro-ketone*, m. p. 168—169°, $[\alpha]_D$ +48·8° (Found: C, 65·0; H, 8·3; Cl, 16·1. $C_{24}H_{36}Cl_2O_3$ requires C, 65·0; H, 8·2; Cl, 16·0%), $\nu_{max.}$ 1732 and 1240 (OAc), 1710 (C=O), and 750 and 660 cm.$^{-1}$ (9,11-Cl_2).

3β-*Acetoxy*-16β-*methyl*-5α-*pregna*-9,17-*dien*-20-*ol* (VIII).—A solution of 3β-acetoxy-16-methyl-5α-pregna-9,16-dien-20-one (100 g.) in tetrahydrofuran (1200 ml.) and triethylamine (200 ml.) was hydrogenated over 10% palladised charcoal (8·5 g.) (uptake 6·5 l. in 9 min.). The solution was filtered cold and evaporated to a dry solid without excessive heating. The residue was suspended in acetone (200 ml.) and the insoluble material filtered off, washed with acetone (3 × 50 ml.), and dried at 60° *in vacuo* to give the crude product (27·8 g.), m. p. 133—136°. A further treatment with boiling acetone (500 ml.) gave the *enol* (VIII) (20·8 g., 20·7%), m. p. 134—140°, $[\alpha]_D$ +30·6°, +30·3° (in dioxan) (Found: C, 77·3; H, 9·7; active H, 0·21. $C_{24}H_{36}O_3$ requires C, 77·4; H, 9·7; active H, 0·27%). The ultraviolet spectrum showed a rapidly increasing absorption at decreasing wavelength; at 220 mμ $E^{1\%}_{1\,cm.}$ was 102. $\nu_{max.}$ (Nujol) were at 3480 (bonded OH), 1716 and 1265 (OAc), 824 (>C=CH–), and 1690 cm.$^{-1}$ (O·C=C). The specimen was stable in Nujol but changed steadily in CS_2. As a comparison 3β-acetoxy-16β-methyl-5α-pregn-9-en-20-one showed no active H, and at 220 mμ $E^{1\%}_{1\,cm.}$ was 5; no 3480 cm.$^{-1}$ band was visible.

When the enol was heated at 100° *in vacuo* for 2 hr. it slowly sintered but it solidified on cooling. A sample recrystallised from methanol then had m. p. 111—115°, $[\alpha]_D$ +20·1°; the infrared spectrum showed it to be a mixture of 17α- and 17β-20-ketones.

Mild Acetylation of the Enol.—The enol (2·0 g.) was suspended in dry pyridine (5·0 ml.) and

acetic anhydride (5·0 ml.) under nitrogen. After 4 hr. at room temperature, a clear solution had been formed and after a further 2 hr. this was evaporated to dryness at 40°/0·5 mm. Crystallisation of the crystalline residue from methanol gave two crops: (1) needles (0·93 g., 41·8%), m. p. 158—160°, $[\alpha]_D$ +34·1°, whose infrared spectrum suggested the presence of the enol acetate group; (2) needles (0·42 g.), m. p. 115—138°, $[\alpha]_D$ +33·7°, whose infrared spectrum showed it to be largely the 20-ketone (1712 cm.$^{-1}$). Recrystallisation of crop (1) from methanol gave the enol acetate (VIIIa) (see below), m. p. 164—166°, $[\alpha]_D$ +34°, the infrared spectrum showing the absence of ketone.

Rearrangement of the Enol.—(*a*) The enol (0·2678 g.) in air-free tetrahydrofuran under nitrogen (total vol. 20·0 ml. at 20°) showed $[\alpha]_D$ +30·6°. This solution was treated with 0·1N-sodium hydroxide in methanol (0·20 ml.). $[\alpha]_D$ fell to 22·4° in less than 30 sec. and was constant (20 min.) after that time. The solution was neutralised with aqueous 0·1N-hydrochloric acid (0·20 ml.) and evaporated to dryness *in vacuo* at room temperature. The infrared spectrum (Nujol mull) showed the product to contain <10% of hydroxyl group (3450 cm.$^{-1}$), indicating that rearrangement to the lower rotating 17α-acetyl compound (Va) as well as to (V) had occurred. (*b*) Treatment of a similar solution to that used in (*a*) with aqueous 0·1N-hydrochloric acid produced no change in the optical rotation of the solution except that due to the slight dilution. The solution was neutralised and evaporated to dryness. The infrared spectrum (Nujol mull) showed <10% of hydroxyl group (3450 cm.$^{-1}$). Rearrangement to the 17β-acetyl compound (V) had thus occurred. (*c*) A sample of the corresponding ketone (V) in tetrahydrofuran showed no change in rotation on treatment with either acid or alkali as under (*a*) and (*b*). (*d*) The enol in air-free tetrahydrofuran (1% solution) was left at room temperature for 30 min. under nitrogen. The solution was evaporated to dryness under reduced pressure at room temperature. The residue showed a slight drop in m. p. and some change in the infrared spectrum (Nujol). (*e*) Tetrahydrofuran (7·0 ml.) containing 14% v/v of triethylamine was flushed with nitrogen, and enol (0·5 g.) and activated charcoal (1·0 g.) (previously washed neutral with water and dried) were added. The suspension was stirred under nitrogen for 30 min. at room temperature, then filtered, and the filtrate was evaporated to dryness at room temperature under reduced pressure, giving a crystalline solid, m. p. 88—94°, $[\alpha]_D$ +31·8°, whose infrared spectrum (Nujol) showed <10% of enol form. Rearrangement to the 17β-acetyl compound (V) was therefore very largely complete.

Oxygenation of 3β-*Acetoxy*-16β-*methyl*-5α-*pregna*-9,17-*dien*-20-*ol* (VIII) (with Miss E. J. Bailey).—The enol (2·0 g.) was dissolved in benzene (200 ml.) by warming. The solution was cooled to room temperature and shaken with oxygen until 1 mol. had been absorbed. The benzene was removed under reduced pressure to give a white solid (2·2 g.), m. p. 120—123°, $[\alpha]_D$ +36° (in MeOH). Crystallisation from aqueous methanol gave 3β-*acetoxy*-17α-*hydroperoxy*-16β-*methyl*-5α-*pregn*-9-*en*-20-*one* (0·95 g.) in two crops. The analytical specimen had m. p. 161—164° (decomp.) (Kofler), $[\alpha]_D$ +57° (in MeOH) (Found: C, 71·1; H, 9·1. $C_{24}H_{36}O_5$ requires C, 71·5; H, 9·0%), $\nu_{max.}$ (in Nujol) 1730 and 1245 (OAc), 1700 (C=O) and 820 cm.$^{-1}$ (>C=CH–).

3β-*Acetoxy*-16β-*methyl*-5α,17α-*pregn*-9-*en*-20-*one* (Va).—3β-Acetoxy-16β-methyl-5α-pregn-9-en-20-one (V) (0·4 g.) in chloroform (20 ml.) was treated with 9·5N-hydrogen chloride in anhydrous ethanol (0·226 ml.). α_D of the solution dropped from +1·20° to −1·33° during 35 min. and then remained constant. The solution was poured into 2% sodium hydrogen carbonate solution (150 ml.), and the chloroform layer washed and evaporated to give a solid which on crystallising from 80% methanol gave the 17α-*compound* (0·23 g., 57·5%), m. p. 121°, $[\alpha]_D$ −41° (Found: C, 77·2; H, 9·9. $C_{24}H_{36}O_3$ requires C, 77·4; H, 9·75%), $\nu_{max.}$ (in CS_2) 1732 and 1240 (OAc), 1705 (C=O), and 822 cm.$^{-1}$ (9-C:C).

3β-*Acetoxy*-9α,11β-*dichloro*-16β-*methyl*-5α,17α-*pregnan*-20-*one* (IVa).—3β-Acetoxy-9α,11β-dichloro-16β-methyl-5α-pregnan-20-one (IV) (5·0 g.) in chloroform (250 ml.) was treated with 9·5N-hydrogen chloride in anhydrous ethanol (2·4 ml.). α_D of the solution fell from +1·71° to −0·13° in 2½ hr. (constant). The product (4·9 g.), m. p. 160—167°, $[\alpha]_D$ −4·2°, obtained as in the previous experiment, crystallised from 75% acetone to give 3β-*acetoxy*-9α,11β-*dichloro*-16β-*methyl*-5α,17α-*pregnan*-20-*one* as prisms, m. p. 173—174°, $[\alpha]_D$ −4·2° (Found: C, 64·9; H, 8·4; Cl, 15·85. $C_{24}H_{36}Cl_2O_3$ requires C, 65·0; H, 8·2; Cl, 16·0%), $\nu_{max.}$ 1732 and 1240 (OAc), 1705 (C=O) and 754 and 660 cm.$^{-1}$ (9,11-Cl_2).

3β,20-*Diacetoxy*-9α,11β-*dichloro*-16β-*methyl*-5α-*pregn*-17-*ene* (VII).—(a) *From* 3β-*acetoxy*-9α,11β-*dichloro*-16β-*methyl*-5α-*pregnan*-20-*one* (IV). To the 20-ketone (5·0 g.) in carbon

tetrachloride (25 ml.) was added, with stirring and cooling, acetic anhydride (17 ml.) containing 60% perchloric acid (0·35 ml.). The mixture was left at room temperature for 2 hr., then water (3·0 ml.) was added dropwise with stirring and cooling. The organic layer was washed and evaporated to a gum which, on trituration with light petroleum (b. p. 40—60°) (15 ml.) and cooling, yielded a solid (3·1 g., 56·6%), m. p. 159—163°, $[\alpha]_D$ +55·5°. Recrystallisation from light petroleum gave a product identical with the analytical specimen of the enol acetate described in experiment (b).

(b) *From* 3β,20-*diacetoxy*-16β-*methyl*-5α-*pregna*-9,17-*diene* (VIIIa) (*isomer* " *A* "; *see below*). The enol acetate (75·3 g.) in carbon tetrachloride (750 ml.) at −9° was treated with 1·96N-chlorine in carbon tetrachloride (190 ml.) during 3 min., the temperature rising to 0°. The solvent was removed under reduced pressure and the residue crystallised from light petroleum (b. p. 100—120°; 186 ml.), to give a crude product (51·5 g., 58·4%), m. p. 167—170°, $[\alpha]_D$ +53·5°. Two further crystallisations from light petroleum gave 3β,20-*diacetoxy*-9α,11β-*dichloro*-16β-*methyl*-5α-*pregn*-17-*ene* (this compound was designated *isomer* " *A* "), m. p. 174—179°, $[\alpha]_D$ +55·1° (Found: C, 64·2; H, 8·2; Cl, 14·2. $C_{26}H_{38}Cl_2O_4$ requires C, 64·3; H, 7·9; Cl, 14·6%), $\nu_{max.}$ 1745 and 1216 (enol-acetate), 1735 and 1240 (OAc), 754 and 654 cm.$^{-1}$ (9,11-Cl_2).

The corresponding 20-isomer (designated *isomer* " *B* ") was obtained in a similar manner from 3β,20-diacetoxy-16β-methyl-5α-pregna-9,17-diene (isomer " B "; see below) in 37% yield, as prisms, m. p. 179—186°, $[\alpha]_D$ +57·8° (Found: C, 64·4; H, 8·1; Cl, 14·5%), $\nu_{max.}$ 1745 and 1212 (enol acetate), 1735 and 1240 (OAc) and 752 and 650 cm.$^{-1}$ (9,11-Cl_2).

3β,20-*Diacetoxy*-16β-*methyl*-5α-*pregna*-9,17-*diene* (VIIIa).—3β-Acetoxy-16β-methyl-5α-pregn-9-en-20-one (V) (10 g.) in carbon tetrachloride (25 ml.) was treated with a mixture (8·5 ml.) of acetic anhydride (10 ml.) and 60% perchloric acid (0·05 ml.) with stirring. The solution, which darkened rapidly, was set aside for 1 hr. at room temperature and water (1·5 ml.) was then added with cooling and stirring. The organic layer was washed and evaporated under reduced pressure (finally from methanol), to give crystals (8·30 g., 74·6%), m. p. 148—157°, $[\alpha]_D$ +33·8°. Recrystallisation several times from acetone gave 3β,20-*diacetoxy*-16β-*methyl*-5α-*pregna*-9,17-*diene*, m. p. 162—165°, $[\alpha]_D$ +34·2° (Found: C, 75·4; H, 9·3. $C_{26}H_{38}O_4$ requires C, 75·3; H, 9·2%), $\nu_{max.}$ (in CS_2) 1745 and 1225 (enol acetate), 1735 and 1240 (OAc), 822 (9-C:C) and 1696 cm.$^{-1}$ ($\Delta^{17(20)}$). This compound was designated isomer " A ".

From a similar experiment (20-g. scale) a second crop (3·14 g., 14·1%) of low-melting solid with $[\alpha]_D$ +38·3° was obtained which after three recrystallisations from methanol gave a compound formulated as the 20-stereoisomer of (VIIIa), m. p. 120—136°, $[\alpha]_D$ +45·8° (in $CHCl_3$) (Found: C, 75·2; H, 9·4%). This compound was designated *isomer* " *B*."

3β,20-*Diacetoxy*-9α,11β-*dichloro*-17α,20-*epoxy*-16β-*methyl*-5α-*pregnane* (IX).—3β,20-Diacetoxy-9α,11β-dichloro-16β-methylpregn-17-ene (VII) (10 g.) (isomer " A ") in chloroform (25 ml.) was treated with 2·4N-monoperphthalic acid in ether (26·5 ml.) at room temperature. The temperature rose to 26·5° after ¾ hr. Next morning the precipitated phthalic acid was filtered off and dissolved in aqueous 2N-sodium hydroxide (24 ml.), and this solution was extracted with chloroform. The combined organic layers were worked up as usual. The product crystallised from acetone (100 ml.) to give a first crop (8·54 g., 82·7%), m. p. 163—165°, $[\alpha]_D$ +68·0°, and a second crop (0·82 g., 7·94%), m. p. 161—162°, $[\alpha]_D$ +61·3°. A sample was recrystallised from acetone to give the 17α,20-*epoxide* (" *A* " *isomer*) as prisms, m. p. 164—165°, $[\alpha]_D$ +68·0° (Found: C, 62·2; H, 7·9; Cl, 14·2. $C_{26}H_{38}Cl_2O_5$ requires C, 62·3; H, 7·6; Cl, 14·1%), $\nu_{max.}$ 1755 and 1240 (epoxy-acetate), 1742 and 1240 (OAc), and 750 and 658 cm.$^{-1}$ (9,11-Cl_2).

The " B " isomer of the enol acetate was epoxidised similarly, to yield the 17α,20-*epoxide* (" *B* " *isomer*), m. p. 180—181°, $[\alpha]_D$ +48·2° (Found: C, 61·8; H, 7·8; Cl, 13·9%), $\nu_{max.}$ 1755 and 1240, 1742 and 1240, and 750 and 658 cm.$^{-1}$. The spectra of the isomers differed in the finger-print region.

9α,11β-*Dichloro*-3β,17-*dihydroxy*-16β-*methyl*-5α-*pregnan*-20-*one* (XII) *from* 3β,20-*Diacetoxy*-9α,11β-*dichloro*-17α,20-*epoxy*-16β-*methyl*-5α-*pregnane* (IX).—(a) *From the* " *A* " *isomer*. The dichloro-diacetate epoxide (10 g.) was left in glacial acetic acid (600 ml.) containing concentrated sulphuric acid (2·95 ml.) and water (20 ml.) at room temperature for 3 hr., then poured into water (2 l.). The steroid was extracted with methylene chloride which was evaporated off under reduced pressure and replaced by light petroleum (b. p. 100—120°). This gave needles (7·2 g., 78·6%), m. p. 180° (decomp.), $[\alpha]_D$ +46°. A sample recrystallised from acetone

gave 3β-*acetoxy*-9α,11β-*dichloro*-17-*hydroxy*-16β-*methyl*-5α-*pregnan*-20-*one* (XIIa), m. p. 183° (decomp.), $[\alpha]_D$ +46·5°, +65·5° (in dioxan) (Found: C, 63·05; H, 7·8; Cl, 15·5. $C_{24}H_{36}Cl_2O_4$ requires C, 62·7; H, 7·9; Cl, 15·4%), $\nu_{max.}$ (in CS_2) 1738 and 1240 (OAc), 1710 and 1678 cm.$^{-1}$ (20-C=O).

This acetate (5·0 g.) in methylene chloride (62·5 ml.) and methanol (54 ml.) was mixed with a solution of concentrated sulphuric acid (11·25 ml.) in water (11·25 ml.) and methanol (54 ml.), then kept at room temperature for 16 hr. The crystalline product was filtered off, washed, and dried *in vacuo* at 60° {0·69 g., 15·2%; m. p. 196° (decomp.), $[\alpha]_D$ +75·2° (in dioxan)}. Diluting the filtrate with water gave a further precipitate (3·05 g., 67·1%), m. p. 198° (decomp.), $[\alpha]_D$ +75·4° (in dioxan). A sample recrystallised from tetrahydrofuran gave the 3β,17-*diol*, m. p. 207° (decomp.), $[\alpha]_D$ +77·1° (in dioxan) (Found: C, 63·2; H, 8·2; Cl, 16·8. $C_{22}H_{24}Cl_2O_3$ requires C, 63·3; H, 8·2; Cl, 17·0%), $\nu_{max.}$ (in Nujol) 1684 (C=O) and 752 and 662 cm.$^{-1}$ (9,11-Cl_2).

The epoxide diacetate (" A " isomer) was also hydrolysed directly to the 3β,17-*diol* in aqueous methanol–sulphuric acid as above, or better by treating a solution (5·0 g.) in methylene chloride (25 ml.) with potassium hydroxide (1·32 g.) in methanol (35 ml.) and water (2·0 ml.) for 1½ hr. at room temperature. The crystalline product was dried *in vacuo* at 60° {4·02 g., 96·5%; m. p. 200—203° (decomp.), $[\alpha]_D$ +75° (in dioxan)}; its infrared spectrum was identical with that of the authentic specimen.

(b) *From the " B " isomer.* The epoxide diacetate " B " isomer was treated with aqueous methanol–sulphuric acid as for the 3-acetate above, yielding the 3β,17-diol (86%), m. p. 196° (decomp.), $[\alpha]_D$ +76·8° (in dioxan), identical in its infrared spectrum with the authentic specimen.

3β-*Acetoxy*-17aβ-*hydroxy*-16ξ,17aα-*dimethyl*-D-*homo*-5α-*pregn*-9-*en*-17-*one* (XIX).—3β,17-Dihydroxy-16β-methyl-5α-pregn-9-en-20-one (XIII) (1·0 g.) was added to methanol (10 ml.) containing 50% aqueous sulphuric acid (0·2 ml.), and the solution refluxed for 10 hr. The clear solution was poured into water (120 ml.), and the product isolated with chloroform. The solvent was evaporated under reduced pressure and the residual gum was left in pyridine (3 ml.) and acetic anhydride (3 ml.) at 60° for 1 hr. This gave (after three crystallisations from methanol) the D-*homo-steroid* (0·218 g.), m. p. 153—155°, $[\alpha]_D$ −81° (in dioxan) (Found: C, 74·4; H, 9·4. $C_{24}H_{36}O_4$ requires C, 74·3; H, 9·35%), $\nu_{max.}$ 1732 and 1240 (OAc), 1708 (C=O), and 820 cm.$^{-1}$ (9-C=C).

3β-*Acetoxy*-17-*hydroxy*-16β-*methyl*-5α-*pregn*-9-*en*-20-*one* (XIIIa).—10% Palladium oxide on charcoal (1·4 g.) was prereduced under hydrogen in tetrahydrofuran (35 ml.). 3β-Acetoxy-9α,11β-dichloro-17-hydroxy-16β-methyl-5α-pregnan-20-one (XIIa) (7·0 g.) in tetrahydrofuran (70 ml.) containing triethylamine (6·35 ml.) was then added and hydrogenation continued until uptake ceased (392 ml., 1·045 mol.) after 35 min. The catalyst was filtered off and washed with methylene chloride, and the combined filtrate and washings were washed with water. Evaporation of the organic phase gave a product (4·11 g., 69·5%), m. p. 175—177° (from methanol), $[\alpha]_D$ +32·6° (dioxan). Two further crystallisations gave 3β-*acetoxy*-17-*hydroxy*-16β-*methyl*-5α-*pregn*-9-*en*-20-*one* as plates (2·96 g., 42%), m. p. 177—179°, $[\alpha]_D$ +3·9°, +34·1° (in dioxan) (Found: C, 73·9; H, 9·45. $C_{24}H_{36}O_4$ requires C, 74·2; H, 9·35%), $\nu_{max.}$ 1735 and 1240 (OAc), 1710 and 1680 (20-C=O), and 820 cm.$^{-1}$ (9-C=C).

3β,17-*Dihydroxy*-16β-*methyl*-5α-*pregnan*-20-*one* (XIV).—10% Palladium oxide on charcoal (0·7 g.) was prereduced under hydrogen in glacial acetic acid. 3β-Acetoxy-17-hydroxy-16β-methyl-5α-pregn-9-en-20-one (XIIIa) (1·0 g.) was added in acetic acid (30 ml.) and hydrogenation continued until the uptake ceased (21 hr.; 66·5 ml., 1·05 mol.). The catalyst was filtered off and the product precipitated with water, collected, washed, and dried (0·96 g.; m. p. 161—163°). Two crystallisations from methanol afforded 3β-acetoxy-17-hydroxy-16β-methyl-5α-pregnan-20-one (XIVa) (0·65 g.), m. p. and mixed m. p. 162—164°, $[\alpha]_D$ +38·5° (in dioxan), $\nu_{max.}$ 1735 and 1245 (OAc), and 1712 and 1680 cm.$^{-1}$ (C=O) (cf. the authentic specimen, m. p. 164—166°). We are indebted to Schering Corporation for authentic samples of compounds (XIV) and (XIVa).

The 3β-acetate (0·43 g.) was hydrolysed by refluxing it in methanol (25·5 ml.) containing water (5·1 ml.) and potassium hydrogen carbonate (0·255 g.) for 1 hr. The product (0·375 g., 97·7%) was isolated by precipitation but could not be purified by crystallisation. The crude material was kept overnight in methanol (40 ml.) containing 50% aqueous sulphuric acid (5·1 ml.). The crystalline product which separated was filtered off, washed, and dried to give

the saturated diol (XIV) (0·25 g., 65·2%), m. p. and mixed m. p. 216—221°, $[\alpha]_D$ +45·5° (in dioxan) (Found: C, 75·6; H, 10·3. Calc. for $C_{22}H_{36}O_3$: C, 75·8; H, 10·4%), $\nu_{max.}$ (in Nujol) 1690 cm.$^{-1}$ (C=O) (authentic specimen, m. p. 212—217°, $[\alpha]_D$ +43° in dioxan).

17β-*Acetoxy*-9α,11β-*dichloro*-3β-*hydroxy*-16β-*methyl*-5α,17α-*pregnan*-20-*one* (X).—The mother-liquors from the acid-catalysed hydrolysis in aqueous methanol of 3β,20-diacetoxy-9α,11β-dichloro-17α,20-epoxy-16β-methyl-5α-pregnane (isomer "A") (IX) (113 g.) were evaporated under reduced pressure to remove as much of the remaining methylene chloride as possible. The residual gum was refluxed with ethyl acetate, and the precipitated white solid (7·47 g.) filtered off and washed with hot ethyl acetate. This material, m. p. 187—193° (decomp.), $[\alpha]_D$ +64° (dioxan), was identified as the dichloro-diol (XII) by its constants and infrared spectrum. The filtrate was cooled and allowed to crystallise {6·6 g., 6·38%; m. p. 200—203° (decomp.), $[\alpha]_D$ +49° (in dioxan)}. Recrystallisation from ethyl acetate–methylene chloride (1 : 1) gave the 17β-*acetate* as flat needles, m. p. 203—204° (decomp.), $[\alpha]_D$ +47° (dioxan) (Found: C, 62·8; H, 7·7; Cl, 15·3. $C_{24}H_{36}Cl_2O_4$ requires C, 62·7; H, 7·9; Cl, 15·4%), $\nu_{max.}$ 1738 and 1244 (OAc), 1710 (C=O), and 670 and 758 cm.$^{-1}$ (9,11-Cl_2) (absence of the 17-hydroxy-20-oxo-system).

3β,17β-*Diacetoxy*-9α,11β-*dichloro*-16β-*methyl*-5α,17α-*pregnan*-20-*one* (Xa).—(a) *From* 17β-*acetoxy*-9α,11β-*dichloro*-3β-*hydroxy*-16β-*methyl*-5α,17α-*pregnan*-20-*one* (X). The steroid (4·37 g.) was suspended in carbon tetrachloride (30 ml.), and acetic anhydride (10 ml.) containing 60% perchloric acid (0·03 ml.) was added. The mixture was shaken for 3 min., the starting material dissolving and the product separating. The mixture was left for 12 min. and water (1·3 ml.) was slowly added while the temperature was kept below 45°. The product (4·0 g.) was filtered off and washed with acetone. Crystallisation of this material (3·0 g.) from methylene chloride–acetone gave the 3β,17β-*diacetate* as prisms (2·59 g., 72·4%), m. p. 229—232° (decomp.), $[\alpha]_D$ +34° (Found: C, 62·2; H, 7·7; Cl, 14·1. $C_{26}H_{38}Cl_2O_5$ requires C, 62·3; H, 7·6; Cl, 14·1%), $\nu_{max.}$ (in Nujol) 1738—1730 and 1254—1240 (OAc), 1710 (C=O), and 756 and 664 cm.$^{-1}$ (9,11-Cl_2).

(b) *From* 3β,20-*diacetoxy*-9α,11β-*dichloro*-17α,20-*epoxy*-16β-*methyl*-5α-*pregnane* (*isomer "A"*) (IX) *by acid catalysis*. The diacetate epoxide (13·0 g.) in methylene chloride (52 ml.) was treated with acetic acid (720 ml.) containing concentrated sulphuric acid (3·8 ml.) and water (13 ml.) at room temperature for 3 hr., after dilution of the solution with water and extraction with chloroform, a crystalline product (6·78 g., 56·9%) was obtained by adding light petroleum (b. p. 100—120°) to the chloroform extract and cooling it at −5° overnight. This was identified as 3β-acetoxy-9α,11β-dichloro-17-hydroxy-16β-methyl-5α-pregnan-20-one (XIIa) by its constants {m. p. 181—183° (decomp.), $[\alpha]_D$ +65° (in dioxan), and infrared spectrum}. A second crop (4·15 g., 34·9%) had m. p. 171—176° (decomp.), $[\alpha]_D$ +59·6° (in dioxan), and an infrared spectrum showing it to be a mixture of the above 3β-acetate and the 3β,17β-diacetate (Xa). This mixture was refluxed with acetone and the insoluble material discarded. Three crops (total 1·25 g.) obtained from the filtrate recrystallised from acetone to give the 3β,17β-diacetate, m. p. 219° (decomp.), $[\alpha]_D$ +34·5°, +42° (in dioxan) (correct infrared spectrum).

(c) *From* 3β,20-*diacetoxy*-9α,11β-*dichloro*-17α,20-*epoxy*-16β-*methyl*-5α-*pregnane* (isomer "*A*") (IX) *by heat*. The diacetate epoxide (6·5 g.) was heated in an open boiling-tube at 185° for 10 min. with stirring. The solid melted slowly to a cloudy liquid and then began to recrystallise. The cold mixture was suspended in acetone. The insoluble material was filtered off, washed with acetone, and recrystallised from acetone–methylene chloride, to give the 3β,17β-diacetate (1·3 g., 20%), m. p. 226° (decomp.), $[\alpha]_D$ +36·5° (correct infrared spectrum).

3β,17-*Diacetoxy*-9α,11β-*dichloro*-16β-*methyl*-5α-*pregnan*-20-*one* (XIIb).—9α,11β-Dichloro-3β,17-dihydroxy-16β-methyl-5α-pregnan-20-one (XII) (5·0 g.) was suspended in carbon tetrachloride (30 ml.), and acetic anhydride (10 ml.) containing 60% w/w perchloric acid (0·03 ml.) was added. The mixture was shaken for 3 min. and left for 12 min. at room temperature. Water (1·3 ml.) was added slowly, the temperature being kept below 45°. The solution was washed and evaporated. The yellow residue recrystallised from acetone as needles (3·11 g., 51·8%), m. p. 170—190° (decomp.), $[\alpha]_D$ +60°. A second recrystallisation from acetone gave the 3β,17-*diacetate* as needles (1·08 g., 18·0%), m. p. 225—228° (decomp.), $[\alpha]_D$ +59·5° (Found: C, 62·3; H, 7·7; Cl, 14·4%), $\nu_{max.}$ 1735 and 1240 (OAc), 1718 (C=O), and 754 and 662 cm.$^{-1}$ (9,11-Cl_2).

3β,17β-*Diacetoxy*-16β-*methyl*-5α,17α-*pregn*-9-*en*-20-*one* (XIa).—17β-Acetoxy-9α,11β-dichloro-3β-hydroxy-16β-methyl-5α,17α-pregnan-20-one (X) (4·0 g.), suspended in acetic acid (39 ml.) containing sodium acetate (2·3 g.), was stirred with zinc dust (7·7 g.; washed with mineral acid,

water, and methanol and dried) at 24—30° for 4 hr. The zinc was filtered off and water added to the filtrate to precipitate the 3-hydroxy-compound (3·17 g., 93·7%), m. p. 215—217°, $[\alpha]_D$ +5°. The 3β-hydroxyl group was acetylated in pyridine (10 ml.) and acetic anhydride (5 ml.) at 50° for 1 hr., to give the crude *diacetate* (3·25 g., 98%), m. p. 154—155°, $[\alpha]_D$ +8·3° (in dioxan). The pure compound was obtained, after two recrystallisations from methanol, as prisms, m. p. 156—157°, $[\alpha]_D$ +6·2°, +9·6° (in dioxan) (Found: C, 72·5; H, 9·0. $C_{26}H_{38}O_5$ requires C, 72·6; H, 9·0%), $\nu_{max.}$ 1738 and 1246 (OAc), 1716 (C=O) and 822 cm.$^{-1}$ (9-C:C).

3β,17-*Diacetoxy*-16β-*methyl*-5α-*pregn*-9-*en*-20-*one* (XIIIb).—3β,17-Diacetoxy-9α,11β-dichloro-16β-methyl-5α-pregnan-20-one (XIIb) (6·0 g.) was treated with zinc dust as in the previous experiment, to give the Δ^9-*compound*, m. p. 156—158°, $[\alpha]_D$ +23·2°, +20° (in dioxan) (Found: C, 72·3; H, 8·9%), $\nu_{max.}$ 1736 and 1246 (OAc), 1722 (C=O), and 822 cm.$^{-1}$ (9-C:C).

21-*Acetoxy*-9α,11β-*dichloro*-3β,17-*dihydroxy*-16β-*methyl*-5α-*pregnan*-20-*one* (XVa).—A 9·2N-solution (110 ml.) of hydrogen chloride in ethanol was added to a suspension of 9α,11β-dichloro-3β,17-dihydroxy-16β-methyl-5α-pregnan-20-one (XII) (60 g.) in chloroform (1·2 l.) and the mixture stirred for 15 min. Bromine (23·5 g.) in chloroform (150 ml.) was then added at such a rate that the bromine was never in great excess. Saturated aqueous sodium hydrogen carbonate solution (920 ml.) was cautiously added and the precipitate was isolated and dried at 45° for 15 hr., to give 21-bromo-9α,11β-dichloro-3β,17-dihydroxy-16β-methyl-5α-pregnan-20-one (57·6 g., 81%), m. p. 185° (decomp.), $[\alpha]_D$ +89° (*c* 0·5 in dioxan). Total halogen: 7·622 mg. gave 7·3% of Ag halide; $C_{22}H_{33}BrCl_2O_3$ requires 7·3%.

The 21-bromide (57·6 g.) was refluxed in acetone (1·3 l.) with anhydrous potassium acetate (142 g.) for 2 hr. The inorganic salts were removed by filtration of the hot solution, the filtrate concentrated to low bulk under reduced pressure, and the product precipitated by addition of water (1·2 l.), yielding 21-*acetoxy*-9α,11β-*dichloro*-3β,17-*dihydroxy*-16β-*methyl*-5α-*pregnan*-20-*one* (55 g.), m. p. 167° (decomp.), $[\alpha]_D$ +95° (in dioxan). Recrystallisation from acetonitrile gave pure material, m. p. 173° (decomp.), $[\alpha]_D$ +100° (in dioxan) (Found: Cl, 14·65. $C_{24}H_{36}O_5Cl_2$ requires Cl, 14·95%). $\nu_{max.}$ (in Nujol) 1735 and 1264 (21-OAc), 1718 (20-C=O), and 754 and 668 cm.$^{-1}$ (9,11-Cl_2).

Dechlorination of 21-*Acetoxy*-9α,11β-*dichloro*-3β,17-*dihydroxy*-16β-*methyl*-5α-*pregnan*-20-*one* (XVa).—(a) *By palladium–charcoal.* The dichloro-compound (57·6 g.) in tetrahydrofuran (290 ml.), water (29 ml.), and triethylamine (49 ml.) was hydrogenated on 10% palladium–charcoal (14 g.) (uptake, 285 ml. in 50 min.). The catalyst was filtered off and the product precipitated by addition of water (1·0 l.) to the concentrated filtrate, and was dried at 40—45° for 16 hr., to yield 21-*acetoxy*-3β,17-*dihydroxy*-16β-*methyl*-5α-*pregn*-9-*en*-20-*one* (XVI) (48·3 g., 98%), m. p. 192—194°, $[\alpha]_D$ +59° (*c* 0·5 in dioxan). Material recrystallised from methanol and again from ethyl acetate had m. p. 197—198°, $[\alpha]_D$ +61·8° (*c* 0·5 in dioxan) (Found: C, 71·1; H, 9·0. $C_{24}H_{36}O_5$ requires C, 71·3; H, 9·0%), $\nu_{max.}$ (in $CHBr_3$) 1744 and 1236 (21-OAc), 1726 (20-C=O), and 820 cm.$^{-1}$ (9-C:C), $\nu_{max.}$ (in Nujol) 1746 and 1236, 1722, and 820 cm.$^{-1}$. When the sample was precipitated from acetic acid by water and dried at 60° *in vacuo* the bands in the Nujol spectrum were displaced to 1728 and 1266 (21-OAc), 1728 (20-C=O), and 818 cm.$^{-1}$ (9-C:C), and the bromoform spectrum showed the presence of water at 1600 cm.$^{-1}$.

(b) *By chromous chloride.* 2·2N-Chromous chloride (2·0 ml.) was added to the dichloro-ketone (1·0 g.) in acetic acid (10 ml.) under an inert atmosphere. The solution was poured into water (100 ml.), and the product extracted in methylene chloride (2 × 50 ml.). The bulked extracts were washed with sodium hydrogen carbonate solution (2 × 50 ml.) and water (2 × 50 ml.). The solvent was distilled off under reduced pressure and the residue diluted with water (50 ml.). The solid was collected and dried *in vacuo* at 100°, to give 21-acetoxy-3β,17α-dihydroxy-16β-methyl-5α-pregn-9-en-20-one (0·72 g.), m. p. 183—189°, $[\alpha]_D$ +63° (*c* 0·48 in dioxan).

(c) *By zinc dust.* The dichloro-compound (1 g.) in acetic acid (25 ml.) was stirred with zinc dust (0·2 g.) at room temperature overnight. The product (0·57 g.), isolated by dilution with water (250 ml.), had m. p. 186—194°, $[\alpha]_D$ +62° (*c* 0·5 in dioxan).

21-*Acetoxy*-9α,11β-*dichloro*-17-*hydroxy*-16β-*methyl*-5α-*pregnane*-3,20-*dione* (XVII).—Anhydrous sodium acetate (52·8 g.) in acetic acid (880 ml.) was stirred with 21-acetoxy-9α,11β-dichloro-3β,17-dihydroxy-16β-methyl-5α-pregnan-20-one (50 g.) in methylene chloride (208 ml.) while chlorine gas was bubbled in at room temperature until 2 mol. had been absorbed (10 min.). The reaction was completed by stirring the mixture for ½ hr. and then setting it aside overnight at room temperature. Water (830 ml.) was added, the organic layer separated, and the aqueous

layer extracted with methylene chloride (3 × 125 ml.). The extracts were bulked and the resulting solution was washed with 1% aqueous sodium pyrosulphite solution (1 × 400 ml.), water (2 × 25 ml.), aqueous sodium hydrogen carbonate (1 × 250 ml.), and water (1 × 250 ml.). The solvent was evaporated under reduced pressure until crystallisation commenced; light petroleum (b. p. 100—120°; 100 ml.) was added and then the evaporation of the methylene chloride was completed. The solid was filtered off and dried *in vacuo* at 60° for 4 hr., to yield 21-*acetoxy*-9α,11β-*dichloro*-17-*hydroxy*-16β-*methyl*-5α-*pregnane*-3,20-*dione* (46·5 g.), m. p. 180° (decomp.), $[\alpha]_D$ +102° (in dioxan) (Found: C, 60·7; H, 7·3; Cl, 15·4. $C_{24}H_{34}Cl_2O_5$ requires C, 60·9; H, 7·2; Cl, 15·0%).

21-*Acetoxy*-17-*hydroxy*-16β-*methyl*-5α-*pregn*-9-*ene*-3,20-*dione* (XVIII).—(a) *By oxidation of* 21-*acetoxy*-3β,17-*dihydroxy*-16β-*methyl*-5α-*pregn*-9-*en*-20-*one* (XVI). The steroid (2·0 g.) in acetone at 50° was agitated and treated with an oxidising mixture (6·1 ml., from 110·8 g. of potassium dichromate per l. of 3N-sulphuric acid) for 15 min. The mixture was concentrated to ~15 ml. and water (200 ml.) added to precipitate the crude product (1·80 g.), m. p. 184—189°. Recrystallisation from acetone gave pure 21-*acetoxy*-17-*hydroxy*-16β-*methyl*-5α-*pregn*-9-*ene*-3,20-*dione*, m. p. 191—193°, $[\alpha]_D$ +81° (*c* 0·5 in dioxan), R_F 0·63 (Zaffaroni-type system) (Found: C, 71·4; H, 8·8. $C_{24}H_{34}O_5$ requires C, 71·6; H, 8·5%), $\nu_{max.}$ 1744 and 1230 (21-OAc), 1726 (20-C=O), and 1706 cm.$^{-1}$ (C=O).

(b) *By dechlorination of* 21-*acetoxy*-9α,11β-*dichloro*-17-*hydroxy*-16β-*methyl*-5α-*pregnane*-3,20-*dione* (XVII). The steroid (10·6 g.) in tetrahydrofuran (106 ml.), dimethylacetamide (120 ml.), and triethylamine (9·27 ml.) was hydrogenated with 5% palladium oxide on kieselguhr (5·3 g.) at atmospheric pressure. Hydrogen uptake (650 ml.) stopped after 30 min. The catalyst was filtered off, the tetrahydrofuran evaporated under reduced pressure, and the product precipitated by water (620 ml.), to give 21-acetoxy-17-hydroxy-16β-methyl-5α-pregn-9-ene-3,20-dione (8·43 g.), m. p. 189—193°, $[\alpha]_D$ +81·2° (*c* 0·5 in dioxan). The infrared spectrum resembled that of the specimen described for experiment (*a*).

Alternatively, 21-acetoxy-9α,11β-dichloro-17-hydroxy-16β-methyl-5α-pregnane-3,20-dione (75 g.) in acetic acid (560 ml.) and methylene chloride (188 ml.) containing anhydrous sodium acetate (47 g.) was stirred with acid-washed zinc dust (150 g.) at 55° for 45 min. The zinc was filtered off from the hot solution and washed with a mixture of acetic acid (50 ml.) and methylene chloride (100 ml.). The combined filtrate and washings were evaporated under reduced pressure to remove the methylene chloride, and the product was precipitated by water (560 ml.), filtered off, washed with water, and dried at 100° *in vacuo* giving 61·0 g. (95·7%) of material, m. p. 186—188°, $[\alpha]_D$ +80·5°.

The authors are indebted to Dr. J. E. Page for interpreting the infrared spectra, also to Messrs. H. A. Crisp, R. E. Grigg, and L. A. Wetherill for experimental assistance.

GLAXO LABORATORIES LTD., GREENFORD, MIDDLESEX. [*Received, April 14th*, 1961.]