809. *Modified Steroid Hormones. Part IV.* 6-Methylpregnane Derivatives.*

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3β-Hydroxy-25*D*-spirost-5-ene (II) has been transformed into its 6-methyl derivative (cf. VI) by two methods. Its degradation gave 3β-acetoxy-6-methylpregna-5 : 16-dien-20-one (VIII; R = Ac), which was transformed into 6-methylpregnenolone (VII; R = H).

Oppenauer oxidation of the last compound gave 6α-methyl-17α-pregn-4-ene-3 : 20-dione and a smaller quantity of 6α-methylprogesterone (X; R = ···Me, ⁻H). The last compound was independently obtained from pregnenolone.

The 16-dehydro-derivative (IV) of 6α-methylprogesterone has been prepared.

Inactivation of steroid hormones in the body occurs, *inter alia*, by hydroxylation at $C_{(6)}$. It was, consequently, of interest to study the effect of a 6-methyl substituent on the properties of some biologically active derivatives of pregnane and androstane. To this end we have examined in some detail the conversion of 3β-hydroxy-25*D*-spirost-5-ene (II) into 3β-hydroxy-6-methylpregna-5 : 16-dien-20-one (VIII; R = H) and 6α-methylprogesterone (X; R = ···Me, ⁻H) hoping thereby to establish a convenient route to 6-methylsteroids and to obtain some intermediates of potential value for later work. In addition, we have converted pregnenolone into 6β-methylprogesterone and thence into the 6α-methyl isomer (above), thereby establishing the stereochemistry of the latter compound at position 6.

Initial experiments were directed to the conversion of the 3β-hydroxy-Δ^5-steroid (II) into the 6-methyl derivative (VI) *via* a 3 : 5-*cyclo*steroid. 3β-Hydroxy-25*D*-spirost-5-ene (II) was converted into the toluene-*p*-sulphonyl derivative (since described by Wall and Serota [1]) which passed smoothly into 6β-hydroxy-3 : 5-*cyclo*-25*D*-spirostan (III; R = ···H, ⁻OH) on being heated with potassium acetate in aqueous acetone or ethyl methyl ketone. Oxidation of the *cyclo*steroid with the pyridine–chromic acid complex [2] furnished 3 : 5-*cyclo*-25*D*-spirostan-6-one (III; R = :O), which was converted by methylmagnesium iodide into 3 : 5-*cyclo*-6ξ-methyl-25*D*-spirostan-6ξ-ol (III; R = Me, OH) and a small quantity of a compound believed to be the $C_{(6)}$-isomer. Treatment of the major reaction product or, better, of the total Grignard product, with acetic acid–sulphuric acid gave the required 3β-acetoxy-6-methyl-25*D*-spirost-5-ene (VI).

The last compound was also prepared from 3β-acetoxy-5α-bromo-25*D*-spirostan-6β-ol (V; R = Ac, R′ = Br, R″ = ···H, ⁻OH), which was readily obtained by the action of hypobromous acid on the acetate of the alcohol (II). Oxidation with the pyridine–chromic acid

* Part III, *J.*, 1956, 1184.

[1] Wall and Serota, *J. Amer. Chem. Soc.*, 1956, **78**, 1747.
[2] Poos, Arth, Beyler, and Sarett, *ibid.*, 1953, **75**, 422.

complex furnished the bromo-ketone (V; R = Ac, R′ = Br, R″ = :O), which was debrominated by zinc dust in acetic acid to 3β-acetoxy-5α : 25*D*-spirostan-6-one (V; R = Ac, R′ = H, R″ = :O). Reaction with methylmagnesium iodide, followed by reacetylation, gave a product assigned the constitution of 3β-acetoxy-6α-methyl-5α : 25*D*-spirostan-6β-ol (V; R = Ac, R′ = H, R″ = ···Me, ⁻OH) by analogy with the work of Fieser and Rigaudy [3] on the Grignard product obtained from 3β-hydroxycholestan-6-one. Dehydration of this material by Darzens's method gave 3β-acetoxy-6-methyl-25*D*-spirost-5-ene (VI), identical with the compound prepared by the 3 : 5-*cyclo*steroid route. Degradation of the spiro-ketal side-chain present in (VI) by the usual methods [4, 5] gave the *pseudo*sapogenin (IX) and thence the required 3β-acetoxy-6-methylpregna-5 : 16-dien-20-one (VIII; R = Ac).

Hydrogenation of the last compound at palladium–calcium carbonate led selectively to 3β-acetoxy-6-methylpregn-5-en-20-one (VII; R = Ac), hydrolysed by methanolic potassium carbonate to the corresponding alcohol (VII; R = H). Oppenauer oxidation of the last compound, followed by chromatography on alumina, gave two isomeric 3-oxo-Δ^4-6-methyl-steroids, *A*, m. p. 105°, $[\alpha]_D^{26}$ +36° (the major product), and *B*, m. p. 123°, $[\alpha]_D^{26}$ +178°. Theoretical considerations lead to the conclusion that in the conversion of a 3β-hydroxy-6-methyl-Δ^5-steroid into the 6-methyl-3-oxo-Δ^4-steroid, the $C_{(6)}$ substituent may be expected to assume the thermodynamically more stable equatorial α-configuration. Compounds *A* and *B* may consequently be regarded as 6α-methyl-3-oxo-steroids. A clue to their structures was furnished by the observation that the minor oxidation product, *B*, was identical with 6α-methylprogesterone (X; R = ···Me, ⁻H), which we had meanwhile synthesised, together with the 6β-methyl isomer (X; R = ···H, ⁻Me), from pregnenolone by the unambiguous route described below.[6] Compound *A*, which differed from the 6β-epimer (X; R = ···H, ⁻Me), as expected, was therefore assigned the constitution of 6α-methyl-17α-pregn-4-ene-3 : 20-dione, a formulation supported by optical-rotational data and by the observation that the compound was transformed into 6α-methylprogesterone (X; R = ···Me, ⁻H) by alcoholic mineral acid.

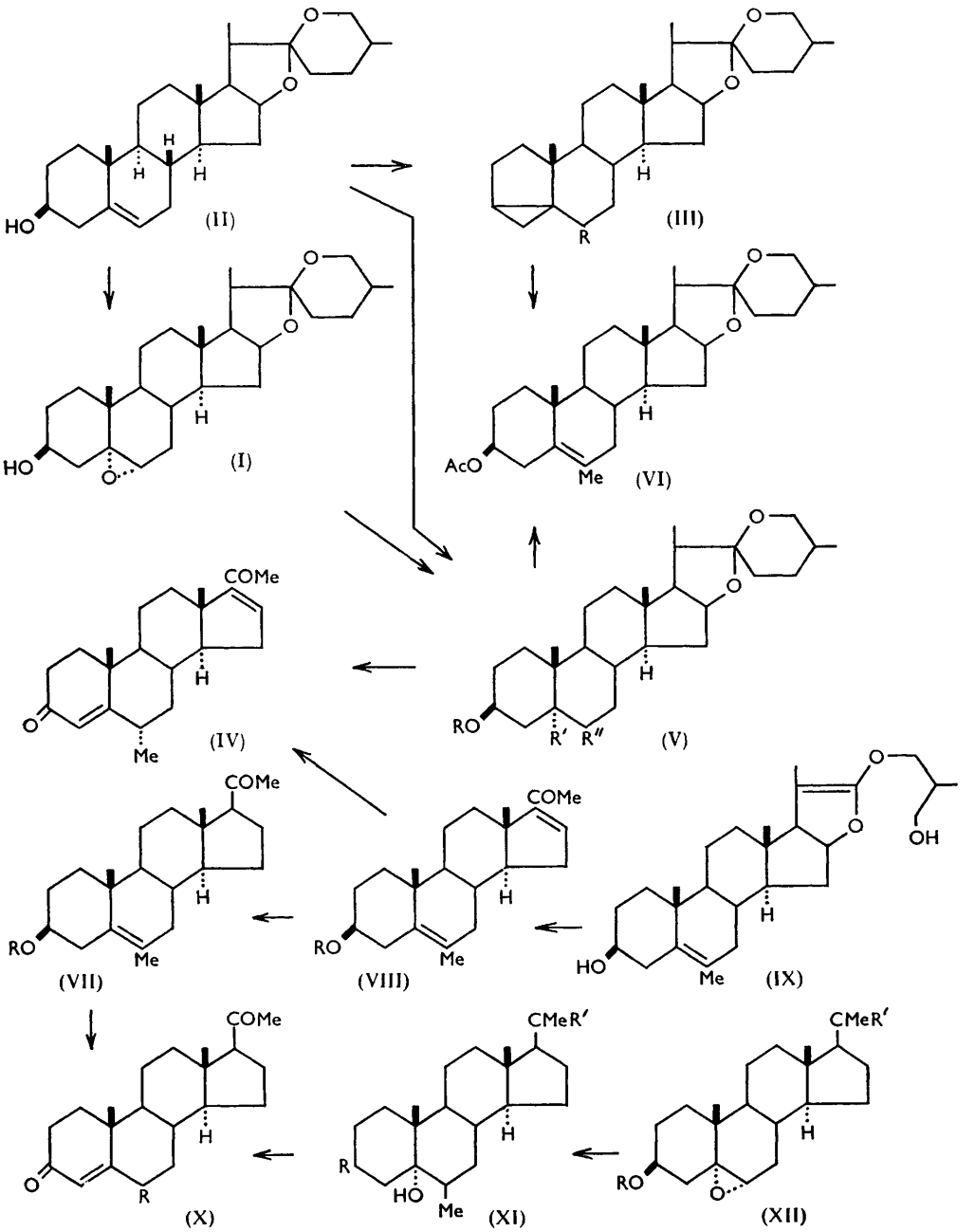
The formation of a 17α-pregnene derivative as major product in the above series of reactions was unexpected. The constitution of a 6-methylpregnenolone (VII; R = H) assigned to the reduction product of 6-methylpregnadienolone (VIII), however, is unequivocally supported by (i) its mode of formation by catalytic hydrogenation of a pregn-16-en-20-one and (ii) its optical rotation. The epimerisation at $C_{(17)}$ must consequently have occurred during the Oppenauer oxidation and must be regarded as due to a vicinal effect of the 6α-methyl group upon the $C_{(17)}$-asymmetric centre.

Conversion of pregnenolone into 6α- and 6β-methylprogesterone utilised pregnenolone 5α : 6α-epoxide [7] (XII; R = H, R′ = :O) as starting material. Ponndorf reduction followed by acetylation furnished 3β : 20(a + b)-diacetoxy-5α : 6α-epoxypregnane (XII; R = Ac, R′ = H, OAc), which was converted by methylmagnesium iodide into 6β-methylpregnane-3β : 5α : 20(a + b)-triol (XI; R = ···H, ⁻OH, R′ = H, OH). Oxidation with chromic acid in acetic acid gave 5α-hydroxy-6β-methylpregnane-3 : 20-dione (XI; R = R′ = :O), which passed into 6β-methylprogesterone (X; R = ···H, ⁻Me) on dehydration by Darzens's method. The last compound was also obtained in low yield by direct Oppenauer oxidation of the mixed triols (XI; R = ···H, ⁻OH, R′ = H, OH).

Epimerisation [8] of 6β-methylprogesterone with hot alcoholic potassium hydroxide furnished 6α-methylprogesterone (X; R = ···Me, ⁻H), also obtained directly from the saturated β-hydroxy-ketone (XI; R = R′ = :O) by heating it with alcoholic mineral acid.

[3] Fieser and Rigaudy, *J. Amer. Chem. Soc.*, 1951, **73**, 4660.
[4] Cameron, Evans, Hamlet, Hunt, Jones, and Long, *J.*, 1955, 2807.
[5] Marker and Rohmann, *J. Amer. Chem. Soc.*, 1940, **62**, 518.
[6] Cf. the preliminary communication of Ringold, Batres, and Rosenkranz, *J. Org. Chem.*, 1957, **22**, 99, which appeared when the present work was in typescript form.
[7] Ehrenstein and Stevens, *J. Org. Chem.*, 1941, **6**, 908; Davis and Petrow, *J.*, 1950, 1185.
[8] Turner, *J. Amer. Chem. Soc.*, 1952, **74**, 5362.

Hydrolysis of 3β-acetoxy-6-methylpregna-5 : 16-dien-20-one (VIII; R = Ac) gave the alcohol (VIII; R = H), which passed into 6α-methylpregna-4 : 16-diene-3 : 20-dione (IV) on Oppenauer oxidation. The last compound was also obtained from 3β-hydroxy-25*D*-spirost-5-ene (II) *via* its 5α : 6α-epoxide (I), which with methylmagnesium iodide gave



6β-methyl-25*D*-spirostan-3β : 5α-diol (V; R = H, R′ = OH, R″ = ···H, –Me). Degradation of the spiro-ketal side-chain gave an oily product which was converted directly into the 6-methyldienedione (IV) by hydrolysis followed by Oppenauer oxidation.

Experimental

Rotations were determined in a 1 dm. tube in $CHCl_3$ unless otherwise stated. Ultraviolet absorption spectra (in EtOH) were kindly determined by Mr. M. T. Davies, B.Sc. Infrared absorption spectra were kindly determined by Dr. A. E. Kellie, Courtauld Institute of Biochemistry. Alumina (B.D.H., chromatography grade) was used throughout.

3β-*Toluene*-p-*sulphonyloxy*-25D-*spirost*-5-*ene*.—3β-Hydroxy-25*D*-spirost-5-ene (II) (10 g.) in pyridine (100 ml.) was left at room temperature for 48 hr. with toluene-*p*-sulphonic acid (10 g.). Ice-cold water was added, and the precipitated solids were collected and dissolved in chloroform. The chloroform solution was washed with water, dried, and evaporated under reduced pressure. The residue was crystallised from acetone, to give the ester, prisms, m. p. 164—165°, $[\alpha]_D^{23}$ −98° (*c* 0·415) (Found: C, 71·6; H, 8·2; S, 6·4. Calc. for $C_{34}H_{48}O_5S$: C, 71·9; H, 8·5; S, 5·6%). Wall and Serota [1] give m. p. 166°, $[\alpha]_D^{25}$ −98°.

3 : 5-cyclo-25D-*Spirostan*-6β-*ol* (III; R = ···H, ⁻OH).—The foregoing ester (25 g.) in ethyl methyl ketone (1·2 l.) was stirred and heated under reflux for 16 hr. with a solution of potassium acetate (31·5 g.) in water (300 ml.). The mixture was poured into water and left overnight, then the product was collected, washed with water, and dried. It was then percolated in benzene through a short column of alumina. After removal of the benzene, the residue was crystallised from acetone, to give 3 : 5-cyclo-25D-*spirostan*-6β-*ol*, plates, m. p. 165—166°, $[\alpha]_D^{23}$ −44° (*c* 0·360) (Found: C, 76·6; H, 10·2. $C_{27}H_{42}O_3,\frac{1}{2}H_2O$ requires C, 76·6; H, 10·2%).

3 : 5-*cyclo*-25D-*Spirostan*-6-*one* (III; R = :O).—The preceding alcohol (23·3 g.) in dry pyridine (233 ml.) was added to the pyridine–chromic acid complex prepared from chromium trioxide (23·3 g.) and pyridine (233 ml.). The mixture was left overnight at room temperature. Hot benzene was added and the mixture filtered through " Hyflo," which was washed repeatedly with hot benzene. The filtrate and washings were combined, washed with dilute hydrochloric acid, dilute sodium hydrogen carbonate solution, and water, dried, and evaporated. The product was purified by passing it in benzene through a short column of alumina. The residue, after evaporation of the benzene, crystallised from acetone, giving 3 : 5-cyclo-25D-*spirostan*-6-*one*, plates, m. p. 185°, $[\alpha]_D^{20}$ −48° (*c* 0·968) (Found: C, 78·3; H, 9·9. $C_{27}H_{40}O_3$ requires C, 78·6; H, 9·7%). The compound formed an orange 2 : 4-dinitrophenylhydrazone.

3 : 5-cyclo-6ξ-*Methyl*-25D-*spirostan*-6ξ-*ol* (III; R = Me, OH).—3 : 5-*cyclo*-25*D*-Spirostan-6-one (1·84 g.) in ether (184 ml.) was added to a Grignard solution prepared from magnesium (1·1 g.), methyl iodide (3 ml.), and ether (50 ml.). The mixture was heated under reflux for 2 hr., cooled, and decomposed with ammonium chloride solution. The product was isolated with chloroform, and chromatographed in benzene on alumina (55 g.). From the benzene–ether (9 : 1) through to pure ether eluates was obtained 3 : 5-cyclo-6ξ-*methyl*-25D-*spirostan*-6ξ-*ol*, needles, m. p. 183—185°, $[\alpha]_D^{20}$ −52° (*c* 0·339) (Found: C, 78·4; H, 10·2. $C_{28}H_{44}O_3$ requires C, 78·5; H, 10·3%), after crystallisation from acetone. The compound gave a negative tetranitromethane test. From the pure benzene eluates was obtained in low yield an isomeric *product*, plates, m. p. 175°, $[\alpha]_D^{21}$ −130° (*c* 0·735) (Found: C, 78·7; H, 10·1%).

3β-*Acetoxy*-6-*methyl*-25D-*spirost*-5-*ene* (VI).—3 : 5-*cyclo*-6ξ-Methyl-25*D*-spirostan-6ξ-ol (2·7 g.), dissolved in acetic acid (20 ml.), was left overnight at room temperature with acetic acid containing concentrated sulphuric acid (2 ml.). The mixture was poured into water and the product collected. Crystallisation from chloroform–methanol gave 3β-*acetoxy*-6-*methyl*-25D-*spirost*-5-*ene*, plates, m. p. 213—214°, $[\alpha]_D^{25}$ −132° (*c* 0·283) (Found: C, 76·3; H, 10·0. $C_{30}H_{46}O_4$ requires C, 76·6; H, 9·8%). The compound gave a positive tetranitromethane test. Subsequently it was found that purification of the Grignard product was not necessary before treating it with acid, the overall yield in the two stages then being 64%.

Saponification with methanolic potassium hydroxide gave the corresponding *alcohol*, needles (from methanol), m. p. 181—182°, $[\alpha]_D^{20}$ −126° (*c* 0·62) (Found: C, 78·0; H, 10·3. $C_{28}H_{44}O_3$ requires C, 78·5, H, 10·3%).

3β-*Acetoxy*-5α-*bromo*-25D-*spirostan*-6β-*ol* (V; R = Ac, R′ = Br, R″ = ···H, ⁻OH).—A solution of 3β-acetoxy-25*D*-spirost-5-ene (12·7 g.) in dioxan (220 ml.) was treated with *N*-bromoacetamide (5·6 g.) in water (20 ml.) and perchloric acid (1·5 ml.) in water (7 ml.). After 1 hour's stirring at room temperature, water was added and the product isolated with ether. The ethereal extracts were washed successively with aqueous solutions of potassium

iodide, potassium thiosulphate, and sodium carbonate. After evaporation of the ether the residue crystallised from chloroform–hexane, giving 3β-*acetoxy*-5α-*bromo*-25D-*spirostan*-6β-*ol*, needles, m. p. 223—226°, $[\alpha]_D^{21}$ −107° (*c* 0·288) (Found: C, 62·9; H, 8·3; Br, 14·2. $C_{29}H_{45}O_5Br$ requires C, 62·9; H, 8·1; Br, 14·6%).

3β-*Acetoxy*-5α-*bromo*-25D-*spirostan*-6-*one* (V; R = Ac, R′ = Br, R″ = :O).—The foregoing bromohydrin (5 g.) in dry pyridine (50 ml.) was left overnight at room temperature with pyridine–chromic acid [from chromium trioxide (5 g.) and pyridine (50 ml.)]. The product was isolated with hot benzene as before (see above), and crystallised from methanol, to give 3β-*acetoxy*-5α-*bromo*-25D-*spirostan*-6-*one*, needles, m. p. 211—212°, $[\alpha]_D^{22}$ −173° (*c* 0·247) (Found: C, 63·0; H, 7·8; Br, 14·1. $C_{29}H_{43}O_5Br$ requires C, 63·1; H, 7·8; Br, 14·5%).

3β-*Acetoxy*-5α : 25D-*spirostan*-6-*one* (V; R = Ac, R′ = H, R″ = :O).—The foregoing compound (3 g.) was debrominated by stirring and heating it on the steam-bath with zinc dust (3 g.) in acetic acid (30 ml.) for 45 min. After removal of the zinc the product was isolated with ether. 3β-*Acetoxy*-5α : 25D-*spirostan*-6-*one* formed prisms, m. p. 222—224°, $[\alpha]_D^{22}$ −93° (*c* 0·283) (Found: C, 73·0; H, 9·2. $C_{29}H_{44}O_5$ requires C, 73·7; H, 9·3%).

3β-*Acetoxy*-6α-*methyl*-5α : 25D-*spirostan*-6β-ol (V; R = Ac, R′ = H, R″ = ···Me, ⁻OH).—The foregoing ketone (4·2 g.) in benzene (100 ml.) was added to a Grignard solution prepared from magnesium (2·4 g.) and methyl iodide (12·6 g.) in ether (50 ml.), and the mixture heated under reflux for 4 hr. After storage overnight at room temperature, ammonium chloride solution was added, and the product isolated with benzene. Reacetylation with acetic anhydride–pyridine (50 ml. of each) gave 3β-*acetoxy*-6α-*methyl*-5α : 25D-*spirostan*-6β-*ol*, needles, m. p. 238—241°, $[\alpha]_D^{25}$ −85° (*c* 0·354) (Found: C, 73·7; H, 10·0. $C_{30}H_{48}O_5$ requires C, 73·7; H, 9·8%), after purification from acetone.

3β-*Acetoxy*-6-*methyl*-25D-*spirost*-5-*ene* (VI).—The foregoing Grignard product (0·5 g.) in dry pyridine (15 ml.) was treated with thionyl chloride (5 ml.) at 0°. After 10 min. the mixture was treated with water, and the precipitated solids were collected, washed with water, and dried. Crystallisation from methanol gave 3β-acetoxy-6-methyl-25*D*-spirost-5-ene, needles, m. p. 218—220°, $[\alpha]_D^{24}$ −129° (*c* 0·356) (Found: C, 76·9; H, 10·2%), identical with a sample prepared by the 3 : 5-*cyclo*-route (above).

6-*Methyl*-25D-*furosta*-5 : 20-*diene*-3β : 26-*diol* (IX).—3β-Acetoxy-6-methyl-25*D*-spirost-5-ene (6·98 g.) was heated under reflux for 2 hr. with *n*-octanoic acid (9·24 ml.) and *n*-octanoic anhydride (4·8 ml.). After cooling, the mixture was diluted with ether, and the ethereal solution washed with water, 2N-sodium hydroxide, and water, dried, and evaporated. The residual gum was hydrolysed under reflux for 30 min. with methanol (70 ml.) and potassium hydroxide (3·5 g.) in water (5 ml.). When hot water was added a solid was precipitated, which, after cooling, was filtered off, washed with water, and dried. Crystallisation from methanol gave 6-*methyl*-25D-*furosta*-5 : 20-*diene*-3β : 26-*diol*, plates, m. p. 179°, 184—186°, $[\alpha]_D^{25}$ −81° (*c* 0·403) (Found: C, 78·3; H, 10·5. $C_{28}H_{44}O_3$ requires C, 78·5; H, 10·3%).

3β-*Acetoxy*-6-*methylpregna*-5 : 16-*dien*-20-*one* (VIII; R = Ac).—The foregoing *pseudo*genin (5·2 g.) was acetylated on the steam-bath for 1 hr. with acetic anhydride–pyridine (20 ml. of each). After addition of water the product was isolated with chloroform, which was removed leaving an oil. To this oil, dissolved in acetic acid (37 ml.), was added dropwise with cooling and stirring chromium trioxide (1·8 g.) in water (3·7 ml.) and acetic acid (37 ml.). The mixture was stirred for 1½ hr. at room temperature, methanol was added, and the mixture poured into water. The product, isolated with chloroform, was an oil which was heated in acetic acid (40 ml.) for 2 hr. Most of the acetic acid was removed under reduced pressure and chloroform added to the residue. The chloroform solution was washed until neutral, dried, and evaporated to an oil, which was dissolved in benzene solution and trickled through a short column of alumina. Evaporation of the residue gave 3β-*acetoxy*-6-*methylpregna*-5 : 16-*dien*-20-*one*, plates, m. p. 121—123°, $[\alpha]_D^{23}$ −60° (*c* 0·505), $\lambda_{max.}$ 240 mμ (ε 9095) (Found: C, 78·0; H, 8·9. $C_{24}H_{34}O_3$ requires C, 77·8; H, 9·2%), after purification from aqueous methanol.

3β-*Acetoxy*-6-*methylpregn*-5-*en*-20-*one* (VII; R = Ac).—The foregoing compound (2·57 g.) was hydrogenated in 95% methanol (100 ml.) by using 2% palladium–calcium carbonate (1·5 g.). Crystallisation of the product from aqueous methanol furnished 3β-*acetoxy*-6-*methylpregn*-5-*en*-20-*one*, needles, m. p. 150—151°, $[\alpha]_D^{26}$ −3° (*c* 0·557) (Found: C, 76·8; H, 10·1. $C_{24}H_{36}O_3$ requires C, 77·4; H, 9·7%).

3β-*Hydroxy*-6-*methylpregn*-5-*en*-20-*one* (VII; R = H).—Hydrolysis of the preceding acetate (1·93 g.) with potassium carbonate (0·32 g.) in methanol (25 ml.) and water (2 ml.) for 1 hr. on

the steam-bath gave 3β-*hydroxy*-6-*methylpregn*-5-*en*-20-*one*, prisms, m. p. 159—160°, $[\alpha]_D^{26}$ +10° (*c* 0·602) (Found: C, 79·4; H, 10·4. $C_{22}H_{34}O_2$ requires C, 80·0; H, 10·3%), after crystallisation from aqueous methanol.

6α-*Methylprogesterone* (X; R = ···Me, ⁻OH).—Oxidation of the last compound (1·25 g.) in *cyclo*hexanone (9 ml.) by heating it under reflux for 30 min. with aluminium *tert.*-butoxide (1·25 g.) in toluene (5 ml.), followed by decomposition with Rochelle salt solution, steam-distillation, and isolation with chloroform gave an oil. This was chromatographed in benzene–hexane (1 : 1) on alumina (35 g.). From the benzene–hexane (1 : 1) to pure benzene eluates, was obtained 6α-methylprogesterone,[6] needles, m. p. 122—123°, $[\alpha]_D^{27}$ +178° (*c* 1·05), $\lambda_{max.}$ 241 mμ (ε 15,700) (Found: C, 80·3; H, 9·9. Calc. for $C_{22}H_{32}O_3$: C, 80·4; H, 9·8%), after crystallisation from acetone–hexane.

6α-*Methyl*-17α-*pregn*-4-*ene*-3 : 20-*dione*.—From the benzene–ether (9 : 1) to benzene–ether (3 : 2) eluates in the preceding experiment was obtained 6α-*methyl*-17α-*pregn*-4-*ene*-3 : 20-*dione*, prisms, m. p. 104—105°, $[\alpha]_D^{24}$ +36° (*c* 0·18), $\lambda_{max.}$ 241 mμ (ε 16,040) (Found: C, 80·4; H, 9·8%), after crystallisation from acetone–hexane. This compound (50 mg.) in ethanol (18 ml.) was heated under reflux for 15 min. with concentrated hydrochloric acid (1·8 ml.). Water was added and the product isolated with ether, as an oil which was passed in benzene through a short column of alumina. Crystallisation from acetone–hexane gave 6α-methylprogesterone, m. p. 120° alone or admixed with a sample prepared as above.

5α-*Hydroxy*-6β-*methyl*-5α-*pregnane*-3 : 20-*dione* (XI; R = R′ = :O).—5α : 6α-Epoxy-3β-hydroxy-5α-pregnan-20-one (13·1 g.) in propan-2-ol (230 ml.) was treated with aluminium *iso*propoxide (13 g.) and the mixture distilled slowly during 6 hr.; 132 ml. of distillate were collected. The product, isolated with ether, was digested with warm acetone, and the insoluble fraction (10·4 g.; m. p. 205—225°), consisting of 5α : 6α-epoxy-5α-pregnane-3β : 20(a + b)-diol, was acetylated in pyridine for 12 hr. at room temperature. The 3β : 20(a + b)-diacetate (11 g.) crystallised from aqueous ethanol in plates, m. p. 150—160°.

The foregoing diacetate (11 g.) in dry benzene (900 ml.) was added rapidly to a solution of Grignard reagent prepared from magnesium (7·2 g.), methyl iodide (18·5 ml.), and ether (300 ml.). The mixture was stirred and distilled until the vapour temperature reached 76°, then refluxing was continued for 5 hr. The product, isolated in the usual way, separated from benzene (yield, 6·3 g.; m. p. 230—240°) and consisted of 6β-methylpregnane-3β : 5α : 20(a + b)-triol. No attempt was made to separate the isomers.

The foregoing triol (5 g.) in acetic acid (50 ml.) was treated for 18 hr. with chromium trioxide (3 g.) in acetic acid (150 ml. of 85%). Dilution with water gave a solid which was purified from ethanol. 5α-Hydroxy-6β-methyl-5α-pregnane-3 : 20-dione [6] formed prisms, m. p. 255—256° (decomp.), $[\alpha]_D^{25}$ +64·5° (*c* 0·5) (Found: C, 75·3; H, 9·9. Calc. for $C_{22}H_{34}O_3$: C, 76·2; H, 9·9%).

6β-*Methylprogesterone* (X; R = ···H, ⁻Me).—(*a*) Thionyl chloride (1·2 ml.) was added dropwise at 0° to an ice-cooled solution of 5α-hydroxy-6β-methyl-5α-pregnane-3 : 20-dione (2 g.) in pyridine (35 ml.). After a further 10 min., the mixture was poured into ice-water, and the product isolated with ether, and crystallised from aqueous methanol. 6β-Methylprogesterone [6] separated in needles, m. p. 169—171°, $[\alpha]_D^{24}$ +141° (*c* 0·95), $\lambda_{max.}$ 242 mμ (ε 19,040) (Found: C, 80·15; H, 9·5. Calc. for $C_{22}H_{32}O_2$: C, 80·4; H, 9·8%).

(*b*) A solution of 6β-methylpregnane-3β : 5α : 20(a + b)-triol (1·5 g.) in toluene (100 ml.) and *cyclo*hexanone (40 ml.) was distilled until 30 ml. of distillate had collected. After the addition of aluminium *iso*propoxide (2·5 g.) in toluene (10 ml.), the mixture was refluxed for 1½ hr., cooled, and washed with dilute sulphuric acid, and the solvents were removed by steam-distillation. The product in benzene was chromatographed on alumina (15 g.), and the early fractions were combined and purified from aqueous methanol. 6β-Methylprogesterone formed needles, m. p. 171°, identified with a specimen prepared by method (*a*) above.

6α-*Methylprogesterone* (X; R = ⁻H, ···Me).—(*a*) 6β-Methylprogesterone (0·6 g.) in methanol (25 ml.) and water (5 ml.) containing potassium hydroxide (0·5 g.) was refluxed under nitrogen for 16 hr. The product, isolated with ether, was chromatographed on alumina (15 g.). Elution with benzene gave a solid which crystallised from aqueous methanol. 6α-Methylprogesterone separated in flakes, m. p. 122—123°, identical (infrared spectrum) with the compound prepared as above.

(*b*) A solution of 5α-hydroxy-6β-methylpregnane-3 : 20-dione (0·5 g.) in ethanol (40 ml.) containing concentrated hydrochloric acid (3 drops) was refluxed for 30 min. The product,

crystallised from aqueous methanol, gave 6α-methylprogesterone, plates, m. p. 121—123°, not depressed in admixture with a specimen prepared by method (*a*) above.

3β-*Hydroxy*-6-*methylpregna*-5 : 16-*dien*-20-*one* (VIII; R = H).—The acetate (VIII; R = Ac) (0·5 g.) was hydrolysed under reflux for 4 hr. with potassium hydroxide (2 g.) in water (5 ml.) and *tert.*-butyl alcohol (30 ml.). Water was added and the product isolated with chloroform. The residue, after evaporation and crystallisation from aqueous methanol, gave 3β-*hydroxy*-6-*methylpregna*-5 : 16-*dien*-20-*one*, needles, m. p. 164—166°, $[\alpha]_D^{25}$ −42° (*c* 0·272) (Found: C, 78·6; H, 9·5. $C_{22}H_{32}O_2,\frac{1}{2}H_2O$ requires C, 78·3; H, 9·8%).

6α-*Methylpregna*-4 : 16-*diene*-3 : 20-*dione* (IV).—The foregoing compound (200 mg.) was heated under reflux for 40 min. with aluminium *tert.*-butoxide (300 mg.) in toluene (3 ml.) and *cyclo*hexanone (5 ml.). Rochelle salt solution was added and the mixture steam-distilled for a few hr. The product was isolated with chloroform, to give 6α-*methylpregna*-4 : 16-*diene*-3 : 20-*dione*, needles, m. p. 179—180°, $[\alpha]_D^{24}$ +145° (*c* 0·138), $\lambda_{max.}$ 240 mμ (ε 28,400) (Found: C, 79·1; H, 9·1. $C_{22}H_{30}O_2,\frac{1}{2}H_2O$ requires C, 78·7; H, 9·2%), after crystallisation from acetone–hexane.

5α : 6α-*Epoxy*-25D-*spirostan*-3β-*ol* (I) (with G. Cooley, B.Sc.).—3β-Hydroxy-25*D*-spirost-5-ene (II) (3 g.) in chloroform (85 ml.) was left overnight at 0° with ethereal monoperphthalic acid (45 ml. containing 2 g. of acid). After the addition of more ether, the solution was washed neutral with potassium carbonate solution and water, dried, and evaporated. The residue, crystallised from chloroform–methanol, gave 5α : 6α-*epoxy*-25D-*spirostan*-3β-*ol*, prisms, m. p. 208—209°, $[\alpha]_D^{26}$ −136° (*c* 0·884) (Found: C, 73·7; H, 9·7. $C_{27}H_{42}O_4,\frac{1}{2}CH_3{\cdot}OH$ requires C, 73·9; H, 9·9%). The infrared absorption spectrum was compatible with this structure.

6β-*Methyl*-25D-*spirostan*-3β : 5α-*diol* (V; R = H, R′ = OH, R″ = ···H, ⁻Me) (with Miss V. Grenville, B. A.).—5α : 6α-Epoxy-25*D*-spirostan-3β-ol (10 g.) in benzene (300 ml.) and ether (200 ml.) was added to a Grignard solution prepared from magnesium (5·0 g.) and methyl iodide (15 ml.) in ether (100 ml.). After 6 hr. under reflux, ammonium chloride solution was added, and the product isolated with ether. Crystallisation from methanol gave 6β-*methyl*-25D-*spirostan*-3β : 5α-*diol*, needles, m. p. 217—218°, $[\alpha]_D^{25}$ −84° (*c* 0·346) (Found: C, 73·3; H, 10·4. $C_{28}H_{46}O_4,\frac{1}{2}H_2O$ requires C, 73·8; H, 10·3%). The infrared spectrum showed the presence of a tertiary hydroxyl group.

6α-*Methylpregna*-4 : 16-*diene*-3 : 20-*dione* (IV).—The foregoing Grignard product was heated in a sealed tube at 185—190° for 18 hr. with acetic anhydride (40 ml.). After cooling, the mixture was concentrated under reduced pressure, and the residue was oxidised with chromium trioxide (9 g.) in water (30 ml.), acetic acid (33 ml.), and methylene dichloride (75 ml.) for 2 hr. at room temperature. Methanol was added and the product was isolated with ether. Hydrolysis of this with potassium hydroxide (12·5 g.) in *tert.*-butyl alcohol (250 ml.) at 30° for 3 hr. gave an oil, after the addition of water and isolation with ether. This was oxidised by heating under reflux for 2 hr. with aluminium *tert.*-butoxide (10 g.) in *cyclo*hexanone (100 ml.) and toluene (80 ml.). Rochelle salt solution was added and the mixture was steam-distilled for 4 hr. The product was isolated with benzene–ether as an oil which was chromatographed on alumina (50 g.). Elution with benzene–hexane (2 : 1) gave 6α-methylpregna-4 : 16-diene-3 : 20-dione, needles, m. p. 180—182°, $[\alpha]_D^{23}$ +152° (*c* 0·293 in EtOH), after crystallisation from methanol. Its infrared spectrum proved its identity with the compound prepared as above.

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