963. *Urinary Steroids and Related Compounds. Part III.*[1] *Side-chain-substituted 5α-Pregnanes Not Carrying Substituents in the Phenanthrene Nucleus.*

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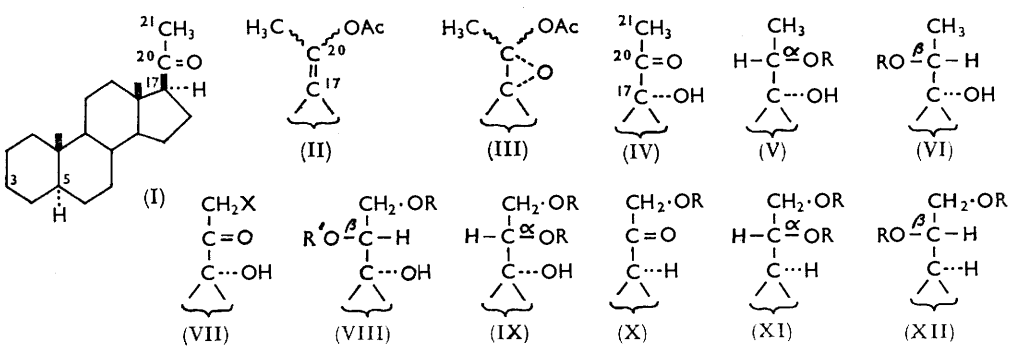
A series of 5α-pregnanes has been prepared not carrying substituents in the phenanthrene nucleus, but with the combinations of substituents at positions 17, 20, and 21 which are characteristic for adrenocortical steroids.

The study of physical properties and chemical reactions in complex compounds, such as the steroids, can be facilitated by the preparation of reference compounds each containing only one individual functional group or a collection of neighbouring groups. Previous work from this laboratory has dealt with 11- and 17-substituted androstanes,[1] 20-monosubstituted pregnanes,[2] and 3-monosubstituted and 3,17-disubstituted androstanes.[3]



[1] Part II, Klyne and Palmer, *J.*, 1958, 4545.
[2] P. M. Jones and Klyne, *J.*, 1960, 871.
[3] Klyne and Marshall-Jones, *J.*, 1961, 5415.

Although an immense amount of work has been done, especially over the last 15 years, on the adrenocortical steroids (for a detailed survey, see Fieser and Fieser [4]), few of the essential reference compounds—those with substituents at positions 17, 20, and 21, but with no other substituents—have been described in the literature. The complete series of these reference compounds is now described in this paper. Most of the compounds were prepared by methods previously used for other compounds carrying substituents in ring A, B, or C (position 3 or elsewhere). The starting material for the series was 5α-pregnan-20-one (I) obtained by selective Clemmensen reduction of the 3-oxo-group of 5α-pregnane-3,20-dione.[5] The 20-monosubstituted compounds are described in the literature; [5,6] their optical rotatory dispersion values are included for completeness (cf. ref. 2).

17α,20-*Disubstituted Compounds.*—Enol acetylation of 5α-pregnan-20-one (I) as described by Marshall *et al.*[7] gave a product from which only one of the two possible isomeric 20-acetoxy-5α-pregn-17-enes (II) was separated. However, on epoxidation and hydrolysis [8] of the crude product, 17α-hydroxy-5α-pregnan-20-one (IV) was obtained in 70% yield.

Epoxidation of the enol acetate (II), followed by reduction of the epoxide [9] (III) by lithium aluminium hydride, acetylation, and chromatography, gave 20α-acetoxy-5α-pregnan-17α-ol (V; R = Ac); hydrolysis gave the diol (V; R = H). Reduction of the ketol (IV) by sodium borohydride afforded 5α-pregnane-17α,20β-diol (VI; R = H).

17α,20,21-*Trisubstituted Compounds.*—The substituent at C-21 was introduced by bromination of the 17,20-ketol (IV) and solvolysis of the product (VII; X = Br) (Romo *et al.*[10]), to give 21-acetoxy-17α-hydroxy-5α-pregnan-20-one (VII; X = OAc). Sodium borohydride reduced this compound to 5α-pregnane-17α,20β,21-triol (VIII; R = R′ = H) identical with the compound prepared by Wagner and Moore.[11] A short cut to this triol was found by Uchibayashi.[12] Sodium borohydride reduced 21-acetoxy-17α-hydroxypregn-4-ene-3,20-dione to pregn-4-ene-3β,17α,20β,21-tetraol which on hydrogenolysis, acetylation, and chromatography afforded 20β,21-diacetoxy-5α-pregnan-17α-ol (VIII; R = R′ = Ac) as main product.

The configuration of 5α-pregnane-17α,20β,21-triol was inverted at C-20, as described by Fukushima and Gallagher.[13] The triol was selectively acetylated at position 21, to give the monoacetate (VIII; R = Ac, R′ = H). Toluene-*p*-sulphonylation at position 20 and forced acetylation at position 17 gave the 20-toluene-*p*-sulphonate 17,21-diacetate, which on rearrangement *via* the cyclic acylonium ion afforded 20α,21-diacetoxy-5α-pregnan-17α-ol (IX; R = Ac). High-pressure hydrogenation of 21-acetoxy-17α-hydroxy-5α-pregnan-20-one with Raney nickel, followed by hydrolysis and benzoylation, gave the two isomeric triol dibenzoates (VIII; R = R′ = Bz) and (IX; R = Bz) directly, but in small yield. A simple two-stage preparation of 17α,20α,21-triols from 17α,21-dihydroxy-20-ketones has recently been described by Gardi *et al.*[14]

20,21-*Disubstituted Compounds.*—Steiger and Reichstein,[15] on reduction of 21-acetoxy-3β-hydroxypregn-5-en-20-one under high pressure with Raney nickel, followed by hydrolysis, obtained 5α-pregnane-3β,20α,21-triol as the sole product in 75% yield.

[4] Fieser and Fieser, " Steroids," Reinhold Publ. Corpn., New York, 1960, chap. 19.
[5] Marker and Lawson, *J. Amer. Chem. Soc.*, 1939, **61**, 852.
[6] Romo, Rosenkranz, and Djerassi, *J. Org. Chem.*, 1952, 17, 1413; Camerino and Albert, *Gazzetta*, 1955, **85**, 51; H. Hirschmann, F. Hirschmann, and Davis, *J. Biol. Chem.*, 1949, **178**, 751; Prelog and Tsatsas, *Helv. Chim. Acta*, 1953, **36**, 1178.
[7] Marshall, Kritchevsky, Lieberman, and Gallagher, *J. Amer. Chem. Soc.*, 1948, **70**, 1837.
[8] Kritchevsky and Gallagher, *J. Amer. Chem. Soc.*, 1951, **73**, 184.
[9] Fukushima and Meyer, *J. Org. Chem.*, 1958, **23**, 174.
[10] Romo, Rosenkranz, Djerassi, and Sondheimer, *J. Amer. Chem. Soc.*, 1953, **75**, 1277.
[11] Wagner and Moore, *J. Amer. Chem. Soc.*, 1950, **72**, 5303.
[12] Uchibayashi, *Chem. and Pharm. Bull.* (*Japan*), 1960, **8**, 122.
[13] Fukushima and Gallagher, *J. Biol. Chem.*, 1955, **212**, 499.
[14] Gardi, Vitali, Ercoli, and Klyne, *Tetrahedron Letters*, 1962, 189.
[15] Steiger and Reichstein, *Helv. Chim. Acta*, 1938, **21**, 161.

Repetition of this experiment confirmed their findings. However, reduction of 21-acetoxy-5α-pregnan-20-one (X; R = Ac), followed by acetylation and chromatography, gave a mixture of 20α,21- (XI; R = Ac) and 20β,21-diacetoxy-5α-pregnane (XII; R = Ac) in 10% and 40% yield, respectively. That the 5,6 double bond influenced the course of reduction at C-20 was indicated by the fact that when 21-acetoxy-3β-hydroxy-5α-pregnan-20-one was reduced in these conditions, a mixture of isomeric triols was obtained in a ratio corresponding more closely with that observed on reducing 21-acetoxy-5α-pregnan-20-one (X; R = Ac).

Infrared Spectra.—Routine measurements were carried out on all compounds with an Infracord spectrophotometer; details are given in the Experimental section. High-resolution measurements on four hydroxy-acetates were carried out by Dr. E. S. Waight and his colleagues at Imperial College—to whom we express our thanks—with a Grubb-Parsons S4 spectrophotometer incorporating a fluorite prism. The results are summarised in Table 1.

TABLE 1.

Infrared spectra (ν in cm.$^{-1}$).

5α-Pregnane derivative	Nujol mull		CCl_4 (less than 0·005M)	
	O–H	C=O	O–H	C=O
17α-OH 20α-OAc	3587	1714	3619	1735
17α-OH 20β-OAc	3623	1730, 1750(sh)	3609	1734, 1750(sh)
17α-OH 20α,21-$(OAc)_2$	3490	1746, 1701 (equal intensity)	3636	1750
17α-OH 20β,21-$(OAc)_2$	3555	1738, 1731 (equal intensity)	3623	1751

TABLE 2.

Rotatory dispersion data of 5α-pregnane derivatives.

For methanol solutions unless indicated otherwise.

Derivative *Non-ketones: Plain curves*	Molecular rotation [φ] at λ (mμ) 600	400	300	Derivative *Non-ketones: Plain curves*	Molecular rotation [φ] at λ (mμ) 600	400	300
20α-OH	+50°	+140°	+310°	20α,21-$(OH)_2$	+50°	+125°	+350°
20α-OAc †	+40	+120	+160	20α,21-$(OAc)_2$	−20	−35	−110
20α-OBz †	+175	+470	+1060	20α,21-$(OBz)_2$ *	+85	+110	+430
20β-OH	+10	+30	+85	20β,21-$(OH)_2$	+20	+120	+230
20β-OAc †	+140	+380	+890	20β-OH 21-OAc	+60	+180	+335
20β-OBz †	−110	−290	−820	20β,21-$(OAc)_2$	+155	+470	+1180
				20β,21-$(OBz)_2$	+15	+80	+260
17α,20α-$(OH)_2$	−80	−120	−210				
17α-OH 20α-OAc	−95	−300	−610	17α,20α,21-$(OH)_3$	−55	−65	−115
17α-OH 20α-OBz	+70	+95	+105	17α-OH 20α,21-$(OAc)_2$ *	−150	−370	−840
17α,20β-$(OH)_2$	−30	−90	−170	17α-OH 20α,21-$(OBz)_2$	−215	−680	−2260
17α-OH 20β-OAc	+120	+300	+710	17α,20β-21$(OH)_3$	+10	+20	0 §
17α-OH 20β-OBz	−55	−155	−540	17α,20β-$(OH)_2$ 21-OAc	+55	+140	+270
				17α-OH 20β-Tos 21-OAc *¶	+200	+530	+1280
				17α,21-$(OAc)_2$ 20β-Tos* ¶	+110	+415	+1110
				17α-OH 20β,21-$(OAc)_2$	+65	+160	+370
				17α-OH 20β,21-$(OBz)_2$	+420	+1120	+3160

Ketones: Cotton effect curves	Peak [φ]	Peak λ (mμ)	Trough [φ]	Trough λ (mμ)	Amplitude *a*
20-CO	+7500°	307·5	−11,620°	262·5	+192 ‖
17α-OH 20-CO	+5580	317·5	−6800	275	+124 ‖
21-OH 20-CO	+7720	307	−8550	261	+163 ‖
21-OAc 20-CO	+10,200	306	−13,550	262·5 ‡	+235 ‡
17α,21-$(OH)_2$ 20-CO	+4950	315	−9150	270	+141 ‖ **
17α-OH 21-OAc 20-CO	+6470	312·5	−11,800	270	+185 **
17α-OH 21-Br 20-CO	+4280	327·5	−7240	270	+115

* Measured in $CHCl_3$. † Measured in $CHCl_3$–MeOH (1 : 4 v/v). ‡ Trough not reached. § −35 at 270 mμ. ¶ Tos = *p*-$C_6H_4Me{\cdot}SO_2{\cdot}O$. ‖ Djerassi *et al.* (*Helv. Chim. Acta*, 1958, **41**, 250) found amplitudes of +178, 127, 163, 150, respectively, for compounds of these four types with substituents in position 3. ** We found amplitudes of +152, 184, respectively, for compounds of these two types with substituents at C-3.

Spectra in carbon tetrachloride gave results very similar to those already reported for compounds substituted at C-3.[16] Although the positions of the O–H bands varied slightly, there was little evidence to indicate intramolecular hydrogen-bonding in any of the four compounds. However, in Nujol mulls strong intermolecular hydrogen-bonding was observed between hydroxyl and ester-carbonyl groups. The interaction appeared to be more pronounced in the 20α- than in the corresponding 20β-isomers. This is particularly evident in the 17α,20α,21-triol diacetate; the hydroxyl band has been displaced by 146 cm.$^{-1}$, and the carbonyl band split into two sharp bands of equal intensity at 1746 cm.$^{-1}$ (unassociated) and 1701 cm.$^{-1}$ (hydrogen-bonded). In the diol monoacetates the ester band for the 20β-isomer was little affected, showing a displacement of only 4 cm.$^{-1}$; the 20α-isomer showed a larger shift of 21 cm.$^{-1}$.

Optical Rotatory Dispersion Curves.—Results are summarised in Table 2.

Experimental

" Usual working up," when referring to an ether or chloroform extract, means that the organic phase was washed with 2N-sulphuric acid, water, saturated sodium hydrogen carbonate solution, and water till neutral, then dried (Na_2SO_4) and evaporated under a vacuum on a steam-bath. Acetylation or benzoylation of a compound in the " usual manner " means that the material (100 mg.) was left in pyridine (1 c.c.) overnight at room temperature with acetic anhydride (0·2 c.c. per OH group) or benzoyl chloride (0·1 c.c. per OH group); the excess of reagent was destroyed by ice, followed by a little water; the suspension was extracted with ether, and the product obtained by the usual working up.

M. p.s were determined on a Kofler apparatus and are corrected.

Infrared spectra, unless otherwise stated, were taken on an Infracord spectrometer as potassium bromide discs.

Optical Rotatory Dispersion.—Measurements were determined on a Rudolph photoelectric spectropolarimeter (model 200A). The procedure used was as described previously [2] except for the following details: the light intensity was increased by using a Siemens xenon arc lamp (500 w A.C., type XC); the symmetrical angle setting was 5° and the usual temperature was 18—21°; concentrations were about 2 mg./c.c. for compounds giving plain curves, and 0·1—0·2 mg./c.c. for ketones. Unless otherwise stated, the solvent was methanol. For a single determination of the molecular rotation for a non-ketonic compound of molecular weight 350, values were reproducible to ±3°; values are in fact given to the nearest 5° (or 10° if over 200°).

Some previous values obtained on the Rudolph instrument at 600 mμ were at variance with published figures obtained with visual polarimeters. However, on decreasing the slit-width of the monochromator which is combined with the Rudolph instrument, apparent rotations were found to change until at slit-widths less than 1 mm. constant values were obtained. These were in agreement with results obtained on a visual instrument for the sodium D-line (no such change in apparent rotation with slit-width was observed below 500 mμ). The small linear dispersion of the monochromator prism in the 600 mμ region necessitates a narrow slit-width to give monochromatic light. This is particularly important in this region, as the light-ouput from the lamp and the sensitivity of the photomultiplier are very dependent on wavelength at this point. The monochromator slit-width was set at 1 mm. at 600 mμ, and at 2 mm. for the rest of the spectrum.

Readings for plain curves were taken at 600, 500, 400, 350, 330 mμ, then at 10 mμ intervals to the lowest limit. For Cotton effects, peaks and troughs were examined at 2·5 mμ intervals.

20-Acetoxy-5α-pregn-17(20)-ene (II).—5α-Pregnan-20-one [1] (I) (1·82 g.) and toluene-*p*-sulphonic acid (1·10 g.) were dissolved in acetic anhydride (240 c.c.). The mixture was slowly distilled through a short unpacked column, over a period of 5 hr., until approximately three-quarters of the solvent had been removed. On cooling, the mixture was diluted with ether. The usual working up gave a residue (2·4 g.) which was chromatographed on alumina. Light petroleum eluted a broad fraction which on repeated recrystallisation from benzene–light petroleum gave *20-acetoxy-5α-pregn-17(20)-ene* (1·01 g.). Recrystallisation from the same

[16] R. N. Jones, Humphries, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2820.

solvent gave needles, m. p. 174—175·5° (Found: C, 80·1; H, 10·4. $C_{23}H_{36}O_2$ requires C, 80·2; H, 10·5%).

20-*Acetoxy*-17α,20-*epoxy*-5α-*pregnane* (III).—20-Acetoxy-5α-pregn-17(20)-ene (II) (422 mg.) was dissolved in 1·32M-monoperphthalic acid [17] in ether (20 c.c.). The mixture was left at room temperature overnight, then diluted with ether. The ether solution was washed with 2N-sodium hydroxide and water. Drying (Na_2SO_4) and evaporation gave a residue (431 mg.) which was used directly for the next stage.

20α-*Acetoxy*-5α-*pregnan*-17α-*ol* (V; R = Ac).—The above crude epoxide in dry ether (40 c.c.) was added with stirring to a suspension of lithium aluminium hydride (280 mg.) in ether (48 c.c.). The mixture was refluxed for 2 hr., then cooled, and the excess of reagent destroyed with ethyl acetate. Acidification with dilute sulphuric acid and extraction with ether, followed by the usual working up, gave a residue (386 mg.). Acetylation in the usual manner followed by recrystallisation from acetone gave 20-*acetoxy*-5α-*pregnan*-17α-*ol* (115 mg.) as plates, m. p. 181—182°. Chromatography of the mother-liquors on alumina and recrystallisation from heptane furnished a further 169 mg., double m. p. 180—181° and 186—187° (63%). A sample recrystallised from the same solvent had m. p. 185—185·5°, $\nu_{max.}$ 1720 cm.$^{-1}$ (ester) (Found: C, 76·1; H, 10·7. $C_{23}H_{38}O_3$ requires C, 76·2; H, 10·6%).

5α-*Pregnane*-17α,20α-*diol* (V; R = H).—The monoacetate (207 mg.) was refluxed with 50% aqueous potassium hydroxide (1·0 c.c.) in methanol (35 c.c.) for 3 hr. The mixture was cooled, diluted with water, and extracted with ether. The residue obtained by the usual working up gave 5α-*pregnane*-17α,20α-*diol*, needles (from hexane), m. p. 170—171° (Found: C, 78·6; H, 11·0. $C_{21}H_{36}O_2$ requires C, 78·7; H, 11·2%). The 20-monobenzoate (V; R = Bz) was prepared in the usual manner. Chromatography on a short column of alumina and recrystallisation from hexane gave plates, m. p. 174—176°, $\nu_{max.}$ 1690 cm.$^{-1}$ (ester) (Found: C, 79·1; H, 9·1. $C_{28}H_{40}O_3$ requires C, 79·2; H, 9·4%).

17α-*Hydroxy*-5α-*pregnan*-20-*one* (IV).—20-Acetoxy-5α-pregn-17(20)-ene (248 mg.) was epoxidised as described above. The crude product was dissolved in ethanol (200 c.c.), and N-sodium hydroxide (100 c.c.) was added. The mixture was kept at 30° for 2 hr., diluted with water, and extracted with ether. The usual working up and recrystallisation from benzene–hexane gave 17α-*hydroxy*-5α-*pregnan*-20-*one* (185 mg., 80%), plates (from acetone–hexane), m. p. 172—173°, $\nu_{max.}$ 1700 cm.$^{-1}$ (C=O) (Found: C, 78·9; H, 11·1. $C_{21}H_{34}O_2$ requires C, 79·2; H, 11·1%).

The ketol (IV) was prepared in 71% yield from the 20-ketone (I) without purification of the intermediates.

5α-*Pregnane*-17α,20β-*diol* (VI; R = H).—17α-Hydroxy-5α-pregnan-20-one (121 mg.), dissolved in methanol (7 c.c.), was added to a solution of sodium borohydride (140 mg.) in methanol (4 c.c.). The mixture was left overnight at room temperature, and the excess of reagent destroyed with 2N-sulphuric acid. Dilution with water, and extraction with ether, followed by the usual working up, gave a residue (124 mg.), which on recrystallisation from methanol–chloroform gave the 17α,20β-*diol* as needles (93 mg., 77%), m. p. 193—193·5° (Found: C, 78·8; H, 11·3. $C_{21}H_{36}O_2$ requires C, 78·7; H, 11·2%).

The 20-*monoacetate* (VI; R = Ac) formed cubes (from hexane), m. p. 175—176°, $\nu_{max.}$ 1730 cm.$^{-1}$ (ester) (Found: C, 76·3; H, 10·5. $C_{23}H_{38}O_3$ requires C, 76·2; H, 10·6%). The 20-*monobenzoate* (VI; R = Bz) formed needles (from hexane), m. p. 152—154°, $\nu_{max.}$ 1700 cm.$^{-1}$ (ester) (Found: C, 79·4; H, 9·5. $C_{28}H_{40}O_3$ requires C, 79·2; H, 9·5%).

21-*Bromo*-17α-*hydroxy*-5α-*pregnan*-20-*one* (VII; X = Br).—Bromine in redistilled acetic acid (2·73 c.c.; 0·430M) was added to a solution of 17α-hydroxy-5α-pregnan-20-one (318 mg.) in acetic acid (12 c.c.) containing a few drops of 50% w/v hydrogen bromide in acetic acid. The solution was left at room temperature for 1·5 hr. by which time it was colourless. The acetic acid was removed under a vacuum, leaving a residue (412 mg.) which on recrystallisation from benzene–light petroleum gave 21-*bromo*-17α-*hydroxy*-5α-*pregnan*-20-*one* (361 mg., 91%), short needles, m. p. 164—165°, $\nu_{max.}$ 1720 cm.$^{-1}$ (Found: C, 63·0; H, 8·7; Br, 19·8. $C_{21}H_{33}BrO_2$ requires C, 63·5; H, 8·4; Br, 20·1%).

21-*Acetoxy*-17α-*hydroxy*-5α-*pregnan*-20-*one* (VII; X = OAc).—The above 21-bromo-compound (450 mg.) was refluxed with potassium iodide (320 mg.) in acetone (25 c.c.). After ½ hr. potassium acetate (made from potassium hydrogen carbonate, 1·65 g., and glacial acetic acid, 0·94 c.c.) was added, and the mixture was refluxed for a further 15 hr. Dilution with water

[17] *Organic Reactions*, 1953, **7**, 395.

and extraction with ether, followed by the usual working up, gave a residue (408 mg.) which on recrystallisation from acetone gave the required 21-*acetate* (321 mg., 76%). A pure sample formed needles, m. p. 222—225°, $\nu_{max.}$ 1770, 1730 cm.$^{-1}$ (Found: C, 73·3; H, 9·7. $C_{23}H_{36}O_4$ requires C, 73·4; H, 9·6%).

17α,21-*Dihydroxy*-5α-*pregnan*-20-*one* (VII; X = OH).—The acetate (VII; X = OAc) (60 mg.) was added as a suspension in methanol (10 c.c.) to a suspension of sodium hydrogen carbonate (100 mg.) in methanol (30 c.c.) containing a few drops of water. The mixture was freed from gas and saturated with nitrogen, and then shaken in the dark until all the material had dissolved (1 hr.). After storage in the dark overnight at room temperature the mixture was diluted with ether. The ether solution was washed with small volumes of water until neutral, dried (Na_2SO_4), and evaporated to dryness at room temperature. The residue was briefly treated with neutral charcoal in methanol; recrystallisation from methanol and then benzene–hexane gave 17α,21-*dihydroxy*-5α-*pregnan*-20-*one* as needles, m. p. 172—175°, recrystallising to plates, m. p. 176—176·5° (Found: C, 75·1; H, 10·9. $C_{21}H_{34}O_3$ requires C, 75·4; H, 10·3%).

5α-*Pregnane*-17α,20β,21-*triol* (VIII; R = R′ = H).—21-Acetoxy-17α-hydroxy-5α-pregnan-20-one (VII; X = OAc) (61 mg.) was treated with sodium borohydride as described for the preparation of the 17α,20β-diol. Recrystallisation of the crude product from benzene–light petroleum gave the required *triol* as needles (30 mg.), m. p. 176—179°. This material did not depress the m. p. of a sample, m. p. 176—177°, kindly provided by Dr. J. A. Moore (of University of Delaware, formerly of Parke Davis, Detroit, Mich.) (cf. ref. 11). The infrared spectra of the two samples were identical.

The 20,21-diacetate (VIII; R = R′ = Ac) was obtained from 21-acetoxy-17α-hydroxypregn-4-ene-3,20-dione by Uchibayashi's method,[12] as needles, m. p. 152—154° (lit., 152—153°).

21-*Acetoxy*-5α-*pregnane*-17α,20β-*diol* (VIII; R = Ac, R′ = H).—The 17α,20β,21-triol (872 mg.) was dissolved in pyridine (15 c.c.). The solution was cooled to 0° and ice-cold acetic anhydride (2·70 c.c., 1·1 equiv.) was added. The mixture was left overnight at 0° in the dark. Ice was added and the suspension extracted with ether. The usual working up gave a residue (932 mg.) which was chromatographed on alumina, elution being with benzene and then ether–benzene mixtures. Benzene eluted a fraction (125 mg.) which on recrystallisation from benzene–light petroleum gave the 20β,21-diacetate as needles, m. p. 152—154°. Elution with benzene–ether (9 : 1) yielded material (560 mg.) which on recrystallisation from acetone–light petroleum gave the 21-*monoacetate* as needles (350 mg.), m. p. 152—154°. Chromatography of the mother-liquors afforded a further 62 mg., m. p. 151—153° (total yield, 42%). A pure sample recrystallised from acetone–hexane had m. p. 152—154°, $\nu_{max.}$ 1735 cm.$^{-1}$ (Found: C, 72·6; H, 10·1. $C_{23}H_{38}O_4$ requires C, 73·0; H, 10·1%). Ethanol eluted mainly unchanged triol (223 mg.).

21-*Acetoxy*-20-*toluene*-p-*sulphonyloxy*-5α-*pregnan*-17α-*ol* (VIII; R = Ac, R′ = Tos).—The above 21-monoacetate (400 mg.) was dissolved in pyridine (1 c.c.), and the solution cooled to 0°. Toluene-*p*-sulphonyl chloride (388 mg.) was added with cooling. The mixture was set aside at 0° in the dark for 3 days, then poured into ice–water, and the product was extracted with chloroform. The usual working up gave a residue which on trituration with ether left a fine white powder (490 mg.). Recrystallisation from acetone gave the required toluene-*p*-sulphonate (460 mg., 82%), needles m. p. 140—141° decomp., $\nu_{max.}$ 1730, 1600 cm.$^{-1}$ (Found: C, 68·4; H, 8·5. $C_{30}H_{44}O_6S$ requires C, 67·7; H, 8·3%).

5α-*Pregnane*-17α,20β,21-*triol* 17α,21-*Diacetate* 20-*Toluene*-p-*sulphonate*.—The 20-toluene-*p*-sulphonate 21-monoacetate (360 mg.) and toluene-*p*-sulphonic acid (74 mg.) were shaken with glacial acetic acid (11 c.c.) and acetic anhydride (5·5 c.c.) for 4 days at room temperature, after which all the compound had dissolved; the mixture was set aside for a further 2 days, then diluted with ether. The usual working up (evaporation under a vacuum at room temperature) afforded a residue which on recrystallisation from ether–light petroleum gave 5α-*pregnane*-17α,20β,21-*triol* 17α,21-*diacetate* 20-*toluene*-p-*sulphonate* (236 mg., 69%). A pure sample formed needles, m. p. 109—110° (decomp.), $\nu_{max.}$ 1750, 1740, 1600 cm.$^{-1}$ (Found: C, 66·8; H, 8·4. $C_{32}H_{46}O_7S$ requires C, 66·9; H, 8·1%).

20α,21-*Diacetoxy*-5α-*pregnan*-17α-*ol* (IX; R = Ac).—The above diacetate toluene-*p*-sulphonate (206 mg.) and potassium acetate (4 g.) were refluxed with 96% aqueous acetic acid (32 c.c.) containing acetic anhydride (1·6 c.c.) for 3 hr. The mixture was left at room temperature overnight, poured into ice–water, and extracted with chloroform. The usual working up

gave a residue (153 mg.), which on recrystallisation from benzene–light petroleum gave the required *diacetate* as fine angular crystals (113 mg.). An analytical sample had m. p. 258—259° (sealed tube), $\nu_{max.}$ 1720, 1750 cm.$^{-1}$ (split ester C=O) (Found: C, 71·4; H, 9·6. $C_{25}H_{40}O_5$ requires C, 71·4; H, 9·5%).

5α-*Pregnane*-17α,20α,21-*triol* (IX; R = H).—The diacetate (95 mg.) was hydrolysed as described for the preparation of the 17α,20α-diol. Recrystallisation from benzene–light petroleum gave 5α-*pregnane*-17α,20α,21-*triol* (69 mg.). Further recrystallisation from benzene gave needles, m. p. 232—233° (sublimation) (Found: C, 74·9; H, 10·8. $C_{21}H_{36}O_3$ requires C, 74·9; H, 10·8%).

5α-*Pregnane*-17α,20α(and 20β),21-*triol* 20,21-*Dibenzoates*.—21-Acetoxy-17α-hydroxy-5α-pregnan-20-one (VII; X = OAc) (266 mg.) was hydrogenated in ethanol (50 c.c.) with Raney nickel at 80°/100 atm. for 4 hr. The mixture was filtered and evaporated to dryness. The residue was hydrolysed as described in the preparation of the 17α,20α-diol, and benzoylated in the usual manner. Several chromatograms on alumina were necessary to separate the isomeric triol dibenzoates. Elution with benzene–light petroleum (50 : 50) gave the 20β,21-*dibenzoate* (112 mg., 31%). A pure sample recrystallised from heptane formed needles, m. p. 154—155°; the melt resolidified immediately to flat needles, m. p. 163—164°, $\nu_{max.}$ 1715 cm.$^{-1}$ (Found: C, 77·2; H, 8·3. $C_{35}H_{44}O_5$ requires C, 77·2; H, 8·1%).

The second product, the 20α,21-*dibenzoate*, was eluted with benzene–light petroleum (55 : 45); it recrystallised from heptane as needles (25 mg., 9%), m. p. 179—180°, $\nu_{max.}$ 1715 cm.$^{-1}$ (Found: C, 77·5; H, 7·9%).

The identities of the two dibenzoates were established by hydrolysis to the triols and acetylation to the diacetates.

21-*Acetoxy- and* 21-*Hydroxy*-5α-*pregnan*-20-*one* (X; R = Ac and H).—The acetate obtained from Messrs. Parke Davis & Co., Detroit, Mich., after recrystallisation from methanol, had m. p. 207—208·5° (lit.,[18] m. p. 197—200°). 21-Hydroxy-5α-pregnane-20-one (X; R = H) obtained by the hydrolysis of the monoacetate under the conditions used for the preparation of (VII; X = OH) had m. p. 120—121° (lit.,[18] 115—117°).

5α-*Pregnane*-20α(and 20β),21-*diol Dibenzoates*.—21-Acetoxy-5α-pregnan-20-one (X; R = Ac) (500 mg.) was hydrogenated over Raney nickel (50 mg.; W-6) at 90°/70 atm. in absolute ethanol for 5 hr. The mixture was filtered and evaporated to dryness. The residue was hydrolysed as described above and benzoylated in the usual manner. The crude dibenzoates were separated on alumina, elution being with increasing proportions of benzene in light petroleum. The less polar 20α,21-*dibenzoate* (XI; R = Bz) (119 mg., 17%) was obtained as flat needles, m. p. 115—116° (from light petroleum), $\nu_{max.}$ 1720 cm.$^{-1}$ (Found: C, 79·3; H, 8·3. $C_{35}H_{44}O_4$ requires C, 79·5; H, 8·4%). The more polar 20β,21-*dibenzoate* (XII; R = Bz) was obtained as long needles (287 mg., 40%), m. p. 175—176° (from acetone–light petroleum), $\nu_{max.}$ 1725 cm.$^{-1}$ (Found: C, 79·6; H, 8·4%).

5α-*Pregnane*-20β,21-*diol* (XII; R = H).—The preceding dibenzoate was hydrolysed as described for the preparation of the diol (V; R = H). The residue (190 mg.), on recrystallisation from acetone–hexane, gave the required *diol* (128 mg.) as needles, which on being heated changed their crystalline form to small plates, m. p. 169—171°. An analytical sample sublimed under a high vacuum had m. p. 173—175° (Found: C, 78·5; H, 11·2. $C_{21}H_{36}O_2$ requires C, 78·7; H, 11·3%). The 20β,21-*diacetate*, prepared in the usual manner, formed needles, m. p. 87—90° (from methanol), $\nu_{max.}$ 1745 cm.$^{-1}$ (Found: C, 74·3; H, 10·0. $C_{25}H_{40}O_4$ requires C, 74·2; H, 9·9%). The last two products were first prepared by Dr. Sheila Palmer at the Postgraduate Medical School of London.

5α-*Pregnane*-20α,21-*diol* (XI; R = H).—The 20α,21-diol dibenzoate was hydrolysed as described for the preparation of the diol (V; R = H). The 20α,21-*diol*, recrystallised from acetone–hexane and acetone, formed needles, double m. p. 185—186° and 191—192° (Found: C, 78·7; H, 11·2. $C_{21}H_{36}O_2$ requires C, 78·5; H, 11·3%). The 20α,21-*diacetate* prepared in the usual manner and recrystallised from pentane formed needles, m. p. 159—159·5°, $\nu_{max.}$ 1745 cm.$^{-1}$ (Found: C, 74·0; H, 10·2. $C_{25}H_{40}O_4$ requires C, 74·2; H, 10·0%).

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[18] Marker, *J. Amer. Chem. Soc.*, 1940, **62**, 2543.

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