229. *Urinary Steroids and Related Compounds. Part VI.*[1] 16,20-*Disubstituted 5α-Pregnanes Carrying no other Substituents in the Phenanthrene Nucleus.*

By J. C. Danilewicz and W. Klyne.

A series of 16,20-disubstituted 5α-pregnanes carrying no other substituents in the phenanthrene nucleus has been prepared. Intramolecular hydrogen bonding in the 16,20-diols and optical rotatory dispersion measurements on 16-substituted 20-ketones have given much information on the preferred conformation of the pregnane side-chain. A method for the inversion of configuration at C-20 in 16,20-diols is described.

The preferred conformation of the two-carbon side-chain of pregnane derivatives has been the subject of speculation for some years.[2] For 20-oxopregnanes (I) early arguments based on the stereochemistry of hydrogenation,[3] and subsequent measurements of optical rotatory dispersion [4-6] and dipole moments,[7] have indicated that the preferred conformation of the acetyl side-chain is that shown in structure (I*a*).*

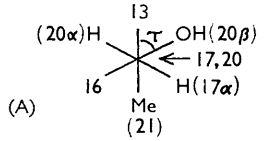
The carbonyl group extends towards C-16, and the C-21 methyl group extends away from ring D towards the rear. Models of 20-hydroxypregnanes indicate that the preferred conformations of the side-chains for 20α- and 20β-ols (II, III) are as shown in formulæ (II*a*) and (III*a*), respectively. In each case the hydrogen atom, being the least bulky substituent, extends over the ring. Two spectroscopic observations substantiate this assumption. Jones *et al.*[9] have shown that in 12α-acetoxy-20-ols only the 20β-isomer exhibits intramolecular hydrogen bonding, while Hirschmann and Daus [10] have shown that in 16α-acetoxy-20-ols only the 20α-isomer shows this phenomenon. (In the latter study, however, spectra were taken in the solid state and should be interpreted with caution.[11])

A series of 5α-pregnane derivatives carrying substituents only at positions 16 and 20 is described in this work. Examination of these simplified structures by infrared spectroscopy and optical rotatory dispersion has given further information on the preferred conformation of the side-chain, in both 20-oxo- and 20-hydroxy-compounds.

Crabbé *et al.*[12] have prepared an extensive series of 16-substituted pregnan-20-ones and

* Roman numerals (I, II, etc.) are employed as usual to designate structural formulæ of compounds. Different *conformations* of the same structure are indicated by *italic* lower-case letters (*a*, *b*, *c*) following the Roman numerals. Octant projections are indicated by the same *italic* lower-case letters doubled (*aa*, *bb*).

The conformations around the C-20, C-17 bond are described in terms of the approximate torsion angle, τ (or the qualitative terms proposed by Klyne and Prelog [8]) between the O–C-20 and the C-17, C-13 bonds, as in (A).



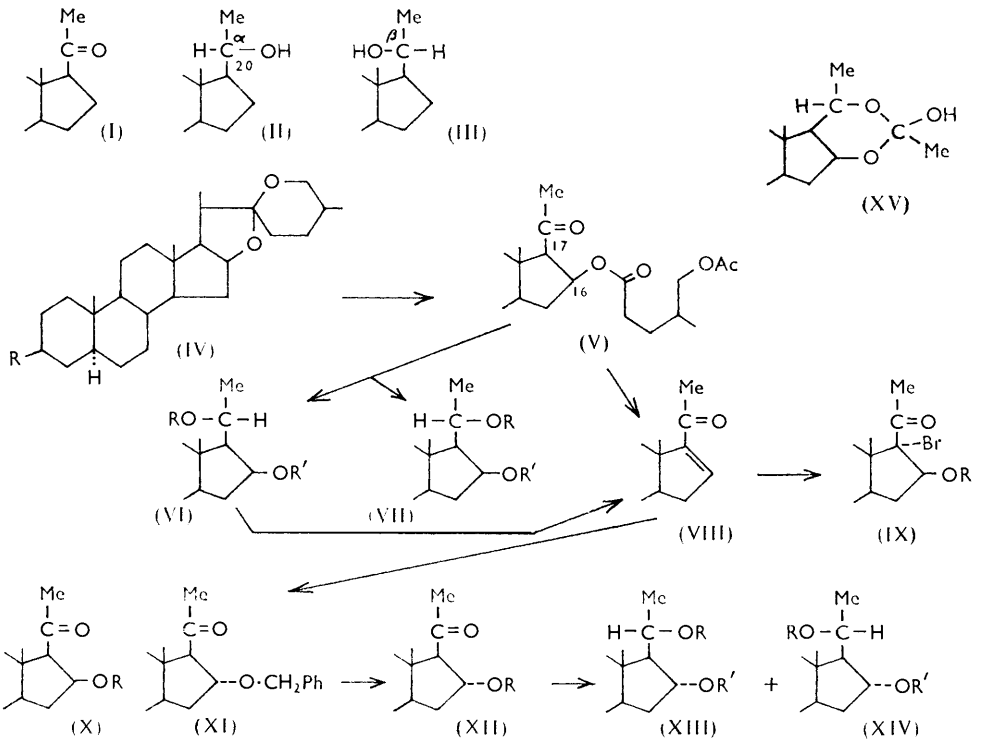
(A) $\tau = -60°$ Conformation O–C-20–C-17–C-13 is — sc (*syn*-clinal)

[1] Part V, Danilewicz, Garbutt, Horeau, and Klyne, *J.*, 1964, 2254.
[2] Rakhit and Engel, *Canad. J. Chem.*, 1962, **40**, 2163.
[3] Klyne, *Ciba Foundation Colloquia on Endocrinology*, 1953, **7**, 127.
[4] Djerassi, Fornaguera, and Mancera, *J. Amer. Chem. Soc.*, 1959, **81**, 2383.
[5] Moffitt, Woodward, Moscowitz, Klyne, and Djerassi, *J. Amer. Chem. Soc.*, 1961, **83**, 4013.
[6] Djerassi and Klyne, *J.*, 1962, 4929.
[7] Allinger and Da Rooge, *J. Amer. Chem. Soc.*, 1961, **83**, 4256.
[8] Klyne and Prelog, *Experientia*, 1960, **16**, 521.
[9] Jones, Humphries, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2820.
[10] Hirschmann and Daus, *J. Org. Chem.*, 1959, **24**, 1114.
[11] Danilewicz and Klyne, *J.*, 1962, 4950.
[12] Crabbé, Guerrero, Romo, and Sanchez-Viesca, *Tetrahedron*, 1963, **19**, 25, 51.
[12a] Crabbé, McCapra, Comer, and Scott, *Tetrahedron*, 1964, **20**, 2455.
[12b] Cross and Beard, *J. Amer. Chem. Soc.*, 1964, **86**, 5317.

17β(H)(17-iso-) pregnan-20-ones (with 5-en-3β-ol or 4-en-3-one groups in the A and B rings), and have studied their optical rotatory dispersion curves. Most of these compounds carry carboxyl and related groups at C-16, but Crabbé's results for 16-methyl compounds are noted in appropriate sections below. Reference is also made to recent work by Snatzke, Pieper, and Tschesche [13] on the circular dichroism of 20-oxo-steroids, including 16α- and 16β-methyl substituted compounds.

The starting material for the series was 3-deoxytigogenin (IV; R = H_2) (5α-spirostan), prepared from tigogenin (IV; R = H,OH) by chromium trioxide oxidation of the 3β-hydroxyl group, formation of the ethylene dithioketal and Raney nickel desulphurisation.

16β,20-*Diols and Related Compounds.*—3-Deoxytigogenin (IV; R = H_2) on treatment with acetic anhydride containing a catalytic amount of toluene-*p*-sulphonic acid afforded the pseudoacetate, which was then degraded to 16β-(γ-methyl-δ-acetoxyvaleroxy)-5α-pregnan-20-one (V).[14] A small portion of this crude product was reduced with lithium aluminium hydride. Careful chromatography afforded 5α-pregnane-16β,20α-diol (VII; R = R′ = H) and 5α-pregnane-16β,20β-diol (VI; R = R′ = H) in 7% and 30% yield, respectively. The 16β,20α-diol was also obtained directly from 3-deoxytigogenin by Marker's peracid degradation.[15] The major part of the 16β-ester (V), dissolved in light petroleum, was placed on a mildly alkaline alumina column, and the 5α-pregn-16-en-20-one

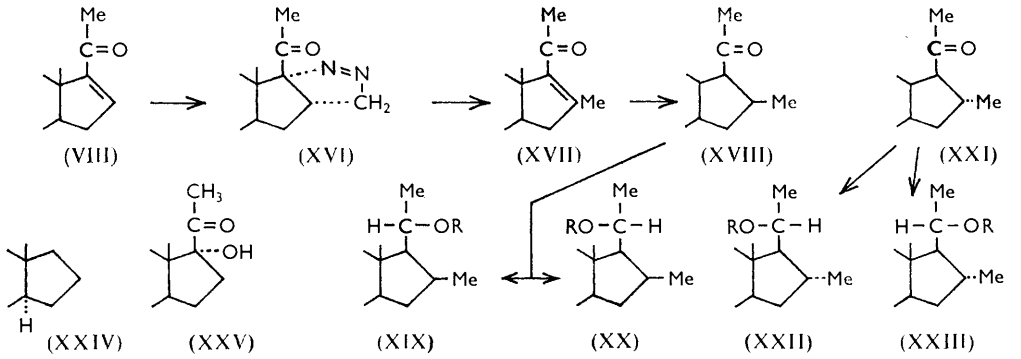


(VIII), which was formed, was eluted with light petroleum (50% overall yield from 3-deoxytigogenin). The action of *N*-bromoacetamide on 5α-pregn-16-en-20-one (VIII) gave 17α-bromo-16β-hydroxy-5α-pregnan-20-one (IX; R = H);[14,16] the acetate (IX; R = Ac) was prepared by the action of acetyl hypobromite on the unsaturated ketone (VIII).[17]

[13] Snatzke, Pieper, and Tschesche, *Tetrahedron*, 1964, **20**, 107.
[14] Löken, Kaufmann, Rosenkranz, and Sondheimer, *J. Amer. Chem. Soc.*, 1956, **78**, 1738.
[15] Marker, Rohrmann, Crooks, Wittle, Jones, and Turner, *J. Amer. Chem. Soc.*, 1940, **62**, 525.
[16] Gansau, Thesis, Technische Universität, Berlin-Charlottenburg, 1952.
[17] Levine and Wall, *J. Amer. Chem. Soc.*, 1959, **81**, 2826, 2829.

The preparation of 16β-hydroxy-5α-pregnan-20-one (X; R = H) by the debromination of the 17α-bromo-derivative (IX; R = H) using palladium-charcoal, as described for another series by Sondheimer and his co-workers,[14] proved unsuccessful. Complete elimination of bromine and the hydroxy-group occurred within five minutes, affording 5α-pregnan-20-one; addition of ammonium acetate, sodium acetate, or pyridine merely served to slow this reaction. Gansau's original method [14,16] involving the use of zinc in acetic acid was therefore employed, and gave a 23% yield of the required ketol (X; R = H). The identity of this compound was verified by its behaviour on brief exposure to alumina, which yielded 5α-pregn-16-en-20-one (VIII), and on reduction with sodium borohydride which gave 5α-pregnane-16β,20β-diol (VI; R = R′ = H).

16α,20-*Diols and Related Compounds.*—The 16α-oxygenated derivatives were prepared *via* 16α-benzyloxy-5α-pregnan-20-one (XI), which was obtained by equilibrating 5α-preg-16-en-20-one (VIII) with potassium hydroxide in benzyl alcohol under nitrogen.[10] Hydrogenolysis of the benzyl ether (XI) using palladium–charcoal gave 16α-hydroxy-5α-pregnan-20-one (XII; R = H) in 97% yield. Catalytic reduction of the acetate (XII; R = Ac) using Adams catalyst in acetic acid, followed by recrystallisation and chromatography, gave two products, 16α-acetoxy-5α-pregnan-20β-ol and -20α-ol (XIV and XIII; R = H, R′ = Ac) in 90% and 2·7% yields, respectively. As the yield of the 20α-isomer in the above reaction was very low, we sought a method for inverting the configuration at C-20 of the abundant 16α-acetoxy-5α-pregnan-20β-ol. Of the methods available, that devised by Fukushima, Gallagher *et al.*[18] for the inversion of the configuration at C-20 in 17α,20β-diols appeared the most hopeful approach. 16α-Acetoxy-5α-pregnan-20β-yl toluene-*p*-sulphonate (XIV; R = Tos, R′ = Ac) was refluxed with sodium acetate in 96% aqueous acetic acid. Rearrangement occurred, presumably *via* an orthoester intermediate (XV),[19,20] and any complications arising from the formation of



the 16α- or 20α-monoacetate were eliminated by hydrolysis of the crude product. Chromatography gave in 26% overall yield 5α-pregnane-16α,20α-diol (XIII; R = R′ = H) identical with the product previously described.

16-*Methyl*-20-*substituted Derivatives.*—5α-Pregn-16-en-20-one (VIII) reacted with diazomethane to form the pyrazoline derivative (XVI), which when heated at its melting point under vacuum decomposed to give 16-methyl-5α-pregn-16-en-20-one (XVII).[21] Catalytic reduction of the double bond gave 16β-methyl-5α-pregnan-20-one (XVIII).[22,23] Reduction of this ketone with lithium aluminium hydride and chromatography on alumina

[18] Fukushima, Leeds, Bradlow, Kritchevsky, Stokem, and Gallagher, *J. Biol. Chem.*, 1955, **212**, 449.
[19] Winstein, Hess, and Buckles, *J. Amer. Chem. Soc.*, 1942, **64**, 2780, 2787, 2796.
[20] Winstein, Grunwald, and Ingraham, *J. Amer. Chem. Soc.*, 1948, **70**, 821.
[21] Wettstein, *Helv. Chim. Acta*, 1944, **27**, 1803.
[22] Taub, Hoffsommer, Slates, Kuo, and Wendler, *J. Amer. Chem. Soc.*, 1960, **82**, 4012.
[23] Attenburrow, Connett, Graham, Oughton, Ritchie, and Wilkinson, *J.*, 1961, 4547.

then gave 16β-methyl-5α-pregnan-20β-ol and -20α-ol (XX and XIX; R = H) in 24% and 53% yields, respectively.

Treatment of 5α-pregn-16-en-20-one with methylmagnesium iodide gave 16α-methyl-5α-pregnan-20-one (XXI).[24] Reduction of this compound with lithium aluminium hydride, followed by careful chromatography on alumina, gave the two isomeric 16α-methyl-20-ols (XXII and XXIII; R = H) in 72 and 12% yield, respectively.

Results and Discussion

Infrared Spectra.—Intramolecular hydrogen bonding in diols. In diols where the O · · · H distance (L) is less than about 2·7 Å (the maximum distance observed at which intramolecular hydrogen bonding occurs, *e.g.*, in ethylene glycol) an intramolecular hydrogen bond is formed, and two bands are observed in the hydroxyl-stretching region of the spectrum (~3620 cm.$^{-1}$).[25] One band is due to the free hydroxyl group absorbing at its normal frequency (a small shift of 1—5 cm.$^{-1}$ to higher frequencies is sometimes observed), and the other band is due to the bonded hydroxyl group, which is displaced to lower frequencies (cf. recent work by Dalton, McDougall, and Meakins [26] on 3,5-disubstituted steroids). The closer the two hydroxyl groups are to one another, the greater the displacement ($\Delta\nu$).[27] It should, however, be pointed out that $\Delta\nu$ is not the difference between the frequencies of the two measured peaks, but the difference between the frequency of the hydrogen-bonded hydroxyl group, and the frequency of the same hydroxyl group when free.[28] This is particularly important because hydroxyl groups absorb at different frequencies varying from 3644 to 3610 cm.$^{-1}$ depending on whether they are primary, secondary, or tertiary, and on their stereochemistry.

Kuhn [25] obtained an inverse empirical relationship between $\Delta\nu$ and the hydrogen-bonding distance (L); his equation has been revised by Brutcher and Bauer [29] as follows:

$$\Delta\nu = [42{\cdot}5/(L - 1{\cdot}4)] - 3{\cdot}5$$

This equation assumes [29] that bond angles and bond lengths remain constant with varying degrees of substitution on the carbon atom, and with strength of the hydrogen bonds. However, in spite of these approximations, it provides a useful guide to the stereochemistry of hydrogen-bonded diols.

Intramolecular hydrogen bonding is also possible in 1,3-diols provided that the hydroxyl groups can approach one another. Cyclohexane-*cis*-1,3-diol exhibits two bands at 3619 and 3544 cm.$^{-1}$ ($\Delta\nu$ = 75 cm.$^{-1}$).[25] Applying the equation we find that L = 1·94 Å, a value which shows that both hydroxyl groups are axial. Strong intramolecular hydrogen bonding has also been shown in bicyclo[2,2,1]heptane-2,7-diol [30] (3621 and 3545 cm.$^{-1}$; $\Delta\nu$ = 76 cm.$^{-1}$) and bicyclo[3,2,1]octane-*cis*-2,8-diol (3620 and 3520 cm.$^{-1}$; $\Delta\nu$ = 100 cm.$^{-1}$).[31]

The results obtained for the four isomeric 16,20-diols are given in Table 1; it is clear that the 16α,20α- and 16β,20α-diols are intramolecularly hydrogen-bonded, while the 20β-isomers are not. Whether the hydrogen of the C-16 or that of the C-20 hydroxyl group is involved in the hydrogen bond is uncertain. However, if the frequency of the bonded hydroxyl group is taken as 3622 cm.$^{-1}$ when free, then the $\Delta\nu$ values for the 16α,20α- and 16β,20α-diols are 54 and 52 cm.$^{-1}$, giving hydrogen-bond lengths of 2·14 and 2·17 Å, respectively. Our results (in solution) confirm the findings of Hirschmann and Daus [10]

[24] Heusler, Kebrle, Meystre, Ueberwasser, Wieland, Anner, and Wettstein, *Helv. Chim. Acta*, 1959, **42**, 2043.
[25] Kuhn, *J. Amer. Chem. Soc.*, 1952, **74**, 2492; 1954, **76**, 4323; 1958, **80**, 5950.
[26] Dalton, McDougall, and Meakins, *J.*, 1963, 4068.
[27] Badger, *J. Chem. Phys.*, 1940, **8**, 288.
[28] Cole and Jeffries, *J.*, 1956, 4391.
[29] Brutcher and Bauer, *J. Amer. Chem. Soc.*, 1962, **84**, 2233, 2236.
[30] Kwartz and Vosburgh, *J. Amer. Chem. Soc.*, 1954, **76**, 5400.
[31] Kwartz and Gatos, *J. Amer. Chem. Soc.*, 1958, **80**, 881.

TABLE 1.

Infrared spectra of 16,20-diols; hydroxyl stretching frequencies.

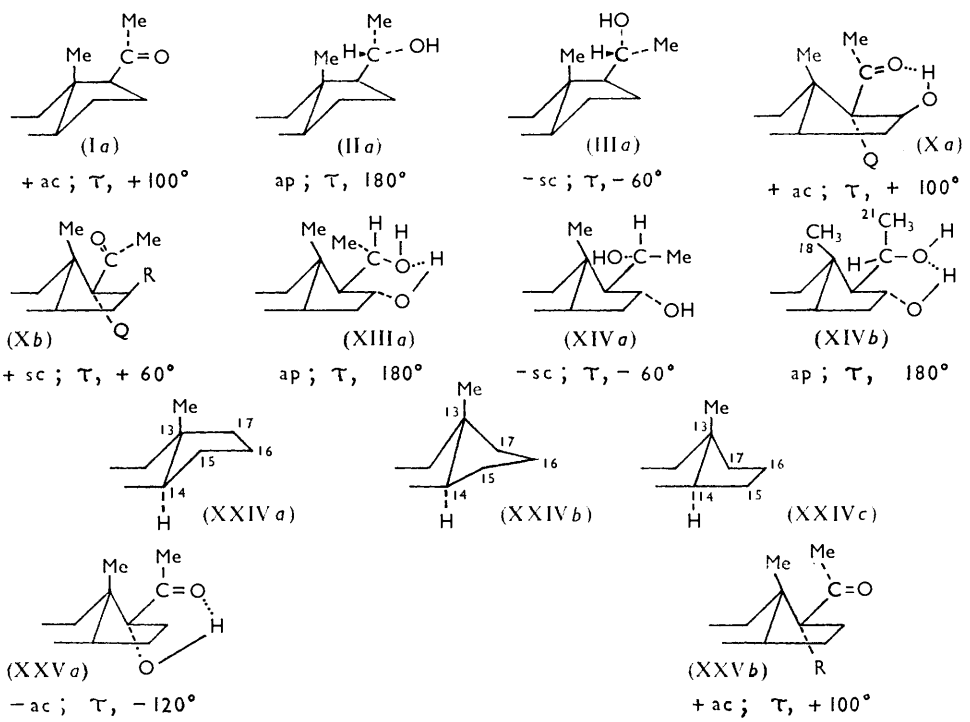
Measured in CCl_4; evidence for intramolecular hydrogen bonding.

Formula no.	R	R′	Compound 5α-Pregnane	Free OH ν (cm.$^{-1}$)	Free OH ε	Bonded OH ν (cm.$^{-1}$)	Bonded OH ε	Δν (free-bonded) (cm.$^{-1}$)	L (Å)
(XIII)	H	H	16α,20α-$(OH)_2$	3626	67	3568	69	54	2·14
(XIV)	H	H	16α,20β-$(OH)_2$	3621	110	None			
(VII)	H	H	16β,20α-$(OH)_2$	3620	65	3570	65	52	2·17
(VI)	H	H	16β,20β-$(OH)_2$	3629	118	None			
(XIII)	H	Ac	16α-OAc,20α-OH	3615		3515		107	
(XIV)	H	Ac	16α-OAc,20β-OH	3621		None			

(using KBr discs) that the pair of 16α-acetoxy-20-ols follow the same pattern; only the 20α-ol forms an intramolecular hydrogen bond.

These results show that the side-chain cannot rotate freely about the C-17,C-20 bond, even when additional energy might be made available by the formation of a hydrogen-bond after rotation. It is therefore suggested that the preferred conformations of the side-chain in 5α-pregnane-16α,20α-diol and its 20β-isomer are as shown in structures (XIII*a*) and (XIV*a*). Intramolecular hydrogen bonding in the latter compound is precluded, because of the interaction between the two methyl groups (C-18 and C-21) which would result if the 16α- and 20β-hydroxyl groups approached one another as shown in structure (XIV*b*).

Brutcher and Bauer [29] have described three idealised symmetrical conformations for a *trans*-fused steroid D-ring (XXIV). The envelope form (XXIV*a*) has C-14 below the



plane described by C-13, 15, 16, and 17; the half-chair form (XXIV*b*) has C-13 and 14 at equal distances above and below the plane of C-15, 16, and 17, and the envelope form (XXIV*c*) has C-13 above the plane of C-14, 15, 16, and 17. Models representing 5α-pregnane-16α,20α-diol show that the minimum intramolecular hydrogen-bonding distances

possible with the D-ring in conformations (XXIV*a*, *b*, and *c*) are 2·9, 2·6, and 2·2 Å, respectively. The D-ring in this diol must therefore tend to the envelope form (XXIV*c*), because only this conformation can accommodate a hydrogen bond-length near to the experimental value of 2·14 Å (Table 1). No comparable conclusions can be reached regarding the preferred conformation of the D-ring in 5α-pregnane-16β,20α-diol, because the models show that the minimum hydrogen-bonding distances for conformations (XXIV*a* and *c*) are 1·1 and 1·3 Å, so that the hydrogen bond length of 2·17 Å (Table 1) can be accommodated by either. Extending the argument to the 12β,20β-diols, models show that these can take up conformations in which their two hydroxyl groups are close together (L ~1·6 Å). 3β-Acetoxy-5α-pregnane-12β,20β-diol exhibits two bands (3613 cm.$^{-1}$, $\varepsilon = 60$; 3446 cm.$^{-1}$, $\varepsilon = 100$; $\Delta\nu = 167$ cm.$^{-1}$). The unusually large $\Delta\nu$ value corresponds

TABLE 2.

Infrared spectra of ketols; hydroxyl and carbonyl stretching frequencies.

Measured in CCl_4; evidence for intramolecular hydrogen bonding. Values (except for that marked *, which is from this laboratory) are from Dr. G. D. Meakins, Oxford.

Formula		Compound	Free OH		Bonded OH		Free C=O		Bonded C=O	
no.	R	5α-Pregnan-20-one	$\nu_{max.}$	ε	$\nu_{max.}$	ε	$\nu_{max.}$	ε	$\nu_{max.}$	ε
(XXV)	—	17α-OH	3618	40	3510	38	1710	300	1693	210
(XII)	H	16α-OH*	3621	82						
(X)	H	16β-OH	3620	15	3472	40	1713	80	1688	545
(IX)	H	17α-Br,16β-OH	3627	15	3526	65				

to a hydrogen-bonding distance between 1·4 and 1·8 Å. A 12β,20α-diol was not available for study, but the above discussion suggests that diols of this type would not form intramolecular hydrogen bonds.

Intramolecular hydrogen bonding in ketols. Jones *et al.*[9] showed that 17α-hydroxy-20-ketones exhibited partial intramolecular hydrogen bonding as doublets were observed in the hydroxyl and carbonyl stretching regions of the spectrum (measured in carbon tetrachloride). Results obtained in the present work for 17α-hydroxy-5α-pregnan-20-one (XXV) are given in Table 2. Hydrogen bonding is incomplete and it is suggested that the side-chain exists in the two conformations (XXV*a* and XXV*b*; R = OH) in approximately equal proportions. In the bonded form (XXV*a*) the keto-group extends towards the 17α-hydroxy group, while in the unbonded form (XXV*b*; R = OH) it extends towards C-16. In 16β-hydroxy-5α-pregnan-20-one and its 17α-bromo-derivative (X*a*; Q = H and Q = Br), the keto and hydroxyl groups in their preferred conformations can come very close together, and virtually complete hydrogen bonding is observed (Table 2). In 16α-hydroxy-5α-pregnan-20-one (XII; R = H) the two functional groups are so far apart that no intramolecular hydrogen bond is observed. These results agree with those of Jones *et al.*[9]

Olson and Alway [32] recently detected hydrogen bonding between 17-hydroxyl and 20-oxo-groups by the study of derivative ultraviolet spectra; Rinehart and Pschigoda [33] have found that in Nujol mulls the carbonyl frequencies of 21-acetoxy-20-oxosteroids are little affected by substituents at C-16 and C-17.

Optical Rotatory Dispersion.—The results obtained are shown in Tables 3, 4, and 5.

Non-ketones. In agreement with the general rule for D-line rotations [34] the 20β-ols on acetylation exhibited a larger molecular rotation increment than their 20α-isomers (cf. 11). Measurements at low wavelengths, for which we thank Mr. J. P. Jennings,[35] show that 20-acetates exhibit a Cotton effect at about 220 mμ. Values obtained for a

[32] Olson and Alway, *Analyt. Chem.*, 1960, **32**, 370.
[33] Rinehart and Pschigoda, *Steroids*, 1963, **2**, 237.
[34] Fieser and Fieser, "Steroids," Reinhold Publ. Corp., New York, 1959, pp. 612—616.
[35] Jennings, *Biochem. J.*, 1963, **86**, 16*P*.; Gillham and King, *J. Sci. Instr.*, 1961, **38**, 21.

TABLE 3.

Rotatory dispersion data for non-ketonic 5α-pregnane derivatives.

Plain curves; determined in methanol.
(Cf. ref. 11)

Formula no.	R	R′	Derivative 5α-Pregnane	Molecular rotation [φ] at λ (mμ) 600	400	300
—			16α-OH	−75	−130	−245
—			16α-OAc	−255	−615	−1240
(XIII)	H	H	16α,20α-$(OH)_2$	−60	−65	−155
,,	H	Ac	16α-OAc,20α-OH	−230	−555	−1115
,,	Ac	Ac	16α,20α-$(OAc)_2$	−290	−600	−1160
(XIV)	H	H	16α,20β-$(OH)_2$	−100	−190	−360
,,	H	Ac	16α-OAc,20β-OH	−280	−680	−1425
,,	Ac	Ac	16α,20β-$(OAc)_2$	−230	−475	−840
(VII)	H	H	16β,20α-$(OH)_2$	+130	+325	+690
,,	Ac	Ac	16β,20α-$(OAc)_2$	+195	+455	+860
(VI)	H	H	16β,20β-$(OH)_2$	+95	+200	+425
,,	Ac	Ac	16β,20β-$(OAc)_2$	+275	+630	+1410
(XXIII)	H	—	16α-Me,20α-OH	+10	+50	+137
,,	Ac	—	16α-Me,20α-OAc	0	−25	−37
(XXII)	H	—	16α-Me,20β-OH	−10	−10	−5
,,	Ac	—	16α-Me,20β-OAc	+110	+270	+735
(XIX)	H	—	16β-Me,20α-OH	+85	+230	+500
,,	Ac	—	16β-Me,20α-OAc	+130	+315	+605
(XX)	H	—	16β-Me,20β-OH	+65	+170	+375
,,	Ac	—	16β-Me,20β-OAc	+215	+480	+1120

TABLE 4.

Rotatory dispersion data for ketonic 5α-pregnane derivatives.

Extrema and amplitudes for Cotton effects, except where stated otherwise (cf. ref. 11).

(A) Measurements in methanol.

Formula no.	R	5α-Pregnan-20-one Saturated ketones	First extremum [φ]	λ (mμ)	Second extremum [φ]	λ (mμ)	Amplitude *a*
(XXI)	—	16α-Me	+9070	309	−11,350	265	+204
(XVIII)	—	16β-Me	+1050	327	+360	290	+7
(XII)	H	16α-OH	+7360	308	−9475	265	+168
(X)	H	16β-OH	Plain curve, see note (*a*)				0
(XII)	Ac	16α-OAc	+7600	307	−9785!*	265!*	+174!*
(X)	Ac	16β-OAc	+715	330	+120	297	+6
(XI)	—	16α-O·CH_2Ph	+7550	309	−10,880!	267!	+184!
(IX)	H	16β-OH,17α-Br	+6660	331	−11,325	275	+180
(IX)	Ac	16β-OAc,17α-Br	+7910	330	−10,225	277	+181
		Miscellaneous					
(XVI)	—	16α,17α-Pyrazoline derivative	+18,500	346	−26,360	315	+450
(VIII)	—	16-ene	+3100	352	−5890	292	+90
(XVII)	—	16-ene,16-Me	+3525	349	−14,700!	285!	+182!

(B) Measurements in hexane.

		5α-Pregnan-20-one Saturated ketones					
(XII)	H	16α-OH	+6460	315	−8290	268	+148
(X)	H	16β-OH	+7425	315	−6000	272	+134
(X)	Ac	16β-OAc	+352	337	−238	310	+7
(XVIII)	—	16β-Me	+850	334	+140	300	+7
(IX)	H	16β-OH,17α-Br	−1750	320	+4350!	280!	−61!
(IX)	Ac	16β-OAc,17α-Br	+8570	335	−11,435	280	+200

!* Indicates lowest wavelength reached, *not* second extremum. Amplitude may be larger than value stated. (*a*) $[\phi]_{600} = +180$, $[\phi]_{400} = +310$, $[\phi]_{280} = +950$.

TABLE 5.

Rotatory dispersion data for 20-acetates in hexane.

Compound 5α-Pregnane	First extremum [φ] (x)	First extremum λ (mμ)	Rotation at lowest wavelength recorded [φ] (y)	Rotation at lowest wavelength recorded λ (mμ)	a!* (x − y)/100
20β-OAc †	+2650	232	+1160	217	+15
20α-OAc †	−725	234	+2750	208	−35
17α-OH,20β-OAc	+2470	238	−1200	208	+37
17α-OH,20α-OAc	−1640	234	0	208	−16
16β-CH_3,20β-OAc	+3260	234	−355	208	+36
16β-CH_3,20α-OAc	−50	236	+3170	208	−32

a!* = Amplitude (incomplete). † Cf. ref. 1.

number of compounds with the Bellingham and Stanley/Bendix-Ericsson spectropolarimeter " Polarmatic '62 " [36] are given in Table 5.

In each of the pairs of compounds studied, the 20α- and 20β-acetates gave negative and positive Cotton effects, respectively. In the future such observations on acetates may serve as better evidence of configuration at C-20 than measurements of rotation at the D-line.[34]

Ketones. Data obtained for the 16-substituted 20-ketones are given in Table 4. The preferred conformation of the acetyl side-chain in 20-ketones not substituted at 16 or 17 is as represented by formula (I*a*); the Octant [5] projection (XXV*bb*; R = H) is in agreement with the large positive Cotton effects obtained [11] for these compounds (*a*, = +192) (cf. ref. 7).

The 16α-substituted 20-ketones prepared in this work all showed large effects of the same magnitude (*a* = +160 to +200). It is reasonable to suggest that 16α-substituents have little effect on the preferred conformation of the side-chain (I*a*) so that Octant projections of the type (XXV*bb*; R = H, with substituent at 16α) are retained (cf. work by Crabbé [12a,*] on O.R.D. curves and Snatzke [13] on C.D. curves of related compounds).

In the three 16β-substituted 20-ketones, however, the amplitudes were much reduced. 16β-Methyl- and 16β-acetoxy-5α-pregnan-20-one gave small positive effects (*a*, = +7), while 16β-hydroxy-5α-pregnan-20-one gave a plain curve in methanol. In these compounds the preferred conformation can no longer be that shown in structure (I*a*), but the keto-group must now extend over the ring in a position approximately equidistant from the C-13 methyl group and the 16β-substituent (X*b*; Q = H). The Octant projection (X*bb*; Q = H) now places the keto-group in a more symmetrical environment, thus rationalising the low amplitude values (cf. small Δε values found by Snatzke [13] for a 16β-methyl-20-one). Crabbé [12] gives a large negative amplitude (−86) for a 16β-methyl-20-one and suggests (no doubt correctly) that in this compound inversion at C-17 has occurred to give the 17β-*H*-compound (cf. refs. 1 and 13).

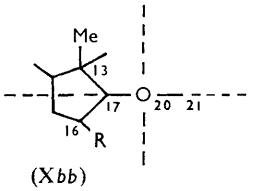
Djerassi *et al.*[4] have previously shown that 17α-bromo-20-ketones give negative Cotton effects, and this finding was explained on the basis of the halogeno-ketone rule (as a forerunner of the Octant rule [5]) in terms of the conformation (XXV*bb*; R = Br). 16β-Hydroxy- and 16β-acetoxy-17α-bromo-5α-pregnan-20-ones (IX; R = H and Ac) appear on first inspection to contradict this finding, since both give large positive effects (*a*, = +180 and +181). If, however, the preferred conformation of the side-chain is that shown as (X*b*; R = OH or OAc, Q = Br), the Octant projection (X*bb*; R = OH or OAc, Q = Br) places the 17α-bromine atom in the horizontal symmetry plane, and a negative effect is no longer expected.

Hydroxy-ketones. We have already indicated (see p. 1311) that 17α-hydroxy-20-ones

* An important parallel study of O.R.D. and C.D. curves by Crabbé, McCapra, Comer, and Scott has just appeared [12a]; see also n.m.r. studies (Cross and Beard [12b]); we are indebted to Dr. P. Crabbé, and Dr. A. D. Cross, Syntex, S.A., for copies of their manuscripts before publication.

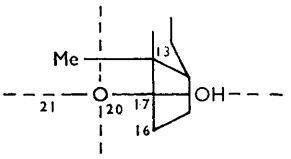
[36] Jennings and Klyne, *Biochem. J.*, 1963, **86**, 12*P*.

exhibit partial intramolecular hydrogen bonding, and that there are at least two preferred conformations of the side-chain represented by (XXV*a*) and (XXV*b*; R = OH). The corresponding Octant projections (XXV*aa*) and (XXV*bb*; R = OH) would indicate negative and positive Cotton effects, respectively. In methanol, where intramolecular

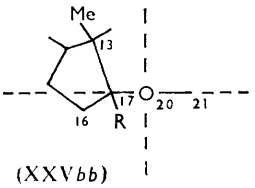


(X*bb*)

(Q lies behind C-17)



(XXV*aa*)



(XXV*bb*)

(If R = H, this is I*aa*)

hydrogen bonding does not take place, a large positive amplitude is obtained (*a*, = +124). In hexane, which was carefully dried for these measurements, both conformations occur, and the negative contribution of (XXV*aa*) results in a much reduced amplitude (*a*, = +40). This behaviour closely resembles that of 1-hydroxy-*p*-menthan-2-one studied by Djerassi and his co-workers.[37] The assumption is made here that the Octant rule can be applied in its original form [5] to hydrogen-bonded carbonyl groups, Dr. G. Snatzke (Bonn) has pointed out to us that this may be unjustifiable, because the shapes of the carbonyl orbitals are certainly modified and made less symmetrical by the hydrogen bonding (*e.g.*, in XXV*a*). However, in the absence of further knowledge about the extent of this distortion, we apply the Octant rule tentatively in its original form.[5]

16β-Hydroxy-5α-pregnan-20-one was shown to form a strong intramolecular hydrogen bond in non-hydroxylic solvents (cf. p. 1311). It may be deduced that in these conditions the keto-group extends towards the 16β-hydroxyl group, the side-chain possessing conformation (X*a*; Q = H), similar to that of unsubstituted 20-ketones. In agreement with this suggestion a large positive Cotton effect (*a* = +134) was found in hexane in contrast with the plain curve (*a* = 0) obtained in methanol (cf. p. 1312). No comparable change in conformation of the side-chain with change in solvent is to be expected for 16β-methyl- and 16β-acetoxy-5α-pregnan-20-one; with these two compounds (XVIII and X; R = Ac) small positive Cotton effects are observed both in methanol and in hexane. Striking solvent differences were also shown by 17α-bromo-16β-hydroxy-5α-pregnan-20-one (IX; R = H). In hexane, the hydroxyl group forms an intramolecular hydrogen bond with the keto-group, and forces the side-chain into a preferred conformation represented by (X*a*; Q = Br). The Octant projection then resembles that of 17α-bromo-20-ketones (XXV*bb*; R = Br), thus explaining the negative Cotton effect observed, in contrast with the large positive effect obtained in methanol. No hydrogen bonding, and no comparable conformational change, are possible for the 16β-acetoxy-compound (IX; R = Ac); the large Cotton effect previously observed in methanol was also found in hexane.

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 vacuum on a steam-bath. Acetylation of a compound in the " usual manner " means that the steroid (100 mg.) was left in pyridine (1 c.c.) overnight at room temperature with acetic anhydride (0·2 c.c. per OH group); the excess of reagent was destroyed with ice, followed by a little water; the suspension was extracted with ether, and the product obtained by the usual working up.

Light petroleum is of b. p. 60—80°. M. p.s were determined on a Kofler apparatus, and are corrected.

Infrared Spectra.—The hydroxyl stretching frequencies reported under " Results and

[37] Djerassi, Records, and Bach, *Chem. and Ind.*, 1961, 258.

Discussion " were recorded by using a Unicam S.P. 700 spectrophotometer. Concentrations were in the order of 0·005—0·002M in AnalaR grade carbon tetrachloride, freshly redistilled from phosphorus pentoxide, and stored over phosphorus pentoxide until used. Measurements were taken using 1 cm. Infrasil cells. The accuracy of any individual measurement was of the order of ± 2 cm.$^{-1}$, and $\Delta\nu$ values for a number of 1,2-diols were identical with those found in the literature. The spectra were comparable in quality with those obtained using an S.P. 100 spectrophotometer in the region of 2—4 μ. The authors are greatly indebted to Dr. G. D. Meakins (Dyson Perrins Laboratory, Oxford University) for this comparison.

Infrared results reported in the Experimental section were obtained in carbon disulphide, using an Infracord spectrophotometer.

Optical Rotatory Dispersion Curves.—These were determined on a Rudolph photoelectric spectropolarimeter (model 200A) as described previously,[11] except for the curves of acetates listed in Table 5 which were measured in hexane on the Bellingham and Stanley/Bendix-Ericsson " Polarmatic '62 " instrument.[35]

Tigogenone.—Tigogenin (59·6 g.) was dissolved in glacial acetic acid (4 l.), 2% chromium trioxide in the same solvent (780 c.c.) was added, and the mixture kept at room temperature overnight. Excess of reagent was destroyed with methanol, and the solvent removed on a rotary evaporator at room temperature. The residue was extracted with ether–chloroform (4 : 1). The usual working up gave a residue which on recrystallisation from benzene–light petroleum gave tigogenone as needles (25 g., 42%), m. p. 204—208° (lit., m. p. 208—210°), $\nu_{max.}$ 1710 cm.$^{-1}$.

3-*Deoxytigogenin* (IV; R = H_2).—Tigonenone (25 g.) was dissolved in dry benzene (1 l.). A small portion (100 c.c.) was distilled off, and the solution cooled. Toluene-*p*-sulphonic acid (200 mg.) and ethane-1,2-dithiol (6 c.c.) were added and the solution refluxed for 4 hr. (continuous water-removal adaptor), after which time no more water was liberated. When the solution was cooled, the ethylene dithioketal crystallised as plates (13·5 g.). The filtrate was evaporated to dryness and extracted with chloroform. The solution was washed with 2N-sodium hydroxide followed by water till neutral. It was then dried (Na_2SO_4), when a white residue (5 g.) was obtained. The whole crude product from this reaction (18·5 g.) was dissolved in ethanol (2 l.) and refluxed for 24 hr. with Raney nickel (from 500 g. alloy). The suspension was filtered hot, and the filtrate evaporated to dryness under vacuum. Recrystallisation from light petroleum gave 3-deoxytigogenin as plates (12 g., 50%), m. p. 174—176° (lit., m. p. 176—177·5°).

5α-*Pregn*-16-*en*-20-*one* (VIII).—3-Deoxytigogenin (11·8 g.; m. p. 174—176°) was dissolved in acetic anhydride (150 c.c.). A small portion (30 c.c.) was distilled off and the solution cooled. Aluminium chloride (1·2 g.) was added, and the solution was refluxed for 4 hr., and allowed to stand overnight. Sodium acetate (3·5 g.) was added to the suspension, which was then diluted with acetic acid (150 c.c.). Chromium trioxide (8·3 g.) in 10% aqueous acetic acid (50 c.c.) was added dropwise over a period of 10 min., the temperature being maintained at 10—12°. After 30 min. the excess of reagent was destroyed with aqueous sodium pyrosulphite, and the solvent removed on a rotary evaporator. The residue was extracted with ether. The usual working-up (at a temperature below 10°) gave crude 16-(γ-methyl-δ-acetoxyvalerate) (V) as a brown gum. A small portion (700 mg.) was set aside for the preparation of diols (VI and VII; R = R′ = H), see below. The remainder was chromatographed on alumina (Savory and Moore, untreated chromatography grade). Light petroleum eluted a fraction which on recrystallisation from the same solvent gave 5α-pregn-16-en-20-one as plates (4·1 g., 50%), m. p. 156—158° (lit., m. p. 156—158°); $\nu_{max.}$ 1670 cm.$^{-1}$; $\lambda_{max.}$ 240 mμ (ε = 10,000).

5α-*Pregnane*-16β,20α-*diol* (VII; R = R′ = H).—3-Deoxytigogenin (1·8 g.) and potassium persulphate (8 g.) were refluxed with 90% aqueous acetic acid (300 c.c.) containing concentrated sulphuric acid (2 c.c.) for 2 hr. Part of the solvent (200 c.c.) was removed at room temperature on a rotary evaporator. The remaining suspension was diluted with water, and extracted with ether. The usual working-up gave a residue which was directly hydrolysed by refluxing with 50% aqueous potassium hydroxide (2 c.c.) in methanol (100 c.c.) for 1 hr. After being cooled the solution was extracted with ether. The ether extract was washed with water until neutral, dried (Na_2SO_4), and evaporated to dryness. The residue (678 mg.) on initial recrystallisation from methanol, followed by chromatography of the mother-liquors gave the required 16β,20α-diol (200 mg., 14%), m. p. 208—211°. An analytical sample recrystallised from benzene–light petroleum formed large plates, m. p. 209—210° (Found: C, 79·0; H, 11·6. Calc. for $C_{21}H_{36}O_2$:

C, 78·7; H, 11·2%). The alkaline washings from the above hydrolysis were acidified and extracted with ether. The ether extract was washed with water until neutral, dried (Na_2SO_4), and evaporated to dryness. The residue (620 mg.) on recrystallisation from methanol gave what is probably 16β-hydroxy-23,24-bisnor-5α-cholanic acid (16 ⟶ 22)-lactone as needles (236 mg., 16%), m. p. 197—201° (lit., m. p. 199°).

5α-*Pregnane*-16β,20α-*diol Diacetate* (VII; R = R′ = Ac).—5α-Pregnane-16β,20α-diol was acetylated in the usual manner. A pure sample crystallised from methanol formed broad needles, m. p. 171—172°, $\nu_{max.}$ 1740 cm.$^{-1}$ (Found: C, 74·0; H, 9·9. Calc. for $C_{25}H_{40}O_4$: C, 74·2; H, 10·0%).

5α-*Pregnane*-16β,20β-*diol* (VI; R = R′ = H).—Crude 16β-hydroxy-5α-pregnan-20-one 16-(γ-methyl-δ-acetoxyvalerate) (700 mg.), obtained as an intermediate in the preparation of 5α-pregn-16-en-20-one, was refluxed with lithium aluminium hydride (600 mg.) in dry ether (25 c.c.). Excess of reagent was destroyed with ethyl acetate followed by water, and the suspension extracted with ether. The usual working up gave a residue which was chromatographed on alumina, and eluted with increasing proportions of ether in benzene. 5α-Pregnane-16β,20α-diol was eluted first; on recrystallisation from benzene–light petroleum it gave plates (32 mg., 7%), m. p. 209—210°), which did not depress the melting point of the product described above. The second fraction eluted was recrystallised from benzene–light petroleum to give the required 16β,20β-*diol* (110 mg., 30%) as small plates, which on heating sublimed to long fine needles, m. p. 209—212°. A pure sample recrystallised from the same solvent behaved in the same way, m. p. 211—212° (Found: C, 79·1; H, 11·4. $C_{21}H_{36}O_2$ requires C, 78·7; H, 11·2%). The *diacetate* (VI; R = R′ = Ac) prepared in the usual manner and recrystallised from methanol formed needles, m. p. 158—159°, $\nu_{max.}$ 1740 cm.$^{-1}$ (Found: C, 73·9; H, 10·0. $C_{25}H_{40}O_4$ requires C, 74·2; H, 10·0%).

16α-*Benzyloxy*-5α-*pregnan*-20-*one* (XI).—A 3% solution of potassium hydroxide in benzyl alcohol (33 c.c.), prepared under nitrogen, was added to 5α-pregn-16-en-20-one (1·06 g.) and the mixture kept at room temperature under nitrogen for 3 hr., and then distributed between ether and water. The organic phase was washed with water until neutral and evaporated to dryness. Most of the benzyl alcohol was removed under high vacuum, and the residue chromatographed on neutral alumina. Light petroleum first eluted starting material (630 mg.) followed by the required 16α-*benzyloxy-compound* (XI; 503 mg.). Recrystallisation from light petroleum gave small plates (408 mg.), m. p. 116—118°, $\nu_{max.}$ 1710 cm.$^{-1}$. A pure sample had m. p. 119—120° (Found: C, 82·7; H, 9·8. $C_{28}H_{40}O_2$ requires C, 82·3; H, 9·9%). Treatment of the mother-liquors and side-fractions again under the same conditions as described above afforded further material (365 mg.), m. p. 116—118°.

16α-*Hydroxy*-5α-*pregnan*-20-*one* (XII; R = H).—16α-Benzyloxy-5α-pregnan-20-one (125 mg.) in methanol (50 c.c.) was shaken with palladium–charcoal (150 mg.) under hydrogen at atmospheric pressure for 2 hr. The suspension was filtered and evaporated to dryness. The residue on crystallisation from benzene–light petroleum gave long needles (89 mg., 97%), m. p. 173—175°, $\nu_{max.}$ 1700 cm.$^{-1}$. A pure sample had m. p. 175·5—176·5° (Found: C, 78·9; H, 10·5. Calc. for $C_{21}H_{34}O_2$: C, 79·2; H, 11·0%). The *acetate* (XII; R = Ac) prepared in the usual manner and recrystallised from methanol had m. p. 193—195°, $\nu_{max.}$ 1745, 1710 cm.$^{-1}$. An analytical sample formed needles, m. p. 194—195° (Found: C, 77·0; H, 10·2. $C_{23}H_{36}O_3$ requires C, 76·6; H, 10·0%).

16α-*Acetoxy*-5α-*pregnan*-20α(*and* 20β)-*ols* (XIII and XIV; R = H, R′ = Ac).—16α-Acetoxy-5α-pregnan-20-one (490 mg.) dissolved in redistilled glacial acetic acid (100 c.c.) was shaken with Adams PtO_2 catalyst in hydrogen at atmospheric pressure for 12 hr. The suspension was filtered and evaporated to dryness at room temperature on a rotary evaporator. The residue (492 mg.) on crystallisation from benzene–light petroleum gave the 16α,20β-*diol* 16-*monoacetate* (416 mg.), m. p. 187—189°. An analytical sample recrystallised from acetone–hexane formed needles, m. p. 190—191°, $\nu_{max.}$ 1730 cm.$^{-1}$ (Found: C, 76·2; H, 10·4. $C_{23}H_{38}O_3$ requires C, 76·2; H, 10·6%). Chromatography of the mother-liquors on neutral alumina, eluting with increasing proportions of benzene in light petroleum, gave more of the 16α,20β-diol 16-monoacetate (36 mg., m. p. 187—189°) and a second fraction, which on recrystallisation from hexane gave the 16α,20α-*diol* 16-*monoacetate* as thick plates (13 mg., 2·7%), m. p. 134—136°, $\nu_{max.}$ 1730 and 1715 cm.$^{-1}$ (Found: C, 76·1; H, 10·8. $C_{23}H_{38}O_3$ requires C, 76·2; H, 10·6%).

5α-*Pregnane*-16α,20β-*diol* (XIV; R = R′ = H).—The 16-acetate (XIV; R = H, R′ = Ac) (56 mg.) dissolved in methanol (2 c.c.) was refluxed with 50% aqueous potassium hydroxide

(0·6 c.c.) for 2 hr. On being cooled the mixture was poured into water and extracted with ether. The ether layer was washed with water until neutral and evaporated to dryness. Crystallisation from benzene–light petroleum gave the *diol* as fine needles (35 mg.), m. p. 210° (Found: C, 78·6; H, 11·4. $C_{21}H_{36}O_2$ requires C, 78·7; H, 11·2%). The *diacetate* (XIV; R = R′ = Ac) was prepared from the 16-monoacetate in the usual manner and on crystallisation from methanol formed short needles, m. p. 117—118°, $\nu_{max.}$ 1740 cm.$^{-1}$ (Found: C, 73·6; H, 9·6. $C_{25}H_{40}O_4$ requires C, 74·2; H, 10·0%).

5α-*Pregnane*-16α,20β-*diol* 16α-*Acetate* 20β-*Toluene*-p-*sulphonate* (XIV; R = Tos, R′ = Ac).—The 16α-monoacetate (XIV; R = H, R′ = Ac) (278 mg.) was dissolved in pyridine (2 c.c.) and cooled to 0°. Toluene-*p*-sulphonyl chloride (210 mg.) was added and the mixture kept at 0° for 2 days; it was then poured on crushed ice and extracted with ether. The usual working-up and crystallisation from methanol gave the required *product* as needles (265 mg., 64%), m. p. 119—122°, $\nu_{max.}$ 1740 cm.$^{-1}$. An analytical sample recrystallised from hexane gave large crystals, m. p. 87—90°; the molten mass recrystallised, on continued heating, to give fine needles, m. p. 119—121° (Found: C, 69·6; H, 8·3. $C_{30}H_{44}O_5S$ requires C, 69·7; H, 8·6%).

5α-*Pregnane*-16α,20α-*diol* (XIII; R = R′ = H).—(*a*) 5α-Pregnane-16α,20α-diol 16α-monoacetate was hydrolysed in the same manner as already described for the preparation of compound (XIV; R = H). A pure sample of the 16α,20α-*diol* recrystallised from hexane formed long needles, which on heating changed in form to plates, m. p. 178·5—179° (Found: C, 78·7; H, 11·2. $C_{21}H_{36}O_2$ requires C, 78·7; H, 11·2%).

(*b*) Inversion at C-20 of 20β-derivative. 5α-Pregnane-16α,20β-diol 16α-monoacetate 20β-toluene-*p*-sulphonate (200 mg.) and potassium acetate (4 g.) were refluxed in 96% aqueous acetic acid containing acetic anhydride (1·6 c.c.) for 2 hr. and kept at room temperature overnight. The mixture was then poured into water, extracted with ether, and worked up as usual. The residue was hydrolysed with 50% aqueous potassium hydroxide in the usual manner. Chromatography of the product on neutral alumina gave the 16α,20α-diol as needles (30 mg., 26%) which on heating crystallised to plates, m. p. 179—180°. This material did not depress the m. p. of the 16α,20α-diol prepared above. The two products also showed identical mobility on thin-layer chromatography. The 16α,20α-*diol diacetate* (XIII; R = R′ = Ac) prepared in the usual manner and recrystallised from methanol, formed plates, m. p. 125—127°, $\nu_{max.}$ 1740 cm.$^{-1}$ (Found: C, 74·0; H, 9·9. $C_{25}H_{40}O_4$ requires C, 74·2; H, 10·0%).

17α-*Bromo*-16β-*hydroxy*-5α-*pregnan*-20-*one* (IX; R = H).—*N*-Bromoacetamide (1·6 g.; m. p. 117—118°; freshly recrystallised from chloroform) was added to 5α-pregn-16-en-20-one (1·35 g.) suspended in 10% aqueous acetone (120 c.c.). The mixture was kept at room temperature for 15 hr. and further *N*-bromoacetamide (1·5 g.) was then added. The mixture was left for 24 hr., poured into water, and extracted with ether. The organic phase was washed with a little aqueous sodium thiosulphate, and with water, dried (Na_2SO_4), and evaporated; the residue, when recrystallised from methanol, gave the required *bromo-compound* as plates (1·33 g., 75%), m. p. 135—138°. A pure sample recrystallised from hexane gave large plates, m. p. 141—143°, $\nu_{max.}$ 1690, 1705w cm.$^{-1}$ (Found: C, 64·0; H, 8·2; Br, 21·0. $C_{21}H_{33}BrO_2$ requires C, 63·5; H, 8·4; Br, 20·1%).

16β-*Acetoxy*-17α-*bromo*-5α-*pregnan*-20-*one* (IX; R = Ac).—Acetyl hypobromite in carbon tetrachloride (8·3 c.c., *ca.* 0·1M; cf. Levine and Wall [17]) was added to 5α-pregn-16-en-20-one (218 mg.) dissolved in carbon tetrachloride (4·0 c.c.) at 0°. After 5 min. the reaction mixture was washed with cold 5% sodium hydrogen sulphite. The organic layer was washed twice with water, dried (Na_2SO_4), and evaporated to dryness. Crystallisation from methanol gave the *acetoxy-bromo-ketone* as small angular crystals (223 mg., 70%), m. p. 178—180° (decomp.), $\nu_{max.}$ 1710 and 1750 cm.$^{-1}$. An analytical sample had the same m. p. (Found: C, 62·8; H, 7·9; Br, 19·1. $C_{23}H_{35}BrO_3$ requires C, 62·9; H, 8·0; Br, 18·4%).

16β-*Hydroxy*-5α-*pregnan*-20-*one* (X; R = H).—Zinc dust (2·2 g.) was slowly added over a period of 30 min. to a solution of 17α-bromo-16β-hydroxy-5α-pregnan-20-one (860 mg.), and sodium acetate (2·2 g.) in glacial acetic acid (50 c.c.). After 1 hr. the suspension was filtered and diluted with water, and the precipitate was filtered and dried. Chromatography on neutral alumina, eluting with increasing proportions of benzene in light petroleum, resolved the reaction product into three fractions. The first (92 mg.) was mainly 5α-pregn-16-en-20-one. The second (345 mg.) was a white gummy solid that failed to crystallise; $\nu_{max.}$ 3600 cm.$^{-1}$ (no C=O). The third (178 mg.) when recrystallised from benzene–light petroleum gave the 16β-*hydroxy*-20-*one* as needles (159 mg., 23%), m. p. 176—179°, $\nu_{max.}$ 1695 cm.$^{-1}$. An analytical sample recrystallised

from hexane had m. p. 179—180° (Found: C, 79·7; H, 10·6. $C_{21}H_{34}O_2$ requires C, 79·2; H, 11·1%). The *acetate* recrystallised from hexane in long needles, m. p. 150—151°, $\nu_{max.}$ 1710 and 1745 cm.$^{-1}$ (Found: C, 76·6; H, 10·2. $C_{23}H_{36}O_3$ requires C, 76·6; H, 10·1%).

16α-*Methyl*-5α-*pregnan*-20-*one* (XXI).—To magnesium turnings (250 mg.), dry ether (10 c.c.), dry tetrahydrofuran (20 c.c.) and a small crystal of iodine, methyl iodide (0·88 c.c.) in dry ether (10 c.c.) was added dropwise, at such a rate that the reaction did not become violent. The mixture was then refluxed for 15 min. and some ether (with a little tetrahydrofuran; 5 c.c.) was distilled off. The suspension of Grignard reagent was cooled to 20°. Cuprous chloride (50 mg.) and 5α-pregn-16-en-20-one (502 mg.) dissolved in tetrahydrofuran (5 c.c.) were added, and the reaction mixture was stirred for 30 min. at room temperature. Saturated aqueous ammonium chloride (12 c.c.) followed by water (2 c.c.) and ether (200 c.c.) were added. The ether layer was washed with a little sodium thiosulphate, saturated ammonium chloride, and water, dried (Na_2SO_4) and evaporated to dryness. Crystallisation from methanol gave small needles (426 mg., 81%), m. p. 111—115°, which on continued heating recrystallised to large plates, m. p. 117—119°. An analytical sample (from methanol) melted in the same manner, m. p. 114—115·5 and 118—118·5°, $\nu_{max.}$ 1700 cm.$^{-1}$ (Found: C, 83·4; H, 11·4. $C_{22}H_{36}O$ requires C, 83·5; H, 11·5%).

16α-*Methyl*-5α-*pregnan*-20β(*and* 20α)-*ols* (XXII and XXIII; R = H).—16α-Methyl-5α-pregnan-20-one (347 mg.) was dissolved in dry ether (35 c.c.). Lithium aluminium hydride (350 mg.) was added, and the mixture refluxed for 2 hr. Excess of reagent was destroyed with ethyl acetate, followed by a little water and the resulting suspension was extracted with ether. The usual working-up and crystallisation from light petroleum gave the 20β-ol as needles (177 mg.), m. p. 110—112°. The mother-liquors were then chromatographed on silica gel, elution being continued with increasing proportions of benzene in light petroleum, and yielded first a further amount of 20β-ol (125 mg.). An analytical sample of the 16α-*methyl*-20β-*ol* recrystallised from hexane had m. p. 114·5—115·5° (Found: C, 83·1; H, 11·9. $C_{22}H_{38}O$ requires C, 83·0; H, 12·0%). A second fraction on recrystallisation from methanol afforded the 16α-*methyl*-20α-*ol* (42 mg., 12%) as short needles, m. p. 127—130°. An analytical sample had m. p. 130·5—131° (Found: C, 83·1; H, 12·0. $C_{22}H_{38}O$ requires C, 83·0; H, 12·0%). The acetates of these compounds were prepared in the usual way. 16α-*Methyl*-5α-*pregnan*-20β-*yl acetate*, recrystallised from methanol, formed needles, m. p. 110—111°, $\nu_{max.}$ 1730 cm.$^{-1}$ (Found: C, 80·3; H, 11·1. $C_{24}H_{40}O_2$ requires C, 79·9; H, 11·2%). 16α-*Methyl*-5α-*pregnan*-20α-*yl acetate*, recrystallised from methanol, formed flat needles, m. p. 76·5—77·5°, $\nu_{max.}$ 1730 cm.$^{-1}$ (Found: C, 79·9; H, 11·4. $C_{21}H_{40}O_2$ requires C, 79·9; H, 11·2%).

Pyrazoline Derivative of 5α-*Pregnan*-20-*one* (XVI).—5α-Pregn-16-en-20-one (1 g.) dissolved in dry tetrahydrofuran (12 c.c.) was added to a ten-fold excess of diazomethane in ether, and kept at room temperature overnight. Excess of reagent and solvent were evaporated under vacuum at room temperature. Crystallisation from ether gave large clear needles (1·05 g., 92%) which on heating became opaque, m. p. 173—178° (decomp.). An analytical sample of the *pyrazoline*, recrystallised from acetone, had m. p. 172—174°, $\nu_{max.}$ 1700 cm.$^{-1}$ (Found: C, 77·8; H, 10·4. $C_{22}H_{34}N_2O$ requires C, 77·1; H, 10·0%).

16-*Methyl*-5α-*pregn*-16-*en*-20-*one* (XVII).—The pyrazoline (XVI) (980 mg.) was heated slowly under vacuum until a temperature of 170° was reached. The temperature was maintained at 170—174° for 10 min., when evolution of nitrogen ceased. The melt was cooled, dissolved in chloroform, filtered through Celite, and evaporated to dryness. Crystallisation from light petroleum afforded needles (534 mg., 60%), m. p. 145—147°, $\nu_{max.}$ 1655 cm.$^{-1}$. An analytical sample of the 16-*en*-20-*one*, recrystallised from hexane, had m. p. 147—148° (Found: C, 84·2; H, 10·9. $C_{22}H_{34}O$ requires C, 84·0; H, 10·9%).

16β-*Methyl*-5α-*pregnan*-20-*one* (XVIII).—16-Methyl-5α-pregn-16-en-20-one (462 mg.) dissolved in methanol was shaken with Adams catalyst in hydrogen at atmospheric pressure. One mole of hydrogen was taken up after 1 hr. The solution was filtered and evaporated to dryness. Crystallisation from light petroleum gave plates (400 mg., 86%), m. p. 133—136°, $\nu_{max.}$ 1705 cm.$^{-1}$. An analytical sample of the 16β-*methyl*-20-*one* recrystallised from hexane had m. p. 136—138° (Found: C, 83·9; H, 11·5. $C_{22}H_{36}O$ requires C, 83·5; H, 11·5%).

16β-*Methyl*-5α-*pregnan*-20β(*and* 20α)-*ols* (XX and XIX; R = H).—16β-Methyl-5α-pregnan-20-one (230 mg.) was reduced with lithium aluminium hydride as described for the preparation of the 16α-methyl-20-ols (see above). The reaction product was resolved into two components by chromatography on silica gel, eluting with increasing proportions of benzene in

light petroleum. The first fraction (80 mg.) eluted afforded the 20β-*ol* as rectangular plates (56 mg., 24%), m. p. 177—178° (hexane). An analytical sample had m. p. 178—179° (Found: C, 83·3; H, 11·9. $C_{22}H_{38}O$ requires C, 83·0; H, 12·0%). The second fraction (130 mg.) on crystallisation from benzene–light petroleum afforded the 20α-*ol* as needles (122 mg., 53%), m. p. 175—178°. An analytical sample recrystallised from hexane had m. p. 177—177·5° (Found: C, 82·7; H, 11·8. $C_{22}H_{38}O$ requires C, 83·0; H, 12·0%). The acetates of these two compounds were prepared in the usual manner. 16β-*Methyl*-5α-*pregnan*-20β-*yl acetate*, recrystallised from methanol, formed needles, m. p. 145—146°, $\nu_{max.}$ 1730 cm.$^{-1}$ (Found: C, 80·2; H, 11·1. $C_{24}H_{40}O_2$ requires C, 79·9; H, 11·2%). 16β-*Methyl*-5α-*pregnan*-20α-*yl acetate*, recrystallised from methanol, formed flat needles which on heating sublimed to long fine needles, m. p. 143—144°, $\nu_{max.}$ 1730 cm.$^{-1}$ (Found: C, 79·3; H, 10·7. $C_{24}H_{40}O_2$ requires C, 79·9; H, 11·2%).

This work has been assisted by grants from the D.S.I.R. and the National Research Development Corporation, and by a contract from the U.S. Army Research and Development Group (Frankfurt-am-Main). The Rudolph polarimeter was a generous loan from the Wellcome Trust. We are indebted to Syntex, S.A., Mexico City, for generous gifts of steroids; and to Dr. G. D. Meakins, Dyson Perrins Laboratory, Oxford University, for valuable discussion, and for the infrared spectral data reported in Table 2.

Medical Research Council, Steroid Reference Collection,
Westfield College, Hampstead, London N.W.3. [*Received, April 1st*, 1964.]