19-Nor and Aromatic Steroids. Part II.[1] Cleavage of 3-Oxygenated 4β,19-Ethers in the Pregnane Series leading to 19-Norprogesterone

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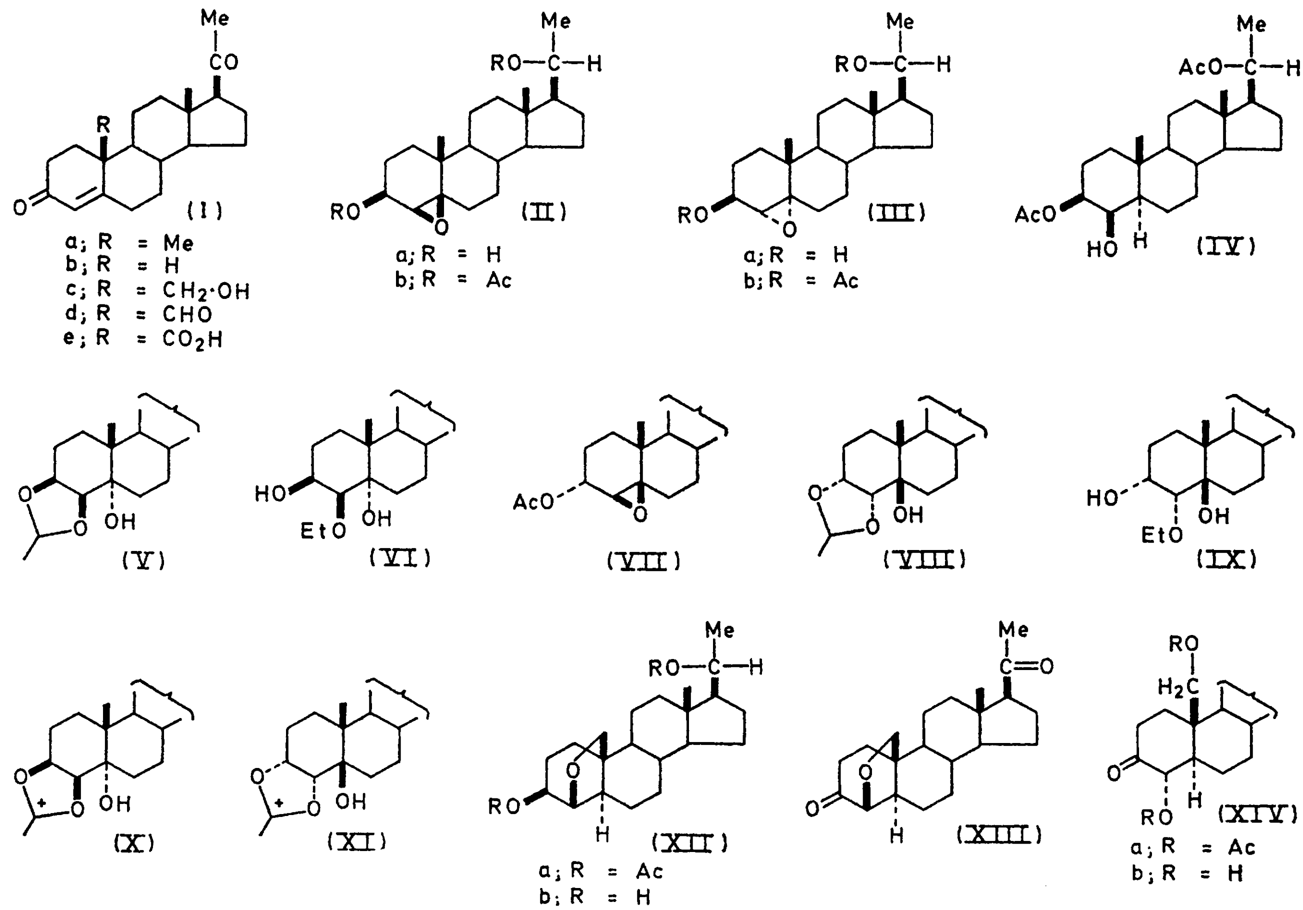
Treatment of pregn-4-ene-3β,20β-diol with *m*-chloroperbenzoic acid gave the 4β,5β-epoxide (IIa), which was separated from the 4α,5α-isomer by recrystallisation. Acetylation of the β-epoxide (IIa) followed by hydrogenation over platinum oxide in acetic acid gave 3β,20β-diacetoxy-5α-pregnan-4β-ol, readily converted into the 4β,19-epoxide (XIIa) by reaction with lead tetra-acetate. Oxidation then gave the epoxy-dione (XIII), cleavage of which with boron trifluoride in acetic anhydride gave mainly 4α,19-diacetoxypregnane-3,20-dione. Careful hydrolysis in methanol for 10 min gave the 4α,19-diol (XIVb); this was converted into 19-hydroxyprogesterone (Ic), which can be converted into 19-norprogesterone.

We have reported the cleavage of 3-oxygenated 2β,19-ethers in the cholestane series,[1] thus providing a route to 19-nor and ring-A-aromatic steroids without involving ring B. We now describe the conversion of progesterone into 19-norprogesterone *via* 3β,20β-diacetoxy-4β,19-epoxypregnane (XIIa).

[1] R. E. Lack and A. B. Ridley, *J. Chem. Soc. (C)*, 1970, 1437.

Treatment of progesterone (Ia) with sodium borohydride in methanol [2-4] gave mainly pregn-4-ene-3β,20β-diol, which with *m*-chloroperbenzoic acid [3] gave the 4β,5β-epoxide (IIa) together with some of the 4α,5α-isomer (IIIa). These two epoxides could be separated only with difficulty by recrystallisation from methanol. Acetylation of the β-epoxide (IIa) with acetic anhydride in pyridine gave 3β,20β-diacetoxy-4β,5β-epoxypregnane the presence of platinum oxide in acetic acid for 3 h gave the 3,4-acetal (VIII) of 20β-acetoxypregnane-3α,4α,5β-triol; prolonged hydrogenation (20 h) gave 20β-acetoxy-4α-ethoxypregnane-3α,5β-diol (IX). The acetals (V) and (VIII) displayed n.m.r. signals indicating the presence of the CH_3·CH grouping (confirmed by double irradiation), and an acetoxy-signal at τ 8·0. Both i.r. and n.m.r. spectroscopy indicated the presence



(IIb), which afforded the 4β-ol (IV) when hydrogenated over platinum oxide in acetic acid.

Hydrogenation of the α-epoxide (IIIb) over platinum oxide in acetic acid for 3 h gave the 3,4-acetal of 20β-acetoxypregnane-3β,4β,5α-triol (V); prolonged hydrogenation (20 h) gave 20β-acetoxy-4β-ethoxypregnane-3β,5α-diol (VI). This ethoxy-diol (VI) was also formed when the intermediate acetal (V) was hydrogenated for 20 h.

For comparison, 3α,20β-diacetoxy-4β,5β-epoxypregnane (VII) was prepared by reduction of 4β,5β-epoxypregnane-3,20-dione [5] with sodium borohydride in methanol followed by acetylation with acetic anhydride in pyridine. Hydrogenation of this 4β,5β-epoxide (VII) in

of one hydroxy-group. The n.m.r. spectra of the ethoxy-compounds (VI) and (IX) confirmed their structures.

The acetals (V) and (VIII) must arise *via* the intermediate acetoxonium ions (X) and (XI), respectively. Hydrolyses of similar 3β-acetoxy-4α,5α-epoxy-derivatives in the cholestane and androstane series [6,7] have been shown to involve participation of the 3β-acetoxy-group to give 4β-acetoxy-3β,5α-diols *via* similar intermediates. It is interesting that the reductive cleavage of the acetals (V) and (VIII) occurs to give the equatorial alcohols (VI) and (IX), since equatorial alcohols have also been shown to be the major products in the hydroly-

[2] S. Julia and J. P. Lavaux, *Bull. Soc. chim. France*, 1963, 1223.
[3] B. Camerino and C. G. Alberti, *Gazzetta*, 1955, **85**, 51.
[4] S. Julia and P. Simon, *Bull. Soc. chim. France*, 1964, 321.
[5] B. Camerino and D. Cattapan, *Il Farmaco (Pavia), Ed. Sci.*, 1958, **13**, 39.
[6] S. Julia and J. P. Lavaux, *Bull. Soc. chim. France*, 1963, 1238.
[7] S. Julia and B. Furer, *Bull. Soc. chim. France*, 1966, 1106.

sis of acetoxonium ions.[8] This would be expected since there would be severe hindrance in both acetals (V) and (VIII) to attack at the axial oxygen atom.

Improved yields of the 4β-ol (IV) could be obtained by hydrogenation of the crude mixture of epoxides (IIb) and (IIIb) over platinum oxide in acetic acid for 3 h; the resulting 4β-ol (IV) and acetal (V) were readily separated by chromatography.

The 4β-ol (IV) was treated with lead tetra-acetate in benzene to give the 4β,19-epoxy-derivative (XIIa), which was hydrolysed to the 3β,20β-diol (XIIb) with methanolic potassium hydroxide. Oxidation of the diol with Jones reagent gave the 3,20-dione (XIII) which was cleaved with boron trifluoride in acetic anhydride [9,10] to give the 4α,19-diacetoxy-3,20-dione (XIVa).

The cleavage of the 4β,19-ether to give only the 4α-acetate (XIVa) indicates that attack by acetic anhydride on the boron-trifluoride-complexed ether is taking place only at C-4 from the less hindered side of the molecule. This result is similar to that observed in the acetolytic cleavage of 2β,19-epoxy-5α-cholestan-3-one,[1] which gave only a 2α-acetate. No evidence was found for the presence of intermediate carbonium ions, which have been observed in the cleavage of methyl ethers at C-2 [11] and C-3 [10] in the absence of adjacent carbonyl groups. This is attributed to the unfavourable formation of a carbonium ion α to a carbonyl group.

When the diacetate (XIVa) was treated with potassium hydroxide in methanol at 20° for 10 min under nitrogen[12] the major product was the required diol (XIVb). Treatment of this diol with naphthalene-β-sulphonic acid in toluene [12] for 3 h gave 19-hydroxypregn-4-ene-3,20-dione (Ic) [13] which has already been converted into 19-norprogesterone (Ib) *via* the 19-al (Id) or the 19-carboxylic acid (Ie).[13]

The structures assigned above were confirmed by spectroscopic methods; comparative data are shown in the Table. In particular, the n.m.r. spectra of the 4β,19-ethers (XIIa and b) showed signals for the 3α- and 20α-hydrogen atoms overlapping at τ 5·38 and 6·38, respectively; that of the equatorial 4α-hydrogen atom appeared at τ 6·25 ($W_{\frac{1}{2}}$ 7 Hz). The 19-methylene signal appeared as an AB quartet, τ 6·48 and 6·16 (J_{AB} 8 Hz). This coupling is characteristic of 2β,19-epoxy- [14] and 4β,19-epoxy- [15] derivatives of cholestane.

N.m.r. data (τ values; *J* in Hz)

Compound	19-H_3	18-H_3	19-H_2 τ	19-H_2 J_{AB}	21-H_3 τ	21-H_3 *J*	20α-H	3α-H	4-H τ	4-H *J*	AcO
Epoxide (IIa)	8·97	9·23			8·85	6	6·28	5·95	6·85	4·5	
Epoxide (IIb)	8·95	9·33			8·85	6	5·55	4·85	6·84	3	7·90, 7·99
4β-Ol (IV)	8·95	9·32					5·2 *	5·2 *	6·15	($W_{\frac{1}{2}}$ 7)	
4β,19-Ether (XIIa)		9·27	6·48, 6·16	8	8·75	6	5·38 *	5·38 *	6·25	($W_{\frac{1}{2}}$ 7)	7·95
4β,19-Ether (XIIb)		9·23	6·47, 6·15	8	8·85	6	6·38 *	6·38 *	6·25	($W_{\frac{1}{2}}$ 7)	
Dione (XIII)		9·23	6·40, 6·11	8	8·80				5·90	7	
4α,19-Diacetate (XIVa)		9·23	5·75, 5 39	10	8 90				4·82	12	7·86, 7·84
4α,19-Diol (XIVb)		9·25	6·12, 5·92	11	8·80				5·87	12	

* Overlapping resonances.

EXPERIMENTAL

M.p.s were determined with a Köfler hot-stage apparatus. U.v. (solvent ethanol) and i.r. spectra (solvent carbon tetrachloride) were measured with Perkin-Elmer 4000A and 221 spectrophotometers, respectively. N.m.r. spectra were measured with Varian A60, HA100, or XL100 instruments with deuteriochloroform as solvent and tetramethylsilane as internal reference. Mass spectra were measured with an A.E.I. MS9 double-focus spectrometer. Column chromatography was performed on alumina (Spence type H, activity II) or on silica (Davison 100—200 mesh). T.l.c. was carried out on silica plates in ether–hexane and the plates were developed by spraying with concentrated sulphuric acid and then heating. Preparative t.l.c. was carried out on silica plates in ether–hexane (1 : 4); the plates were sprayed with berberine hydrochloride and examined in u.v. light. G.l.c. was performed with an F & M 400 instrument fitted with a disc integrator. Columns used were 1% XE60 on acid-washed, silanised GasChrom P (mesh 100—140) (length 1·64 m, diam. 3 mm) and 3·8% W98 on Diatoport S (mesh 80—100) (length 1·5 m, diam. 4 mm). The temperature of the injection port and detector was *ca.* 60° higher than that of the column and helium was used as the carrier gas (flow rate 75 ml min^{-1}).

4β,5β-*Epoxypregnane*-3β,20β-*diol* (IIa).—Pregn-4-ene-3β,20β-diol [2–4] (5·0 g) in chloroform (100 ml) was treated with *m*-chloroperbenzoic acid (5·0 g) at 20° for 0·5 h to give, after recrystallisation from methanol and then further recrystallisation from benzene, the 4β,5β-epoxide (IIa) (2·0 g), m.p. 218—232° (lit.,[16] 235—237°), $\nu_{max.}$ 3400, 1100, 980, and 890 cm^{-1}; τ 9·23 (18-H_3), 8·97 (19-H_3), 8·85 (21-H_3, *J* 6 Hz), 8·35 (2 × OH, exchanged by D_2O), 6·85 (4α-H, $J_{3\alpha,4\alpha}$ 4·5 Hz), and 6·28 and 5·95 (3α-H and 20α-H).

3β,20β-*Diacetoxy*-4β,5β-*epoxypregnane* (IIb).—The diol (IIa) (5·0 g) was treated with acetic anhydride (12·5 ml) and pyridine (10 ml) for 17 h at 20° to give a viscous oil (5·5 g). This was dissolved in aqueous acetic acid (90%; 200 ml)

[8] J. Atkin, R. E. Gall, and A. M. Slee, *J.C.S. Perkin II*, 1972, 1185.
[9] B. Kamber, G. Cainelli, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, 1960, **43**, 347.
[10] C. R. Naryanan and K. N. Iyer, *Tetrahedron Letters*, 1964, 759; R. O. Youssefyeh and Y. Mazur, *ibid.*, 1962, 1287.
[11] S. E. Bruce and R. E. Gall, *J.C.S. Perkin I*, 1972, 2319.
[12] R. E. Lack and A. B. Ridley, *J. Chem. Soc.* (*C*), 1968, 3017.
[13] A. Bowers, R. Villotti, J. A. Edwards, E. Denot, and O. Halpern, *J. Amer. Chem. Soc.*, 1962, **84**, 3204.
[14] C. W. Shoppee, T. E. Bellas, J. C. Coll, and R. E. Lack, *J. Chem. Soc.* (*C*), 1969, 2734.
[15] R. E. Lack, J. E. Nemorin, and A. B. Ridley, *J. Chem. Soc.* (*B*), 1971, 629.
[16] B. Camerino and B. Patelli, *Il. Farmaco* (*Pavia*), *Ed. Sci.*, 1956, **11**, 579.

and stirred for 18 h; after the usual isolation, the crude product was adsorbed on a column of silica gel. Elution with ether–pentane (1 : 1) gave 3β,20β-*diacetoxy*-4β,5β-*epoxypregnane* (IIb) as a glass, $\nu_{max.}$ 1725, 1250, and 1025 cm^{-1}; τ 9·33 (18-H_3), 8·95 (19-H_3), 8·85 (21-H_3, *J* 6 Hz), 7·99 and 7·90 (acetates), 6·84 (4α-H, $J_{3\alpha,4\alpha}$ 3 Hz), and 5·55 and 4·85 (3α- and 20α-H) (Found: C, 71·85; H, 9·3; O, 19·1. $C_{25}H_{38}O_5$ requires C, 71·8; H, 9·1; O, 19·1%).

3β,20β-*Diacetoxy*-5β-*pregnan*-4β-*ol* (IV).—(*a*) Pure epoxide (IIb) (2·0 g) in acetic acid (150 ml) was hydrogenated over Adams catalyst (0·2 g) for 8 h. The mixture was filtered and the solvent removed to give, on trituration with pentane, a white solid. Recrystallisation from pentane gave the 4β-*ol* (IV) (0·75 g), m.p. 190—191°, $\nu_{max.}$ 3610, 1727, 1245, 1070, 1025, and 960 cm^{-1}, τ 9·38 (18-H_3), 8·95 (19-H_3), 8·88 (21-H_3, *J* 6 Hz), 8·80 and 7·93 (acetates), 6·15 (4α-H, $W_{\frac{1}{2}}$ 7 Hz), and 5·2 (2α- and 20α-H) (Found: C, 71·65; H, 9·6; O, 18·8. $C_{25}H_{40}O_5$ requires C, 71·5; H, 9·5; O, 19·0%).

(b) Crude β-epoxide (IIb) (1·0 g) containing some of the α-epoxide in acetic acid (150 ml) was hydrogenated as in (*a*). T.l.c. revealed some unchanged epoxide (IIb), the 4β-ol (IV), and the acetal (V). These were separated on a column of neutral alumina in benzene–pentane to give the 4β-ol (IV) (0·5 mg), m.p. 190—191° (from benzene–pentane), identical with the sample prepared in (*a*).

Hydrogenation of 3β,20β-*Diacetoxy*-4α,5α-*epoxypregnane* (IIIb).—(*a*) The epoxide [6] (IIIb) (m.p. 156—157°) (1·0 g) in acetic acid (50 ml) was hydrogenated over Adams catalyst (0·2 g) for 2 h. The solution was filtered to give 20β-*acetoxy*-3β,4β-*ethylidenedioxypregnan*-5α-*ol* (V) (0·7 g), m.p. 235—236° (from methanol), $\nu_{max.}$ 3500, 1720, and 1270 cm^{-1}, τ 9·35 (18-H_3), 8·84 (19-H_3), 8·85 (21-H_3, *J* 6 Hz), 8·60 (acetal Me, *J* 5 Hz), 8·0 (acetate), 6·36 (4α-H, *J* 6 Hz), 5·8 and 5·2 (3α- and 20α-H), and 4·93 (MeC*H*, q, *J* 5 Hz) (on irradiation at 4·93 the signal at τ 8·58 collapsed to a singlet) (Found: C, 71·35; H, 9·7; O, 19·0. $C_{25}H_{40}O_5$ requires C, 71·4; H, 9·5; O, 19·0%).

(*b*) When the hydrogenation was allowed to proceed for 48 h, the usual isolation gave 20β-*acetoxy*-4β-*ethoxypregnane*-3β,5α-*diol* (VI) (0·6 g), m.p. 259—261° (from methanol), $\nu_{max.}$ 3500, 1720, and 1270 cm^{-1}, τ 9·37 (18-H_3), 8·90 (19-H_3), 8·85 (21-H_3, *J* 6 Hz), 8·80 (CH_3·CH_2, t, *J* 5·0 Hz), 8·0 (acetate), 6·81 (4α-H, *J* 4 Hz), 6·3br (CH_3·CH_2), and 6·0 and 5·2 (3α- and 20α-H) (Found: C, 71·3; H, 10·1; O, 18·8. $C_{25}H_{42}O_5$ requires C, 71·1; H, 9·9; O, 18·9%).

Hydrogenation of 3α,20β-*Diacetoxy*-4β,5β-*epoxypregnane* (VII).—(*a*) The epoxide [5] (VII) (1·0 g) in acetic acid (50 ml) was hydrogenated over Adams catalyst (0·2 g). The usual isolation gave 20β-*acetoxy*-3α,4α-*ethylidenedioxypregnan*-5β-*ol* (VIII) (0·6 g), m.p. 189—190° (from methanol), $\nu_{max.}$ 3550, 1720, 1270, 1120, 1080, 1030, 1000, and 890 cm^{-1}; τ 9·37 (18-H_3), 9·07 (19-H_3), 8·85 (21-H_3, *J* 6 Hz), 8·60 (acetal Me, *J* 5 Hz), 8·0 (acetate), 6·23 (4α-H, *J* 5·5 Hz), 5·8 and 5·2 (3α-H and 20α-H), and 4·97 (CH_3·C*H*, q, *J* 5 Hz) (Found: C, 71·4; H, 9·7; O, 19·1. $C_{25}H_{40}O_5$ requires C, 71·4; H, 9·5; O, 19·0%).

(*b*) When the hydrogenation was allowed to proceed for 48 h, the usual isolation gave 20β-*acetoxy*-4α-*ethoxypregnane*-3α,5β-*diol* (IX) (0·5 g), m.p. 236—238°, $\nu_{max.}$ 3620, 1726, 1250, and 1070 cm^{-1}; τ 9·38 (18-H_3), 9·13 (19-H_3), 8·86 (21-H_3, *J* 6 Hz), 8·75 (CH_3·CH_2, t, *J* 7·5 Hz), 8·0 (acetate), 6·68 (4α-H, *J* 4 Hz), 6·25 and 5·2 (3α-H and 20α-H), and 6·3br (CH_2·CH_3) (Found: C, 71·0; H, 9·9; O, 18·8. $C_{25}H_{42}O_5$ requires C, 71·7; H, 9·9; O, 18·9%). This product could also be isolated if the acetal (VIII) was hydrogenated for 48 h.

3β,20β-*Diacetoxy*-4β,19-*epoxy*-5α-*pregnane* (XIIa).—The 4β-ol (IV) (0·5 g) in dry benzene (75 ml) was heated under reflux for 10 h with freshly recrystallised lead tetra-acetate (1·5 g). The cooled mixture was poured into saturated sodium thiosulphate solution and extracted into dichloromethane to give an oil (300 mg) which, after preparative t.l.c. on silica (benzene–ethyl acetate, 9 : 1), gave the 4β,19-*epoxide* (XIIa), m.p. 160—162° (from methanol), $\nu_{max.}$ 1725 and 1250 cm^{-1}; τ 9·27 (18-H_3), 8·75 (21-H_3, *J* 6 Hz), 8·00 and 7·95 (acetates), 6·48 and 6·16 (19-H_2, J_{AB} 8 Hz), 6·25 (4α-H), 5·38 (3α-H and 20α-H); *m/e* 418 (Found: C, 71·7; H, 9·1. $C_{25}H_{38}O_5$ requires C, 71·75; H, 9·1%).

4β,19-*Epoxy*-5α-*pregnane*-3β,20β-*diol* (XIIb).—The diacetate (XIIa) (0·5 g) was treated with methanolic 5% potassium hydroxide for 12 h at 20° and the product extracted into ethyl acetate to give the 3β,20β-*diol* (XIIb) (400 mg), m.p. 240—241° (from methanol); $\nu_{max.}$ 3600 cm^{-1}; τ 9·23 (18-H_3), 8·85 (21-H_3, *J* 6 Hz), 8·38 (2 OH, readily exchanged by D_2O), 6·47 and 6·15 (19-H_2, J_{AB} 8 Hz),[2] 6·38 (3α- and 20α-H), and 6·25 (4α-H) (Found: C, 75·5; H, 10·2. $C_{21}H_{34}O_3$ requires C, 75·45; H, 10·2%).

4β,19-*Epoxy*-5α-*pregnane*-3,20-*dione* (XIII).—The diol (XIIb) (0·5 g) in acetone was treated with Jones reagent. After quenching with methanol and extracting with ethyl acetate, the crude product was filtered through a column of alumina in benzene to give the 3,20-*dione* (XIII) (300 mg), m.p. 160—162° (from methanol); $\nu_{max.}$ 1710 cm^{-1}; τ 9·23 (18-H_3), 8·80 (21-H_3), 6·40 and 6·11 (19-H_2, J_{AB} 8 Hz), and 5·90 (4α-H, *J* 7 Hz) (Found: M^+, 330·2192. $C_{21}H_{30}O_3$ requires *M*, 330·2194).

4α,19-*Diacetoxy*-5α-*pregnane*-3,20-*dione* (XIVa).—The 3,20-dione (XIII) (300 mg) in acetic anhydride was treated with boron trifluoride–ether (15 drops) at 0° for 1 h. Ice was added and the product was extracted into ethyl acetate to give 4α,19-*diacetoxy*-5α-*pregnane*-3,20-*dione* as an oil (280 mg) which failed to crystallise after chromatography through a column of neutral alumina; $\nu_{max.}$ 1750 and 1735 cm^{-1}; τ 9·23 (18-H_3), 8·90 (21-H_3), 7·86 and 7·84 (acetates), 5·75 and 5·39 (19-H_2, J_{AB} 10 Hz), and 4·82 (4β-H, $J_{4\beta,5\alpha}$ 12 Hz) (Found: M^+, 432·2512. $C_{25}H_{36}O_6$ requires *M*, 432·2512).

4α,19-*Dihydroxy*-5α-*pregnane*-3,20-*dione* (XIVb).—The dione (XIVa) (40 mg) in methanol (15 ml) was added to methanolic 10% potassium hydroxide (20 ml) under nitrogen at 20°. After 10 min the mixture was neutralised. Extraction with chloroform gave the 4α,19-*diol* (XIVb) (25 mg), m.p. 228—231° (from methanol); $\nu_{max.}$ 3600 and 1710 cm^{-1}; τ 9·25 (18-H_3), 8·80 (21-H_3), 6·12 and 5·92 (19-H_2, J_{AB} 11 Hz), and 5·87 (4β-H, $J_{4\beta,5\alpha}$ 12 Hz) (Found: M^+, 348·2302. $C_{21}H_{32}O_4$ requires *M*, 348·2300).

19-*Hydroxyprogesterone* (Ic).—Naphthalene-β-sulphonic acid (80 mg) in dry toluene (100 ml) was distilled until 90 ml of distillate had been collected. The diol (XIVb) (40 mg) was then added and the mixture was heated for 3 h. Extraction with ether gave the 19-ol (Ic), m.p. 168—170° (lit.,[13] 169—171°); τ 9·25 (18-H_3), 8·80 (21-H_3), and 5·65 and 5·38 (19-H_2, J_{AB} 4·08).

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