1345. *Compounds Related to the Steroid Hormones. Part XV.*[1] *Proton Magnetic Resonance Spectra of* 11-*Oxo-steroids*

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The proton magnetic resonance spectra of deuterochloroform, pyridine, and benzene solutions of 40 assorted 11-oxo-steroids and of eight 9α-halogeno-11β-hydroxy- and 9α,11β-dihalogeno-17α-hydroxy-pregnan-20-ones have been recorded and the effect of various ring-C and -D substituents on the proton resonances of the 12-methylene, 10-methyl, and 13-methyl groups examined. Unexpected changes in the behaviour of the 12-methylene protons were observed and are discussed.

Recent proton magnetic resonance (p.m.r.) measurements have shown that the 12-methylene protons of simple 5α-androstan-11-ones in chloroform solution give rise to a two-proton singlet at τ 7·62—7·73 [2,3] and that the equatorial 1β-proton, which is deshielded by the 11-oxo-group, gives a pair of smeared triplets centred at τ 7·55.[4] In benzene solution, the 12α-proton (axial) is displaced upfield whereas the 12β-proton (equatorial) either is barely moved or is displaced downfield; these displacements are attributed to the formation of a 1 : 1 collision complex.[5,6]

We have examined the p.m.r. spectra of a much wider range of 11-oxo- and of certain related 11β-hydroxy- and 11β-halogeno-steroids and have studied the effect of various ring-C and -D substituents on the proton resonances of the 12-methylene, the 10-methyl,

[1] Part XIV, S. Eardley, A. G. Long, and C. H. Robinson, *J.*, 1965, 156.
[2] J. N. Shoolery and M. T. Rogers, *J. Amer. Chem. Soc.*, 1958, **80**, 5121.
[3] (*a*) J. S. G. Cox, E. O. Bishop, and R. E. Richards, *J.*, 1960, 5118; (*b*) Sir Ewart R. H. Jones and D. A. Wilson, *J.*, 1965, 2933.
[4] D. H. Williams, N. S. Bhacca, and C. Djerassi, *J. Amer. Chem. Soc.*, 1963, **85**, 2810.
[5] N. S. Bhacca and D. H. Williams, "Applications of N.M.R. Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, 1964, ch. 7; *Tetrahedron Letters*, 1964, 3127.
[6] N. S. Bhacca, J. E. Gurst, and D. H. Williams, *J. Amer. Chem. Soc.*, 1965, **87**, 302.

and the 13-methyl groups. Our measurements were conducted on deuterochloroform and pyridine solutions and, sometimes, on benzene solutions. Pyridine was favoured, rather than benzene, since many steroids are insoluble in benzene, and pyridine is a useful solvent for steroids, which are insoluble in deuterochloroform and the solvents commonly used in p.m.r. measurements.

For the purposes of this discussion, we have divided the 11-oxo-steroids into three groups (cf. Tables 1—3), depending on the p.m.r. behaviour of the 12-methylene protons and on the substitution pattern at C-17. Earlier measurements on 5α- and 2β,3β-epoxy-5α-androstan-11-one [5] have been included in Table 1 for comparison purposes. To simplify the Tables, we have omitted the negative sign for the geminal coupling constants.

Group 1.—The first group (Table 1) consists of 11-oxo-steroids, which, when examined in deuterochloroform solution, show a two-proton singlet for the 12-methylene protons; the group includes simple androstan-11-ones,[3] pregnane-11,20-diones, 11-oxo-25D-sapogenins, and certain 11-oxo-D-homo-steroids.

The two-proton singlet for androstan-11-ones unsubstituted at C-17 and for simple 11-oxo-25D-sapogenins in deuterochloroform solution appears at τ 7·70—7·73. Introduction of a 17-oxo- or a 17β-acetyl group into androstan-11-one displaces the two-proton singlet to τ 7·62—7·63 and 7·41—7·47, respectively; in 17a-oxo-D-homosteroids, the singlet appears at τ 7·48—7·51.

In pyridine and benzene, the 12-methylene protons of androstan-11-ones unsubstituted at C-17 form an AB system and give rise to pairs of doublets (J = −12 to −12·5 c./sec.) centred at τ 7·62 and 7·84 and at τ 7·68—7·71 and 8·10—8·18, respectively, *i.e.*, 0·22 and 0·40—0·50 τ-units apart. The corresponding doublets for pyridine and benzene solutions of simple pregnane-11,20-diones are centred at τ 7·22—7·26 and τ 7·47—7·54 and at τ 7·52 and 8·11, respectively. The 12-methylene protons of the 11-oxo-25D-sapogenins in pyridine solution show, rather surprisingly, a broad singlet at τ 7·63—7·67; the 12-methylene protons of 3β-acetoxy-5α,9β-pregnane-11,20-dione (No. 9) and 3β-acetoxy-8α,9α-epoxy-7,11-dioxo-5α-ergost-22-ene (No. 12) likewise do not give an AB quartet. However, in the spectra of some of these compounds it is difficult to distinguish between a pair of doublets and a broad singlet.

The doublets at low and high magnetic field in the pyridine and benzene solution spectra are attributed to the 12β-proton (equatorial) and 12α-proton (axial), respectively.[3b,5,6] This assignment is supported by the observation that the low-field doublet for the 12β-proton is sharper than the high-field doublet and the 10-methyl peak is sharper than the 13-methyl peak, indicating that the axial 12α-proton is long-range coupled with the 13-methyl protons.[5,7] It is surprising that, when examined in deuterochloroform solution, both 12-protons for the 11-oxo-steroids in this group show the same chemical shift.[5] On going from deuterochloroform to pyridine solution, the signals for the 12α- and 12β-protons are usually displaced upfield and downfield, respectively.

The doublets for the 12β-protons of the two 11-oxo-steroids (No. 4 and 8) examined in both benzene and pyridine showed a smaller downfield shift in going from deuterochloroform to benzene (τ −0·01 to −0·06) than in going from deuterochloroform to pyridine (τ −0·10 to −0·20), whereas those for the 12α-proton showed a bigger upfield shift in going from deuterochloroform to benzene (τ 0·44 to 0·65) than in going from deuterochloroform to pyridine (τ 0·08 to 0·12). Thus, benzene has a larger shielding effect on the axial proton and a slightly smaller deshielding effect on the equatorial proton than has pyridine; this variation in shielding causes the two doublets to be further apart in benzene (τ 0·45 to 0·59) than in pyridine solution (τ 0·22 to 0·28). The 12β- and 12α-protons of the 11-oxo-D-homo-steroid (No. 14) underwent larger shifts to low field (τ −0·35 and −0·07, respectively) in going from deuterochloroform to pyridine solution than did those for the other steroids in Group 1.

The 1β-proton gave rise to two smeared triplets (J = −12 to −13 and 2·5 to 3 c./sec.)

[7] C. W. Shoppee, F. P. Johnson, R. Lack, and S. Sternhell, *Tetrahedron Letters*, 1964, 2319.

TABLE 1

Proton-resonance lines (τ values) for simple 11-oxo-steroids (Group 1) (*J* values in c./sec. in parentheses)

No.	Compound	Ref.	Solvent	10-Me	12-H (12α-)	12-H (12β-)	13-Me	21-H	Other peaks
1	5α-Androstan-11-one	*a*	$CDCl_3$	8·97	7·73		9·33b	—	—
			C_6H_6	8·83	8·10bd	7·70d	9·44b	—	—
2	2β,3β-Epoxy-5α-androstan-11-one	*a*	$CDCl_3$	8·93	7·70		9·33b	—	—
			C_6H_6	8·67	8·18(bd, 12·5)	7·68(d, 12·5)	9·50b	—	—
3	5α-Pregnane-11,20-dione	*b*	$CDCl_3$	8·98	7·46		9·41b	7·89	—
4	3β-Acetoxy-5α-androstan-11-one	*c*	$CDCl_3$	8·95	7·72		9·32b	—	—
			C_6H_6	8·93	8·16(bd, 12)	7·71(d, 12)	9·48b	—	—
			Pyridine	8·90	7·84(bd, 12)	7·62(d, 12)	9·38b	—	—
5	3β-Acetoxy-5α-androstane-11,17-dione	*d*	$CDCl_3$	8·95	7·63		9·18b	—	—
6	3α-Hydroxy-5β-pregnane-11,20-dione	*e*	$CDCl_3$	8·87	7·46		9·45b	7·91	—
7	3α-Acetoxy-5β-pregnane-11,20-dione	*e*	$CDCl_3$	8·83	7·43		9·42b	7·90	—
			Pyridine	8·78	7·47(bd, 12)	7·22(d, 12)	9·38b	7·94	—
8	3β-Acetoxy-5α-pregnane-11,20-dione	*f*	$CDCl_3$	8·96	7·46		9·42b	7·90	—
			C_6H_6	9·00	8·11(bd, 12)	7·52(d, 12)	9·53b	8·32	—
			Pyridine	8·92	7·54(bd, 12)	7·26(d, 12)	9·39b	7·95	—
9	3β-Acetoxy-5α,9β-pregnane-11,20-dione	*f*	$CDCl_3$	8·91	7·47		9·06b	7·90	7·20(d, 8) *
			Pyridine	8·95	7·41		9·12b	7·94	7·18(d, 8) *
10	5α-Pregnane-3,11,20-trione	*g*	$CDCl_3$	8·78	7·41		9·37b	7·89	—
11	3β-Acetoxy-11-oxo-22-bisnor-5α-cholanic acid	*f*	$CDCl_3$	8·96	7·56		9·35b	8·81(d, 6·5)	—
			Pyridine	8·90	7·68(bd, 12·5)	7·38(d, 12·5)	9·33b	8·72(d, 6·5)	—
12	3β-Acetoxy-8α,9α-epoxy-7,11-dioxo-5α-ergost-22-ene	*h*	$CDCl_3$	8·75	7·46		9·23b	9·00(d, 6·5)	—
			Pyridine	8·69	7·39b		9·19b	9·06(d, 6·5)	—
13	3βAcetoxy-16β-acetyl-16α-methyl-5α-androstane-11,17-dione	*i*	$CDCl_3$	8·95	7·62		9·26b	7·75 ×	8·53 †
14	3β,17α-Dihydroxy-17β-methyl-5α-D-homo-androstane-11,17a-dione	*c*	$CDCl_3$	8·97	7·51		8·97b	—	8·58 ‡
			Pyridine	8·83	7·44(bd, 12·5)	7·16(d, 12·5)	8·99b	—	8·51 ‡
15	3β-Acetoxy-17α-hydroxy-16α,17β-dimethyl-16β-fluoro-5α-D-homoandrostane-11,17a-dione	*i*	$CDCl_3$	8·95	7·48		8·95b	—	8·63 ‡ 8·50(d, 23) †
16	11-Oxotigogenin acetate	*j*	$CDCl_3$	8·94	7·73		9·27b	9·05(d, 7)	—
			Pyridine	8·90	7·67		9·21b	8·95(d, 6)	—
17	3,11-Dioxodeoxytigogenin (11-oxotigogenone)	*k*	$CDCl_3$	8·76	7·70		9·25b	9·05(d, 6·5)	—
			Pyridine	8·73	7·63		9·18b	8·94(d, 6·5)	—
18	3β,9α,20β-Triacetoxy-5α-pregnane-11-one	*l*	$CDCl_3$	8·80	7·54		9·38b	8·86(d, 6)	7·80, 7·96 §

Unless otherwise indicated, values refer to singlet absorptions. For multiplets, d = doublet, dd = two doublets, t = triplet, b = broad. * 9β-H, † 16-methyl, ‡ 17-methyl, § 9α-OAc and 20-OAc, × 16-Ac.

a, Calculated from values given in ref. (5). *b*, J. C. Babcock (Upjohn), U.S.P. 2,868,808. *c*, J. D. Cocker, J. Elks, P. J. May, F. A. Nice, G. H. Phillipps, and W. F. Wall, *J. Med. Chem.*, 1964, **8**, 417. *d*, T. Reichstein, *Helv. Chim. Acta*, 1937, **20**, 978. *e*, J. von Euw, A. Lardon, and T. Reichstein, *ibid.*, 1944, **27**, 821. *f*, A. F. B. Cameron, J. S. Hunt, J. F. Oughton, P. A. Wilkinson, and B. M. Wilson, *J.*, 1953, 3864. *g*, M. Steiger and T. Reichstein, *Helv. Chim. Acta*, 1938, **21**, 161. *h*, H. Heusser, K. Eichenberger, P. Kurath, H. R. Dällenbach, and O. Jeger, *ibid.*, 1951, **34**, 2106. *i*, P. J. May, F. A. Nice, and G. H. Phillipps, *J.*, to be submitted for publication. *j*, J. W. Cornforth, J. M. Osbond, and G. H. Phillipps, *J.*, 1954, 907. *k*, S. G. Brooks, J. S. Hunt, A. G. Long, and B. Mooney, *J.*, 1957, 1175. *l*, J. D. Cocker, H. B. Henbest, G. H. Phillipps, G. P. Slater, and D. A. Thomas, *J.*, 1965, 6.

TABLE 2

Proton-resonance lines (τ values) for simple 11-oxo-steroids (Group 2) (*J* values in c./sec. in parentheses)

No.	Compound	Ref.	Solvent	10-Me	12-H (12α-)	12-H (12β-)	13-Me	21-H	Other peaks
19	3β-Acetoxy-5α-ergostan-11-one	*a*	$CDCl_3$	8·97	7·78(bd, 12)	7·42(d, 12)	9·37b	9·16(d, 6)	—
			Pyridine	8·88	7·77(bd, 12)	7·35(d, 12)	9·38b	9·12(d, 6)	—
20	3β-Acetoxy-5α,9β-ergostan-11-one	*a*	$CDCl_3$	8·88	7·88(bd, 16)	7·57(d, 16)	9·07b	9·14(d, 6)	7·13(d, 8) *
			Pyridine	8·93	7·82(bd, 15)	7·54(d, 15)	9·08b	9·13(d, 6)	7·11(d, 8) *
21	3β-Acetoxy-5α-ergostane-7,11-dione	*b*	$CDCl_3$	8·71	7·79(bd, 12)	7·36(d, 12)	9·37b	9·15(d, 6)	—
			Pyridine	8·63	7·72(bd, 12)	7·30(d, 12)	9·33b	9·12(d, 6)	—
22	3β-Acetoxy-5α-ergost-22-ene-7,11-dione	*c*	$CDCl_3$	8·71	7·78(bd, 12)	7·40(d, 12)	9·35b	9·03(d, 6·5)	—
			Pyridine	8·63	7·71(bd, 12)	7·32(d, 12)	9·32b	9·04(d, 6)	—
23	3β-Acetoxy-5α-ergosta-8(9),22-dien-11-one	*a*	$CDCl_3$	8·89	7·69(bd, 14·5)	7·22(d, 14·5)	9·28b	9·01(d, 6·5)	—
			Pyridine	8·75	7·62 (bd, 14·5)	7·09(d, 14·5)	9·27b	9·04(d, 6·5)	—
24	3β-Acetoxy-5α,9β-ergosta-7,22-dien-11-one	*a*	$CDCl_3$	8·84	7·75(bd, 17)	7·38(d, 17)	9·08b	9·03(d, 6·5)	6·64b *
			Pyridine	8·86	7·70(bd, 16)	7·33(d, 16)	9·07b	9·02(d, 6)	6·54b *
25	3β,21-Diacetoxy-5α-pregnane-11,20-dione	*d*	$CDCl_3$	8·97	7·61(bd, 12)	7·37(d, 12)	9·38b	5·43	7·83 †
			C_6H_6	9·00	8·15(bd, 12)	7·43(d, 12·5)	9·46b	5·61(d, 16·5) 5·92(d, 16·5)	8·19 †
			Pyridine	8·92	7·50(bd, 12)	7·17(d, 12)	9·29b	5·20	7·90 †
26	21-Acetoxy-5α-pregnane-3,11,20-trione	*e*	$CDCl_3$	8·78	7·59(bd, 12)	7·34(d, 12)	9·33b	5·43	7·83 †
27	3β-Acetoxy-16β-methyl-5α-pregnane-11,20-dione	*f*	$CDCl_3$	8·97	7·87(bd, 12)	7·50(d, 12)	9·06b	7·90	8·95(d, 6·5) ‡
			Pyridine	8·90	7·79(bd, 12)	7·33(d, 12)	8·97b	7·95	7·98(d, 6) ‡

* 9β-H, † 21-AcO, ‡ 16β-Me.

a, P. Bladon, H. B. Henbest, E. R. H. Jones, B. J. Lovell, G. W. Wood, G. F. Woods, J. Elks, R. M. Evans, D. E. Hathway, J. F. Oughton, and G. H. Thomas, *J.*, 1953, 2921. *b*, J. Elks, R. M. Evans, A. G. Long, and G. H. Thomas, *J.*, 1954, 451. *c*, Ref. *h*, Table 1. *d*, J. von Euw and T. Reichstein, *Helv. Chim. Acta*, 1942, **25**, 988. *e*, O. Mancera, G. Rosenkranz, and F. Sondheimer, *J. Amer. Chem. Soc.*, 1955, **77**, 5669. *f*, P. De Ruggien, *Farmaco* (*Pavia*), *Ed. Sci.*, 1961, **16**, 583.

TABLE 3

Proton-resonance lines (τ values) for 17,17-disubstituted-11-oxo-steroids (Group 3) (J values in c./sec. in parentheses)

No.	Compound	Ref.	Solvent	10-Me	12-H (12α-)	12-H (12β-)	13-Me	16-H	21-H	21-AcO
28	3β-Acetoxy-16-methyl-5α-pregn-16-ene-11,20-dione	*a*	$CDCl_3$	8·96	7·68(bd, 12·5)	7·10(d, 12·5)	9·12b	7·90 †	7·70	—
29	21-Acetoxy-5α-pregn-16-ene-3,11,20-trione	*b*	$CDCl_3$	8·77	7·58(bd, 12·5)	6·93(d, 12·5)	9·12b	3·17	5·04	7·82
30	21-Acetoxypregna-1,4,16-triene-3,11,20-trione	*c*	$CDCl_3$	8·54	7·62(bd, 13)	6·88(d, 13)	9·07b	3·18	5·05	7·82
			Pyridine	8·59	7·48(bd, 13)	6·71(d, 13)	9·10b	3·15	4·67(d, 16) 4·98(d, 16)	7·87
31	3β-Acetoxy-16α,17α-epoxy-5α-pregnane-11,20-dione	*d*	$CDCl_3$	8·98	7·61(bd, 12)	7·30(d, 12)	9·03b	6·22	7·97	—
			Pyridine	8·93	7·47(bd, 12)	7·12(d, 12)	8·98b	6·17	7·99	—
32	3β,16α-Diacetoxy-17α-hydroxy-5α-pregnane-11,20-dione	*d*	$CDCl_3$	8·98	7·02(bd, 12·5)	7·95(d, 12·5)	9·35b	7·92 ‡	7·76	—
33	3β,21-Diacetoxy-17α-hydroxy-5α-pregnane-11,20-dione (Figure 1)	*e*	$CDCl_3$	8·97	7·10(bd, 12)	7·83(d, 12)	9·40b	—	4·82(d, 17) 5·35(d, 17)	7·84
			Pyridine	8·89	6·70(bd, 12)	7·33(d, 12)	9·18b	—	4·50(d, 17) 4·88(d, 17)	7·90
34	21-Acetoxy-17α-hydroxy-5α-pregnane-3,11,20-trione	*f*	$CDCl_3$	8·78	7·07(bd, 12)	7·78(d, 12)	9·37b	—	4·80(d, 17·5) 5·36(d, 17·5)	7·83
35	21-Acetoxy-17α-hydroxy-16β-methyl-5α-pregnane-3,11,20-trione	*g*	$CDCl_3$	8·78	7·16(bd, 12·5)	7·84(d, 12·5)	9·20b	8·87(d, 7) †	4·89(d, 18) 5·28(d, 18)	7·82
			Pyridine	8·73	6·73(bd, 12)	7·47(d, 12)	9·02b	8·71(d, 7) †	4·50(d, 18) 4·83(d, 18)	7·87
36	21-Acetoxy-17α-hydroxy-pregn-4-ene-3,11,20-trione	*f*	$CDCl_3$	8·59	7·07(bd, 12·5)	7·81(d, 12·5)	9·33b	—	4·84(d, 18) 5·33(d, 18)	7·83
37	21-Acetoxy-17α-hydroxy-pregna-1,4-diene-3,11,20-trione	*h*	$CDCl_3$	8·56	7·06(bd, 12·5)	7·69(d, 12·5)	9·31b	—	4·87(d, 18) 5·30(d, 18)	7·83
			Pyridine	8·55	6·67(bd, 12)	7·24(d, 12)	9·12b	—	4·52(d, 17·5) 4·88(d, 17·5)	7·88
38	21-Acetoxy-17α-hydroxy-16β-methylpregna-1,4-diene-3,11,20-trione	*g*	$CDCl_3$	8·55	7·14(bd, 12·5)	7·78(d, 12·5)	9·14b	8·89(d, 6·5) †	4·89(d, 18) 5·22(d, 18)	7·82
			Pyridine	8·56	6·73(bd, 12·5)	7·42(d, 12·5)	8·98b	8·73(d, 7) †	4·67	7·86
39	21-Acetoxy-16α,17α-isopropylidenedioxy-5α-pregnane-3,11,20-trione	*b*	$CDCl_3$	8·46	7·14(bd, 12)	7·72(d, 12)	9·39b	—	4·88(d, 18) 5·40(d, 18)	7·83
40	21-Acetoxy-9α-fluoro-17α-hydroxy-16β-methylpregna-1,4-diene-3,11,20-trione	*i*	Pyridine	8·44	6·25(bdd, 12, 6·5)	7·40(dd, 12, 1·5)	8·97b	8·73(d, 7·5) †	4·70	7·85
41	17α,21-Diacetoxy-9α-fluoro-16β-methylpregna-1,4-diene-3,11,20-trione	*i*	$CDCl_3$	8·44	6·59(bdd, 12, 6·5)	7·45(dd, 12, 2)	9·23b	8·67(d, 7) †	5·23(d, 16·5) 5·67(d, 16·5)	7·83 *
42	21-Acetoxy-9α-bromo-17α-hydroxy-5α-pregnane-3,11,20-trione	*j*	$CDCl_3$	8·66	6·03(bd, 13)	7·75(d, 13)	9·37b	—	4·86(d, 17·5) 5·34(d, 17·5)	7·82
			Pyridine	8·62	5·60(bd, 13)	7·26(d, 13)	9·15b	—	4·52(d, 17·5) 4·87(d, 17·5)	7·88

† 16-Me, ‡ 16α-AcO, * includes 17α-AcO.

a, G. H. Phillipps, W. Graham, G. I. Gregory, and J. Elks (Glaxo), U.S.P. 3,040,070. *b*, S. Eardley and A. G. Long, *J.*, 1965, 130. *c*, H. L. Herzog and E. P. Oliveto (Schering), U.S.P. 2,874,172. *d*, S. Eardley, W. Graham, A. G. Long, and J. F. Oughton, *J.*, 1965, 142. *e*, Ref. *e*, Table 2. *f*, J. Romo, G. Rosenkranz, C. Djerassi, and F. Sondheimer, *J. Amer. Chem. Soc.*, 1953, **75**, 1277. *g*, D. Taub, R. D. Hoffsommer, H. L. Slates, C. H. Kuo, and N. L. Wendler, *ibid.*, 1960, **82**, 4012. *h*, H. L. Herzog, C. C. Payne, M. A. Jevnik, D. Gould, E. L. Shapiro, E. P. Oliveto, and E. B. Hershberg, *ibid.*, 1955, **77**, 4781. *i*, Unpublished observations. *j*, J. Fried and E. F. Sabo, *J. Amer. Chem. Soc.*, 1953, **75**, 2273.

centred at τ 7·44—7·55, 7·22—7·23, and 7·30—7·35 in deuterochloroform, benzene, and pyridine solution, respectively;[4] the peaks, which are not listed in the Tables, were, however, often partially obscured by other absorption. The peaks for the 3β-acetoxy-protons appeared at τ 7·97—7·98, 8·22—8·23, and 7·95—7·97 and those for the corresponding 3α-protons at τ 5·20—5·33, 5·13—5·15, and 5·03—5·22 in deuterochloroform, benzene, and pyridine solution, respectively. The 21-protons of the pregnane-11,20-diones shift from τ 7·89—7·91 in deuterochloroform solution to τ 8·32 and 7·94—7·95 in benzene and pyridine solution, respectively.

Group 2.—The second group (Table 2) consists of 11-oxo-steroids that do not have a 17α-substituent and for which the 12-methylene protons in both deuterochloroform and pyridine solution give an AB quartet; this group includes certain 21-acetoxypregnane-11,20-diones, 16β-methylpregnane-11,20-diones, and 9α- and 9β-ergostan-11-ones.

The 12β- and 12α-protons for 11-oxo-9α-steroids with a saturated ring system show doublets (J = −12 c./sec.) centred at τ 7·34—7·50 and 7·59—7·87, respectively, in deuterochloroform and at τ 7·17—7·35 and 7·50—7·79, respectively, in pyridine solution. A 21-acetoxypregnane-11,20-dione (No. 25), which was examined in deuterochloroform, pyridine, and benzene solution, gave solvent shifts similar to those observed for the androstan-11-ones (Table 1), the centres of the 12β- and 12α-doublets being 0·24, 0·33, and 0·72 τ-units apart, respectively. Once again, long-range coupling between the 12α- and the 13-methyl protons causes the high-field doublet for the 12α-proton, both in deuterochloroform and pyridine solution, to be less sharp than that for the 12β-proton.

It is to be noted that the 12-methylene group for the 16β-methylpregnane-11,20-dione (No. 27) gives a pair of doublets in deuterochloroform solution, whereas the corresponding compound without a 16-substituent (No. 8) gives a singlet (Table 1). This effect must be associated with the change in the orientation of the 17β-acetyl side-chain caused by the introduction of the 16β-methyl group.[8]

In deuterochloroform solution the 9β-ergostan-11-ones (No. 20 and 24) give the expected 12-methylene doublets centred at τ 7·38—7·57 and 7·75—7·88, but with a geminal coupling constant of −16 to −17 c./sec. instead of −12 c./sec., as shown by 9α-steroids. This effect is attributed to a change in the conformation of ring-c. The 9β-proton of 3β-acetoxy-5α,9β-ergostan-11-one (No. 20), due to vicinal coupling with the 8β-proton, gives rise to a doublet centred at τ 7·13 (J = 8 c./sec.). A Dreiding model shows that the 9β-proton lies in the same plane as the 11-ketone and would therefore be deshielded. The corresponding 7,22-diene derivative (No. 24) likewise shows a 9β-proton peak at τ 6·64.

The 1β-proton multiplet, when observable, was centred at τ 7·40—7·47 and 7·24—7·36 in deuterochloroform and pyridine solution, respectively; this solvent effect is similar to that shown by the 1β-proton multiplet for the 11-oxo-steroids included in group 1. The 3β-acetoxy and 3α-proton peaks were likewise in the same ranges as in group 1.

Group 3.—The third group (Table 3) consists of pregnane-11,20-diones either disubstituted at C-17 (*e.g.*, Figure 1) or with a 16-olefinic linkage. The 12-methylene protons for these steroids in both deuterochloroform and pyridine solution give rise to an AB quartet (J = −12 to −12·5 c./sec.); the compounds were insufficiently soluble for reliable measurements in benzene.

The centres of the doublets for these steroids in deuterochloroform and pyridine solution are farther apart than those for the corresponding 11-oxo-steroids monosubstituted at C-17; a 16β-methyl group displaces the doublets by about 0·10 τ-units to higher field. In the 16-olefinic and 16α,17α-epoxy-pregnane-11,20-diones, as for the simpler 11-oxo-steroids (Tables 1 and 2), the doublet at higher magnetic field is broader than that at lower field; the reverse occurs with the 17α-hydroxy- and 17α-acetoxy-pregnane-11,20-diones. This behaviour was confirmed by measurements on cortisone acetate (No. 36) at 100 Mc./sec. The 13-methyl peak remains broader than the 10-methyl peak, suggesting

[8] A. D. Cross and C. Beard, *J. Amer. Chem. Soc.*, 1964, **86**, 5317.

that the 13-methyl protons are long-range coupled with the low-field doublet, which must be assigned to the 12α-proton (axial); the axial proton now absorbs at lower field than the equatorial.

The introduction of a 9α-halogen atom leads to 1,3-diaxial deshielding of the 12α-proton.[3b] The centre of the broad doublet for the 12α-proton of 21-acetoxy-9α-bromo-17α-hydroxy-5α-pregnane-3,11,20-trione (No. 42) moves downfield to τ 6·03 (deuterochloroform solution), but the sharp doublet for the 12β-proton remains near τ 7·75. It is noteworthy that a 9α-fluorine (No. 40 and 41) splits the doublets for the 12α- and 12β-protons to give quartets (J = −12 and 6·5 c./sec. and −12 and 1·5—2 c./sec., respectively). This splitting is rather unexpected, since long-range coupling through carbonyl is usually greatest when the interacting nuclei are pseudo-equatorial.[9]

The 1-protons for the 11-oxo-, 11β-hydroxy-, and 11β-chloro-3-oxo-$\Delta^{1,4}$-9α-steroids named in Tables 3 and 4 give rise in deuterochloroform solution to doublets (J = 10 c./sec.)

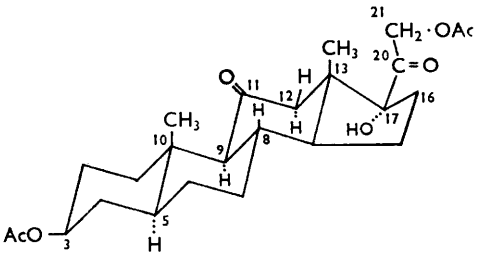

FIGURE 1. 3β,21-Diacetoxy-17α-hydroxy-5α-pregnane-11,20-dione (No. 33)

centred at τ 2·22—2·25, 2·74—2·76, and 2·81, respectively, whereas the 1-protons for the corresponding steroids unsubstituted at C-11 absorb at about τ 2·9 (the 1-proton peaks for the 11-oxo-steroids and for the steroids unsubstituted at C-11 are not listed in the Tables); this effect indicates a deshielding action by the 11-ketone similar to that observed for 5α-androstan-11-one.[4] The 1-proton doublet for the 3,11-dioxo-$\Delta^{1,4}$-9α-fluoro-steroid (No. 41) is, however, centred at τ 2·58. In pyridine solution, the 1-proton peaks are obscured by solvent absorption.

11β-*Hydroxy- and* 11β-*Halogeno-steroids*.—The 12α-protons of 9α-halogeno-11β-hydroxy- and 9α,11β-dihalogeno-17α-hydroxypregnan-20-ones (*e.g.*, Figure 2) are also deshielded more than the corresponding 12β-protons (Table 4). 9α,11β-Dichloro-17α-hydroxypregnan-20-ones show one pair of doublets in the τ 5 region for the 11α-proton and two pairs of doublets at higher field for the two 12-methylene protons. The spectra for the 9α-halogeno-11β,17α-dihydroxy-steroids are similar except that the 11α-proton of the 9α-fluoro-steroids (No. 43 and 44) couples with the 9α-fluorine to give a pair of multiplets (J = 9—10 c./sec.).

The pairs of doublets centred at τ 7·16, 6·83, and 6·65 in the pyridine-solution spectra of the 9α-fluoro-, 9α-chloro-, and 9α-bromo-11β-hydroxy-compounds (No. 44—46), respectively, are assigned to the 12α-proton; the doublets for the 12β-proton for all three 9α-halogeno-11β-hydroxy-steroids are partly obscured by other absorption, but the doublets have their centres in the same region, namely, τ 7·69—7·71. This 1,3-diaxial deshielding of the 12α-proton by 9α-halogen is similar to that found for 9α-halogeno-11-oxo-steroids (Table 3).[3b]

The 11α-proton of a 9α,11β-dichloro-17α-hydroxypregnan-20-one (cf. Figure 2) couples with the 12α- and 12β-protons to give an ABX system with coupling constants of 4·5—5 and 2 c./sec., respectively. The low-field 12-proton peaks have a geminal coupling constant of −14·5 to −15 c./sec. and a vicinal one of 4·5 to 5 c./sec., whereas the corresponding high-field peaks, which are sharper, have the same geminal constant but a vicinal constant of 2 c./sec., indicating that the protons are 12α and 12β, respectively. Similar assignments

[9] T. A. Wittstruck, S. K. Malhotra, H. J. Ringold, and A. D. Cross, *J. Amer. Chem. Soc.*, 1963, **85**, 3038.

TABLE 4

Proton-resonance lines (τ values) for 9α-halogeno-11β-hydroxy- and 9α,11β-dihalogeno-steroids (J values in c./sec. in parentheses)

No.	Compound	Ref.	Solvent	1-H	10-Me	11α-H	12-H (12α-)	12-H (12β-)	13-Me	16-Me	21-H	21-AcO
43	21-Acetoxy-9α-fluoro-11β,17α-dihydroxy-16α-methyl pregna-1,4-diene-3,20-dione	*a*	$CDCl_3$	2·76 (d, 10)	8·45	5·65 (dm, 10)	7·62(dd, 15, 3)	n.o.	8·94b	9·08(d, 7·5)	5·10	7·82
44	21-Acetoxy-9α-fluoro-11β,17α-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione	*b*	$CDCl_3$	2·74 (d, 10)	8·46	5·65 (dm, 9)	7·62(dd, 15, 3)	n.o.	8·92b	8·83(d, 7)	5·03	7·82
			Pyridine	n.o.	8·22	5·28 (dm, 10)	7·16(dd, 14, 4·5)	7·71(d, 14)	8·49b	8·62(d, 7)	4·62	7·86
45	21-Acetoxy-9α-chloro-11β,17α-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione	*c*	Pyridine	n.o.	8·11	5·10 (m)	6·83(dd, 14, 3)	7·70(d, 14)	8·48b	8·62(d, 7)	4·60	7·85
46	21-Acetoxy-9α-bromo-11β,17α-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione	*b*	Pyridine	n.o.	8·07	4·90 (m)	6·65(dd, 14, 3·5)	7·69(d, 14)	8·49b	8·62(d, 7)	4·59	7·85
47	3β-Acetoxy-9α,11β-dichloro-17α-hydroxy-16β-methyl-5α-pregnan-20-one (Figure 2)	*d*	$CDCl_3$	n.o.	8·62	5·28 (dd, 5, 2)	6·95(dd, 14·5, 5)	8·01(dd, 14·5, 2)	8·82b	8·69(d, 7)	7·73	—
48	9α,11β-Dichloro-17α,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione	*e*	Pyridine	n.o.	8·33	5·01 (dd, 5, 2)	6·57(dd, 15, 5)	7·98(dd, 15, 2)	8·76b	8·90(d, 7)	4·77(d, 19) 5·29(d, 19)	—
49	9α,11β-Dichloro-17α,21-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione	*d*	Pyridine	n.o.	8·32	5·04 (m)	6·62(dd, 15, 5)	8·10(dd, 15, 2)	8·63b	8·70(d, 7)	4·85(d, 19) 5·22(d, 19)	—
50	9α,11β-Dichloro-17α,21-isopropylidenedioxy-16α-methylpregna-1,4-diene-3,20-dione	*e*	$CDCl_3$	2·81 (d, 10)	8·26	5·17 (dd, 4·5, 2)	6·68(bdd, 15, 4·5)	8·16(dd, 15, 2)	8·98b	9·13(d, 7)	5·63(d, 19) 6·03(d, 19)	—

n.o. = not observed, m = multiplet.

a, E. P. Oliveto, R. Rausser, L. Weber, A. L. Nussbaum, W. Gebert, C. T. Coniglio, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *J. Amer. Chem. Soc.*, 1958, **80**, 4431. *b*, Ref. *g*, Table 3. *c*, Merck, B.P. 912,378. *d*, J. Attenburrow, J. E. Connett, W. Graham, J. F. Oughton, A. C. Ritchie, and P. A. Wilkinson, *J.*, 1961, 4547. *e*, C. H. Robinson, L. E. Finckenor, R. Tiberi, and E. P. Oliveto, *J. Org. Chem.*, 1961, **26**, 2863.

are made for the 11β-hydroxy-9α-halogeno-steroids; the vicinal coupling constants between the 11α- and the 12α-protons and between the 11α- and the 12β-protons of simple 5α-androstan- and 20-oxo-5α-pregnan-11β-ols are, however, both about 2·5 c./sec.[10]

Further support for our assignments for the 12α- and 12β-proton resonances came from 100 Mc./sec. and spin-decoupling measurements on a pyridine solution of 21-acetoxy-9α-chloro-11β,17α-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione (No. 45) and on a deuterochloroform solution of 9α,11β-dichloro-17α,21-isopropylidenedioxy-16α-methylpregna-1,4-diene-3,20-dione (No. 50). Double irradiation at the frequency of the 11α-proton of the 11β,17α-dihydroxy-steroid reduces the 12β- and 12α-proton resonances to doublets ($J = -14$ c./sec.); irradiation at the frequency of the 12β-proton reduces the 12α-proton peaks to a doublet ($J = 4$ c./sec.). Double irradiation at the frequency of the

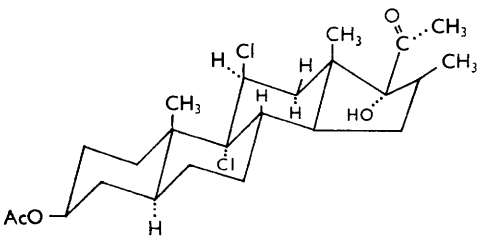

FIGURE 2. 3β-Acetoxy-9α,11β-dichloro-17α-hydroxy-16β-methyl-5α-pregnan-20-one (No. 47)

12α- but not at that of the 12β-proton of the 9α,11β-dichloro-steroid leads to a sharpening of the 13-methyl protons. The 16β-proton peaks are incidentally shown to be centred at about τ 6·85, since on irradiation at this frequency the doublet for the 16α-methyl protons collapses to a singlet.

Discussion.—The positions of the 10- and 13-methyl peaks for 11-oxo-steroids without 17α- and 16β-substituents (Tables 1 and 2) agree well with those calculated from Zürcher's Tables.[11] The frequency-shift additivity-principle cannot be applied to steroids polysubstituted in the D-ring, since distortion of the D-ring probably occurs.[8] The shifts in the position of the 13-methyl peak observed in going from a steroid unsubstituted at C-16 to one with a 16β-methyl (Table 3) agree with those reported by Cross and Beard.[8]

The 10- and 13-methyl peaks of simple steroids usually undergo a small paramagnetic shift in going from deuterochloroform to pyridine solution [12] and a larger diamagnetic shift in going from deuterochloroform to benzene.[5] In simple androstan-11-ones, a change from deuterochloroform to benzene causes a small deshielding of the 10- and a small shielding of the 13-methyl protons; this is attributed to the formation of a 1 : 1 collision complex.[5] A change to pyridine solution produces a small deshielding of the 10- and 13-methyl protons and, when present, of the 16- and 21-methyl protons; a number of exceptions are, however, recorded in the Tables.

The downfield shift of the 12α- and 12β-protons of 11-oxo-steroids is affected by the nature of the 9- and 17-substituents. A 17β-substituent causes deshielding of the equatorial 12-proton, whereas a 20-ketone also deshields the axial 12-proton. Introduction of 17α-hydroxyl, but not of 16-olefin or 16α,17α-epoxide, into a pregnane-11,20-dione causes a large downfield shift of the 12-axial but an upfield shift of the 12-equatorial proton; the 12α-proton now absorbs at lower field than the 12β-proton. A 16β-methyl group appears to decrease the paramagnetic shift of the 12-axial proton, probably because of the reorientation of the 17β-acetyl side-chain.

The unexpected deshielding of the 12α-proton compared with the 12β-proton in the

[10] K. Tori, T. Tomita, H. Itazaki, M. Narisada, and W. Nagata, *Chem. and Pharm. Bull.* (*Japan*), 1963, **11**, 956; D. H. Williams and N. S. Bhacca, *J. Amer. Chem. Soc.*, 1964, **86**, 2742.

[11] R. F. Zürcher, *Helv. Chim. Acta*, 1963, **46**, 2054.

[12] G. Slomp and F. MacKellar, *J. Amer. Chem. Soc.*, 1960, **82**, 999; J. P. Kutney, W. McCrae, and A. By, *Canad. J. Chem.*, 1962, **40**, 982.

spectra of 17α-hydroxypregnan-20-ones suggests that the 17α-hydroxyl interacts with the 12α-proton. A Courtauld model shows that the oxygen of the 17α-hydroxyl comes close to the 12-axial proton and deshields it, whereas the 20-ketone shields the 12-equatorial proton (see Figure 1). The corresponding 16-olefinic and 16α,17α-epoxy-steroids cannot show these effects. The interaction between the 12α-proton and the 17α-hydroxyl provides another example of 1,3-diaxial deshielding. It is noteworthy that the introduction of a 17α-hydroxyl causes the relative positions of the 12α- and 12β-hydrogen peaks of a pregnane-11,20-dione to accord with the original " rule " that an axial proton adjacent to the carbonyl group in a cyclohexanone ring appears at lower field than the corresponding equatorial proton (see *inter al.* Bhacca, Gurst, and Williams [6]).

The large downfield shift of the 12-axial proton of 11-oxo- (Table 3), 11β-hydroxy-, and 11β-chloro-steroids (Table 4) in the presence of a 9α-halogen is attributed to 1,3-diaxial deshielding (see Figure 2); the size of the paramagnetic shift increases with increasing size of the halogen atom (see No. 44—46).

It is of interest that the geminal coupling constant for the 12-methylene protons of 11-oxo-9α-steroids is about −12 to −13 c./sec., but that it rises to −15 to −17 c./sec. in 11-oxo-9β-steroids (cf. −15 c./sec. in 9,19-cycloandrostan-11-one [13]), to −14·5 c./sec. in 11-oxo-$\Delta^{8(9)}$-steroids, and to −14 to −15 c./sec. in 11β-hydroxy- and 11β-chloro-9α-halogeno-steroids.[14]

The 21-methylene protons of 21-substituted pregnan-20-ones are rendered non-equivalent by virtue of restricted rotation around the C-20–C-21 bond and, sometimes, give rise to an AB quartet in the τ 5 region. When splitting occurred, the geminal coupling constants for the 21-methylene protons of our 17α,21-dihydroxy- (−19 c./sec.), 17α-hydrogen-21-acetoxy- (−16·5 c./sec.), 17α-hydroxy-21-acetoxy- (−17 to −18 c./sec.), and 17α,21-diacetoxy-steroids (−16·5 c./sec.) were close to those (−19·5, −16·9, −17·6, and −16·8 c./sec., respectively) reported by Takahashi.[15] The peaks were displaced by τ 0·2—0·4 downfield in going from deuterochloroform to pyridine solution. However, as will be seen from the Tables, splitting does not always occur. The 21-methylene protons of 21-acetoxypregna-1,4,16-triene-3,11,20-trione (No. 30) give an AB quartet in pyridine but not in deuterochloroform solution, whereas those of 21-acetoxy-17α-hydroxy-16β-methylpregna-1,4-diene-3,11,20-trione (No. 38) are split in deuterochloroform but not in pyridine solution.

Experimental

The p.m.r. spectra were measured at 38° with a Varian Associates A-60 spectrometer at a sweep-rate of 1 c./sec./sec. Tetramethylsilane ($SiMe_4$ = τ 10) was used as an internal standard; a few measurements were conducted on a Varian Associates HA-100 spectrometer. The steroids were studied as 5—10% w/v solutions in deuterochloroform, pyridine, and benzene.

The compounds, which were prepared by colleagues in these laboratories, gave satisfactory infrared spectra and had the physical properties described in the references listed in the Tables.

We thank Dr. J. Feeney of Varian Associates Ltd. for recording the 100 Mc./sec. spectra and for the spin decoupling measurements.

Glaxo Research Ltd., Greenford, Middlesex. [*Received, June 10th,* 1965.]

[13] D. H. Williams and N. S. Bhacca, *J. Amer. Chem. Soc.*, 1963, **85**, 2861.
[14] D. H. Williams and N. S. Bhacca, *Chem. and Ind.*, 1965, 506.
[15] T. Takahashi, *Tetrahedron Letters*, 1964, 565.