Fourier Transform ^{13}C Nuclear Magnetic Resonance Studies of Steroids. Part I. Some Substituted 17β-(2,5-Dihydro-5-oxo-3-furyl) Steroids

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The natural abundance ^{13}C n.m.r. spectra of several substituted (2,5-dihydro-5-oxo-3-furyl) steroids, having hydroxy-groups at various positions in the steroid nucleus, have been measured. The effects of changes in the structure of the steroid nucleus upon substituent chemical shifts are evaluated and discussed.

THE steroid nucleus provides an ideal rigid system for the study of the spacial dependence of substituent effects. Although the early work of Roberts *et al.*[1] showed the sensitivity of the ^{13}C spectra of steroids towards substituent and structural modification few further investigations have appeared. The early work was concerned totally with the assignment of the resonances and it is only recently that substituent effects have been discussed in any detail.[2-4]

Although the effects upon the ^{13}C spectra of substituting hydroxy-groups at various positions in the steroid nucleus may be deduced from the literature, the dependence of these effects upon the presence of substituents elsewhere in the molecule and upon the structure of the steroid nucleus as a whole has not been considered. Such a study is necessary, as ' conformational transmission ' of long-range structural effects is well known in the reactions of steroids.[5]

In the present work we have studied the ^{13}C n.m.r. of the substituted 17β-(2,5-dihydro-5-oxo-3-furyl) steroids (1)—(13), having hydroxy-groups in various positions in the molecule, in order to investigate the influences of structural modification upon substituent effects.

EXPERIMENTAL

The steroids (1), (1a), (2), (2a), (3), (6a), (9), (10), and (13) were prepared synthetically while (4), (5), (7), (8), (11), and (12) were produced as fungal metabolites. Steroid (6) was produced by both procedures. Experimental details will appear elsewhere. The structure of each was confirmed by mass spectrometry, i.r. spectroscopy, ^{1}H and ^{13}C n.m.r. spectroscopy, and elemental analysis.

All spectra were recorded on a Varian XL-100-12 spectrometer operating in the Fourier transform mode at 25·16 MHz and locked to the deuterium resonance (15·40 MHz) of the solvent. The instrument was controlled with a Varian 620-L computer equipped with a moving head disc together with complementary software. Parameters were chosen except where indicated, to yield a 12 K transform which gave 0·90 Hz per channel for 5500 Hz sweep widths. Peak positions were determined by a software centroid

[1] H. J. Reich, M. Jautelat, M. T. Messe, F. J. Weigert, and J. D. Roberts, *J. Amer. Chem. Soc.*, 1969, **91**, 7445.

[2] N. S. Bhacca, D. D. Giannini, W. S. Jankowski, and M. E. Wolff, *J. Amer. Chem. Soc.*, 1973, **95**, 8421.

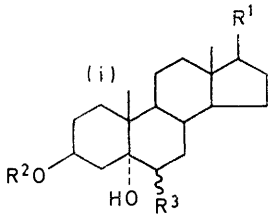
[3] S. H. Grover and J. B. Stothers, *Canad. J. Chem.*, 1974, **52**, 870.

[4] R. J. Abraham and J. R. Monasterios, *J.C.S. Perkin II*, 1974, 662.

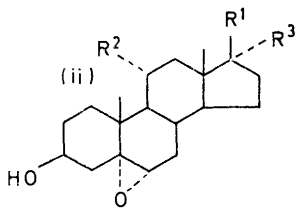
[5] N. L. Allinger and G. A. Lane, *J. Amer. Chem. Soc.*, 1974, **96**, 2937 and references therein.

function and are considered to be accurate to within ±0·04 p.p.m.

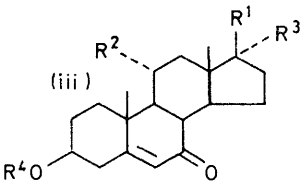
A sample of each steroid, at a concentration of 0·07—0·15M, was dissolved in deuteriated solvent (0·5 ml). Noise-decoupled and off-resonance proton decoupled spectra [6]



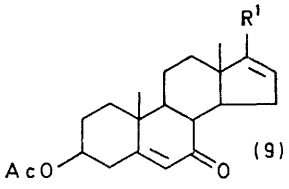
(1) R^2 = H, R^3 = 6β-OH
(1a) R^2 = Ac, R^3 = 6β-Ac
(2) R^2 = H, R^3 = 6α-OH
(2a) R^2 = Ac, R^3 = 6α-Ac



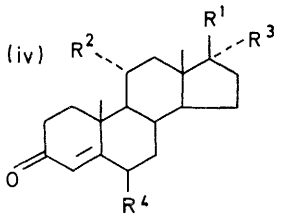
(3) R^2 = R^3 = H
(4) R^2 = H, R^3 = OH
(5) R^2 = OH, R^3 = H



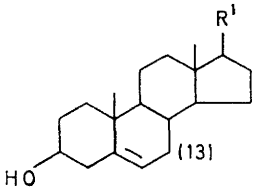
(6) R^2 = R^3 = R^4 = H
(6a) R^2 = R^3 = H, R^4 = Ac
(7) R^2 = R^4 = H, R^3 = OH
(8) R^3 = R^4 = H, R^2 = OH



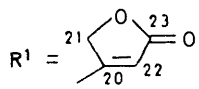
(9)



(10) R^2 = R^3 = R^4 = H
(11) R^2 = R^4 = H, R^3 = OH
(12) R^3 = H, R^2 = R^4 = OH



(13)



were obtained at 37° with internal tetramethylsilane as standard in 5 mm sample tubes. Typically between 30 and 50 K transients were accumulated.

Our filing of all the known literature data for steroids on magnetic tape enabled us to compare and evaluate substituent effects in a quick and accurate way.

RESULTS

The spectral assignments were made by the use of the off-resonance spectra, by acetylation of hydroxy-groups, by shift considerations, and by comparison with literature data. The shifts and assignments are shown in Table 1 and in the correlation diagrams, Figures 1 and 2. The multiplicity of the resonances in the off-resonance proton decoupled spectra allowed the assignment of most signals to either primary, secondary, tertiary, or quaternary carbons. The replacement of a hydrogen atom with a hydroxy-group causes a downfield shift of *ca.* 43 p.p.m. for a secondary carbon atom in the cyclohexane system [7] and a smaller shift for a tertiary carbon atom. This together with chemical shift considerations [8] and the results of the off-resonance experiments allowed the resonances of C-3, -5, -10, -11, -13, -18, -19, -21, and -22 in all compounds to be unambiguously assigned. The resonances of C-6 [except for (10) and (11)], -8 [except for (1), (2), and (13)], -9 [except for (5)—(9)], -14 [except for (6)—(9)], -15 [except for (6), (8), and (9)], -16 [except for (4) and (6)—(8)], and -17 [except for (5), (6), and (8)] were assigned by the same methods.

The resonances of C-23 and -20 were assigned as indicated (Figure 2) to give a self-consistent set of shifts in agreement with a previous tentative assignment of these carbons.[9] The resonance that remained constant at 175·4 ± 0·1 p.p.m. in methanol–chloroform as solvent and at 174·3 ± 0·4 p.p.m. in either pyridine–acetone or chloroform was assigned to C-23, while the resonance that showed substantial substituent effects upon hydroxylation at C-17 [(4) and (7)] and 16-ene formation [(9)] was assigned to C-20. The resonance of C-20 in (12) and (11) was distinguished from that of C-5 by comparison with (13) and (6a) (in methanol–chloroform) respectively; the shift difference of 3·00 p.p.m. between C-20 and -23 for (6a) in chloroform was used to distinguish C-23 from C-5 in (10) (shift difference 3·09 p.p.m.).

The remaining resonances were assigned as follows.

Compounds (1) *and* (2).—Only resonances of C-1, -2, -4, -7, -8, and -12 remain to be assigned. C-8 Could not be assigned from the off-resonance experiment. Spectra of the 3,6-diacetylated compounds [(1a) and (2a), Table 1] showed the expected two-bond upfield shifts for three of the six resonances (those of C-2, -4, and -7) while three resonances remained essentially unchanged (those of C-1, -8, and -12). Of the former C-2 was assigned to the resonance at 30·5 ± 0·2 p.p.m. by comparison with literature data.[1-4] From the work of Grover and Stothers [3] the effect of an axial hydroxy-group upon carbons two and three bonds removed from this group may be calculated as +5·9 p.p.m. (downfield, average of 12 observations) and −6·2 p.p.m. (11 observations) respectively. The effect of introducing a 5α-hydroxy-group may be calculated from these substituent shifts and the reported data for the cholestane-3β,6-diols.[3] The calculated shifts for C-4 and -7 are 41·3 and 33·4, and 38·2 and 35·5 p.p.m. for the 3β,5α,-6β-triol and 3β,5α,6α-triol respectively. Hence C-4 and -7 in (1) and (2) were assigned as shown at 40·4 and 34·2, and 38·1 and 34·6 p.p.m. respectively. Of the remaining three resonances the one unaffected on going from (1) to (2) was assigned to C-12, and this was confirmed by its characteristic shift from a comparison with literature data.[2,4] The last two resonances, of C-1 and -8, were assigned as shown, since C-1 appears as a triplet in the off-resonance spectra for both the parent compounds and their acetylated derivatives.

Compound (3)—(5).—Of the secondary carbon resonances only those of C-4 and -7 would be expected to remain

[6] R. R. Ernst, *J. Chem. Phys.*, 1966, **45**, 3845; K. G. R Pachler, *J. Magnetic Resonance*, 1972, **7**, 442.
[7] J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, *J. Amer. Chem. Soc.*, 1970, **92**, 1338.
[8] J. B. Stothers, 'Carbon-13 N.M.R. Spectroscopy,' Academic Press, London, 1972.
[9] K. Tori, H. Ishii, Z. W. Wolkowski, C. Chachaty, M. Sangare, F. Piriou, and G. Lukacs, *Tetrahedron Letters*, 1973, 1077.

constant throughout this series; thus they were assigned by comparison with (1) and (2). Of the remaining secondary carbon resonances, two would remain unaffected by the introduction of a 17α-hydroxy-group (those of C-1 and -2) and were assigned by comparison with (1) and (2). This assignment was confirmed by the effects of the introduction of an 11α-hydroxy-group in (5), which caused a greater downfield shift for C-1 than for C-2. The resonance of C-12 in (3) was assigned by comparison with (1) and (2), while the two remaining unassigned resonances of (4) arise from C-12 and -16. Although these cannot be unambiguously distinguished, they have been assigned as shown, since substantial upfield and downfield shifts for C-12 and -16, respectively, were expected upon the introduction of the 17α-hydroxy-group (ref. 1; and see above).

Hydroxy-substitution at C-11 caused an expected downfield shift for C-12 in (5).[2] This resonance was differentiated from C-9 and -17 by an off-resonance experiment in pyridine. A change of solvent from I to II is accompanied

TABLE 1

^{13}C Chemical shifts (p.p.m.) of steroids [a]

Compound	(1)	(1)	(1a)	(2)	(2)	(2a)	(3)	(3)	(4)	(4)	(5)	(5)	(6)
Carbon													
1	32·6	33·2	32·11	31·5	32·0	31·50	32·8	33·2	32·7	33·1	34·56	35·40	36·94 [e]
2	30·7	31·4	26·94	30·4	31·5	26·79	28·8	29·1	28·9	29·3	29·71	30·00	32·08
3	67·5	67·4	71·65	67·2	67·0	71·36	68·2	68·2	68·2	68·2	68·18	68·22	70·17
4	40·4	42·0	36·62	38·1	39·2	34·71	39·7	40·6	39·7	40·3	40·05	41·34	42·94
5	75·6	75·8	74·34	77·1	77·0	75·69	66·6	66·0	66·6	66·3	67·26	66·54	166·94
6	75·9	75·8	76·68	70·5	70·4	74·46	59·7	59·1	59·7	59·3	60·15	59·54	125·79
7	34·2	35·2	31·46	34·6	35·4	30·99	30·9	31·9	30·8	31·6	31·17	32·59	200·81
8	31·1	32·0	31·46	34·3	34·5	34·32	30·5	30·5	30·7	30·8	30·33	30·30	45·82
9	45·6	45·8	45·02	44·7	44·9	44·60	43·0	43·2	42·7	43·2	49·84	50·23	50·39 [e]
10	38·5	39·0	38·83	39·4	39·7	40·18	35·3	35·4	35·2	35·3	36·75	37·07	38·77
11	21·3	21·5	21·13	21·3	21·5	21·15	20·8	20·9	20·5	20·7	67·41	67·15	21·35
12	38·5	38·4	38·40	38·4	38·3	38·29	38·0	37·8	30·1	30·3	46·69	49·51	37·10 [e]
13	45·1	44·9	45·02	45·0	44·9	45·02	44·7	44·4	48·5	48·5	44·61	44·37	45·02
14	56·2	56·3	55·96	56·2	56·1	55·96	57·0	56·9	50·9	51·4	55·97	55·99	50·28 [e]
15	24·5	24·7	24·53	24·5	24·5	24·43	24·4	24·4	23·7	23·9	24·48	24·40	26·58 [d]
16	26·3	26·2	26·22	26·2	26·1	26·19	26·1	26·0	37·1	37·2	26·22	26·00	26·98 [d]
17	51·3	51·1	51·14	51·1	50·9	51·08	50·9	50·7	82·4	82·4	50·61	50·45	49·91
18	13·5	13·3	13·60	13·5	13·3	13·50	13·3	13·0	15·8	15·6	14·07	13·77	13·05
19	16·7	17·1	16·48	15·7	15·8	15·80	16·0	16·0	16·0	16·0	16·64	16·79	17·37
20	173·2	173·0	172·95	173·0	173·0	172·81	172·8	172·6	175·3		172·33	171·59	172·05
21	74·4	74·1	74·34	74·3	74·1	74·29	74·3	74·0	73·4	73·4	74·21	73·64	73·91
22	115·8	115·8	115·93	115·9	115·8	116·00	116·0	116·0	115·6	115·8	116·12	116·16	116·38
23	175·7		175·60	175·6		175·55	175·5		175·3	175·7	175·45	174·06	
			171·95 [f]			172·02 [f]							
			171·21 [f]			171·56 [f]							
			21·54 [g]			21·47 [g]							
			21·45 [g]			21·15 [g]							
Solvent [b]	I	II	I	I	II	I	I	II	I	II	I	IV	II

Compound	(6a)	(6a)	(7)	(7)	(8)	(9)	(10)	(10)	(11)	(11)	(12)	(13)
Carbon												
1	36·35 [e]	36·08 [e]	36·70	36·94	39·04	35·90	35·79	35·77	37·52	38·06	38·89 [e]	37·93
2	27·58	27·33	30·98	32·08	31·90	27·33	32·72 [e]	32·70 [e]	34·03 [e]	33·71 [e]	35·09	32·10
3	72·70	72·04	70·12	70·18	70·55	72·01	199·17	198·24	202·01	199·10	200·18	71·25
4	38·14	37·84	42·00	42·91	43·15	37·92	124·11	124·24	124·38	124·74	126·56	43·39
5	165·96	164·38	168·22	166·96	167·28	165·16	170·40	170·17	173·53	171·00	170·21	142·16
6	126·49	126·48	125·53	125·78	125·09	126·54	33·94 [e]	34·35 [e]	34·32 [e]	34·80 [e]	72·82	120·94
7	202·10	200·68	203·15	201·35	201·32	200·45	31·85	32·05	31·91	31·97	39·87 [e]	32·55
8	45·93	45·53	46·18	46·25	45·28	43·57	35·92	35·89	35·73	35·47	29·48	32·55
9	50·27 [d]	49·91	50·07	50·28	55·74	49·97	53·73	53·78	58·96	59·35	59·84	50·94
10	38·88	38·45	38·84	38·78	40·93	38·42	38·61	38·67	40·47	40·41	40·11	37·04
11	21·31	21·20	21·11	21·24	67·62	21·09	20·87	20·98	68·28	68·13	68·34	21·26
12	37·25 [e]	36·99 [e]	29·69	29·97	48·16	34·62 [e]	37·90	37·69	49·22	49·72	49·85	38·05
13	45·34	44·92	49·25	49·19	45·03	47·91	44·34	44·22	44·88	44·60	44·92	44·35
14	50·14 [d]	49·75	44·61	45·08	49·46 [d]	50·82	55·75	55·64	55·37	55·30	55·53	56·69
15	26·68	26·42 [d]	26·04	26·56	26·47 [e]	34·22 [e]	24·31	24·39	24·50	24·36	24·58	24·66
16	26·68	26·37 [d]	37·69	37·95	26·68 [e]	138·09	25·93	26·02	26·27	26·07	26·20	26·17
17	50·05 [d]	49·70	81·67	81·74	49·58 [d]	144·63	50·72	50·69	50·81	50·60	50·80	50·58
18	13·37	13·23	15·84	15·64	14·03	15·83	13·25	13·02	14·49	14·28	14·34	12·99
19	17·47	17·32	17·51	17·40	17·09	17·38	17·42	17·13	18·43	18·44	20·53	19·61
20	172·55	170·86		175·26	172·32	158·34	170·78	171·77	172·27	171·53	171·76	171·92
21	74·35	73·53	73·57	73·18	74·02	71·53	73·43	73·72	74·19	73·61	73·71	73·76
22	116·36	116·42	115·83	116·17	116·17	111·30	116·28	116·20	116·16	116·25	116·22	116·09
23	175·44	173·86	175·47	174·12	174·68	174·55	173·87	174·10	175·44	174·10	174·07	173·96
	171·22 [f]	170·23 [f]				170·26 [f]						
	21·22 [g]	20·98 [g]				21·20 [g]						
Solvent	I	III	I	II	II	III	III	IV	I	IV	II	II

[a] Shifts are given to one decimal place for 8 K transforms and two decimal places for 12 K transforms (see Experimental section). [b] Solvents are as follows: I, $CDCl_3$–CD_3OD (7 : 3); II, [$^2H_5$]pyridine–[$^2H_6$]acetone (4 : 1); III, $CDCl_3$; IV, [$^2H_5$]pyridine. [c–e] Assignments may be reversed in vertical column. [f] Carbonyl resonance of Ac group. [g] Methyl resonance of Ac group.

by a small downfield shift for the resonance of C-9 and an upfield shift for that of C-17 in (1)—(4). A comparison of the shifts of resonances from C-9 and -17 in solvents I and IV allows them to be differentiated as shown (Table 1).

Compounds (6)—(9).—The resonance of C-7 was at lowest field. The expected upfield shifts of the resonances of upon 11α-hydroxy-substitution (8) was assigned to C-1. The remaining secondary carbon resonance in (6), that could not be distinguished from that of C-1, was that of C-12. The resonances of C-12 and -16 in (7) and of C-12 in (8) were assigned by comparison with (4) and (5) respectively. The alternative assignment of C-12 and -16

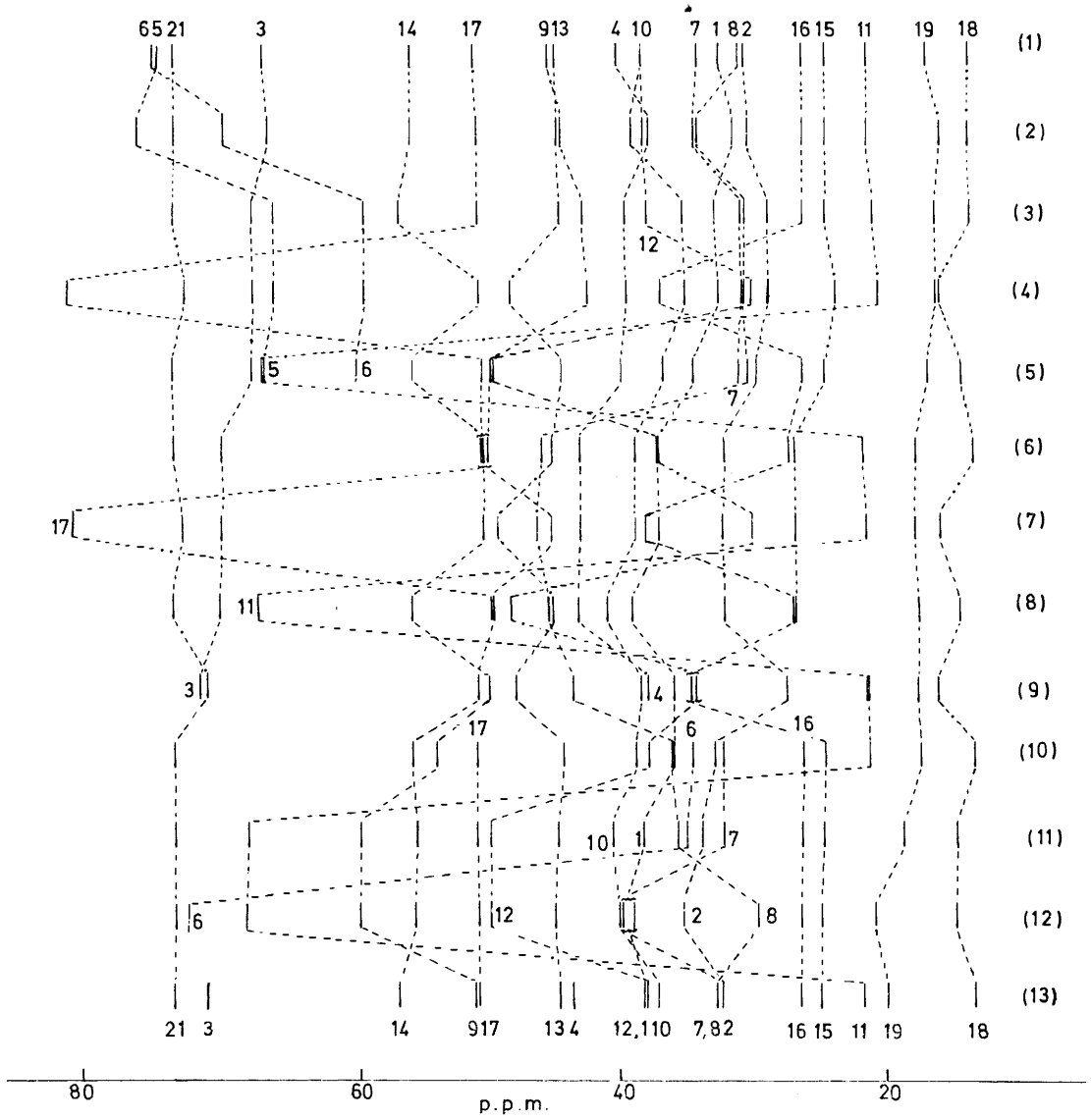


FIGURE 1 Correlation diagram of the chemical shifts (high field) for compounds (1)—(13)

C-2 and -4 in (6) upon acetylation (6a), followed by comparison with (1)—(5), allowed identification and assignment of these resonances in (6)—(8). A comparison of (9) with (6a) in solvent III identifies the resonances of C-2 and -4. [This also indicates that the resonance of C-2 in (6a) was to low field of that of C-16 and -15 and that these overlap in solvent I.] The resonances of C-15 and -16 in (6) and (8), and of C-15 in (7) were identified by comparison with (1)—(5) although unambiguous assignment was impossible. The secondary carbon resonance that showed only small changes (<1·1 p.p.m.) upon acetylation of the 3β-hydroxy-group (6a), 17α-hydroxy-substitution (7), and 16-ene formation (9), and a downfield shift in (7) is untenable, as 17α-hydroxy-substitution (pseudo-axial) would then have to give rise to a downfield shift of C-12, which is unlikely (see above). The remaining secondary resonances of (9) were assigned to C-12 and -15 although unambiguous assignment was impossible.

The resonance of C-17 of (6) was assigned, as only this resonance could show a downfield shift on going to (6a) in solvent I (see above). Unambiguous assignment of C-17, -14, and -9 in (6a), of C-14 and -9 in (6), and of C-17 and -14 in (8) was impossible. The resonance that was unaffected by 17α-hydroxy-substitution in (7) was assigned to C-9, while only this resonance was shifted upon 11α-hydroxy-substitution in (8). The resonance of C-14 was

distinguished from that of C-9 in (9) by comparison with (6a) in solvent III and (7).

Compounds (10)—(13).—The resonance of C-4 in (10)—(12) was assigned from off-resonance experiments and chemical shift considerations. The assignment of the

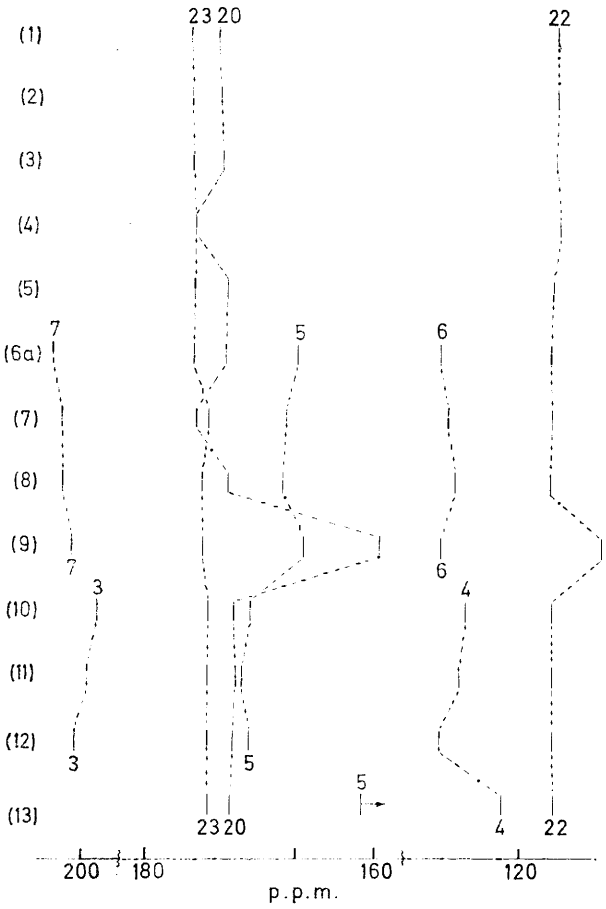


FIGURE 2 Correlation diagram of the chemical shifts (low field) for compounds (1)—(13)

resonance of C-12 in (10) and (13), and in (11) and (12) was made by comparison with (1)—(3), and (5) and (8) respectively.

The remaining resonances of C-1, -2, -6, and -7 were more difficult to assign. The resonances of C-1 and -7 of (10) and (11) are taken from the literature;[1,2] the resonance of C-7 was unaffected by 11α-hydroxy-substitution (11). The resonances of C-2 and -6 could not be unambiguously assigned in (10) and (11); comparison with the literature data for progesterone was inadequate as these assignments appear ambiguous.[1,2] The resonance that was least affected by 11α-hydroxy-substitution was tentatively assigned to C-6. The resonance that was but little affected upon dihydroxylation in (12) was assigned to C-2, while C-7 and -1 were close together and could not be unambiguously assigned.

The remaining resonances of (13) (C-1, -2, -7, and -8) were assigned from the off-resonance experiments and by comparison with the literature data for cholesterol.

DISCUSSION

Solvent effects in ^{13}C n.m.r. are not well documented; there is only one study, by Mantsch and Smith,[10] of this phenomenon with a steroid, cholesterol. In the present work the problems caused by solubility and overlapping of resonances necessitated the use of various solvents and solvent mixtures. Although it was impracticable to carry out a thorough study of solvent effects in these systems it can be seen, from a comparison of the data for compounds (1)—(5), (6a), (7), (10), and (11) in the various solvents (Table 1), that in contrast to previous results, a change of solvent causes both upfield and downfield shifts. Carbons carrying the substituents are not always the ones having the largest shifts. In the following discussion substituent effects are evaluated from compounds in the same solvent whenever this is possible.

The substituent chemical shifts (SCS) produced by substitution of a hydroxy-group in the 11α-, 17α-, 5α-, and 6β-positions in the various systems are shown in Table 2. The values for 5α-hydroxy-substitution were calculated with the data of Grover and Stothers [3] for cholestane-3β,6-diols in $CDCl_3$ as the parent compounds and our data for (1) and (2) in solvent I. These SCS should be accurate to within ± 1 p.p.m. when solvent effects are taken into account, while the SCS for 11α- and 17α-hydroxy-substitution in system (ii) are solvent independent to within ±0·2 p.p.m. (Table 2).

The only previous work on the effects of 11α- and 17α-hydroxy-substitution was that of Roberts *et al.*[1] and Wolff *et al.*[2] in the progesterone system; while the effects of 5α- and 6β-hydroxy-substitution have been evaluated by Abraham and Monasterios [4] in ergosta-7,9,22-triene-3β,5α-diol and by Grover and Stothers [3] in cholestan-3β-ol, respectively. These values are included for comparison in Table 2.

11α-Hydroxy-substitution.—When the SCS for progesterone and system (iv) are compared, they appear very similar, as is to be expected, since the only difference between the two systems is the 17β-substituent. It can be seen that structural changes in rings A, B, and D have little effect upon the SCS of C-11 and -12, while that of C-9 is considerably affected. Similarly, smaller changes can be seen for C-2, -3, -6, -10, and -19. These effects, caused by changes in the atom positions on going from system to system, may arise from changes either in polar effects (through-space field effects and/or through-bond effects), steric effects, or differing modifications of the solvent shell upon hydroxy-introduction. Although polar effects may be the cause of the change in the SCS for C-9, -10, and -19, it is unlikely that they are the cause for those of C-2, -3, and -6 which are a considerable distance from the site of substitution.

17α-Hydroxy-substitution.—There are considerable differences between the SCS for the directly bonded carbon of the present data and those of the literature.[2] As the differences between our two systems, (ii) and (iii), are small (suggesting that changes in the structure of rings A and B have little effect upon this SCS), the change found on going to the progesterone system

[10] H. H. Mantsch and I. C. P. Smith, *Canad. J. Chem.*, 1973, **51**, 1384.

must arise from the change of the 17β-substituent. This is supported by the fact that both 21-hydroxy-substituted progesterone derivatives (C and D) have similar SCS, but are different from those of the non-hydroxylated side chain derivatives (A and B, Table 2). Similarly vicinal and three-bond effects are modified by the different 17β-substituents, while the presence of the 11α-hydroxy-substituent (B and D) increases the magnitude of the C-12 SCS compared to the non-hydroxylated compounds (A and C).

5α-Hydroxy-substitution.—One can estimate the one-bond SCS, in the absence of other effects, from the effect of hydroxy-substitution upon the shift of the in the other vicinal SCS are also noted (C-4 and -10) together with a substantial decrease in the effect upon C-19; the effect on C-19 in our system is comparable with the effect of 17α-hydroxy-substitution upon C-18 (see above).

The shift differences between (1) and (2) are compared with those for similar compounds in Table 3. The large differences found between our results and those of Grover and Stothers [3] for C-5 and -6 undoubtedly arise from the presence of the 5α-hydroxy-group. The shift differences between the α- and β-anomers for C-1 and -2 of D-mannose [11] and 2-deoxy-D-glucose [12] may be likened to those of C-6 and -5 of our compounds

TABLE 2

Substituent chemical shifts (p.p.m.) for hydroxy-group substitution in the 11α-, 17α-, 5α-, and 6β-positions in the steroid nucleus

Compounds	Solvent	Carbon	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	Ref.
11α-Hydroxy-substitution																					
(5)—(3)	I		1·8	0·9	0·0	0·3	0·7	0·4	0·3	−0·2	6·8	1·5	46·6	11·7	−0·1	−1·0	0·1	0·1	−0·3	0·8	0·6	*
(5)—(3)	II		2·2	0·9	0·0	0·7	0·5	0·4	0·7	−0·2	7·0	1·7	46·3	11·7	0·0	−0·9	0·0	0·0	−0·2	0·8	0·8	*
(8)—(6)	II		2·1	−0·2	0·4	0·2	0·3	−0·7	0·5	−0·5	5·3	2·2	46·3	11·1	0·0	−0·8	−0·1	−0·3	−0·3	1·0	−0·3	*
(11)—(10)	IV		2·3	1·0	0·9	0·5	0·8	0·4	−0·1	−0·4	5·6	1·7	47·1	12·0	0·4	−0·3	0·0	0·1	−0·1	1·3	1·3	*
A	DMSO		1·8	0·3	0·7	0·3	0·7	0·9	0·1	−0·7	5·0	1·4	46·6	11·5	0·3	−0·5	−0·1	−0·1	−0·2	1·2	1·1	2
17α-Hydroxy-substitution																					
(4)—(3)	I		−0·1	0·1	0·0	0·0	0·0	0·0	−0·1	0·2	−0·3	−0·1	−0·3	−7·9	3·8	−6·1	−0·7	11·0	31·5	2·5	0·0	*
(4)—(3)	II		−0·1	0·2	0·0	−0·3	0·3	0·2	−0·3	0·3	0·0	−0·1	−0·2	−7·5	4·1	−5·5	−0·5	11·2	31·7	2·6	0·0	*
(7)—(6)	II		0·0	0·0	0·0	0·0	0·0	0·0	0·5	0·4	−0·1	0·0	−0·1	−7·1	4·2	−5·2	0·0	11·0	31·8	2·6	0·0	*
A	DMSO		0·0	0·0	0·5	−0·1	0·6	0·0	−1·2	0·2	0·0	0·1	−0·2	−5·6	3·1	−5·5	0·8	8·3	26·7	1·6	0·2	2
B	DMSO		0·0	0·0	0·1	0·0	0·1	0·3	0·1	0·1	0·0	0·0	0·3	−7·5	2·9	−5·4	1·4	8·0	26·2	1·5	0·1	2
C	DMSO		0·2	0·0	−0·1	0·0	0·0	0·1	−1·4	0·4	0·1	0·1	−0·1	−4·1	3·5	−5·4	0·9	8·2	31·0	1·4	0·3	2
D	DMSO		−0·2	−0·1	0·0	−0·1	0·1	0·1	−0·2	−0·1	−0·2	−0·1	0·1	−7·8	3·0	−5·6	1·3	8·7	30·1	1·1	−0·1	2

Compounds	Solvent	Carbon	1	2	3	4	5	6	7	8	9	10	19	Ref.
5α-Hydroxy-substitution														
E—(1)	$CDCl_3$, I		−5·9	−0·8	−4·0	5·0	28·3	4·0	−5·4	0·7	−8·6	3·1	0·9	3, *
F—(2)	$CDCl_3$, I		−6·9	−0·9	−3·9	5·8	25·5	1·2	−0·7	0·0	−9·0	3·2	2·2	3, *
G	$CDCl_3$		−4·9	−0·8	−3·3	4·1	34·5	8·6	−2·2	0·6	−3·3	5·5	5·7	4
6β-Hydroxy-substitution														
(11)—(12)	II, IV		0·8	1·3	1·0	1·8	−0·8	38·0	7·9	−6·0	0·5	−0·3	2·1	*
H	$CDCl_3$		1·4	−0·1	0·3	−2·9	2·3	43·1	7·5	−5·2	−0·2	−0·1	3·4	3

* Present work.

A = Progesterone system, B = 11α-hydroxyprogesterone system, C = 21-hydroxyprogesterone system, D = corticosterone system, E = cholestane-3β,6β-diol, F = cholestane-3β,6α-diol, G = ergosta-7,9,22-trien-3β-ol system, H = cholestan-3β-ol system.

TABLE 3

Chemical shift differences (p.p.m.) between the axial and equatorial 6-hydroxy-group in A, system (i); B, cholestane-3β,6-diol; and C, *trans*-decalin

System	Solvent	Carbon	1	2	3	4	5	6	7	8	9	10	19
A	I		−1·1	−0·3	−0·3	−2·3	1·5	−5·4	0·4	3·2	−0·9	0·9	−1·0
A	II		−1·2	0·1	−0·4	−2·8	1·2	−5·4	0·2	2·5	−0·9	0·7	−1·3
B *	$CDCl_3$		−1·2	−0·2	−0·4	−3·1	4·3	−2·6	2·1	3·9	−0·5	0·8	−2·3
C *	$CDCl_3$		0·2	−0·2	−0·6	−3·0	3·9	−1·8	2·5	3·5	−2·5	1·1	−2·3

* Ref. 3.

C-2 of $(CH_3)_2CHC(CH_3)_3$.[7] The value of 36·3 p.p.m. agrees with the values of Abraham and Monasterios.[4] Thus our data indicate that this SCS is dependent upon both the nature and the orientation of a substituent on the adjacent C-6. A decrease in the magnitude of the one- and two-bond SCS (for the adjacent carbon carrying the hydroxy-group permanently present) can also be seen in aliphatic systems: the magnitude of these SCS for hydroxy-substitution in ethane (51·4 and 12·0 p.p.m. respectively) are larger than those in ethanol (45·5 and 6·1 p.p.m. respectively).[8] Changes and those of Grover and Stothers respectively. From these data one predicts, that relative to their results, both C-5 and -6 of our compounds should have shift differences that are more negative by 2·0 and 2·6 p.p.m. respectively, which are close to the values found. The remaining smaller shift differences may arise from distortion effects caused by the introduction of the 5α-hydroxy-group. By analogy with the *X*-ray data of Wolff *et al.*[13] for 9-fluorocortisol, the introduction of a 5α-hydroxy-group would be expected to cause some

[11] D. E. Dorman and J. D. Roberts, *J. Amer. Chem. Soc.*, 1970, **92**, 1355.

[12] L. D. Hall and L. F. Johnson, *Chem. Comm.*, 1969, 509.

[13] C. M. Weeks, W. L. Duax, and M. E. Wolff, *J. Amer. Chem. Soc.*, 1973, **95**, 2865.

flattening of rings A and B in order to relieve the interactions of 3α-H and 7α-H with 5α-OH.

6β-Hydroxy-substitution.—As expected the presence of the 4-en-3-one system causes severe modifications of the SCS compared to those for the cholestan-3β-ol system. The effect upon the quaternary carbon C-5 is not consistent with the behaviour of similar compounds, *e.g.* allyl alcohol, C-2 139·1, and propane, 133·1 p.p.m.,[8] although there is a possibility that both conformers are significantly populated.

Other Effects.—The results for the introduction of the 16,17-double bond in system (iii) may be compared with those of Tori *et al.*[9] for the digitoxigenin system ergosta-7,9,22-triene-3β,5α-diol.[4] The results for the acetylation of the 6α-equatorial hydroxy-group are, as expected, similar to those of 3β-acetylation, with C-7 showing an upfield shift similar to that of C-2 while C-5 has a smaller shift as it has a greater degree of substitution. Acetylation of the axial 6β-hydroxy-group produces a much smaller SCS for the directly bonded carbon than those normally associated with axial acetylation (4·4 ± 0·2 p.p.m.) although the two-bond effect upon C-7 is normal.[9] These results again suggest that the 5α-hydroxy-group has the more pronounced effect when it is in a *trans*-planar orientation with respect to the 6-hydroxy-group.

TABLE 4

Substituent chemical shifts (p.p.m.) for the introduction of the 16,17-double bond in system (iii) and the digitoxigenin system

Compound	Carbon / Solvent	10	11	12	13	14	15	16	17	18	19	20	21	22	23
(6)—(9)	III	0·0	−0·1	−2·4	3·0	1·1	7·8	111·7	94·9	2·6	0·1	−12·5	−2·0	−5·1	0·7
Digitoxigenin system *	CD_3OD–$CDCl_3$	−0·4	−0·3	0·3	2·3	0·1	5·8	106·5	109·7	0·6	0·2	−4·3	−2·1	−5·7	0·0

* Ref. 9.

TABLE 5

Substituent chemical shifts (p.p.m.) for 3β-acetylation and 3β,6-diacetylation

Compound	Carbon / Solvent	1	2	3	4	5	6	7	8	9	10
3β-Acetylation											
(6a)—(6)	III, II	−0·6	−5·4	2·5	−4·8	−1·0	0·7	1·3	0·1	−0·3	0·1
(9)—(6)	III, II	−1·0	−4·7	1·8	−5·0	−1·8	0·8	−0·4	−2·2	−0·4	−0·3
A *	Dioxan	−0·2	−3·4	2·4	−4·0	−1·3	1·3	0·2	0·2	−0·1	0·2
B *	Dioxan	−0·4	−4·2	2·8	−4·4	−0·4	−0·2	−0·2	−0·1	−0·2	0·0
3β,6-Diacetylation											
(1a)—(1)	I	−0·5	−3·8	4·1	−3·8	−1·3	0·8	−2·7	0·4	−0·6	0·3
(2a)—(2)	I	0·0	−3·6	4·2	−3·4	−1·4	4·0	−3·6	0·0	−0·1	0·8

* A is the cholestan-3β-ol system and B the cholesterol system (ref. 1).

(Table 4). It is immediately obvious that the presence of the 14β-hydroxy-group and consequent *cis*-fusion of rings C and D in the latter has considerable consequences upon all the SCS. The largest is for C-20, which suggests that the orientation of the 17β-substituent may be entirely different in the two systems.

The effects of 3-acetylation and 3,6-diacetylation of hydroxy-groups are given in Table 5. When solvent differences are taken into account, the effects of 3-acetylation are in agreement with previous results.[1,4] Diacetylation of the triol system increases the magnitude of the SCS for the directly-bonded carbon from that normally associated with 3β-equatorial acetylation of 2·5 ± 0·3 to 4·1 ± 0·1 p.p.m. This effect is also discernible in previous data for the acetylation of

We must therefore conclude that structural change within the steroid nucleus does cause modification of substituent chemical shifts. In particular 11α-hydroxy-substitution effects are influenced by changes in rings A and B, while 17α-hydroxy-substitution appears to be little affected by such changes. The occurrence of another substituent one or two carbon bonds away, in particular a hydroxy-group, causes substantial change to the directly bonded SCS and these effects depend upon orientation.

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