

- [8] *R. M. Barrer, J. W. Baynham, F. W. Bultitude & W. M. Meier*, *J. chem. Soc.* 1956, 2882.  
[9] *W. M. Meier*, 'Molecular Sieves', *Soc. Chem. Ind.*, London 1968, p. 10.  
[10] cf. *D. W. Breck & E. M. Flanigen*, 'Molecular Sieves', *Soc. Chem. Ind.*, London 1968, p. 47.  
[11] *B. D. McNicol, G. T. Pott, K. R. Loos & N. Mulder*, *Adv. Chemistry Ser.* 121, 140 (1973).  
[12] *R. M. Barrer & P. J. Denny*, *J. chem. Soc.* 1961, 971.  
[13] *R. M. Barrer, P. J. Denny & E. M. Flanigen*, *U. S. Pat.* 3 306 922 (1967).  
[14] *G. T. Kerr*, *Inorg. Chemistry* 5, 1539 (1966).  
[15] *Ch. Baerlocher & W. M. Meier*, *Helv.* 52, 1853 (1969); *ibid.* 53, 1285 (1970).  
[16] *W. Sieber*, Ph. D. Thesis ETH Zürich, 1972.  
[17] *J. von Braun*, *Chem. Ber.* 49, 966 (1916).  
[18] *F. F. Blicke & E. B. Hotelling*, *J. Amer. chem. Soc.* 76, 5099 (1954).  
[19] *K. Jewers & J. McKenna*, *J. chem. Soc.* 1958, 2209.  
[20] *H. C. Brown & W. H. Bonner*, *J. Amer. chem. Soc.* 75, 14 (1953).  
[21] *V. M. Micović & M. L. Mihailović*, *J. org. Chemistry* 18, 1190 (1953).  
[22] *H. Borer*, Ph. D. Thesis ETH Zürich, 1969; *H. Borer & W. M. Meier*, *Adv. Chemistry Ser.* 101, 122 (1971).  
[23] *W. M. Meier*, unpublished file.  
[24] *Ch. Baerlocher & W. M. Meier*, *Z. Kristallogr.* 135, 339 (1972).  
[25] *A. J. Regis, L. B. Sand, C. Calmon & M. E. Gilwood*, *J. phys. Chemistry* 64, 1567 (1960).  
[26] *D. W. Breck, W. G. Eversole, R. M. Milton, T. B. Reed & T. L. Thomas*, *J. Amer. chem. Soc.* 78, 5963 (1956).  
[27] *R. M. Barrer, J. F. Cole & H. Sticher*, *J. chem. Soc. A* 1968, 2475.  
[28] *O. Jarchow*, *Z. Kristallogr.* 122, 407 (1965).  
[29] *W. Thoeni*, Ph. D. Thesis ETH Zürich, 1973.  
[30] *W. M. Meier & H. Villiger*, *Z. Kristallogr.* 129, 411 (1969).  
[31] cf. *H. S. Sherry*, *Adv. Chem. Ser.* 101, 350 (1971).  
[32] *H. H. Weldes & K. R. Lange*, *Ind. Eng. Chemistry* 61, 29 (1969).  
[33] *R. Aiello, R. M. Barrer & I. S. Kerr*, *Adv. Chemistry Ser.* 101, 44 (1971).

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## 170. Substituent Increments for the $^1\text{H}$ -NMR. Chemical Shifts of the 18- and 19-Methyl Protons of Steroids. Part I: $9\beta$ , $10\alpha$ (*Retro*)-Steroids

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Dedicated to Professor *Pl. A. Plattner* on his 70th birthday

(22. V. 74)

*Summary.* This paper reports 261 substituent increments for the  $^1\text{H}$ -NMR. chemical shifts (solvent:  $\text{CDCl}_3$ ) of the 18- and 19-methyl protons of  $9\beta$ ,  $10\alpha$ (*retro*)-steroids relative to  $5\beta$ ,  $9\beta$ ,  $10\alpha$ ,-androstane. The increments were calculated by a least-squares procedure from 1334 spectra of 759 different steroids.

**1. Introduction.** – Since *Shoolery & Rogers* [1] reported on the application of  $^1\text{H}$ -NMR. spectroscopy to the study of steroids, this technique has proved extremely useful for the elucidation of unknown structures. Especially the fact that the chemical shifts of the angular methyl protons can in many cases be calculated from additive shift increments of the substituents (or of suitably chosen combinations thereof)

has found numerous applications in steroid chemistry. This method has the advantage that the prediction of the chemical shifts of the 18- and 19-methyl protons of a larger number of new products can be made from the spectra of a few compounds of known structure.

Some years ago, *Zürcher* [2] [3] published comprehensive tables of substituent increments for steroids of natural  $9\alpha, 10\beta$ -configuration. His work was extended later by others and the empirical additivity relationship was also successfully applied to steroids having modified basic skeletons (for a recent review see [4]).

For some years we have been interested in the chemistry of  $9\beta, 10\alpha$ (*retro*)-steroids. In the beginning, no shift increments for these compounds were available in the literature. At an early stage in our work the shift increments were calculated manually as described by *Zürcher*. As the number of spectra increased, however, it soon became evident that computer handling of the experimental data would be desirable. Our results obtained in this manner for *retro*-steroids are presented herein. In the following paper [5] calculations carried out for  $9\alpha, 10\beta$ -steroids, *i.e.* with 'normal' configuration are reported.

Computer methods for the calculation of shift increments have already been applied by others [6] [7]. This paper reports the calculation of shift increments for 261 functional groups, denoted as substituents. The values were calculated by a standard least-squares procedure from the chemical shifts of 759 different *retro*-steroids obtained from 1334 spectra. For the application of the shift increments in structural elucidations it seemed sufficient to us to report only the increments themselves, and therefore a separate listing of all the compounds and their chemical shifts will not be presented here.

Although the shift increments were derived from a very specific class of steroids, they might be useful even for steroids of different basic skeletons. It is known [6] that the magnitude of a shift increment mainly depends on the relative geometry of the substituent and the angular methyl group, and that similar geometric relations may also occur with steroids of different stereochemistry. For example, this is true for substituents in all positions from 11 to 17 of *retro*- and normal-steroids, and similar substituent effects on the chemical shifts of the 18-methyl protons are indeed observed in these cases [5]. It is also known that the chemical shift increments for substituents in several positions of the same basic skeleton may be similar in magnitude due to structural symmetry. These findings may be helpful in the elucidation of the structure of unknown steroidal products.

No attempt was made to discuss the voluminous literature on chemical shift increments determined for the various types of steroids. Furthermore, in order to reduce experimental errors, no previously published experimental data on the chemical shifts of *retro*-steroids were incorporated and no attempt was made to interpret the reported shift increments on the basis of a physical model, although some preliminary investigations into a deeper understanding of the cause of the chemical shift increments are available (see *e.g.* [4] [6] [7] and references cited therein).

**2. Experimental.** – All spectra were routinely taken in our laboratories using  $\text{CDCl}_3$  as solvent with internal TMS. Spectra were measured at 60 MHz (*Varian* A-60 and A-60 D), 90 MHz (*Brüker* HX 90/15 FT), or 100 MHz (*Varian* HA 100). The concentrations used were between *ca.* 0.05 and 0.5M. The sweepwidth of the 60 MHz instruments was calibrated once every day.

Chemical shifts of the angular methyl groups measured at 90 and 100 MHz were determined in most cases directly with the aid of a frequency counter or from a computer print-out of the shifts. In order to improve the accuracy of the experimental data, in some cases more than one spectrum of the same compound was included in the data set.

The chemical shift of the angular methyl protons of the unsubstituted compound, 5 $\beta$ ,9 $\beta$ ,10 $\alpha$ ,-androstane, was obtained from 20 measurements as 0.719 ppm (18-methyl) and 0.944 ppm (19-methyl).

The compounds used for the calculation of the increments were synthesized in our Chemical Research Department. Some substances were obtained by microbiological transformations. In addition to the <sup>1</sup>H-NMR. spectrum the compounds were characterized, in general, by several additional techniques: microanalysis and/or MS., UV., IR., and in some cases ORD./CD.

**3. Computations.** – The details of the program ADDIT 2 are not given here. The basic assumption used in the calculation was that the chemical shifts of the 18- and 19-methyl protons can be calculated from additive contributions of the substituents and of suitably combined groups of substituents including double bonds. These increments were calculated in such a way that the sum of the squared deviations of the calculated shifts from the experimental shifts was minimized (least-squares method). The results of the computations of several data sets from an increasing number of spectra were in all cases checked by inspection of the calculated deviations. If these deviations were considered to be too great, new combinations of substituents were used until internal consistency of the input data was achieved. Compounds with  $\Delta^{8(9)}$  and  $\Delta^{8(14)}$  double bonds and epoxides were not included since, in these cases, difficulties were encountered which were caused by changes of the geometry of the basic skeleton.

The computations were done *via* teleprocessing on an IBM 370/155 computer. The program ADDIT in its latest version needed a computer memory of 600 K bytes. Typical C.P.U. times of up to 30 min were necessary for the last computations.

**4. Results.** – In Table 1 are listed the chemical shift increments (in ppm; solvent: CDCl<sub>3</sub>) for 261 substituents or combinations of substituents, calculated from 1334 spectra of 759 *retro*-steroids. The values are arranged according to the position of the substituted carbon atom (position 1 to 17). Column 3 indicates the number of times the substituent occurred in the used set of spectra. Some abbreviations used in Table 1 are explained in Table 2.

Although a detailed discussion of the results presented in Table 1 seems to be unnecessary, a few remarks must be made with regard to the choice of some of the substituent combinations. In all cases where simultaneous occurrence of two or more substituents are either known to or are expected to result in deviations from additivity, these substituents were combined to form a new 'substituent'. In some cases the reasons and justifications have already been presented in *Zürcher's* paper [3]. Examples are the combination of substituents at 3-C and double bonds as  $\Delta^4$  or  $\Delta^5$ . Two substituents at the same carbon (geminal substitution) or two substituents on neighboring carbon atoms (vicinal substitution, *e.g.* 16,17-disubstitution) had to be treated as single 'substituents'. Substituents at double bonds were specified according to the position of the double bond. As was mentioned above, compounds with  $\Delta^{8(9)}$  and  $\Delta^{8(14)}$  double bonds were omitted as well as epoxides since in these cases stronger changes of the geometry of the basic skeleton cause the substituent effects to be non-additive.

Hydroxylated compounds were included even if there was more than one OH-group present. However, in some cases difficulties were encountered for such compounds. Thus it was found that 8 $\beta$ -OH steroids afforded different increments depending on the presence of double bonds in rings A and/or B (entries 129, 130 and

Table 1. *Substituent Increments* (in ppm; Solvent: CDCl<sub>3</sub>) *for the Chemical Shifts of the 18- and 19-Methyl Protons of 9 $\beta$ ,10 $\alpha$ (Retro)-Steroids* (Plus Sign Represents a Downfield Shift)

No.	Substituent	Quantity	18-Methyl Protons	19-Methyl Protons
–	5 $\beta$ , 9 $\beta$ , 10 $\alpha$ , -androstane		0.719	0.944
1	1 $\beta$ -CH <sub>3</sub>	4	–0.003	0.064
2	1 $\beta$ -OH	4	0.008	0.006
3	1 $\alpha$ -OH	1	0.006	0.040
4	1 $\beta$ -O-ac	3	–0.005	0.070
5	1 $\alpha$ -O-ac	1	–0.015	0.062
6	1 $\beta$ -Cl	1	0.002	0.314
7	1 $\beta$ -CN	2	0.024	0.087
8	1 $\beta$ -S-CH <sub>3</sub>	2	0.007	0.138
9	1 $\beta$ -S-C <sub>2</sub> H <sub>5</sub>	11	0.005	0.135
10	1 $\beta$ -S-isopropyl	2	–0.003	0.131
11	1 $\beta$ -S-allyl	1	–0.002	0.130
12	1 $\beta$ -S-ac	9	–0.019	0.181
13	1 $\beta$ -S-CSCH <sub>3</sub>	1	–0.026	0.209
14	1 $\beta$ -S-COCH <sub>2</sub> CH <sub>3</sub>	1	–0.022	0.180
15	1 $\beta$ -S-CH <sub>2</sub> CH <sub>2</sub> OH	1	–0.002	0.137
16	1 $\beta$ -S-benzyl	2	–0.037	0.048
17	A <sup>2,4,6</sup>	3	0.048	0.173
18	2 $\beta$ -CH <sub>3</sub>	3	0.000	0.055
19	2 $\beta$ -OH	2	–0.005	0.113
20	2 $\alpha$ -OH	2	0.000	–0.058
21	2 $\beta$ -O-ac	6	–0.004	0.147
22	2 $\alpha$ -O-ac	1	–0.005	–0.044
23	2 $\beta$ -OCH <sub>3</sub>	10	–0.005	0.108
24	2 $\beta$ -Cl	20	0.003	0.097
25	2 $\alpha$ -Cl	4	0.009	0.081
26	2 $\beta$ -Br	13	0.000	0.081
27	2 $\beta$ -I	12	–0.003	0.058
28	2 $\alpha$ -F	6	0.003	0.142
29	2 $\beta$ -F + 3-oxo + A <sup>4</sup>	8	0.045	0.520
30	2 $\beta$ -F + 3-oxo + A <sup>4,6</sup>	9	0.091	0.423
31	2-CH <sub>3</sub> (at A <sup>1</sup> )	2	–0.004	–0.031
32	2-OH (at A <sup>1</sup> )	2	–0.008	0.015
33	2-OCH <sub>3</sub> (at A <sup>1</sup> )	1	0.006	0.031
34	2-Cl (at A <sup>1</sup> )	11	0.007	0.057
35	2-Br (at A <sup>1</sup> )	2	0.006	0.043
36	2, 2-di-Cl	1	–0.034	0.249
37	A <sup>3,5</sup>	4	0.055	0.059
38	3-oxo	42	0.023	0.227
39	3-oxo + A <sup>1</sup>	5	0.046	0.220
40	3-oxo + A <sup>1,4</sup>	52	0.062	0.402
41	3-oxo + A <sup>1,4,6</sup>	116	0.083	0.408
42	3-oxo + A <sup>1,4</sup> + 6- = CH <sub>2</sub>	1	0.068	0.313
43	3-oxo + A <sup>4</sup>	546	0.053	0.396
44	3-oxo + A <sup>4,6</sup>	316	0.086	0.331
45	3-oxo + A <sup>4</sup> + 6-oxo	7	0.094	0.408
46	3-oxo + A <sup>4</sup> + 6- = CH <sub>2</sub>	5	0.057	0.324
47	3-oxo + A <sup>6</sup>	1	0.054	0.131

Table 1. (continued)

No.	Substituent	Quantity	18-Methyl Protons	19-Methyl Protons
–	5 $\beta$ , 9 $\beta$ , 10 $\alpha$ , -androstane		0.719	0.944
48	3 $\alpha$ -OH	11	0.007	0.031
49	3 $\alpha$ -O-ac	16	0.013	0.037
50	3 $\alpha$ -OSO <sub>2</sub> CH <sub>3</sub>	1	– 0.004	0.052
51	3-OC <sub>2</sub> H <sub>5</sub> (at $\Delta^3$ )	2	0.000	0.034
52	3 $\alpha$ -OH + $\Delta^4$	5	0.012	0.269
53	3 $\alpha$ -OH + $\Delta^{4,6}$	8	0.047	0.219
54	3 $\alpha$ -OH + $\Delta^5$	13	0.049	0.263
55	3 $\beta$ -OH + $\Delta^5$	6	0.056	0.262
56	3 $\beta$ -OH + $\Delta^{5,7}$	1	– 0.049	– 0.202
57	3 $\beta$ -O-ac + $\Delta^5$	3	0.055	0.255
58	3 $\alpha$ -O-ac + $\Delta^5$	20	0.050	0.277
59	3 $\alpha$ -O-ac + $\Delta^{4,6}$	5	0.046	0.220
60	3-O-ac + $\Delta^{2,4,6}$	5	0.049	0.275
61	3-O-ac + $\Delta^{3,5}$	6	0.061	0.137
62	3-O-ac + $\Delta^{3,5,7}$	1	– 0.054	– 0.127
63	3 $\beta$ -OCH <sub>3</sub> + $\Delta^4$	2	0.025	0.187
64	3 $\alpha$ -OCH <sub>3</sub> + $\Delta^4$	3	0.019	0.271
65	3 $\beta$ -OC <sub>2</sub> H <sub>5</sub> + $\Delta^{4,6}$	2	0.042	0.127
66	3 $\alpha$ -OC <sub>2</sub> H <sub>5</sub> + $\Delta^{4,6}$	4	0.041	0.199
67	3 $\alpha$ -OCOCH <sub>2</sub> CH <sub>3</sub> + $\Delta^5$	1	0.047	0.277
68	3 $\alpha$ -Cl + $\Delta^5$	3	0.044	0.281
69	3, 3-ethylenedioxy	9	– 0.018	0.059
70	3, 3-ethylenedioxy + $\Delta^{1,4,6}$	1	0.044	0.274
71	3, 3-ethylenedioxy + $\Delta^4$	8	0.016	0.248
72	3, 3-ethylenedioxy + $\Delta^{4,6}$	5	0.040	0.186
73	3, 3-ethylenedioxy + $\Delta^4$ + 6-oxo	1	0.057	0.190
74	3, 3-ethylenedioxy + $\Delta^4$ + 6=CH <sub>2</sub>	1	0.029	0.160
75	3, 3-ethylenedioxy + $\Delta^5$	21	0.054	0.281
76	3, 3-ethylenedioxy + $\Delta^{5,7}$	6	– 0.064	– 0.175
77	3, 3-ethylenedioxy + $\Delta^6$	1	0.034	– 0.049
78	3, 3-ethylenedithio + $\Delta^4$	1	0.013	0.225
79	3, 3-ethylenedithio + $\Delta^{4,6}$	3	0.042	0.180
80	$\Delta^{4,6}$	2	0.050	0.192
81	4-CH <sub>3</sub> (at $\Delta^3$ or $\Delta^4$ )	21	0.001	– 0.045
82	4-C <sub>2</sub> H <sub>5</sub> (at $\Delta^4$ )	3	– 0.003	– 0.043
83	4-propyl (at $\Delta^4$ )	3	0.002	– 0.039
84	4-isopropyl (at $\Delta^4$ )	3	0.003	– 0.045
85	4-allyl (at $\Delta^4$ )	2	0.001	– 0.006
86	4-benzyl (at $\Delta^4$ )	3	– 0.023	0.004
87	4 $\alpha$ -OH	1	– 0.029	0.180
88	4 $\alpha$ -O-ac	2	– 0.038	0.147
89	4 $\beta$ -Br	4	0.007	0.039
90	4-OH (at $\Delta^4$ )	11	0.000	– 0.022
91	4-O-ac (at $\Delta^4$ )	10	– 0.006	0.053
92	4-OCH <sub>3</sub> (at $\Delta^4$ )	3	0.004	– 0.003
93	4-SH (at $\Delta^4$ )	2	0.005	– 0.038
94	4-S-C <sub>2</sub> H <sub>5</sub> (at $\Delta^4$ )	2	0.001	0.018
95	4-S-ac (at $\Delta^4$ )	2	0.014	0.087
96	4-F (at $\Delta^4$ )	8	0.006	0.031

Table 1. (continued)

No.	Substituent	Quantity	18-Methyl Protons	19-Methyl Protons
–	5 $\beta$ , 9 $\beta$ , 10 $\alpha$ , -androstane		0.719	0.944
97	4-Cl (at $\Delta^4$ )	22	0.006	0.019
98	4-Br (at $\Delta^4$ )	4	0.014	0.016
99	5 $\beta$ -OH	6	0.049	0.077
100	6-oxo	16	0.077	–0.134
101	6-oxo + $\Delta^7$	8	0.083	–0.240
102	6 $\beta$ -OH	18	–0.007	0.011
103	6 $\alpha$ -OH	19	–0.019	0.130
104	6 $\beta$ -O-ac	1	0.002	0.065
105	6 $\alpha$ -O-ac	2	–0.005	0.071
106	6 $\beta$ -F	11	0.005	0.032
107	6 $\alpha$ -F	10	–0.015	0.131
108	6 $\beta$ -Cl	32	0.002	0.041
109	6 $\alpha$ -Cl	2	0.004	0.212
110	6 $\beta$ -Br	8	0.005	0.021
111	6 $\beta$ -NO <sub>2</sub>	3	0.019	0.089
112	6 $\beta$ -CH <sub>2</sub> OH	4	0.007	0.014
113	6 $\beta$ -CH <sub>2</sub> O-ac	1	0.009	0.007
114	6-CH <sub>3</sub> (at $\Delta^5$ or $\Delta^6$ )	15	–0.008	–0.039
115	6-O-ac (at $\Delta^6$ )	1	–0.005	0.082
116	6-OCH <sub>3</sub> (at $\Delta^6$ )	3	–0.002	0.012
117	6-OC <sub>2</sub> H <sub>5</sub> (at $\Delta^6$ )	1	–0.006	0.019
118	6-F (at $\Delta^6$ )	5	–0.003	0.050
119	6-Cl (at $\Delta^5$ or $\Delta^6$ )	125	–0.003	0.033
120	6-Br (at $\Delta^6$ )	2	–0.010	0.034
121	7 $\beta$ -CH <sub>3</sub>	5	–0.004	–0.009
122	7 $\alpha$ -CH <sub>3</sub>	2	0.026	–0.001
123	7-CH <sub>3</sub> (at $\Delta^6$ )	2	0.031	0.046
124	7-oxo + $\Delta^{3,5}$	6	0.107	0.338
125	7-oxo + $\Delta^5$	8	0.079	0.423
126	7 $\beta$ -S-CH <sub>3</sub>	1	0.021	0.015
127	7 $\beta$ -S-C <sub>2</sub> H <sub>5</sub>	3	0.014	0.015
128	7 $\beta$ -S-ac	3	–0.007	0.021
129	8 $\beta$ -OH (from 3-oxo + $\Delta^4$ )	15	0.247	–0.047
130	8 $\beta$ -OH (from 3-oxo + $\Delta^{1,4}$ )	7	0.200	–0.095
131	8 $\beta$ -OH (from 3-oxo + $\Delta^{4,6}$ )	6	0.245	0.022
132	9 $\beta$ -OH	68	0.096	0.099
133	11-oxo	10	–0.015	0.020
134	11 $\beta$ -OH	57	0.202	–0.071
135	11 $\alpha$ -OH	32	0.037	0.187
136	11 $\beta$ -O-ac	9	0.120	–0.028
137	11 $\alpha$ -O-ac	5	0.097	0.191
138	11 $\alpha$ -OCOCH <sub>2</sub> Br	1	0.103	0.178
139	12 $\beta$ -OH	6	0.007	–0.047
140	15-oxo	2	0.097	–0.014
141	15 $\beta$ -OH	5	0.281	–0.017

Table 1. (continued)

No.	Substituent	Quantity	18-Methyl Protons	19-Methyl Protons
–	5 $\beta$ ,9 $\beta$ ,10 $\alpha$ ,-androstande		0.719	0.944
142	15 $\alpha$ -OH	13	0.017	0.029
143	15 $\beta$ -O-ac	5	0.232	–0.006
144	15 $\alpha$ -O-ac	2	0.077	0.048
145	$\Delta^{16}$	1	0.065	–0.002
146	$\Delta^{16}$ + 17-ac	24	0.186	–0.005
147	$\Delta^{16}$ + 17-(me-dioxolanyl)	5	0.225	0.018
148	$\Delta^{16}$ + 17-cyclopropyl	1	0.116	0.015
149	16 $\alpha$ -OH	37	0.011	0.035
150	16 $\beta$ -O-ac	2	0.239	–0.015
151	16 $\alpha$ -O-ac	12	0.044	0.047
152	16 $\alpha$ -OCH <sub>3</sub>	5	0.003	0.027
153	16 $\alpha$ -OCH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub>	2	–0.011	0.010
154	16 $\alpha$ -O-allyl	1	–0.004	0.030
155	16 $\alpha$ -O-prop-2-ynyl	1	–0.003	0.029
156	16 $\beta$ -Cl	1	0.504	–0.052
157	16 $\alpha$ -Cl	9	–0.008	0.052
158	16 $\beta$ -Br	1	0.554	–0.055
159	16 $\alpha$ -CN	2	–0.045	0.031
160	16 $\alpha$ -CONH <sub>2</sub>	1	0.014	0.017
161	16 $\alpha$ -NHCH <sub>3</sub>	1	0.031	0.012
162	16 $\alpha$ -NH-OCH <sub>3</sub>	1	0.052	0.029
163	16 $\alpha$ -SH	1	–0.011	0.030
164	16 $\alpha$ -SCN	1	–0.026	0.054
165	16 $\alpha$ -S-CH <sub>3</sub>	1	0.014	0.029
166	16 $\alpha$ -S-C <sub>3</sub> H <sub>5</sub>	21	0.011	0.031
167	16 $\alpha$ -S-isopropyl	1	0.012	0.025
168	16 $\alpha$ -S-allyl	1	0.011	0.037
169	16 $\alpha$ -S-prop-2-ynyl	1	0.024	0.030
170	16 $\alpha$ -S-CH <sub>2</sub> CH <sub>2</sub> OH	1	–0.003	0.030
171	16 $\alpha$ -S-ac	2	0.049	0.046
172	16 $\alpha$ -S-C <sub>8</sub> H <sub>17</sub> (n)	1	0.002	0.020
173	16 $\alpha$ -S-C <sub>18</sub> H <sub>37</sub> (n)	1	0.001	0.019
174	16 $\alpha$ -S-C <sub>6</sub> H <sub>5</sub>	1	0.009	–0.021
175	16 $\alpha$ -S-benzyl	1	–0.036	0.015
176	16 $\alpha$ -S-furfuryl	1	–0.014	0.017
177	16 $\alpha$ -SO <sub>2</sub> -C <sub>2</sub> H <sub>5</sub>	1	0.027	0.017
178	16 $\alpha$ -OH + 17 $\beta$ -OH	7	0.060	–0.001
179	16 $\alpha$ ,17 $\alpha$ -isopropylidenedioxy + 17 $\beta$ -ac	24	–0.111	0.106
180	17 $\beta$ -C <sub>8</sub> H <sub>17</sub>	27	–0.036	0.001
181	17 $\beta$ -C <sub>9</sub> H <sub>19</sub>	3	–0.052	–0.008
182	17- =CHCOOCH <sub>3</sub> ( <i>trans</i> )	6	0.122	–0.041
183	17- =CHCOOCH <sub>3</sub> ( <i>cis</i> )	3	0.296	–0.037
184	17-oxo	56	0.171	–0.031
185	17 $\beta$ -OH	99	0.036	–0.023
186	17 $\beta$ -OCH <sub>3</sub>	1	0.041	–0.006
187	17 $\beta$ -O-isobutyl	2	–0.001	–0.011
188	17 $\beta$ -OC(CH <sub>3</sub> ) <sub>3</sub>	2	–0.004	–0.005
189	17 $\beta$ -OCHO	1	0.106	–0.013

Table 1. (continued)

No.	Substituent	Quantity	18-Methyl Protons	19-Methyl Protons
-	5 $\beta$ , 9 $\beta$ , 10 $\alpha$ , -androstane		0.719	0.944
190	17 $\beta$ -O-ac	57	0.084	-0.014
191	17 $\alpha$ -O-ac	1	0.041	0.047
192	17 $\beta$ -OCOCH <sub>2</sub> OH	1	0.084	-0.010
193	17 $\beta$ -OCOCH <sub>2</sub> Br	3	0.116	-0.016
194	17 $\beta$ -OCOC <sub>9</sub> H <sub>19</sub> (n)	4	0.081	-0.018
195	17 $\beta$ -OCOCH <sub>2</sub> O-benzyl	1	0.067	-0.028
196	17 $\alpha$ -Cl	7	0.091	0.063
197	17 $\beta$ -COOH	1	0.027	0.014
198	17 $\beta$ -ac	406	-0.086	0.038
199	17 $\alpha$ -ac	4	0.180	-0.067
200	17 $\beta$ -ac-oxime	3	-0.078	0.024
201	17 $\beta$ -(me-dioxolanyl)	34	0.056	-0.001
202	17 $\beta$ -COCH <sub>2</sub> OH	34	-0.066	0.019
203	17 $\beta$ -COCH <sub>2</sub> O-ac	19	-0.046	0.029
204	17 $\beta$ -COCH <sub>2</sub> OCH <sub>3</sub>	2	-0.095	0.038
205	17 $\beta$ -COCH <sub>2</sub> F	7	-0.049	0.035
206	17 $\beta$ -COCHF <sub>2</sub>	11	-0.020	0.038
207	17 $\alpha$ -COCHF <sub>2</sub>	2	0.244	-0.079
208	17 $\beta$ -CH(OH)CH <sub>3</sub> ( $\beta$ )	24	0.043	0.008
209	17 $\beta$ -CH(OH)CH <sub>3</sub> ( $\alpha$ )	3	-0.043	-0.007
210	17 $\beta$ -CH(O-ac)CH <sub>3</sub> ( $\beta$ )	10	-0.071	0.015
211	17 $\beta$ -CH(O-ac)CH <sub>3</sub> ( $\alpha$ )	8	-0.034	0.000
212	17 $\beta$ -CH(OCH <sub>2</sub> OCH <sub>3</sub> )CH <sub>3</sub> ( $\beta$ )	1	0.001	0.004
213	17 $\beta$ -CH(OCOCH <sub>2</sub> CH <sub>2</sub> COOH)CH <sub>3</sub> ( $\beta$ )	2	-0.084	0.009
214	17,17-ethylenedioxy	7	0.133	0.047
215	17 $\beta$ -CH(OH)CH <sub>3</sub> ( $\beta$ ) + 17 $\alpha$ -CH <sub>3</sub>	2	0.162	0.025
216	17 $\beta$ -CH(O-ac)CH <sub>3</sub> ( $\alpha$ ) + 17 $\alpha$ -CH <sub>3</sub>	1	0.105	0.013
217	17 $\beta$ -CH(OH)CH <sub>3</sub> ( $\alpha$ ) + 17 $\alpha$ -CH <sub>3</sub>	1	0.039	0.008
218	17 $\beta$ -CH(O-ac)CH <sub>3</sub> ( $\beta$ ) + 17 $\alpha$ -CH <sub>3</sub>	2	0.009	0.034
219	17 $\beta$ -CH <sub>3</sub> + 17 $\alpha$ -ac	1	0.107	-0.165
220	17 $\beta$ -OH + 17 $\alpha$ -ClH <sub>3</sub>	99	0.155	0.003
221	17 $\beta$ -OH + 17 $\alpha$ -ethynyl	20	0.143	0.027
222	17 $\beta$ -OH + 17 $\alpha$ -(Cl-ethynyl)	2	0.126	0.021
223	17 $\beta$ -OH + 17 $\alpha$ -vinyl	4	0.208	-0.063
224	17 $\beta$ -OH + 17 $\alpha$ -C <sub>2</sub> H <sub>5</sub>	14	0.177	-0.004
225	17 $\beta$ -OH + 17 $\alpha$ -ac	1	0.227	-0.116
226	17 $\beta$ -OH + 17 $\alpha$ -CH <sub>2</sub> COCH <sub>3</sub>	1	0.176	0.007
227	17 $\beta$ -OH + 17 $\alpha$ -allyl	5	0.192	0.005
228	17 $\beta$ -OH + 17 $\alpha$ -(1-me-allyl)	4	0.191	0.004
229	17 $\beta$ -OH + 17 $\alpha$ -(2-me-allyl)	2	0.191	0.004
230	17 $\beta$ -OH + 17 $\alpha$ -(3-OH-prop-1-enyl)	1	0.196	-0.040
231	17 $\beta$ -OH + 17 $\alpha$ -prop-1-ynyl	2	0.119	0.034
232	17 $\beta$ -OH + 17 $\alpha$ -prop-2-ynyl	2	0.212	-0.006
233	17 $\beta$ -OH + 17 $\alpha$ -(3-trifluoro-prop-1-ynyl)	1	0.167	0.007
234	17 $\beta$ -OH + 17 $\alpha$ -(1-me-prop-2-ynyl)	4	0.201	0.025
235	17 $\beta$ -OH + 17 $\alpha$ -(3-OH-prop-1-ynyl)	1	0.137	0.030
236	17 $\beta$ -OH + 17 $\alpha$ -cyclopropyl	1	0.174	0.015
237	17 $\beta$ -OH + 17 $\alpha$ -CH <sub>2</sub> -cyclopropyl	1	0.189	-0.023
238	17 $\beta$ -OH + 17 $\alpha$ -CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH	3	0.179	-0.014



Table 1. (continued)

No.	Substituent	Quantity	18-Methyl Protons	19-Methyl Protons
–	5 $\beta$ , 9 $\beta$ , 10 $\alpha$ , -androstane		0.719	0.944
239	17 $\beta$ -OH + 17 $\alpha$ -CH <sub>2</sub> C(OH)(CH <sub>3</sub> ) <sub>2</sub>	2	0.155	0.126
240	17 $\beta$ -OH + 17 $\alpha$ -epoxyisobutyl	1	0.154	–0.053
241	17 $\beta$ -OCH <sub>3</sub> + 17 $\alpha$ -cyclopropyl	1	0.204	0.037
242	17 $\beta$ -O-ac + 17 $\alpha$ -CH <sub>3</sub>	69	0.137	0.009
243	17 $\beta$ -O-ac + 17 $\alpha$ -vinyl	9	0.216	–0.100
244	17 $\beta$ -O-ac + 17 $\alpha$ -C <sub>2</sub> H <sub>5</sub>	11	0.103	0.008
245	17 $\beta$ -O-ac + 17 $\alpha$ -ac	2	0.292	–0.131
246	17 $\beta$ -O-ac + 17 $\alpha$ -ethynyl	30	0.156	0.034
247	17 $\beta$ -O-ac + 17 $\alpha$ -(Cl-ethynyl)	5	0.142	0.044
248	17 $\beta$ -O-ac + 17 $\alpha$ -prop-1-ynyl	5	0.123	0.043
249	17 $\beta$ -O-ac + 17 $\alpha$ -(3-trifluoro-prop-1-ynyl)	3	0.186	0.016
250	17 $\beta$ -ac + 17 $\alpha$ -CH <sub>3</sub>	17	–0.041	0.049
251	17 $\beta$ -ac + 17 $\alpha$ -OH	17	0.008	0.067
252	17 $\beta$ -ac + 17 $\alpha$ -O-ac	13	–0.066	0.116
253	17 $\beta$ -ac + 17 $\alpha$ -OC <sub>2</sub> H <sub>5</sub>	7	–0.143	0.072
254	17 $\beta$ -ac + 17 $\alpha$ -Br	20	0.063	0.113
255	17 $\beta$ -COOCH <sub>3</sub> + 17 $\alpha$ -CH <sub>3</sub>	3	–0.019	0.023
256	17 $\beta$ -COCH <sub>2</sub> CH <sub>3</sub> + 17 $\alpha$ -CH <sub>3</sub>	2	–0.078	0.043
257	17 $\beta$ -COCH <sub>2</sub> OH + 17 $\alpha$ -OH	8	–0.054	0.058
258	17 $\beta$ -COCH <sub>2</sub> O-ac + 17 $\alpha$ -OH	11	–0.043	0.061
259	17 $\beta$ -COCH <sub>2</sub> Br + 17 $\alpha$ -Br	2	0.125	0.114
260	17 $\beta$ -COCHBr <sub>2</sub> + 17 $\alpha$ -Br	1	0.205	0.105
261	17 $\beta$ -COCH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> + 17 $\alpha$ -OH	1	–0.023	0.062

131 of Table 1). The non-additive property of these substituents is probably caused by slight changes of the overall shape of the basic molecular skeleton; therefore, the shift increments were also specified according to their chemical origin. The influence of the 9 $\beta$ -OH substituent on both angular methyl shifts was found to be small enough to ensure that no significant dependence of its increment on different chemical structures could be observed.

It is interesting to note that within the class of *retro*-steroids some of the  $\alpha$ -substituents in ring D, for example in position 16 and 17, may also strongly contribute to the chemical shift of the 19-methyl protons. This finding is in contrast to the results found for normal steroids and is attributed to the closer approach of the  $\alpha$ -substituents and the 19-methyl protons in these molecules of bent shape.

The accuracy of the reported increments is difficult to be estimated. Some indications, however, on the reliability of the values can be gathered from the differences between calculated and observed chemical shifts obtained for the 1334 spectra. The average deviation found was 0.004 ppm for both the methyl shifts. Most of the deviations (94% for the 18-methyls, 91% for the 19-methyls) were  $\leq 0.01$  ppm, thus demonstrating the internal consistency of the data. In judging these values, however, one has to take into account, that 70 of the 263 substituents occurred only once in the data set, meaning that 70 out of 1334 spectra of compounds containing these substituents necessarily have a zero deviation between calculated and experimental

Table 2. Abbreviations and Notations used in Table 1

me	$-\text{CH}_3$	$\text{C}_9\text{H}_{17}$	
ac	$-\text{COCH}_3$	$\text{C}_9\text{H}_{19}$	
ac-oxime	$-\text{C}(\text{CH}_3)=\text{NOH}$	17- $=\text{CH}-\text{R}$	
epoxyisobutyl		<i>trans</i> <sup>a)</sup>	
furfuryl	$-\text{CH}_2-$	<i>cis</i> <sup>a)</sup>	
isopropylidenedioxy		configuration at 20-C:	
ethylenedioxy		( $\alpha$ )	
ethylenedithio		( $\beta$ )	
me-dioxolanyl			

a) Tentative assignment under the assumption that in the *cis* compounds the 18-methyl protons are deshielded compared to the *trans* compounds.

chemical shifts. Nevertheless, it can be seen that, with the aid of the reported increments, the chemical shifts of  $5\beta, 9\beta, 10\alpha$ -steroids without too many interacting substituents may, in many cases, be predicted fairly accurately. Together with other NMR. techniques, e.g. application of lanthanide shift reagents, measurement of solvent effects and  $^{13}\text{C}$ -NMR., the reported shift increments are believed to be very helpful for the elucidation of the chemical structure of steroids.

## REFERENCES

- [1] J. N. Shoolery & M. T. Rogers, J. Amer. chem. Soc. 80, 5121 (1958).
- [2] R. F. Zürcher, Helv. 44, 1380 (1961).
- [3] R. F. Zürcher, Helv. 46, 2054 (1963).
- [4] J. E. Page, NMR. Spectra of Steroids, in: Annual Reports on NMR. Spectroscopy, ed. by E. F. Mooney, Vol. 3, p. 149, Academic Press, London and New York, 1970.
- [5] W. Arnold, W. Meister & G. Englert, Helv. 57, 1559 (1974).
- [6] A. I. Cohen & S. R. Roch, Steroids 3, 243 (1964).
- [7] E. R. Molinowski, M. S. Manhas, G. H. Miller & A. K. Bose, Tetrahedron Letters 1963, 1161.
- [8] R. F. Zürcher, Progress in Nuclear Magnetic Resonance Spectroscopy, ed. by J. W. Emsley, J. Feeney & L. H. Sutcliffe, Vol. 2, p. 205, Pergamon Press, Oxford, 1967.