Tetrahedron, 1965, Vol. 21, pp. 3171 to 3183. Pergamon Press Ltd. Printed in Northern Ireland

NUCLEAR MAGNETIC RESONANCE SPECTRA OF LANOSTANE DERIVATIVES

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(*Received* 12 *April* 1965)

Abstract—The chemical shift values for all of the methyl groups of 59 steroids of the lanostane series are presented. The effects of 11 nuclear substituents and of 18 different side chains on these chemical shifts are analyzed. The additivity principle is shown to hold satisfactorily, and the contributions of functional groups in "equivalent positions" show reasonable agreement.

IN THE course of recent studies[2] concerned with the transformation of eburicoic acid, a tetracyclic triterpene of the lanostane type to analogs of steroid hormones a large number of compounds became available for NMR studies. The information to be gained from a systematic analysis of the spectra was considered to be most helpful for further chemical studies with this group of substances, and, indeed the structural elucidation of the triterpenoid acid sulfurenic acid[3] was greatly aided by the data presented in this paper.

The spectra of steroids and triterpenes are generally complex because of the presence of a large number of aliphatic and alicyclic methylene groups. However, the three-proton signals of the methyl groups are usually readily discernible as relatively sharp peaks, which rise above the background of methylene and methine protons in the region 8·5–9·5 τ. Substituents as well as stereochemical and conformational changes can have a profound influence on the chemical shift of these methyl groups and this has been recognized during the early phases of the application of NMR spectroscopy to structural problems[4] and refined to a remarkable extent by subsequent workers both in the steroid[5] and triterpene[6] fields. The data reported in this paper are confined to the correlation of the chemical shifts of these methyl groups with changes in their chemical environment. The eburicane (24-methyllanostane) skeleton (I) possesses nine methyl groups, numbered as shown, and this may be contrasted with the presence of but two or three such groups in the steroid hormones of the androstane and pregnane series. The

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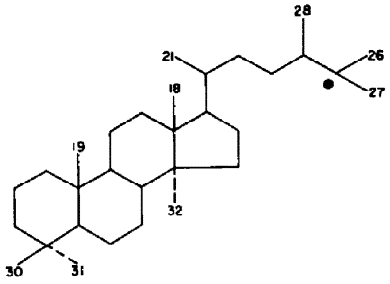
[2] See Part V of this series and earlier papers: A. I. Laskin, P. Grabowich, C. de Lisle Meyers and J. Fried, *J. Med. Chem.* **7**, 406 (1964).

[3] J. Fried, P. Grabowich, E. F. Sabo and A. I. Cohen, *Tetrahedron* **20**, 2297 (1964).

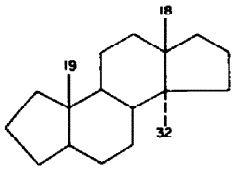
[4] J. N. Shoolery and M. T. Rogers, *J. Amer. Chem. Soc.* **80**, 5121 (1958).

[5a] R. F. Zürcher, *Helv. Chim. Acta* **44**, 1380 (1961); [b] R. F. Zürcher, *Ibid.* **46**, 2054 (1963); [c] A. I. Cohen and S. Rock, Jr., *Steroids* **3**, 243 (1964); [d] N. S. Bhacca and D. H. Williams, *Applications of NMR Spectroscopy in Organic Chemistry*. Holden-Day, San Francisco (1964).

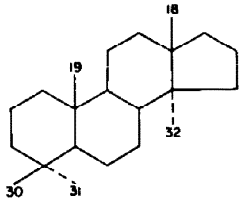
[6a] J. M. Lehn and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1137 (1962); [b] J. M. Lehn, *Ibid.* 1832 (1962); [c] S. Huneck and J. M. Lehn, *Ibid.* 1702 (1963); [d] D. Lavie, B. S. Benjaminov and Y. Shvo, *Tetrahedron* **20**, 2585 (1964).



I



II



III

intricate problem of assigning the appropriate chemical shifts to the various methyl groups present, many of them in rather similar environment and often giving rise to overlapping signals, was attacked in the following way: From an analysis of the spectra of relatively simple derivatives containing only the nuclear methyl groups, namely, those possessing the A-norandrostane skeleton (II), it was possible with the aid of published data[5] to make assignments for the 18 and 19-methyl protons. The third signal arising from the 32-methyl group could now be assigned to produce a consistent pattern. Consideration was then given to derivatives of the trimethylandrostane series (III), which contain, in addition, the 30 and 31-methyl groups, and, finally, after all the previous assignments had been made, substances possessing the various side chains were analyzed until a consistent set of assignments had been achieved.

RESULTS AND DISCUSSION[7]

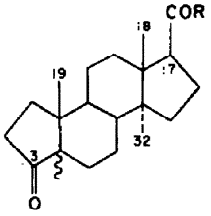
Our results are presented in tabular form, each Table combining related compounds and the sequence of Tables arranged in the order of increasing complexity of the spectra. Thus, Tables 1 and 2 list compounds possessing only nuclear methyl groups; in Table 3 various side chains are added, but the complexity has been reduced by contracting ring A and attaching the 30 and 31-methyl groups as an isopropylidene grouping, thereby shifting these methyl groups to lower field. Table 4 combines the most complex spectra arising from the intact ring system and an 8 or 9 carbon side chain, and interpretable only on the basis of the preceding spectra. Tables 5 and 6, utilizing all the available data, list the contributions of individual nuclear substituents and of different side chains, respectively, to the chemical shifts of the angular 18, 19 and 32-methyl groups. Finally, Table 7 compares the contributions of functional groups located in "equivalent" positions[6b] to the chemical shifts of these same methyl groups.

A-nor Derivatives (*Tables* 1 *and* 2). In contrast to normal 3-keto-steroids, which show no significant difference in the 19-methyl signals of their 5α- and 5β-isomers[8] the A-nor-3-ketones of the 5α- and 5β-series exhibit the C-19 proton signals 0·20–0·25 ppm

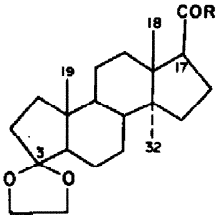
[7] All spectra were obtained with a Varian Associates model A-60 NMR spectrometer using ca. 0·1 M solutions of the sample in $CDCl_3$ containing 1% v/v tetramethylsilane as an internal reference standard. The spectra were scanned at a rate of two c/s per second. The reproducibility of the chemical shifts was ±0·01 ppm.

[8] Shoolery and Rogers (Ref. 4) report 8·99 and 8·98τ for 5α and 5β-pregnane 3,20-dione, respectively, and the same values may be derived from Zürcher's correlations.

TABLE 1. NMR SPECTRA OF A-NOR-3-KETO AND 3,3-ETHYLENDIOXY DERIVATIVES POSSESSING ONE AND TWO CARBON SIDE CHAINS AT C_{17}[a]



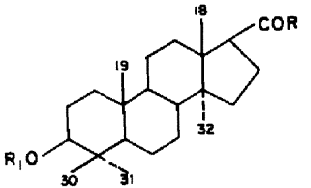
	R	Other substituents	C-18CH_3 τ	C-19CH_3 τ	C-32CH_3 τ	Others	τ[b]
1.	OCH_3	5βH, $\Delta^{6,9(11)}$	9·38	8·70	9·28	C-6, 7, 11 H	4·48, 4·32, 4·16
2.	OCH_3	5αH, 11-keto	9·30	8·88	9·12		
3.	OCH_3	5βH, 11-keto	9·29	8·63	8·98		
4.	OCH_3	5βH, Δ^6, 11-keto	9·24	8·71	8·96	C-6, 7H	4·37, 4·52
5.	OCH_3	Δ^5, 11-keto	9·22	8·88	8·88	C-6H	3·45(m, 3)
6.	OCH_3	5αBr, 11-keto	9·29	8·74	8·91		
7.	OCH_3	5βBr, 11-keto	9·28	8·51	9·00		
8.	CH_3	Δ^5, 11-keto	9·26	8·86	8·86	C-6H	3·41(m, 3)
						C-21 CH_3	7·88
9.	CH_3	5βH, Δ^6	9·32	8·77	9·09	C-21 CH_3	7·88
10.	CH_2OAc	5αH, Δ^5	9·28	8·99	9·09	C-21 CH_2	5·43(d, 17)
							5·23(d, 17)
11.	CH_2OAc	5βH, Δ^6	9·28	8·76	9·08	C-21 CH_2	5·45(d, 17)
							5·22(d, 17)



12.	OCH_3	5βH, $\Delta^{6,9(11)}$	9·29	8·86	9·22	C-6, 7H	4·38(m, ~1)
						C-11 H	4·53(m)
13.	OCH_3	5βH, 11-keto	9·32	8·82	8·91		
14.	OCH_3	Δ^5, 11-keto	9·28	8·96	8·88	C-6H	4·20(t, 3)
15.	OH	Δ^5, 11-keto	9·16	8·92	8·85	C-6H	4·18(t, 3)
16.	OCH_3	5βH, Δ^6, 11-keto	9·28	8·88	8·88	C-6, 7H	4·34(s)
17.	OH	5βH, Δ^6, 11-keto	9·18	8·86	8·86	C-6, 7H	4·33(s)

[a] J. Fried and E. F. Sabo, *J. Amer. Chem. Soc.* **84**, 4356 (1962); [b] In parentheses: m-multiplet, s-singlet, d-doublet, t-triplet, J in c/s.

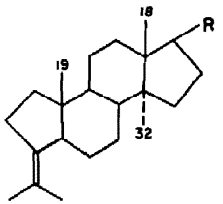
TABLE 2. NMR SPECTRA OF 3β-HYDROXY DERIVATIVES POSSESSING ONE AND TWO CARBON SIDE CHAINS AT C_{17}



	R	R_1	Other substituents	C-18CH_3 τ	C-19CH_3 τ	C-30CH_3 τ	C-31CH_3 τ	C-32CH_3 τ	Others τ	Ref.
18.	OCH_3	Ac[a]	11β-ol	9·04	8·80	9·10	9·15	9·20	5·75(m)[b]	*c*
19.	OCH_3	Ac	$\Delta^{9(11)}$	9·38	8·95	9·12	9·13	9·23	4·75(m)[b]	*c*
20.	OCH_3	Ac	9α, 11α-oxido	9·21	8·78	9·12		9·07	6·85(d, 5)[b]	*c*
21.	OCH_3	H	11-keto	9·33	8·94	9·03	9·20	8·90		*d*
22.	OCH_3	Ac	11-keto	9·34	8·92	9·14		8·90		*d*
23.	OCH_3	Ac	Δ^8-7, 11-diketo	9·24	8·68	9·05	9·10	8·79		*d*
24.	OH	Ac	Δ^8-7, 11-diketo	9·17	8·67	9·04	9·09	8·78		*d*
25.	CH_2OH	H	Δ^8	9·37	9·01	9·03	9·20	9·03		*h*
26.	CH_2OAc	H	Δ^8	9·33	9·00	9·02	9·18	9·02		*e*
27.	CH_2OAc	Ac	Δ^8	9·34	9·00	9·12		9·03		*e*
28.	CH_3	H	Δ^8	9·38	8·99	9·02	9·18	9·02		*e*
29.	[f]	Ac	11-keto	9·19	8·91	9·13	9·15	8·88	4·90(m)[g]	*h*

[a] Ac = CH_3CO; [b] C-11 H; [c] Unpublished work; [d] J. Fried and E. F. Sabo, *J. Amer. Chem. Soc.* **84**, 4356 (1962); [e] D. Rosenthal, P. Grabowich, E. F. Sabo and J. Fried, *Ibid.* **85**, 3971 (1963); [f] COR = 17β-$OCOCH_3$; [g] C-17α H; [h] G. W. Krakower, J. W. Brown and J. Fried, *J. Org. Chem.* **27**, 4710 (1962).

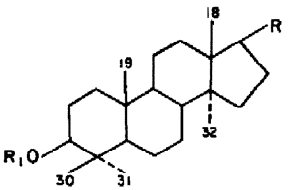
TABLE 3. NMR SPECTRA OF A-NOR-3-ISOPROPYLIDENE DERIVATIVES

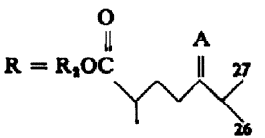


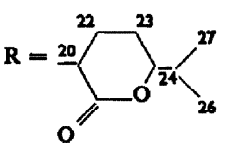
		R	C-18CH_3 τ	C-19CH_3 τ	C-32CH_3 τ	C-26, 27CH_3 τ	Ref.
30.	11-keto	CO_2CH_3	9·32	9·24	8·91		*a*
31.	Δ^8	$HOCH_2C{=}CHCH{=}CHCH(CH_3)_2$	9·39	9·22	9·03	8·98(d, 6·3)	*b*
32.	Δ^8	$HO_2C{-}C{=}CHCH{=}CHCH(CH_3)_2$	9·35	9·21	9·00	8·96(d, 6)	*b*
33.	Δ^8	$COC{=}CHCH{=}CCH(CH_3)_2$	9·41	9·24	8·94	8·78(d, 7)	*b*
34.	Δ^8	$CH_3O_2C{-}CHCH_2CH_2CH(CH_3)CH(CH_3)_2$	9·21	9·21	9·21	47·5, 54[c]	*d*

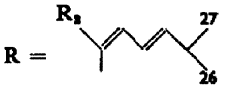
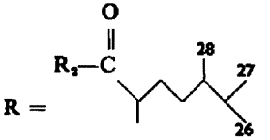
[a] J. Fried and E. F. Sabo, *J. Amer. Chem. Soc.* **84**, 4356 (1962); [b] D. Rosenthal, P. Grabowich, E. F. Sabo and J. Fried, *Ibid.* **85**, 3971 (1963); [c] C-26, C-27, C-28 CH_3 groups; cps from TMS; [d] R. M. Gascoigne, J. S. E. Holker, B. J. Ralph and A. Robertson, *J. Chem. Soc.* 2346 (1951).

TABLE 4. NMR SPECTRA OF 3β-HYDROXY DERIVATIVES CONTAINING EIGHT AND NINE CARBON SIDE CHAINS



	R_1	R_2		Other substituents	C-18CH_3 τ	C-19CH_3 τ	C-30CH_3 τ	C-31CH_3 τ	C-32CH_3 τ	C-26, 27 CH_3 τ	Ref.
											
				A							
35.	H	CH_3	Δ^5	CH_2	9·27	9·01	9·04	9·20	9·12	8·99(d, 6)	*a*
36.	Ac	H	Δ^5	CH_2	9·22	9·00	9·12		9·12	8·99(d, 6)	*a*
37.	Ac	CH_3	Δ^5	CH_2	9·27	9·00	9·12		9·12	9·00(d, 6)	*a*
38.	Ac	H	Δ^5	O	9·23	9·00	9·11		9·11	8·91(d, 7)	*b*



39.	H		$\Delta^{8,20(22),23}$		9·44	8·94	9·04	9·19	8·99	8·77(d, 6)	*b*
40.	Ac		$\Delta^{8,20(22),23}$		9·44	8·95	9.12		9·02	8·78(d, 7)	*b*
41.	Ac		$\Delta^{8,24}$		9·18	9·00	9·12		9·16	8·36 8·27	*b*
42.	Ac		$\Delta^{8,23}$	R = 	9·17	9·01	9·14		9·17	8·89(d, 7)	*b*
43.	H	CHO	Δ^{8}		9·46	8·98	9·04	9·19	8·98	8·92(d, 7)	*b*
44.	H	CH_2OH	Δ^{8}		9·42	9·01	9·03	9·18	9·03	8·98(d, 7)	*b*
45.	Ac	CH_2OAc	Δ^{8}	R = 	9·41	8·99	9·10		9·03	8·98(d, 7)	*b*
										C-26, 27, 28 CH_3 cps from TMS	
46.	Ac	OCH_3			9·20	9·14	9·14	9·17	9·20	48, 54	*c*
47.	H	OCH_3	Δ^{8}		9·27	9·00	9·03	9·18	9·12	49, 53	*b*
48.	Ac	OCH_3	Δ^{8}		9·28	9·01	9·13		9·13	49, 52	*d*
49.	Ac	OCH_3	$\Delta^{8(11)}$		9·31	8·95	9·12		9·25	49, 53	*d*
50.	Ac	OCH_3	11β-ol		8·97	8·80	9·10	9·16	9·23	54	*d*
51.	H	OCH_3	11-keto		9·26	8·95	9·03	9·20	8·92	48, 53	*e*
52.	Ac	OCH_3	11-keto		9·27	8·92	9·14-5		8·92	48·5, 51	*e*
53.	Ac	OCH_3	11-keto, 7-dithioethylene		9·18	8·88	9·14		8·60	49, 51·5	*e*
54.	Ac	OCH_3	7, 11-diketo		9·29	8·74	9·18		8·81	49, 53·5	*e*
55.	Ac	OCH_3	Δ^{8}, 7-keto		9·30	8·83	9·12		9·05	48·5, 54·5	*e*
56.	Ac	OCH_3	Δ^{8}, 7, 11-diketo		9·20	8·70	9·06	9·12	8·84	48, 53	*e*
57.	Ac	H	11-keto		9·29	8·93	9·13		8·91	52	*e*
58.	Ac	Cl	Δ^{8}		9·25	9·00	9·12		9·08	48·5, 53	*f*
59.	Ac	Cl	11-keto		9·25	8·93	9·15		8·89	51	*e*

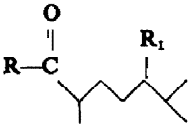
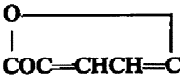
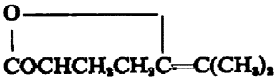
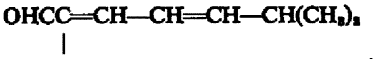
[a] R. M. Gascoigne, J. S. E. Holker, B. J. Ralph and A. Robertson, *J. Chem. Soc.* 2346 (1951); [b] D. Rosenthal, P. Grabowich, E. F. Sabo and J. Fried, *J. Amer. Chem. Soc.* **85**, 3971 (1962); [c] Unpublished work; [d] F. N. Lahey and P. H. A. Strasser, *J. Chem. Soc.* 873 (1951); [e] G. W. Krakower, J. W. Brown and J. Fried, *J. Org. Chem.* **27**, 4710 (1962); [f] J. S. E. Holker, A. D. G. Powell, A. Robertson, J. J. H. Simes and R. S. Wright, *J. Chem. Soc.* 2414 (1963).

TABLE 5. INFLUENCE OF VARIOUS FUNCTIONAL GROUPS ON THE CHEMICAL SHIFT OF THE AXIAL METHYL GROUPS

Functional group	$\Delta\tau^a CH_3$ C-18	C-19	C-32	No. of examples
Δ^8	+0·08	−0·13	−0·07	2[c]
7-Keto	+0·02	−0·18	−0·10	2[d]
11-Keto	+0·07	−0·22	−0·28	4[e]
7-Dithioethylene	−0·09	−0·04	−0·32	1[e]
Δ^8-7-Keto	+0·10	−0·31	−0·15	1[c]
7, 11-Diketo	+0·09	−0·40	−0·39	1[e]
Δ^8-7, 11-Diketo	0·00	−0·44	−0·34	1[e]
11β-Ol	−0·23	−0·34	−0·03	1[c]
$\Delta^{9(11)}$	+0·11	−0·19	+0·05	1[c]
15α-Ol[b]	−0·05	−0·01	−0·11	1[f]
15α-Acetoxy[b]	−0·09	−0·02	−0·13	1[f]
15-Keto[b]	−0·09	−0·03	−0·12	1[f]

[a] +upfield shift; −downfield shift; [b] J. Fried, P. Grabowich, E. F. Sabo and A. I. Cohen, *Tetrahedron* **20**, 2297 (1964); [c] Compared with compound 46; [d] Compared with compound 48 and 52; [e] Compared with compound 52; [f] Compared with compounds 35, 36 or 37.

TABLE 6. INFLUENCE OF SIDE CHAIN ON THE CHEMICAL SHIFT OF THE ANGULAR METHYL GROUPS

17β-Side chain	R	R_1	$\Delta\tau^a CH_3$ C-18	C-19	C-32	No. of examples
	OCH_3	CH_3	0·00[b]	0·00[b]	0·00[b]	
	H	CH_3	+0·02	+0·01	−0·01	1
	Cl	CH_3	−0·03	0·00	−0·04	2
	OCH_3	$=CH_2$	0·00	0·00	0·00	2
	OH	$=CH_2$	−0·06	−0·01	−0·01	1
	OH	$=O$	−0·05	−0·01	−0·02	1
			+0·17	−0·06	−0·12	2
			−0·10	−0·01	+0·03	1
			−0·11	0·00	+0·04	1
			+0·19	−0·02	−0·15	1
			+0·15	+0·01	−0·09	1
			+0·07	−0·01	−0·03	5
$-CO_2H$			−0·03	−0·03	−0·05	1
$-COCH_2OH$			+0·10	+0·01	−0·09	1
$-COCH_2OAc$			+0·06	0·00	−0·10	2
$-COCH_3$			+0·10	−0·01	−0·10	1
$-OCOCH_3$			−0·08	−0·01	−0·04	1

[a] +upfield shift; −downfield shift; [b] The differences are relative to these chemical shifts.

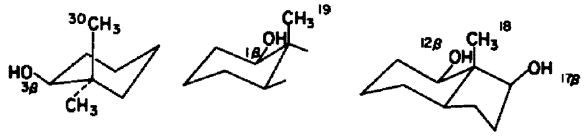
TABLE 7. CONTRIBUTION OF FUNCTIONAL GROUPS IN EQUIVALENT POSITIONS TO CHEMICAL SHIFT OF 18, 19 AND 32-METHYL PROTONS

Equivalent set	Functional groups	Angular methyl affected	Chemical shift contribution $\Delta\tau$
1	$\Delta^{9(11)}$	19	−0·19
	Δ^{8}	19	−0·13
	Δ^{8}	32	−0·07
2	$\Delta^{9(11)}$	18	+0·11
	$\Delta^{9(11)}$	32	+0·06
3	11-keto	19	−0·22
	7-keto	32	−0·10
	15-keto	18	−0·09
4	11-keto	32	−0·28
	7-keto	19	−0·18

apart, which makes it possible to distinguish between them with ease. Although displaced to lower field differences of the same magnitude were found for the corresponding 5-bromo derivatives. An example of long range deshielding by bromine was observed with the 5α-bromo-compound 6, whose 32-methyl signal is shifted downfield by 0·21 ppm. No such shift was found with the corresponding 5β-bromo epimer 7, which possesses the bromine atom and the 32-methyl group on opposite sides of the steroid nucleus. The effect of the α-bromine atom may be ascribed to the distortion of the molecule caused by the 1-3-diaxial interactions between the axial bromine and the 7α- and 9α-protons on the one hand, and between the latter and the axial 32-methyl group on the other. Substituting a carbon-carbon double bond for the magnetically more highly anisotropic carbonyl group at C_3 in compound 2 (e.g. compound 30, Table 3) causes an upfield shift of the C-19 methyl signal by 0·36 ppm.[6a] This latter signal appears between 9·21 and 9·24 τ in 5 compounds (Table 3).

C-30 *and* C-31 *Methyl groups.* Of the 27 3β-acetoxy derivatives measured, 19 possess both the C-30 and C-31 methyl signals at the same average τ value of 9·13 ± 0·02 ppm (Tables 2 and 4). Notable exceptions are the Δ^{8}-7,11-diketones 23, 24 and 56, which show the two methyl groups as discrete peaks at 9·05 and 9·10 τ ± 0·01, and the 11β-hydroxy derivatives 18 and 50 which absorb at 9·10 and 9·15 τ. On the other hand, the signals for these same methyl groups in 10 3β-hydroxy derivatives consistently appeared as separate peaks at 9·03 and 9·19 τ with an average deviation of ±0·01 ppm. Similar observations have been made in these laboratories (unpublished results) with 4,4-dimethylcholestanol (3-proton peaks at 9·05 and 9·20 τ) and its acetate (6-proton peak at 9·13 τ), and these findings are also in line with those derived from reports by Lehn and Ourisson[6a] in the lupane series and by Lehn[6b] in the dammarane series. We have tentatively assigned the lower field signal in the free hydroxy derivatives to the axial 30-methyl group for the following reasons: The hydrocarbon lupane shows signals attributed to the 30 and 31-methyl groups at 9·16 and 9·19 τ.[6b] It is fair to assume that the lower field signal represents the 30-methyl group, which is slightly deshielded as a result of its diaxial interaction with the 19-methyl group. The effect on the former of adding the equatorial 3β-hydroxyl function should be "equivalent" in the sense discussed by Zürcher[5b] to that observed when an equatorial hydroxyl group is placed on a

carbon atom contiguous to that bearing one of the angular methyl groups. Thus, a 1β-hydroxyl group produces a downfield shift of the 19-methyl signal by 0·05 ppm and the presence of a 12β- or 17β-hydroxyl group causes a shift of the 18-methyl group in the same direction by 0·07 and 0·03 ppm, respectively.[5a] The steric equivalence of these structures is illustrated below. Applying the average of these three values (—0·05 ppm)



to the chemical shift of the 30-methyl group lowers it to 9·11 τ as compared to 9·19 τ for the 31-methyl groups, thereby approaching the observed separation of the two peaks. The above considerations do not take account of any possible effect of the 3β-hydroxyl group on the signal of the equatorial 31-methyl group, no equivalent structures being available to evaluate such an effect. The merging of the two methyl signals in the 3-acetoxy derivatives would then be the net effect on the 30 and 31-methyl groups resulting from time averaging of all the possible conformations of the acetyl group.

Functional groups in equivalent position. The concept of functional groups in equivalent positions introduced by Zürcher,[5b] was designed to extend the range of validity of chemical shift data gathered for one specific functional group-angular methyl relationship to other situations displaying similar steric relationships. We have, therefore, gathered in Table 7 all those sets possessing structural equivalence that can be derived with the aid of Table 5. Inspection of this table shows that for each equivalent set the direction of the chemical shift is the same. Yet, within individual sets the differences range from 0·01 to 0·13 τ. It should be noted, however, that smaller differences are always encountered ($<0{\cdot}06\ \tau$) when comparing the effects on the same methyl group or on methyl groups both located at the C, D-ring junction than when comparing the effects on methyl groups located at different ring junctions ($>0{\cdot}06\ \tau$).

C-26, C-27 *and* C-28-*Methyl groups.* In compounds possessing a $\Delta^{24(28)}$-methylene grouping the 26 and 27-methyl groups appear as a doublet centered at 9·00 τ (J = 7 c/s). This assignment was confirmed by determining the spectrum of compound 37 at 100 mc, under which conditions the separation of peaks was clearly defined as being due to spin–spin coupling.[9] Other compounds in which carbon atom 24 is the terminus of either a carbon-carbon or carbon-oxygen double bond likewise show the isopropyl grouping as a well defined doublet (J = 7) below 9·00 τ. This includes the 24-ketone 38, the α-pyrones 33, 39 and 40, the dihydropyrone 42 and several substances possessing the dienic side chains listed in Tables 3 and 4.

Greater difficulty was encountered in the assignment of the proper signals to the 26, 27 and 28-methyl groups in derivatives 46–59, which possess a saturated side chain.

[9] It was particularly important to make an unambiguous assignment for the 26 and 27-methyl groups in compound 37 so as to be able to correlate the chemical shift data for the nuclear methyl groups obtained on derivatives possessing one and two carbon side chains listed in Tables 1 and 2 with those possessing eight and nine carbon side chains (Table 4). We wish to thank Dr. Leroy F. Johnson of Varian Associates for carrying out this determination.

These signals are expected to appear as two doublets with coupling constants of 6–7 c/s in the range of 9·07–9·13 τ.[10] Actually, the spectra of most of the compounds of this series show signals at about 49 and 55 c/s. It is suggested that the signal at lower field, in addition to one peak due to the C_{26}, C_{27} protons, contains the "filled-in" doublet arising from the C_{28} protons. A similar situation obtains in the cholesterol case, in which the C_{21} proton doublet is found bracketing the lower field peak of the terminal isopropyl group.[11]

Influence of 7- *and* 11-*keto groups on the chemical shift of angular methyl groups.* The 7 and 11-keto groups are strategically located on the steroid nucleus so as to profoundly affect the degree of shielding of all the angular methyl groups. Thus, the C-19 and C-32 methyl protons attached to carbon atoms located in γ-position with regard to the respective carbonyl groups are strongly deshielded. This is shown in Fig. 1 (To "convert" the 11-ketone shown into a 7-ketone turn page upside down). This effect is a consequence of the magnetic anisotropy of the carbonyl group, the above methyl groups lying outside the cone of positive shielding.[12] A more complex picture is found

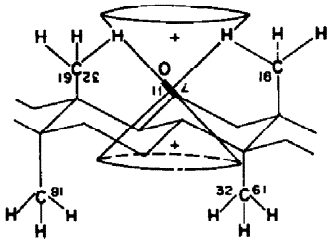


FIG. 1

when attempting to rationalize the chemical shifts of the methyl groups attached in β-position with respect to the two carbonyl groups. Both the 18- and 19-methyl groups would be expected to be shielded by the 11-keto group, and so would the 32-methyl group as a result of the anisotropy of the 7-keto group (Fig. 1). Yet in 11-keto steroids only the 18-methyl group is shielded, the 19-methyl group being deshielded as is the 32-methyl group in 7-keto steroids. The effects observed in these latter cases are more readily understood when considering in addition to its anisotropy the dipolar character of the carbonyl group. Whenever the electronegative end of the C=O dipole is directed towards the β-methyl group—the 19-methyl in 11- and the 32-methyl group in 7-ketones—deshielding will result, the latter effect outweighing the contribution due to anisotropy.

The deshielding effect of the 11-keto group on the 32-methyl group is all but abolished when the *trans*-fused six-membered A ring is replaced by a *trans*-fused five-membered ring as in compound 2. One would expect that the more highly strained *trans*-indanone system would cause distortion of ring C as well, thus altering the spatial relationship between the 11-keto and the 32-methyl groups. When the five-membered

[10] G. Slomp and F. A. McKellar, *J. Amer. Chem. Soc.* **84**, 204 (1962). Cf. also page 34 of Ref. *5d*.

[11] For purposes of practicality we have chosen to list these signals in Table 4 in terms of c/s for the peaks actually observed, rather than report the chemical shift values, which latter cannot be derived with any degree of certainty.

[12] L. M. Jackman, *Applications of NMR Spectroscopy in Organic Chemistry* p. 124. Pergamon Press, London (1959).

A-ring is *cis*-fused as in compounds 3, 13, 16 and 17 or if a 5,6-double bond is present, the C-32 methyl group is again strongly deshielded. That it is indeed the 11-keto group, which is responsible for these effects, is seen from a comparison of the *cis-trans*-pair 10 and 11, which lacks the 11-keto group, and which shows identical chemical shifts for the 32-methyl group.

Additivity of functional group effects. The principle of the additivity of functional group effects on the chemical shifts of angular methyl groups, which has been so well established and documented by Zürcher[5a,b] is applicable to the present series of compounds as well. The effects of various functional groups on the C-18, C-19 and C-32 signals are shown in Table 5. These values as well as those in Table 6 were arrived at by pairing compounds, which differ by only a single chemical grouping, namely, the one shown in the first column. Moreover, only values for compounds possessing a 6-membered A-ring were used in the compilation of these Tables. The last column in both of these Tables indicates the number of pairs meeting these criteria and that were, therefore, utilized to arrive at the figures listed. As has been discussed by others,[5a,b] conjugated systems cannot always be treated as the sum of their individual components, and this is evident from a comparison of the observed chemical shifts for the Δ^8-7,11-diketone system with those calculated by adding the contributions for the 7,11-diketone system and the 8,9-double bond. On the other hand, the values for the Δ^8-7-ketone grouping closely approximate the sums of the Δ^8- and 7-ketone shifts.

Influence of the side chain on the chemical shift of angular methyl groups. A great variety of side chains have been available for this study, some of which showed a considerable effect on the chemical shifts of the nuclear methyl groups. Again based on the principle of additivity, so well established for nuclear substituents, the contributions of the various side chains have been determined, and these are listed in Table 6. Effects of considerable magnitude, particularly on the C-18 and C-32-methyl groups were found with side chains possessing highly delocalized π-electron systems. Thus, the α-pyrone, dienal and dienol side chains (e.g. compounds 39, 43 and 44, respectively) show increased shielding of the 18-methyl group by 0·15–0·19 ppm, and deshielding of the 32-methyl group by 0·09–0·15 ppm, versus the standard saturated carboxylic acid side chain. These effects can be readily rationalized if one orients the side chain as shown for the α-pyrone side chain in Fig. 2a. (Or by rotating it about the 17,20-bond by 180°.)

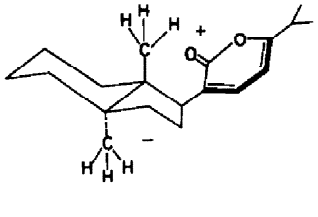


FIG. 2a

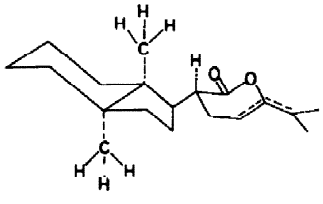


FIG. 2b

Similar orientation of the extended dienic side chains (e.g. compounds 43 and 44) should produce parallel effects. The reverse effects, namely, deshielding of the 18 and slight shielding of the 32-methyl group are observed with the dihydropyrones 41 and 42, Fig. 2b. No unique interpretation of these data is possible because of the conformational flexibility and rotational degrees of freedom of this type of side chain.

Tables 5 and 6 in combination with each other may serve for the calculation of chemical shift values for compounds in this series, whether or not they are listed in Tables 1–4. Calculating, for example, the chemical shifts of the 18, 19 and 32-methyl protons for the 11-keto 17-carboxylic ester 22, using compound 46 (Table 4) as the reference compound, by adding the appropriate $\Delta\tau$ values for the 11-keto group and the carbomethoxy side chain taken from Tables 5 and 6, we obtain values of 9·34, 8·91 and 8·89 τ, in good agreement with the observed values of 9·34, 8·92 and 8·90 τ, respectively.