# NMR—THE CHEMICAL SHIFT—IV THE ANISOTROPIES OF THE CARBONYL GROUP

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Abstract—The calculation of chemical shift values by the method used in Part I has been extended to a derivation of the shielding effect of the ketonic CO group. The calculations include consideration of both the magnetic anisotropy screening and the electric field screening effect in this substituent. Using the complete series of monoketoandrostanes, the values of the anisotropies of the C=O double bond and of K, a parameter descriptive of the electric screening effect, have been derived for various, coincidental locations

of the magnetic and electric dipoles along the >C=O bond.

As with the C=C double bond, our results necessitate a substantial modification of the conventional picture of the shielding 'cone' around the CO group.

The general validity of these concepts has been illustrated by their application to a variety of substances, including a selection of diterpenes and their ketonic derivatives.

**PRECEDING** papers in this series  $^{1-3}$  have described the derivation of values for the magnetic anisotropies of C—C, C—H and C=C bonds and have demonstrated the use of these parameters in the prediction of chemical shift differences and their potential value for the solution of conformational problems. The extension of these ideas to the CO group has been the subject of a preliminary communication<sup>4</sup> and is elaborated in this paper.

In contrast to the C—C, C—H and C=C bonds, it is assumed (vide infra) that the long range screening effect of a CO group includes not only a magnetic anisotropy screening term but also an electric field screening effect, which is a consequence of the polarization of the CO bond.

Earlier studies<sup>5, 6</sup> using amides as model compounds must be accepted with reserve since amides may not necessarily yield anisotropy values which are applicable to the CO bond in ketones. Moreover, these studies<sup>5, 6</sup> involved the use of McConnell's equation<sup>7</sup> even though the distance between the proton observed and the CO function responsible for the shielding was much less than 3 Å: this is approximately the distance below which McConnell's equation is no longer considered valid.<sup>1, 7, 8</sup> In a more recent communication<sup>9</sup> anisotropy values for the CO group were derived from a consideration of a series of keto-androstanes assuming that the C—H bonds displaced upon the introduction of the CO group have a small or negligible anisotropy. We believe this assumption to be unjustified since the magnetic anisotropy of the C—H bond, and therefore its screening effect, has previously been shown<sup>1</sup> to be significant. Because of these limitations associated with previous derivations we have felt it necessary to revaluate the anisotropy of the CO group and have used the complete series of keto-androstanes as models. The magnitude of the electric field effect has also been investigated. In addition, our calculations include the effect of varying the position, within the bond, of the magnetic and electric dipoles. The effect of solvent shifts between cyclohexane and deuteriochloroform has also been taken into account.

Our mathematical approach to this problem, therefore, consists of an evaluation of (a) the magnetic anisotropy and (b) the electric field effects. The derivation of Eq. (1) used for the former has been described.<sup>2</sup>

$$\sigma = 1/3 R^3 [\Delta \chi_1^{C=0} (1-3\cos^2 \theta) + \Delta \chi_2^{C=0} (1-3\sin^2 \theta \sin^2 \gamma)]$$
(1)

In Eq. (1),  $\Delta \chi_1^{C=0}$  is the anisotropy between the axis perpendicular to the nodal plane of the  $\pi$  orbitals and the axis in the C=O  $\sigma$  bond direction while  $\Delta \chi_2^{C=0}$  is the anisotropy between the axis perpendicular to the  $\sigma$  bond direction in the nodal plane of the  $\pi$  orbitals and the axis in the C=O  $\sigma$  bond direction.

The electric screening effect,  $\sigma_{\rm E}$ , resulting from the C=O dipole is given by the expression<sup>4</sup>

$$\sigma_{\rm E} = kE_z = km[\cos\omega \left(3\cos\beta\cos\psi - \cos\phi\right)]R^{-3}$$
(2)

where k is a constant whose theoretical value is not readily assessed. In this work, km, has been written as K which has been evaluated from the data by the least squares method. The magnitude of m, the electrical dipole moment of the C=O bond has not been used in these calculations except in Table 6, where values of k have been estimated from the values of K. The symbols are defined and the derivation of Eq. (2) is outlined in Appendix I.

The total screening effect of a CO bond on a distant, essentially freely rotating Me group is found from the algebraic sum of the effects calculated by Eqs. (1) and (2).

Our approach, as in previous studies,<sup>1-4</sup> to the problem of calculating chemical shift differences, consists in the algebraic subtraction of the screening contribution of the displaced C—H bonds from the screening contribution of the anisotropic group introduced. For the CO function, two screening mechanisms, namely a magnetic anisotropy and an electric field effect,<sup>10</sup> must be considered. Since the CO group lacks axial symmetry, estimation of the contribution from the magnetic anisotropy must be obtained by application of Eq. (1).

Thus, the net, calculated chemical shift difference  $(\Delta \sigma)$  resulting from the introduction of a CO bond, in place of a methylene group, can be written as follows:

$$Term I i Term I ii Term I I$$

$$\Delta \sigma = \left[ \Delta \chi_1^{C=0} f(\theta_1 R_1) + \Delta \chi_2^{C=0} f(\theta_1 R_1 \gamma_1) + K_1 f(R_1 \omega \beta \psi \phi) \right]$$

$$Term III i Term III ii$$

$$-\left[ \Delta \chi^{CH} f(\theta_2 R_2) + \Delta \chi^{CH} f(\theta_3 R_3) \right] (3)$$

Terms I (i) and (ii) are the screening contributions due to the magnetic anisotropy of the CO group [Eq. (1)]; Term II is the screening contribution from the electric field effect of the CO bond [Eq. (2)] and Terms (III) (i) and (ii),\* are the contributions due to the magnetic anisotropy of the C—H bonds (axial and equatorial) displaced by the C==O group.

The symbols  $f(R, \theta)$  etc are geometric factors calculated from measurements on Dreiding models; for simplicity they may be replaced by a, b, c, d, as in Eq. (4).

$$\Delta\sigma \text{ observed (ppm)} = \left[ a \,\Delta\chi_1^{\rm CO} + b \Delta\chi_2^{\rm CO} + cK \right] - \left[ d \Delta\chi^{\rm CH} + e \Delta\chi^{\rm CH} \right] \tag{4}$$

whence

$$a\Delta\chi_1^{\rm CO} + b\Delta\chi_2^{\rm CO} + cK = \Delta\sigma \text{ observed (ppm)} + \Delta\chi^{\rm CH}(d+e)$$
 (5)

The anisotropy,  $\Delta \chi^{CH}$ , of the C—H bond has previously been determined and the value (see note added in proof ref. 2) used in the present work was  $\Delta \chi_{CH} = +7.54 \times 10^{-30} \text{ cm}^3 \text{ molecule}^{-1}$ .

The requisite data for the present study were derived as follows: chemical shift positions of the C-18 and C-19 Me groups for those keto-androstanes synthesized by us (Experimental) were observed in cyclohexane and carbon tetrachloride solution (Table 1). Table 2 shows the chemical shift data for these ketones, together with the

TABLE 1. OBSERVED METHYL RESONANCE POSITIONS FOR KETO-5 $\alpha$ -ANDROSTANES (in Hz from TMS at 60 MHz)

0		C-19		C-18				
Compound	Cyclohexane	CCl4	CDCl <sub>3</sub>	Cyclohexane	CCl4	CDCl <sub>3</sub>		
Androstane	49-4	47.2	47-9	43.3	41-6	42-0		
1-one	67.5	67·3	<del>69</del> -8	43-1	41-6	42-0		
2-one	44-0	44·3	45-4	43-6	42-0	41-9		
3-one	61·3	61.3	61.4	<b>45</b> ·1	43.7	44-0		
4-one	44-6	<b>44</b> ·3	45-6	44.3	<b>42</b> ·5	42.6		
6-one	43-9	43.7	45-6	<b>43</b> ·8	43.7	43-9		
7-one	63·8	63·5	63-9	42.5	41.5	42·3		
11-one	63-0	59·8	61.7	39-8	40-0	40-4		
12-one	53-4	52.4	52.7	58·2	58-8	61-3		
15-one (14α)	49-5	48-6	<b>48</b> ·7	46-1	<b>47</b> ·2	47.7		
16-one (14a)	51·2	49.5	4 <del>9-6</del>	52-8	52·7	52.7		
17-one (14a)	50-5	<b>48</b> -9	49.5	48-1	48-9	52-1		

shift values obtained from the literature for the remainder. Since chloroform and carbon tetrachloride produce solvent screening effects on protons in oxygenated solutes, <sup>11, 12</sup> the chemical shifts taken from literature sources have been suitably adjusted to give a value for solutions in cyclohexane. Table 1 clearly indicates, as expected, that the solvent shift is largest (4–5 Hz) when the CO group is adjacent to the Me group (5 $\alpha$ -androstan-1-one, -12-one and -17-one), but decreases rapidly as the ketonic function moves further away from the proton observed. The data in Table 1 were thus used as the basis for the adjustment of the requisite literature shift values measured in chloroform.

\* These take the form of McConnell's original equation  $\Delta \sigma = \frac{1}{2} \Delta \chi^{CH} (1-3\cos^2\theta)/\mathbb{R}^3$ .

Conhanyl maritian		С	-19		C-18					
aroonyi position -	Example No	Cyclohexane	CCl₄	CDCl <sub>3</sub>	Lit.*	Example No.	Cyclohexane	CCl₄	CDCl <sub>3</sub>	Lit.*
1-one(5α)	1	- 18-0	- 20-1	- 21-9	- 22.5	17	+0-2	0-0	0.0	-1-0
1-one(5β)	2	- <b>8·8†</b>			-13-0	18	0-0			0-0
2-onc(5α)	3	+ 5.4	+2.9	+ 2.5	+1-6	19	-03	-04	+0-1	-0-5
3-one(5a)	4	-11.9	-14.2	-13.5	-14.5	20	-1.8	-2.1	-2-0	-2.5
3-one(5β)	5	- 5.4†			-7-0	21	2.5			-2.5
4-one(5a)	6	+ 4.8	+2.9	+ 2.3	+ 2.0	22	-1-0	-09	-0-6	-1-0
4-one(5β)	7	- <b>9</b> -6*			- 12-0	23	0-0			0-0
6-one(5a)	8	+ 5.5	+3.5	+ 2.3	+ 3-0	24	-05	-2.1	-1.9	-1-0
7-one(5a)	9	- 14-4	-16-3	-16-0	-16-5	25	+08	+01	-0-3	-0-5
11-onc(5a)	10	-13-6	- 12-6	-13·8	-13-0	26	+ 3.5	+1.6	+1.6	+2-0
12-one(5a)	11	-4-0	- <b>5</b> ·2	-4.8	-60	27	-14-9	-17.2	- 19-3	-22.5
15-one(14a)	12	-0-1	-1.4	-0-3	-0-6	28	-2.8	- 5-6	- 5.7	-4.5
15-one(148)	13	+ 2.5*			+2.5	29	-9.5*			-11.5
16-one(14α)	14	- 1.8	-2.3	-1.7	. – •	30	-9.5	-11.1	- 10-7	
17-one(14a)	15	-1.1	-1.7	- 1.5	-1.0	31	-4.8	-7.3	-10-1	- 10-0
17-onc(148)	16	-1.0*			-1.0	32	-3.0*			- 5-0

### TABLE 2. OBSERVED ME SHIFTS UPON INTRODUCTION OF C==O GROUP IN ANDROSTANE (in Hz at 60 MHz) (a + sign indicates an upfield shift - towards TMS)

\* Literature values taken from R. F. Zürcher, Helv. Chim. Acta, 44, 2054 (1963).

† Lit. value corrected for solvent (CDCl<sub>3</sub>) shift.

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In our measurements of distances and angles we have assumed that the magnetic and electrical dipoles arise at the same point in the CO bond. Since the exact location of this point is uncertain<sup>4, 9</sup> calculations were carried out for the three cases where the point dipoles are placed 1.2 Å, 0.9 Å and 0.6 Å from the C atom along the direction of the C=O bond. Table 3 lists the necessary measurements and the calculated geometric factors for the C--H bonds in the keto-androstanes; Table 4 gives the relevant data for the anisotropy calculations on the CO group; Table 5 lists measurements and the calculated geometric factors for the electric field effect of the CO group. These Tables were then used to set up 32 equations of the form given in Eq. (5) and the best values of  $\Delta \chi_1^{c=0}$ ,  $\Delta \chi_2^{c=0}$  and K were obtained by the least squares method. These values were then substituted into the original equations in the form of Eq. (4) and the chemical shift  $\Delta \sigma$ , ( $\Delta \sigma$  and rostane  $-\Delta \sigma$  keto-androstane) calculated: the results thus obtained were compared with the observed values.

Initial calculations, which included *all* the keto-androstanes indicated that the effect of the 11-keto-function on the C-19 Me group (example No. 10; see Tables) was anomalous: the discrepancy between the observed and calculated shifts for this situation was of the order of 20 Hz and is to be ascribed to the lack of conformational parity between the parent hydrocarbon and the ketone occasioned by the interference between the C-1  $\beta$  H atom and the 11-keto substituent. The reality of this interaction has been elegantly illustrated,<sup>13</sup> and is further supported by the observation<sup>14</sup> that the CD curve of 5 $\alpha$ -androstan-11-one is temperature dependent.

Example 10 was therefore excluded from the calculations in our derivation of values for K,  $\Delta \chi_1^{C=0}$  and  $\Delta \chi_2^{C=0}$  listed in Table 6.

Substitution of these anisotropies and K values into the original equations then furnished a comparison of observed and calculated shift values. Tables 7, 8 and 9 give the results for each of the dipole locations chosen and show the contribution from each term of Eq. (3). A plot of observed against calculated shift values ( $\sigma$  and rostane- $\sigma$ keto-androstane) for the case of the dipole located on the O atom (1.2 Å from the C atom) is shown in Fig. 1. Three points only lie outside +4 Hz range of the theoretical line. Several important facts emerge (cf. Tables 7, 8 and 9). Thus, within experimental error, equally good agreement between observed and calculated values is obtained for each of the three locations of the dipole along the C-O bond. However, as the position of the magnetic and electric dipoles moves from the centre of the bond towards the O atom, the value of K decreases. When the dipole is centred on the O ator, K becomes small enough  $(-0.2 \times 10^{30})$  to be considered insignificant (cf. Table 6). This implies that if the electrical and magnetic dipoles be placed on the O atom, electric field effects may be ignored in our type of calculation. This is further illustrated by omitting Term II from Eq. (3) and solving the three sets of 31 equations in terms of only two unknowns, namely  $\Delta \chi_1^{c=0}$  and  $\Delta \chi_2^{c=0}$ . The anisotropy values calculated in this manner are shown in Table 10.

If these anisotropies be now used to calculate chemical shift differences [Eq. (3) with Term II omitted], agreement between observed and calculated values is satisfactory when the dipole is placed on the O atom: three cases only lie outside  $\pm 4$  Hz of the observed value. Agreement is less satisfactory when the dipole is placed 0.6 Å from the C atom: then eight values fall outside  $\pm 4$  Hz of the experimental figure. Despite this and in view of the small number of cases examined, we deem it prudent to include the electric field effect in calculations. The present data indicate no preferred position

TABLE 3	\$.	
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Experimental Parameters and Calculations for effect of Carbon-Hydrogen Bonds on C-19 Methyl Group in Keto-Androstanes

Example*	Example* CH No Bond R(Å)		θ	Geometric Sector d	CH Bond	R(Å)	θ	Geometric Factor e	<b>Term</b> • III [Eq. (3)] $\times 10^{6}$		Obs. Shift
INO.	Posn.		(degrees)	$cm^{-3} \times 10^{22}$	Posn.		(degrees)	$\mathrm{cm}^{-3} \times 10^{22}$	dx ∆χ <sup>c</sup> —н	ех ∆χ <sup>с</sup> -н	p.p.m.
1	1α	3.52	21	1.2341	1β	2.90	75	+ 1.0921	-0-093	+0-082	-0.300
2	1α	2-90	75	+1-0921	1β	2.90	75	+1-0921	+0-082	+0-082	-0147
3	2α	3.76	22	-0.9902	28	2.74	65	+07522	-0-075	+0-057	+0-090
4	3α	4.36	40	-0-3059	3β	4.20	48	-01544	-0-023	-0.012	-0-198
5	3α	5.50	12	-0-3747	3β	4.66	83	+0-3147	-0-028	+0-024	-0-090
6	4α	3.76	22	- 0-9902	4 <b>B</b>	2.74	65	+0.7522	-0-075	+0-057	+0-080
7	4α	4.42	70	+0-2506	4β	4.70	45	-0-1605	+0-019	-0-012	-0-160
8	6a	3.76	22	0-9902	6β	2.74	65	+0.7522	-0-075	+0-057	+0-092
9	7α	4.36	40	-0-3059	7B	4.20	48	-0.1544	-0-023	-0.012	-0.240
10	11α	3-56	62	+0.2503	11 <b>β</b>	2.88	65	+0.6477	+0-019	+ 0-049	-0-228
11	12a	5.10	48	-0-0862	128	5.04	57	+0-0287	-0-007	+0-002	-0-067
12	15α	6-00	50	-0-0370	15B	5.27	76	+0-1878	-0-003	+0-014	-0.002
13	15α	5.50	78	+01744	15B	6-00	60	+ 0-0386	+0-013	+0-003	+0.042
14	16a	7-30	28	-01147	16 <b>B</b>	6.82	67	+0-0570	0-009	+0-004	-0.030
15	17a	6.60	52	-0-0159	178	6.50	68	+0.0703	-0.001	+0-005	-0.018
16	17α	6.88	62	+ 0-0347	17β	6.92	53	-0.0087	+0-003	-0-001	-0.017

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17	1α	6-00	56	+0-0096	1 <b>β</b>	5-25	77	+01954	+ 0-001	+0-015	+0-003
18	1α	5.24	78	+0-2016	1β	5·98	40	-0-1185	+0-015	-0.009	0.000
19	2a	7·24	39	-0-0713	2β	6-42	80	+01146	-0-005	+0-009	-0.005
20	3α	7.70	59	+0-0149	3β	7.95	33	+0-0736	+0-001	-0-006	-0-030
21	3α	7.60	44	-0-0419	3β	7.46	55	+0-0010	-0-003	0-000	-0-042
22	<b>4</b> α	7·24	39	-0-0713	4β	6.42	80	+01146	-0-005	+0-009	-0-017
23	4α	6.00	66	+0-0777	4β	7.00	37	-0-0888	+ 0-006	-0-007	0-000
24	6α	6-00	21	-0.2492	6β	5-00	84	+0-2579	-0-019	-0-019	-0.008
25	7 <b>a</b> c	4.92	45	-0-1399	7β	4-45	80	+0-3441	-0-011	+0-026	+0-013
26	11α	3.76	20	-1-0341	11β	2.74	65	+0.7522	-0.078	+0-057	+ 0-058
27	12α	3.58	20	- 1·1980	12β	2·90	75	+1.0921	0-090	+0-082	-0-248
28	15α	<b>4</b> ·10	7	- 0 <b>-94</b> 57	15 <b>β</b>	3-09	83	+1.0795	-0-071	+0-081	-0-047
29	15a	4.62	48	-0-1160	15 <b>B</b>	4.60	48	-01175	0-009	-0.009	-0-158
30	16a	4.12	12	-0.8915	16 <b>B</b>	3.37	82	+0-8203	-0-067	+0-062	-0158
31	17α	3-51	24	- 1·1 <b>59</b> 1	17β	2.80	85	+ 1.4839	-0-087	+0112	-0.080
32	17α	3.15	58	+0-1680	17β	2.76	89	+1.5840	+0-013	+0119	-0-050

Experimental Parameters and Calculations for effect of Carbon-Hydrogen Bonds on C-18 Methyl Group in Keto-Androstanes

\* In this and all subsequent tables in this paper the compound corresponding to any given example number can be found by reference to Table 2.  $\Delta \chi^{C-H} = +7.5 \times 10^{-30} \text{ cm}^3 \text{ molecule}^{-1}$  is the value used in these calculations (cf. ref. 2).

	Distance of Dipole Position from Carbon Atom										
Example No.	10	2 Å	0.9	9 A	0-0	5 <b>A</b>					
Example 140.	Geometric Factor a $cm^{-3} \times 10^{22}$	Geometric Factor b $cm^{-3} \times 10^{22}$	Geometric  Factor a  cm-3 × 1022	Geometric Factor b $cm^{-3} \times 10^{22}$	Geometric Factor a cm <sup>-3</sup> × 10 <sup>22</sup>	Geometric Factor b $cm^{-3} \times 10^{22}$					
1	+03685	+0.4160	+0-3468	+0-3815	+0-2473	+0.3290					
2	+1.3667	-2.3830	+1.4399	- <b>2</b> ·6931	+1.5185	- 2 <b>·948</b> 7					
3	-0-4852	+0-4601	-0-6421	+0-4663	-0.8591	+0-5023					
4	+0-2966	+0-2977	+0-3481	+0-3562	+0.4061	+0-4312					
5	+0-0862	+0.1858	+0-0808	+0-2117	+0-0720	+0-2440					
6	-0-4852	+0-4601	-0-6421	+ 0-4663	-0.8591	+0-5023					
7	+0-2195	+0-0283	+0-2424	-0.0207	+0.2684	+0-0850					
8	-0-4852	+0•4601	-0-6421	+0-4663	-0.8591	+0-5023					
9	+0-2966	+0-2977	+0-3481	+0-3562	+0-4061	+0-4312					
10	+0-0713	- <b>1·1974</b>	-0-0997	- 1-0463	-0-2759	-0.8761					
11	+0-1958	+0-1017	+0-2178	+0-1058	+0-2444	+0-1105					
12	+0-0531	-0.1537	+0-0462	-01727	+0-0388	-0-1886					
13	+0-0662	-0-2044	+0-0597	-0-2047	+0-0450	-0-2013					
14	+0-0661	+0-0680	+0-0712	+0-0736	+0-0744	+0-0799					
15	+0-0949	-0-0169	+0.1009	-0-0283	+0.1071	-0-0475					
16	+0-0827	+0-0015	+0-0906	-0-0073	+0-0994	-0-0232					
17	+0-0643	-0-2281	+ 0-0679	-0-2568	+0-0808	-0.2900					
18	+0-0023	0-0918	-0.0160	-01057	-0-0455	-0-1014					
19	+0-0191	-0-0380	+0-0154	-0-0439	+0-0113	-0-0532					
20	+0-0456	+0-0524	+0-0494	+0-0583	+0-0537	+0-0651					
21	+0-0591	+0-0605	+0-0636	+0-0651	+0-0686	+0-0702					
22	+ 0-0102	-0-0288	-0-0036	-0-0250	-0-0253	-0-0191					
23	- 0-0494	-0-0074	-0-0514	-0-0215	-0-0533	-0-0376					
24	0-0399	+01019	-0-0624	+01198	0-0892	+0-1398					
25	+0-1999	-0.1299	+0-2022	+0-1546	+0.1634	-0.1744					
26	-0.6375	+0.6105	-0-7621	+0.5983	- 1-0297	+0-6560					
27	+0.6460	+0.2520	+0.4053	+0.5230	+0-3847	+0-5131					
28	-0.1010	+0-4947	-0-2118	+0.5487	-0-3572	+ 0-6009					
29	+0-2376	+0-1627	+0.2780	+01611	+0-3273	+0-1386					
30	+0.1504	+0.3710	+0.1192	+04504	+0-0359	+0.5436					
31	+0.2634	+0-2089	+0.1894	+01871	+0-0146	+0.1883					
32	+0.8420	-1.4403	+07752	- 1.6295	+06755	-1.8242					

TABLE 4. GBOMETRIC FACTORS FOR ANISOTROPY EFFECT OF CARBONYL BOND IN KETO-ANDROSTANES FOR VARYING POSITIONS OF THE DIPOLE

for the induced electric and magnetic dipoles and in applications of this work, each location, (1.2 Å, 0.9 Å, 0.6 Å) would best be examined in turn.

Susceptibilities corresponding to the anisotropies of Table 6 may be obtained (cf Ref. 2) using the mean susceptibility  $(-1.7 \times 10^{-30})$  for the CO bond.<sup>16</sup> Table 11 gives the appropriate values.

The paramagnetic nature of  $\chi_x$  is in agreement with the conclusion<sup>17</sup> that the CO bond in aldehydes has a paramagnetic contribution in the XZ plane. The present work, moreover, is supported by the molar susceptibility data for urea<sup>18</sup> where the susceptibility perpendicular to the plane of the CO bond is large and diamagnetic.

	C-19: Dista	nce of dipole p carbon atom	osition from		C-18: Distance of dipole position from carbon atom				
Example	1·2 Å	0-9 Å	0-6 Å	Example	1·2 Å	0-9 Å	0-6 Å		
NO.	Geometric Factor c $cm^{-3} \times 10^{22}$	Geometric Factor c $cm^{-3} \times 10^{22}$	Geometric Factor c cm <sup>-3</sup> × 10 <sup>22</sup>	- NO.	Geometric Factor c cm <sup>-3</sup> × 10 <sup>22</sup>	Geometric Factor c $cm^{-3} \times 10^{22}$	Geometric Factor c cm <sup>-3</sup> ×10 <sup>22</sup>		
1	+ 1-0576	+1.2326	+ 1.4367	17	-0-0534	-0-0720	-0-0964		
2	+1.5669	+1.4555	+1.2561	18	+0-1489	+01551	+0-1594		
3	+0-8123	+0-8868	+0-9374	19	+0-0562	+0-0606	+0-0650		
4	+0-3607	+04325	+0.5430	20	+0-0110	+0-0122	+0-0102		
5	+0-3368	+0-3829	+0-4341	21	+0-0622	+0-0670	+0-0724		
6	+0-8123	+0-8868	+0.9374	22	+0-0605	+0-0688	+0-0768		
7	+04279	+0-4748	+0-5177	23	+0-0103	-0-0004	-0-0117		
8	+0-8123	+0-8868	+0-9374	24	+0-1467	+01684	+0.1914		
9	+0-3607	+04325	+0-5430	25	+0.1420	+0-1301	+0-1166		
10	+07038	+0-5270	+0-3291	26	+07821	+0-8751	+1-0296		
11	+0-1722	+01856	+0-2009	27	+1.0674	+ 1-2537	+1.4748		
12	+0-0912	+0-0871	+0-0826	28	+0-7007	+0-8128	+0-9623		
13	+0-0227	+0-0039	-0-0159	29	+0-4154	+04761	+0-5493		
14	+0-0610	+0-0675	+0-0744	30	+0.5414	+0-6623	+0-8200		
15	+0-0557	+0-0607	+0-0667	31	+1.1521	+1.3409	+ 1-5641		
16	+0-0952	+0-1108	+0-1270	32	+ 1· <b>4695</b>	+ 1.4739	+1.4118		

TABLE 5. GEOMETRIC FACTOR FOR ELECTRIC FIELD EFFECT OF CO GROUP IN KETO-ANDROSTANES FOR VARYING POSITIONS OF THE DIPOLE

TABLE 6

Location of dipoles Distance from C atom Å	$\Delta \chi_1^{C=0} \times 10^{30}$	$\Delta \chi_2^{C=0} \times 10^{30}$	$K^{\dagger} \times 10^{30}$	$k \times 10^{12}$
1.2	- 39-9	- 25-9	-0-2	-0-07 to -0-09
0-9	- 33-2	-21 <del>·9</del>	- 3-8	-1.3 to $-1.7$
0-6	-27-0	- 18.4	-69	-2.4 to $-3.0$

\* The value of k derived depends on the magnitude of the dipole moment used. Values reported for the CO bond dipole range from 2.3 to 2.9 Debyes.<sup>15</sup>

 $\dagger K = km$  where m equals dipole moment of >C=O bond.

The chemical shift difference,  $\Delta\sigma$ , i.e. ( $\sigma$  and rostane- $\sigma$  keto-and rostane) consists of two parts, (i) the shielding effects of the two C—H bonds displaced (their contribution is subtracted) and (ii) the sum of the magnetic and electric shielding effects of the CO group. Table 12 shows the contributions from these two sources. In two examples, namely 1-keto-5 $\beta$ -and rostane (C-19 Me group) and 17-keto-14 $\beta$ -and rostane (C-18 Me), out of 31, the contribution from the two C—H bonds displaced is greater than v at from the CO group introduced. In five cases the shielding contributions from

Example	Shii fro	ft contribut om C=O b	tions ond	Shift cont from C—	ributions H bonds	Calc. Shift	Obs. Shift	۸•
No.			TERM II	TERM III		Hz	Hz	
	(I)	(u)			(II)			
C-19								
1	- 8.8	-6.5	0-1	- 5.6	+ 4-9	-14.7	- 18-0	3.3
2	- 32.7	+ 37-0	-0-2	+4.9	+4.9	- 5·7	- <b>8</b> ·8	3.1
3	+11.6	-7.1	-01	-4.5	+ 3.4	+ 5.5	+ 5.4	0-1
4	-7.1	-4-6	0-0	-1.4	-0.7	-96	-11·9	2.3
5	-2.1	- 2-9	0-0	-1.7	+1.4	- <b>4</b> ·7	-5-4	ው7
6	+11.6	- 7.1	-01	-4.5	+3.4	+ 5.5	+4.8	0-7
7	- 5.3	-04	-01	+1.1	-0-7	-6.2	- 9.6	3.4
8	+11.6	- 7.1	-0-1	-4.5	+3.4	+ 5·5	+ 5.5	0-0
9	-7.1	-4.6	0-0	-1.4	-0-7	-9.6	- <b>14</b> ·4	4.8
10			Exclude	d from Lea	st Squares A	Analysis		
11	- 4.7	-1-6	0-0	-04	+01	-60	-4-0	2.0
12	-1.3	+2.4	0-0	-0-2	+0-8	+05	-0-1	0-6
13	-1.6	+3.2	0-0	+0-8	+0-2	+0-6	+ 2.5	1.9
14	-1.6	- 1.1	0-0	-0-5	+03	- 2.5	- 1.8	0-7
15	-2.3	+0-3	0-0	-0-1	+0-3	- 2·2	- 1·1	1.1
16	-2.0	0-0	0-0	+0-2	0-0	- 2·2	-1.0	1.2
C-18								
17	-1.5	+ 3.5	0-0	0-0	+09	+1.1	+0-2	0-9
18	-01	+1.4	0-0	+0-9	-0-5	+0-9	0-0	0-9
19	-0-5	+0-6	0-0	-0-3	+0-5	-0-1	-0-3	0-2
20	-1.1	-0-8	0-0	+01	-0-3	- 1·7	-1·8	0-1
21	-1.4	-0.9	0-0	-0-2	0-0	-2.1	- 2.5	0-4
22	-0-2	+0-4	0-0	-0-3	+05	0-0	-1-0	1-0
23	+1.2	+0-1	0-0	+04	-04	+ 1.3	0-0	1.3
24	+1-0	- 1.6	0-0	-1·1	+1.2	-0-7	-0-5	0-2
25	- 5.3	+1.7	0-0	-0-6	+1.6	-4-6	+0-8	3∙8
26	+15.2	-9.5	-0.1	<b>- 4</b> ·7	+ 3•4	+ 6.9	+ 3.2	3-4
27	<b>-9</b> ·1	-80	-0-1	<b> 5</b> ∙4	+4-9	-1 <del>6</del> .7	- 14-9	1.8
28	+ 2•4	- <b>7</b> ·7	-0-1	-4-3	+ 4-9	-6-0	-2.8	3-2
29	<u> </u>	- 2.5	0-0	-0-5	-0-5	- 7.2	<b>-9</b> ∙5	2.3
30	- 3.6	<b> 5</b> ∙8	-01	-4-0	+ 3.7	- 9·2	<b>-9</b> ∙5	0-3
31	-6.3	- 3·2	-0-1	- 5·2	+6.7	-11-1	<b>4</b> ·8	6.3
32	-20-1	+ 22.4	-0-2	+0-8	+ 7·2	- 5.9	- <b>3</b> ·0	2.9

# TABLE 7. CHEMICAL SHIFT CONTRIBUTIONS (Hz) FROM EACH TERM OF EQUATION (3) TO THE TOTAL CALCULATED SHIFT OF METHYL RESONANCES. DIPOLE POSITION CA. $1\cdot 2$ Å from Carbon atom

•  $\Delta = /obs-calc/.$ 

Example	Shi fro	ft contribut m C—O B	ions ond	Shift cont from C—	ributions H Bonds	Calc. Shift	Obs. Shift	۸•
No.	TER	MI	TERM II	TERMIN		Hz	Hz	-
	(i)	(ii)		(i)	(ii)			
C-19								
1	-6.9	- 5.0	-2·8	- 5.6	+ 4.9	-14-0	18-0	4-0
2	- 28.6	+ 35.4	- 3·3	+ 4.9	+ 4.8	- 6.3	- <b>8</b> ·8	2.5
3	+12.8	<b>-6</b> ·1	-2.0	<b>-4</b> ·5	+ 3.4	+ 5.8	+ 5.4	0-4
4	- 6-9	- <b>4</b> ·7	-1·0	-1.4	-0-7	-10-5	- 11.9	1.4
5	-1.6	- 2.8	-0-9	-1.7	+1.4	-50	- 5.4	0-4
6	+ 12.8	-6.1	-2-0	- <b>4</b> ·5	+ 3.4	+ 5.8	+ 4.8	1.0
7	-4.8	+0-3	-1.1	+1.1	-0.7	-60	<b>-9.6</b>	3.6
8	+12.8	- 6.1	-2-0	-4.5	+ 3.4	+ 5.8	+ 5.2	0-3
9	-6.9	-4.7	-1-0	-1.4	-0-7	-10-5	- 14.5	3.9
10			Exclude	d from Lea	st Squ <mark>ares</mark> A	Analysis		
11	- <b>4</b> ·3	-1.4	-0-4	-0-4	+0-1	- 5.8	-4-0	1.8
12	-09	+ 2.3	-0-2	-0-2	+0-8	+0-6	-0-1	0.7
13	-1.2	+ 2.7	0-0	+0-8	+0-2	+05	+ 2.5	2-0
14	-1.4	-1.0	-0-2	-0-5	+0-3	-2·4	-1.8	0-6
15	-2.0	+0-4	-0-1	-0-1	+0-3	- 1.9	-1.1	0-8
16	-1.8	+01	-0-3	+0-2	0-0	-2·2	-1-0	1.2
C-18								
17	-1.4	+ 3.4	+0-2	0-0	+09	+1.3	+0-2	1.1
18	+0-3	+1.4	-04	+0-9	-0.5	+09	0-0	0.9
19	-0-3	+0-6	-0-1	-0-3	+05	0-0	-0.3	0-3
20	-1.0	-0-8	0-0	+01	-0-3	-1-6	-1·8	0-2
21	-1.3	-09	-0-2	-0-2	0-0	- 2·2	- 2.5	0-3
22	+01	+0-3	-0.2	-0-3	+05	0-0	-1-0	1-0
23	+1.0	+0-3	0-0	+04	-0-4	+1.3	0-0	1.3
24	+1.2	-1.6	-0-4	-1.1	+1·2	-09	-0.5	0-4
25	-4-0	+2-0	-0-3	-0-6	+1.6	- 3·3	+0.8	<b>4</b> ·1
26	+15.2	- <b>7·9</b>	-2-0	<b>-4</b> ·7	+ 3•4	+6-6	+ 3.5	3.1
27	-8.0	- 6-9	- <b>2</b> ·8	- 5.4	+ 4-9	-17·2	- 1 <b>4·9</b>	2.3
28	+4.2	- 7.2	- 1.8	-4.3	+ 4 9	- 5.4	-2.8	2.6
29	- 5.5	- 2·1	-1.1	-0-5	-0-5	- 7.7	9.5	1-8
30	- 2.4	- <b>5</b> ·9	-1.5	-4-0	+ 3.7	-9.5	-9.5	0-0
31	- 3.8	-2.5	-3-0	- 5·2	+ 6.7	- 10-8	- <b>4</b> ·8	6-0
32	-15.4	+21.4	- 3·3	+08	+ 7·2	- 5-3	-3-0	2.3

TABLE 8. CHEMICAL SHIFT CONTRIBUTIONS (Hz) FROM EACH TERM OF BQUATION (3) TO THE TOTAL CALC	JLATED
shift of methyl resonances. Dipole position ca, $0.9$ Å from carbon atom	

\*  $\Delta = /obs.-calc./$ 

Example	Shi fro	ft contribution C=O b	tions ond	Shift cont from C—	ributions H bonds	Calc.	Obs.	٨٠
No.	TERM I		TERM II	TERM III		Hz	Hz	Δ.
	(i)	(ii)		(i)	(ii)	-	_	
C-19								
1	4.0	- 3-6	- 5 <del>-9</del>	- 5-6	+4.9	-12·8	- 18-0	5.2
2	- 24.6	+ 32.5	- 5.2	+4.9	+4.9	- <b>7</b> ·1	8.8	1.7
3	+ 13-9	- 5·5	- 3-9	-4.5	+ 3.4	+ 5-6	+ 5.4	0-2
4	-6.6	- <b>4</b> ·7	-2.5	-1.4	-07	- 11·4	- 11·9	0.5
5	- 1.2	- 2.7	— 1·8	-1.7	+1.4	- 5.4	- 5·4	0-0
6	+13·9	- 5.5	- <b>3</b> ·9	-4.5	+ 3.4	+ 5-6	+ 4.8	0-8
7	4.4	+09	-2.1	+1.1	-0-7	-6-0	-9.6	3-6
8	+13-9	- 5.5	<b>-3</b> ·9	-4.5	+ 3.4	+5.6	+ 5-5	0-1
9	- 6.6	-4.7	-2·2	- 1.4	-07	-11.4	- 14.4	3-0
10			Exclude	d from Lea	st Squares /	Analysis		
11	4-0	-1·2	-0-8	-04	+01	- 5·7	-4-0	1.7
12	-06	+ 2.1	-0-3	-0-2	+08	+0-6	-0-1	0-7
13	-07	+ 2-2	+01	+0-8	+0-2	+0-6	+ 2.2	1.9
14	-1.2	-0-9	-0-3	-05	+0-3	-2·2	- 1·8	0-4
15	1.7	+0-5	-0-3	-0-1	+0.3	-1·7	- <b>1</b> ·1	0.6
16	-1.6	+03	-05	+0.5	0-0	-20	-1.0	1.0
C-18								
17	-1.3	+ 3.2	+04	0-0	+09	+1.4	+0-2	1.2
18	+07	+1.1	-07	+09	-05	+07	0-0	0.7
19	-0-2	+0-6	-03	-0-3	+05	-01	-0-3	0-2
20	-09	-0.7	0-0	+01	-0-3	-1.4	-1.8	0-4
21	-1.1	-0.8	-03	-0-2	0-0	-2.0	- 2.5	0.5
22	+04	+0.5	-03	-0-3	+05	+01	-1-0	1.1
23	+0.9	+0.4	0.0	+0.4	-0.4	+1.3	0.0	1.3
24	+1.4	-1.5	0.8	-1.1	+1.2	-1.0	-0·5	0.2
25		+1.9	<b>—0</b> ·5	0.6	+1.6	-2.3	+0.8	3.1
26	+16.7	_7·2	-4·2	-4.7	+ 3.4	+6.6	+3.5	3.1
27	6-2	<b>5</b> .7	<b>—6·1</b>	5·4	+4.9	-17·5	-14.9	2.6
28	+ 5.8	<b>—6</b> ·6		<b>4</b> ·3	+4.9	<u>_5·4</u>	<b>2</b> ·8	2.6
29	-5·3	-1.2	<b>2</b> · <b>3</b>	<b>0</b> ·5	<b>_0</b> ∙5	-8.1	<del>9</del> ·5	1.4
30	0-6	<b>—6</b> ∙0	<u>-3·4</u>	<b>—4</b> ∙0	+3.7	<u>-9</u> .7	<u> </u>	0.2
31	0-2	-2·0	<u>-6·5</u>	-5.2	+6.7	-10·2	<b>-4</b> ·8	5-4
32	-11·0	+ 20 · 1	—5·8	+0.8	+7·2	<b>_4</b> ·7	<b>—3</b> ∙0	1.7

TABLE 9. CHEMICAL SHIPT CONTRIBUTIONS (Hz) FROM EACH TERM OF EQ. (3) TO THE TOTAL CALCULATED SHIPT OF ME RESONANCES, DIPOLE POSITION CA. 0-6 Å FROM C ATOM

\*  $\Delta = /obs.--calc./.$ 

both sources are approximately equal (in one case opposite in sign). For the remainder the contribution from the CO group is dominant since the screening effects from the axial and equatorial bonds involved are approximately equal in magnitude but opposite in sign.

By employing Eq. (1) and the values<sup>2</sup> for the anisotropies of the C—C bond, together with those obtained in the present study for the C—O bond, the screening



FIG. 1 Plot of calculated/observed shift values for the androstane/keto-androstane series

volumes around the C—C and C—O bonds have been derived.\* In Eq. (1),  $1/3R^3$  was set equal to 1, and  $\theta$  and  $\gamma$  were varied in units of 1° from 0° to 90°. Thus 8100 values (i.e. 90 × 90) were calculated for  $\sigma$ . A plot of  $\theta$  against  $\gamma$  reveals the sign of  $\sigma$  (cf Fig. 2) for any given combination of  $\theta$  and  $\gamma$ . The volume inside either curve (Fig. 3) is deshielding whilst the volume outside is shielding.

	IAB	LEIU			
Location of di Distance from C Å	pole $\Delta \chi_1^{C}$	° × 10 <sup>30</sup>	Δχ2 <sup>C=</sup>	<sup>o</sup> × 10 <sup>30</sup>	
1.2	_	39.7	_	27-9	
· 0 <del>.9</del>		35.7		24.7	
0-6		- <b>28</b> ·1		20-5	
	TAB	LE I I			
Location of dipole Distance from C atom Å	$\chi_s^{C=0} \times 10^{30}$	, <sup>معر</sup> يد	< 10 <sup>30</sup>	$\chi_s^{C=0} \times 10^{30}$	
1.2	+20-8	- 18	3-9	- 5.4	
0-9	+ 18-3	-17	1-4	-6.4	
0-6	+10-6	-17	1.5	<b>-9-9</b>	

\* Using the IBM 360 computer at the Lilly Research Laboratories, Indianapolis.

Example Carbonyl			ition			
Example No.	Carbonyl position	Fo	or carbonyl bo Introduced erm I + Term	bad II	For C—H bonds Displaced Term III	Obs. shift Hz
	~ ~	1·2 Å	0-9 Å	0-6 Å		
C-19	-			<u> </u>		
1	1-one	-15.4	-14.7	- 13.5	-07	- 18.0
2	1-one	+ 4.1	+ 3.2	+2.7	+9.8	- <b>8</b> ·8
3	2-one	+ 4.4	+ 4-7	+4.2	-1.1	+ 5-4
4	3-one	-11.7	- 12.6	- 13-5	-2.1	-11·9
5	3-0 <b>ne</b>	-50	5·3	<i>−</i> 5·7	-0-3	- <b>5</b> ·4
6	4-one	+ 4-4	+ 4.7	+ 4.5	-1.1	+ 4.8
7	4-one	<b>5</b> •8	- <b>5</b> ·6	- <b>5</b> ·6	+04	<b>-9</b> -6
8	6-one	+ 4·4	+ 4.7	+4.5	-1.1	+ 5.5
9	7-one	-11.7	- 12-6	- 13-5	<b>-2</b> ·1	- <b>14</b> ·4
10	11-one		Exclude	d from Least	Squares Analysis	
11	12-one	-6.3	-6.1	-60	-0-3	-4-0
12	15-one	+1.1	+1.2	+1.5	+0-6	-0.1
13	15-one	+1.6	+1.5	+1.6	+1-0	+ 2.5
14	16-one	- 2·7	- 2.6	-2.4	-0-2	— 1·8
15	17-one	-2-0	-1·7	-1.5	+0-2	-1.1
16	17-one	-2.0	-2.0	- 1·8	+0-2	-1-0
C-18						
17	1-one	+2.0	+ 2.2	+2.3	+09	+0-2
18	1-one	+1.3	+1.3	+1.1	+0-4	0.0
19	2-one	+01	+0-2	+0-1	+0-2	-0-3
20	3-one	-1.9	- 1.8	- 1.6	-0-2	-1.8
21	3-one	-2.3	-2·4	-2.2	-0-2	- 2.5
22	4-one	+0-2	+0-2	+0-3	+0-2	-1.0
23	4-one	+1.3	+1.3	+1.3	0-0	0-0
24	6-one	-0.6	-0-8	-0-9	+0-1	-05
25	7-one	- 3.6	-2.3	-1.3	+1-0	+0-8
26	11-one	+ 5.6	+ 5.3	+ 5-3	-1.3	+ 3.5
27	12-one	-17.2	-17.7	18-0	-0-5	14.9
28	15-one	- 5.4	<b>-4·8</b>	4.8	+0-6	-2.8
29	15-one	-8.2	-8.7	<b>-9</b> ·1	-1.0	<b>-9</b> •5
30	16-one	-9.5	-9.8	- 10-0	-0-3	-9.5
31	17-one	-9.6	-9-3	-8·7	+1.2	- <b>4·8</b>
32	17-one	+2.1	+2.7	+ 3.3	+8-0	- 3-0
-					. – –	

TABLE 12. CONTRIBUTION FROM EACH BOND (Hz) TO TOTAL CALCULATED CHEMICAL SHIFT

The most obvious point to emerge from this study is that the screening "cone" or environment around a C=C or C=O bond, derived from Eq. (1) (Fig. 3), is considerably different from the one presented by Jackman.<sup>19</sup> The plot of  $\theta$  against  $\gamma$  in Fig. 2, which indicates the shielding and deshielding regions around C=C and C=O bonds, clearly implies that, contrary to Jackman's model, it can no longer be considered a general rule that a proton situated in the plane of a C=C or C=O bond is always deshielded. Indeed, it is quite possible that the reverse may be the case and very recently evidence has been presented<sup>20</sup> in support of our model.







The general validity of our conclusions is illustrated by a selection of examples. Thus, the agreement between the calculated and observed<sup>21, 22</sup> values of the chemical shift differences for the process camphane (I)  $\rightarrow$  camphor (II) is satisfactory.

Similar agreement is obtained for the pair<sup>23</sup> of adamantane derivatives (III and IV) where  $\Delta\sigma$  obs.  $(H_t) = -31.2$  Hz and  $\Delta\sigma H_t$  calc.  $(H_t) = -27.8$  Hz.



Another interesting example is provided by dimethyl formamide (V). From nuclear Overhauser studies Anet<sup>24</sup> has unambiguously demonstrated that the highest field Me signal corresponds to the Me group which is *cis* to the CO group. Thus, the low field Me signal must be assigned to the Me protons *trans* to the amide CO. This is in contrast to the predictions using Jackman's treatment.<sup>19</sup> With our approach (and recognising the potential perils of applying anisotropies derived for the CO in ketones, to CO functions in amides), satisfactory agreement is obtained.



Thus:

Me (cis);  $\Delta \sigma$  calc. = -3.4 Hz Me (trans);  $\Delta \sigma$  calc. = -12.6 Hz

 $\Delta \sigma$  calc. (trans)  $\rightarrow$  (cis) = -9.2 Hz

whilst

...

$$\Delta \sigma$$
 obs. (trans)  $\rightarrow$  (cis) =  $-11.9$  Hz

In the ketone  $(VI)^{25}$  the C-4 and C-6 protons resonate at  $\tau$  7.43 but in the hydrocarbon (VII) this signal has moved *downfield* to  $\tau$  7.16. It has not been possible to calculate the shift differences in this example because of uncertainties introduced into the measurements by the strain in the molecules, but the experimental results are in satisfactory general agreement with our predictions, although it is prudent to emphasise that the ring-strain may be a contributory factor (of unknown significance) to the chemical shift differences.









A much larger group of compounds to which our calculations have been applied is provided by a selection of diterpenoids. Table 13 lists the relevant Me resonance signals—those of compounds VIII to XII inclusive were measured in carbon tetrachloride, deuteriochloroform and benzene. The data for the remainder, XIII to XVIII inclusive were taken from the literature and are recorded in deuteriochloroform. All resonances were referred to carbon tetrachloride as the standard solvent and the literature values were adjusted (cf. Table 19) as required (cf. the similar operation with the androstanes).

Using the values of  $\Delta \chi_1^{C=0}$ ,  $\Delta \chi_2^{C=0}$  and K derived in the earlier part of this paper from the androstane/keto-androstane series the chemical shift differences produced when a CO group is introduced into the systems VIII, X, XIII, XV and XVII were

Compound		CCl <sub>4</sub>	CDCl <sub>3</sub>	Benzene
Tetrahydropimaric acid	(VIII)	47·5, 53·0, 69·7	47.1, 54.0, 71.2	
14-Keto-tetrahydropimaric acid	(IX)	54·2, 59·3, 69·9	57.8, 60.2, 71.5	41-0, 63-7, 73-0
Tetrahydrosandaracopimaric acid	(X)	48.4, 53.7, 70.0	48.2, 54.0, 71.6	45.7, 48.2, 75-0
14-Keto-tetrahydrosandaracopimaric	acid (XI)	59-2, 64-0, 70-1	59-9, 66-0, 71-5	41.3, 52.1, 72.8
7-Keto-tetrahydro-isopimaric acid	(XII)	47.8, 66.0, 72.0	47.8, 67.4, 74.4	40-5, 50-8, 73.1
• •	(XIII)	52.1, 68-5	52.2, 70.2	
	(XIV)	40-0, 69-3	41.1, 71.5	43·3, 65·5
	(XV)		57-0, 66-0	
	(XVI)		49-2, 66-0	
	(XVII)		46-8, 60-6, 71-0	
	(XVIII)		58.8, 66-0, 73-6	

TABLE 13. TABLE OF OBSERVED MC RESONANCE POSITIONS (HZ FROM TMS AT 60 MHz) FOR THE DITERPENE SERIES

calculated. The location of the induced magnetic and electric dipoles along the  $\sigma$  axis of the CO bond was treated as a parameter (i.e. 1.2, 0.9, and 0.6 Å from the C atom). Consequently three shift differences were calculated (as with the keto-androstanes) for each Me group in every compound examined. The relevant data are collected in Tables 14–16 (inclusive). The calculated chemical shift differences were utilised<sup>3</sup> to assign Me resonances (Table 17) and to compare calculated with observed results (Tables 14–16). In accord with established precedent, the lowest field Me signal in each case was allocated to the C-20 Me protons (cf. Table 17).

<b>P</b> 1	N. 4 . 11 . 1	Carbonyl Position	Keto-derivative			Hydrocarbon		Calc.*	Obs.
Example	Group		TERM I		TERM II	TERM III		Shift Hz	Shift Hz
			(1)	(n)		(1) aH	(1) <b>PH</b>		
VIII → IX	C-18	C(14)	- 4.9	-1.1		-0.4	0-0	-5.6	-6.3
VIII → IX	C-17	C(14)	- 31.6	+ 36-6	_	+7-0	+7.0	-9.0	-4.4†
VIII → IX	C-20	C(14)	-2.3	+0-8		+03	+03	-2.1	-0-2
X → XI	C-17	C(14)	- 8.9	- 6.8		- 8.3	+7.9	- 15-3	-13.3†
X → XII	C-18	C(7)	-6.9	- 5-0	—	-1.3	-1-0	-9.6	-10-2
X → XII	C-17	C(7)	-4.8	+ 2.8	—	-0-5	+ 2.4	<u> </u>	+0-6
X → XII	C-20	C(7)	- 4.8	-1.0	—	-0-5	+0-4	- 5.7	-2-0
XIII → XIV	C-18	C(12)	+ 55-1	- 26-2	_	- 9-1	-15.2	+ 53-2	+11-2
XIII → XIV	C-20	C(12)	+2.2	-1·2		-0-8	0-0	+ 1.8	-0-8
XV → XVI	C-18	C(16)	+11.1	- 8.1		+ 5.2	-6.6	+ 4.4	+7.8
XV → XVI	C-20	C(16)	+ 2.3	-2-0		+1.2	-1.1	+0-2	0-0
XVII → XVIII	C-18	C(7)	-6.9	-50	_	-1.3	-1.0	-9.6	-10-4†
XVII → XVIII	C-17	C(7)	<u>-4·4</u>	+ 5-5	—	+1.7	+1.0	-1.6	- 5.4
XVII → XVIII	C-20	<b>C</b> (7)	- <b>4</b> ·8	-10		-05	+04	- 5.7	-2.6

TABLE 14. DITERPENES—CHEMICAL SHIFT CONTRIBUTIONS (Hz) FROM EACH TERM OF BQ. (3) TO TOTAL CAL-CULATED SHIFT OF MC RESONANCE (DIPOLE POSITION CA. 1.2 Å FROM C ATOM)

\* Anisotropies used were  $\Delta \chi_1^{C=0} - 39.8 \times 10^{-30}, \Delta \chi_2^{C=0} - 25.9 \times 10^{-30}$ ; K, 0.0 (Table 6).

† Corrected for solvent shift (see Table 19).

The assignment of the C-17 and C-18 Me protons was more involved. Thus, the two unassigned Me resonances of 14-keto-tetrahydropimaric acid (IX) can be combined with the previously assigned<sup>3</sup> Me resonances of tetrahydropimaric acid (VIII) as follows:

		A	B		
	C-17	C-18	C-17	C-18	
IX	59-3	54.2	54-2	59·3	
VIII	47.5	53-0	<b>47</b> ·5	53-0	
$\Delta \sigma \text{ VIII} \rightarrow 1 \text{X}$	-11.8	-1.2	-67	-6.3	

	Mathul	Carbonyl Position		Keto-derivative			Hydrocarbon		Obs.
Example	Group		TER (i)	XM I (ii)	TERM II	TER (i) aH	M III (ii) βH	Hz	Shift Hz
VIII → IX	C-18	C(14)	- <b>4</b> ·6	-0-6	-0-4	-04	0-0	- 5.2	-6.3
VIII → IX	C-17	C(14)	- 27.7	+ 37.8	-2-4	+7-0	+7.0	-6.3	- <b>4·4</b> †
VIII → IX	C-20	C(14)	-2·2	+1.1	0-0	+03	+03	-1.7	-0.2
$X \rightarrow XI$	C-17	C(14)	- 6.3	-6.6	-2·1	- 8·3	+7·9	- 14.6	- 13·3†
X → XII	C-18	<b>C</b> (7)	- 6.8	<b>5</b> ·1	-0-7	-1.3	-1.0	-10-3	-10-2†
X → XII	C-17	C(7)	- 3.8	+ 3.1	-0-2	-05	+ 2.4	- 2.8	+0-6
$X \rightarrow XII$	C-20	<b>C</b> (7)	-4.5	-0-6	-04	-0-5	+0-4	- 5.4	-2.0
XIII → XIV	C-18	C(12)	+ 54-2	-23·2	- 1·4	<b>9</b> ·1	-15·2	+ 53-9	+11.2
XIII → XIV	C-20	C(12)	+2.1	-1.1	-0-1	-0-8	0-0	+1· <b>9</b>	-0-8
XV → XVI	C-18	C(16)	+17.1	- <b>8</b> ·8	-1.1	+ 5.2	-6.6	+8.6	+ 7.8
XV → XVI	C-20	C(16)	+2.7	-1.7	-0-3	+1.2	-1.1	+0-6	0-0
XVII → XVIII	C-18	C(7)	- 6.8	- 5.1	-0.7	-1.3	-1-0	-10-3	- 10-4†
XVII → XVIII	C-17	C(7)	<b>-4</b> ·1	+ 5.7	-1.1	+ 1.7	+1.0	- 2·2	- 5.4
XVII → XVIII	C-20	C(7)	<b>-4</b> ·5	-0-6	-04	-0-5	+04	- 5.4	- 2-6

TABLE 15. CHEMICAL SHIFT CONTRIBUTIONS (Hz) FROM EACH TERM OF BQ. (3) TO TOTAL CALCULATED SHIFT OF MC RESONANCES (DIPOLE POSITION CA. 0.9 Å FROM C ATOM)

\* Anisotropies used were  $\Delta \chi_1^{C=0} - 33.2 \times 10^{-30}$ ,  $\Delta \chi_2^{C=0} - 21.9 \times 10^{-30}$ ;  $K = -3.8 \times 10^{-30}$ Table 6).

† Corrected for solvent shift (see Table 19).

TABLE 16. CHEMICAL SHIFT CONTRIBUTIONS (Hz) FROM EACH TERM OF EQ. (3) TO TOTAL CALCULATED SHIFT OF MC RESONANCES (DIPOLE POSITION CA. 0-6 Å FROM C ATOM)

	Mathail	Carbonyl Position	K	Keto-derivative			Hydrocarbon		Obs.
Example	Group		TEF (i)	RM 1 (ii)	TERM II	TER (i)αH	M III (ii)βH	Shift Hz	Shift Hz
VIII → IX	C-18	C(14)	-4·3	-0-2	-0-8	-04	0-0	- <b>4</b> ·9	-6.3
VIII → IX	C-17	C(14)	- 24-0	+ 36.3	<b>- 4</b> ·5	+7-0	+7.0	-6.2	<u> </u>
VIII → IX	C-20	C(14)	- 1·9	+ 1.4	-01	+0-3	+03	-1·2	-0.5
$X \rightarrow XI$	C-17	C(14)	-3.4	- 6-1	<b>- 5</b> ·1	- 8.3	+ 7·9	-14·2	- 13·3
$X \rightarrow XII$	C-18	C(7)	-6.4	- 5·1	-1.9	- 1.3	-1-0	-11-1	-10-2
$X \rightarrow XII$	C-17	C(7)	- 2.5	+ 3.2	-04	-0-5	+ 2.4	-1.6	+06
$X \rightarrow XII$	C-20	C(7)	-4·2	-0-2	-0-8	-05	+04	- 5·1	-2.0
XIII → XIV	C-18	C(12)	+ 51-5	- 20-8	-3.6	-9-1	-15·2	+ 51•4	+11.2
XIII → XIV	C-20	C(12)	+ 2.1	-1-0	-02	-0-8	0-0	+ 1.7	-0-8
XV → XVI	C-18	C(16)	+20-6	-9.5	- 3·3	+ 5-2	-6-6	+9.2	+ 7.8
$XV \rightarrow XVI$	C-20	C(16)	+ 3-0	-0-8	- 2·2	-1·2	-1.1	-0-1	0-0
XVII → XVIII	C-18	C(7)	- 6.4	- <b>5</b> ·1	-1.9	-1-3	-1.0	-11.1	- 10-4
XVII → XVIII	C-17	C(7)	- 3·6	+ 5•4	-2-0	+1.7	+1-0	- 2·9	- 5·4
XVII → XVIII	C-20	C(7)	- <b>4</b> ·2	-0-2	-08	-05	+0-4	- 5.1	-2.6

• Anisotropies used were  $\Delta \chi_1^{C=0} - 27.0 \times 10^{-30}$ ,  $\Delta \chi_2^{C=0} - 18.4 \times 10^{-30}$ ;  $K - 6.9 \times 10^{-30}$ (Table 6).

† Corrected for solvent shift (see Table 19).

C 1	C-18			C-17			C-20		
Compound	CCl4	CDCl,	φH	CCl4	CDCl,	φH	CCl <sub>4</sub>	CDCl <sub>3</sub>	φH
VIII	53-0	54-0		47.5	47.1		<del>69</del> ·7	71-2	
IX	59·3	60-2	41-0	54·2	57.8	63·7	69-9	71.5	73·0
XI	5 <del>9-</del> 2	59-9	41-3	64-0	66-0	52.1	70-1	71.5	72·8
XII	66-0	67-4	40-5	47.8	<b>47</b> ·8	50-8	72-0	74-4	73·1
XIV	40-0	41-1	43·3				<del>69</del> ·3	71-5	65·5
xv		57-0						66-0	
XVI		49.2						66-0	
XVII		46.8			60-6			71-0	
XVIII		58.8			66-0			73-6	

TABLE 17. DITERPENES-TABLE OF ASSIGNED MC RESONANCE POSITIONS (HZ FROM TMS AT 60 M HZ)

The calculated shift differences for the dipole positioned at 1.2, 0.9 and 0.6 Å along the CO bond axis are  $\Delta\sigma$  C-17 = -9.0, -6.3, -6.2 Hz and  $\Delta\sigma$  C-18 = -5.6, -5.2, -5.2, -4.9 Hz. These shifts agree better with combination B, which was thus chosen as the correct assignment. Supporting evidence for this choice is presented later (page 140).

Similarly, the two unassigned C-17 and C-18 Me resonances (59.2 and 64.0 Hz) of 14-keto-tetrahydrosandaracopimaric acid (XI) and of 7-keto-tetrahydro-isopimaric acid (66.0 and 47.8 Hz) (XII) can be combined with the previously assigned C-17 and C-18 Me resonances of tetrahydrosandaracopimaric acid<sup>3</sup> (X) in the following ways:

	c	2	I	)
	C-17	C-18	C-17	C-18
XI	<u> </u>	64.0	64.0	59.2
х	48·4	53.7	<b>48</b> • <b>4</b>	53-7
$\Delta \sigma X \rightarrow XI$	-10-8	- 10-3	-15·6	- 5.5
	]	E	F	
	C-17	C-18	C-17	C-18
	66-0	47.8	47.8	66-0
XII	~~~			
	48·4	53.7	<b>48</b> ·4	53·7

The calculated shift differences for the Me protons are  $\Delta\sigma$  C-17 = -15.3, -14.6, -14.2 and  $\Delta\sigma$  C-18 = -5.6, -5.2, -4.9 for X  $\rightarrow$  XI and  $\Delta\sigma$  C-17 = -3.9, -2.8, -1.6 and  $\Delta\sigma$  C-18 = -9.6, -10.3, -11.1 for X  $\rightarrow$  XII. These calculated values clearly indicate that the correct assignments for 14-keto-tetrahydrosandaracopimaric acid (XI) and 7-keto-tetrahydro-isopimaric acid (XII) are combinations D and F, respectively. Further evidence for the validity of combinations B, D and F is provided from a study of the benzene-induced solvent shift of the three keto-diterpenoid acids (IX, XI and XII).

Thus, it has been shown<sup>26</sup> that if a reference plane "P" be drawn through the CO carbon atom at right angles to the plane of the C—O double bond those protons situated close to "P" show very small shifts on going from carbon tetrachloride to benzene as solvent; protons in front of "P", i.e. on the same side of the plane as the CO oxygen are deshielded, while protons behind "P" are shielded.

Thus, if the assignments of Me resonances for IX, XI and XII be correct, models indicate that on going from carbon tetrachloride to benzene the following solvent shifts should be observed:

- (a) The benzene induced solvent shift for the C-18 Me protons of 14-keto-tetrahydropimaric acid (IX) and 14-keto-tetrahydrosandaracopimaric acid (XI) should (within experimental limits) be identical since the C-18 Me group in both compounds is identically situated with respect to the CO bond at C(14).
- (b) The equatorial C-17 Me protons in 14-keto-tetrahydropimaric acid (IX) should experience a deshielding effect: in 14-keto-tetrahydrosandaracopimaric acid (XI) the axial C-17 Me group should experience a shielding effect.
- (c) The solvent shift observed for the C-18 Me protons of 7-keto-tetrahydro-isopimaric acid (XII) should be approximately equivalent to the C-19 Me shift observed for 4,4-dimethyl-5α-androstan-3-one.<sup>26</sup>

Tables 17 and 18 illustrate that the observed benzene induced solvent shifts for IX, XI and XII satisfy these criteria. Thus, in accordance with (a), the observed shifts for the C-18 Me protons in IX and XI are +18.3 and +17.9 Hz respectively; as required by (b), the C-17 Me protons in IX are deshielded (-9.5 Hz) while the C-17 protons in XI are shielded (+11.9 Hz); the C-18 Me protons in XII are shielded by +15.5 Hz which compares favourably with the shift of +22.0 Hz observed for the C-19 Me protons in 2,2-dimethyl-5 $\alpha$ -androstan-3-one, in accordance with (c). A complete assignment of the C-17, C-18 and C-20 Me protons in IX, XI and XII may thus be made (cf Table 17).

Commenced		$\Delta \sigma \operatorname{CCl}_4 - \phi \mathrm{H}$	I
Compound	C-18	C-17	C-20
IX	+ 18.3	-9.5	3·1
XI	+17.9	+11.9	-2.7
XII	+15.5	-30	-2.1
XIII	- 3·3		+3.8

TABLE	18.	TABLE OF	SOLVENT	SHIFTS	FOR	KETO-DITERPENES
			<b>(H</b>	Iz)		

No problem is encountered in assigning the Me resonances in compounds XV and XVI. The lowest field signals are assigned to the C-20 Me protons thus giving a resultant observed shift of 0.0 Hz as compared to a calculated shift difference of  $\Delta\sigma$  C-20 = +0.2, +0.6, -0.1 Hz. The signals at 57.0 Hz in XV and 49.2 Hz in XVI are thus assigned to the C-18 Me protons giving an observed shift difference of +7.8

Hz upon introduction of the CO bond into XV as compared to a calculated value of  $\Delta \sigma C-18 = +4.4, +8.6, +9.2$  Hz.

In compounds XVII and XVIII difficulty is again encountered in distinguishing between the C-18 and C-17 Me resonances. The C-20 Me protons give signals at 71.0 Hz (XVII) and 73.6 Hz (XVIII) which result in an observed shift difference of -2.6 Hz on going from XVII to XVIII; the calculated value of  $\Delta\sigma$  C-20 = 5.7, -5.4, -5.1 Hz. The observed C-17 and C-18 Me resonance positions can be combined in the following ways:

	G		H		Ι		J	
	C-17	C-18	C-17	C-18	C-17	C-18	C-17	C-18
xviii	66-0	58.8	66-0	58·8	58.8	66-0	58.8	66-0
XVII	60-6	<b>46</b> ·8	<del>46</del> ·8	60-6	60-6	46.8	<b>46</b> ·8	60-6
$\Delta \sigma XVII \rightarrow XVIII$	- 5.4	-12-0	- <b>19</b> ·2	- <b>1·8</b>	- 1·8	- 19·2	-12-0	- 5.4

The corresponding calculated shift differences for the C-17 and C-18 Me protons are  $\Delta\sigma$  C-17 = -1.6, -2.2, -2.2 Hz and  $\Delta\sigma$  C-18 = -9.6, -10.3, -11.1 Hz and clearly point to combination G as the correct assignments for XVII and XVIII. Further evidence for these assignments is provided by the close similarity (predicted on geometrical grounds) between the observed shifts of the C-18 Me protons in example XVII  $\rightarrow$  XVIII, -12.0 Hz and example X  $\rightarrow$  XII, -12.3 Hz.

One anomaly is the example XIII  $\rightarrow$  XIV. In this case, the observed C-18 Me shift difference is +11.2 Hz in contrast to a calculated value of  $\Delta\sigma$  C-18 = +53.2, +53.9, +51.4 Hz. The observed C-20 Me shift difference is -0.8 Hz as compared to a calculated value of  $\Delta\sigma$  C-20 = +1.8, +1.9, +1.7 Hz. The discrepancy between the observed and calculated values for the C-18 Me protons is to be attributed, as with the similar cases involving double bonds,<sup>3</sup> to a combination of several factors, including the inapplicability of McConnell's equation at distances less than 3 Å, the non-inclusion of Van der Waals deshielding terms at the short distances involved and to a probable lack of conformational parity between XIV and XIII.

Example	C-18		C-17		C-20	
	CCl	CDCl <sub>3</sub>	CCI.	CDCl <sub>3</sub>	CCI4	CDCl <sub>3</sub>
VIII → IX	-6.3	-6.2	-6.7	-10-7	-0.2	-0-3
$X \rightarrow XI$	<b>- 5</b> ∙5	- 5.9	-15.6	- 17.8	-0-1	+0-1
X → XII	- 12.3	- 13-4	+0-6	+04	-2-0	-2·8
XIII → XIV	+11.2	+11.1			-0-8	-1.3
$XV \rightarrow XVI$		+ 7.8				0-0
XVII → XVIII		-12.0		- 5.6		-2.6

TABLE 19. OBSERVED SHIPT FOR C-18 AND C-19 METHYLS FROM PARENT TERPENOID TO KETO-TERPENOID

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#### APPENDIX I

The derivation of the screening effect of an electric dipole on a distant protons begins from the general expression derived by Buckingham<sup>10</sup>  $E_{(spen)} = ke_x 10^{-12}$  where  $e_x$  is the component in the C--H bond direction of the electric field at the proton concerned caused by a substituent with unit dipole moment, and k, is a proportionality constant; to avoid confusion with the z axis of Fig. 4,  $e_x$  is written  $E_{CH}$  subsequently.

In the case of the keto-androstanes we have utilised the Me group resonances and have made the reasonable assumption that the energy barriers to rotation are such that the conformations of the Me groups are not clearly defined. Requirements of mathematical simplicity have led us to redefine the electric field effect on such a distant group as that component of the electric field at the centre of the circle of rotation of the H atoms, resolved parallel to one of the C—H bonds and averaged over all angles of rotation.





In Fig. 4, AE is an electrical dipole, m, not necessarily in the plane of the paper. The line CB, perpendicular to the plane of "rotation" of the methyl H atoms and passing through the Me group C atom at C, is taken as the y-axis of a system of Cartesian co-ordinates. The point at which a line drawn from the centre of the dipole at A cuts CB at right angles is taken as the origin, O. OA is then the x-axis and the z-axis is perpendicular to both OA and OC. D is any position of a methyl H atom.

Angle 
$$HBD = 0$$

Angle  $HCB = \omega$  the angle between a C-H bond and the line of OC produced (70° 32')

Angle  $OCA = \beta$ 

Angle  $CAE = \psi$  the angle between the electric dipole and  $AC(\mathbf{R})$ 

Angle  $EAF = \phi$  the angle between the dipole direction and the Y axis

Neither  $\phi$  nor  $\psi$  are necessarily in the plane of the paper.

As a first approximation, the field at C is found and is resolved along CD; the result is then averaged over all values of  $\alpha$ , to give a mean value of  $E_z$ 

The field E at C due to the dipole is given by the standard equation.

$$E = \hat{\mathbf{R}} \frac{2m}{R^3} \cos \psi + \hat{\psi} \frac{m}{R^3} \sin \psi \tag{6}$$

where *m* is the dipole moment and **R** is the unit vector in the direction  $AC; \psi$  is the unit vector perpendicular to **R** in the direction of increasing  $\psi$  and in the same plane as **R** and **m** (the dipole); it is therefore not necessarily in the plane of the paper.

The field given by (6) is resolved along CD to give  $E_{CH}$ 

$$E_{\rm CH} = \frac{2m}{R^3} \cos \psi$$
. cos (angle between R and CD)

+ 
$$\frac{m}{R^3}\sin\psi$$
. cos (angle between  $\psi$  and CD)

The direction cosines are: **R**;  $-\sin\beta$ ,  $\cos\beta$ , 0;

CD,  $\sin \omega \cos \alpha$ ,  $\cos \omega$ ,  $\sin \omega \sin \alpha$ ; let those of *m* be *L*, *M*, *N* and those of  $\psi$  be *P*, *Q*, *S*. then,  $\cos (\text{angle between } R \text{ and } CD) = -\sin \beta \sin \omega \cos \alpha + \cos \beta \cdot \cos \omega$ 

cos (angle between  $\hat{\psi}$  and CD) =  $P \sin \omega \cdot \cos \alpha + Q \cos \omega + S \sin \omega \sin \alpha$ . When these values are substituted into  $E_{CH}$  and the resulting expression is averaged over all values of  $\alpha$  from 0 to  $2\pi$ , all the terms containing trigonometric functions of  $\alpha$  vanish leaving

$$\overline{E}_{CH} = \frac{2m}{R^3} \cos \psi \cdot \cos \beta \cdot \cos \omega + \frac{m}{R^3} Q \cos \omega \cdot \sin \psi = \frac{m \cos \omega}{R^3} [2 \cos \psi \cdot \cos \beta + Q \sin \psi]$$
(7)

To evaluate Q in terms of the dipole direction, the following equations are used:

Since 
$$\hat{\psi}$$
 is perpendicular to  $R$ ,  $-P \sin \beta + Q \cos \beta = 0$  (8)

Since  $\hat{\Psi}$  is coplanar with R and m,

$$\frac{N}{L\cos\beta + M\sin\beta} = \frac{S}{P\cos\beta + Q\sin\beta}$$
(9)

Since the angle between m and R is  $\psi$ 

$$\cos\psi = -L\,\sin\beta + M\cos\beta \tag{10}$$

Also by the properties of direction cosines

$$N^2 = 1 - L^2 - M^2; \quad S^2 = 1 - P^2 - Q^2$$
 (11)

Squaring Eq. (9), eliminating N and S by (11), P by (8) and L by (10) gives

$$Q^2 = \frac{(M - \cos \psi \cdot \cos \beta)^2}{\sin^2 \psi}$$

whence

$$Q = \pm \left(\frac{M - \cos\psi \cdot \cos\beta}{\sin\psi}\right) \tag{12}$$

Substituting into (7)

$$E_{\rm CH} = \frac{m\cos\omega}{R^3} \left[ 2\cos\psi \cdot \cos\beta \pm (M - \cos\psi \cdot \cos\beta) \right]$$

Because  $M = \cos \phi$ 

$$\therefore \overline{E}_{CH} = \frac{m\cos\psi}{R^3} \left[ 2\cos\psi \cdot \cos\beta \pm (\cos\phi - \cos\psi \cdot \cos\beta) \right]$$
(13)

The sign ambiguity can be resolved (in favour of the negative option) by considering the case in which  $\phi = 0$ ; then  $\psi = \beta$ : for this condition it is well known that the field component parallel to the dipole is  $m/R^3$  ( $3\cos^2\beta - 1$ ).

With the negative option in Eq. (13)

$$E_{\rm CH} = m [\cos \omega (3 \cos \beta . \cos \psi - \cos \phi)] R^{-3}$$
<sup>(2)</sup>

#### **APPENDIX II**

Zürcher<sup>9</sup> has suggested that a more appropriate model for a steroid may be that in which the Mc groups are "staggered" in relatively fixed conformations, rather than more freely rotating. Since our derivation had used the concept of more freely rotating Mc groups it appeared desirable to examine the implications of the Zürcher model upon our conclusions. This examination indicated that our approximate formula for assessing the contribution of the electrical dipole of a CO group to the shielding of Me protons, is not altogether satisfactory in one relative conformation of the CO and Me groups. A more exact equation is derived by assessing the electrical potentials due to the dipole at the carbon atom  $(\psi_c)$  of the Me group and at a Me hydrogen  $(\psi_H)$ . The electrical field which affects the shielding is then

$$E_{\rm CH} = \frac{\psi_{\rm H} - \psi_{\rm C}}{l}$$

where *l* is the bond length.

When this expression is averaged over three positions of the Me protons it leads to an intractable integral which can be solved by measurements on a molecular model followed by integration by computation.

However, a more direct and in many ways more rapid method is to use the molecular model to assess the electrical field in the direction of the C—H bond for each Me proton, repeating the measurements for at least two conformations of the Me group unless there is some reason for a preferred conformation. For each proton, the following quantities are required:

(a) The length and polar co-ordinate angles for the line joining the centre of the dipole to the proton; from these measurements the direction cosines for the unit vectors  $\hat{\mathbf{R}}$  and  $\hat{\theta}$  in the electrical dipole field equation.

$$\mathbf{E} = M \left[ \frac{\hat{\mathbf{R}} 2 \cos \theta}{R^3} + \frac{\hat{\theta} \sin \theta}{R^3} \right] \text{ are calculated}$$

(b) The polar co-ordinate angles for the C—H bond, from which the direction cosines of this bond are calculated. From these values the cosines of the angles,  $\gamma_1$ , between the C—H bond and  $\hat{\mathbf{k}}$ , and  $\gamma_2$ , between the C—H bond and  $\hat{\theta}$  are estimated.

The final result for the electrical field in the direction of the C-H bond is thus:

$$E_{\rm CH} = \frac{m}{R^3} [2\cos\theta\cos\gamma_1 + \sin\theta\cos\gamma_2]$$

The calculation of the geometrical factor for each protons has been made for Me groups in various situations proximate to the CO group using this formula (cf. Table 20).

	Geometric factor ( $\dot{A}^{-3} \times 10^3$ )							
	<u>H</u> 1	<u>H</u> 2	<u>H</u> 3	Average	Value derived from formula (3)			
—CO . CH(C <u>H</u> 3) ax	1.194	1.881	1.308	1.46	1.38			
$-CO \cdot CH(CH_3) eq$	0.206	3.373	2.516	2.03	1.50			
-CO. CH <sub>2</sub> CH(C <u>H</u> <sub>3</sub> ) ax	0-144	1· <b>248</b>	1.108	0-83	0-80			

TABLE 20

The angles were assessed from measurements of the polar co-ordinate angles for the directions concerned using a molecular goniometer devised by Dr. J. N. T. Gilbert of The School of Pharmacy. The results were computed by a three card programme for the Olivetti 101 Calculator. The Me protons were placed in staggered conformations relative to adjacent atoms and bonds. A complete determination for a Me group together with the computation takes about 1 hr.

The results averaged over three protons were compared with those calculated by the more approximate formula<sup>4</sup> for pertinent situations and are summarized in Table 20.

Except in the case of an equatorial Me group attached to a C atom adjacent to a CO function, the agreement is within the limits of expected error. Since the series of examples (the keto-androstanes) used in our derivation of the CO anisotropies does not contain Me groups in equatorial situations with respect to the CO functions, it is clear that the two methods of approach lead (within the limits of experimental error) to the same values for the CO anisotropies.

#### **EXPERIMENTAL**

The NMR spectra were measured in CCl<sub>4</sub>, in CDCl<sub>3</sub>, in benzene (as required) and in cyclohexane, where solubility permitted, in 10% w/v concentration and at room temp (20°). Measurements for each compound were made at 100 Hz sweep width on a Varian A-60 Spectrometer and the values recorded in the relevant Tables represent the mean of four determinations. The spectrometer was calibrated using benzene (436 Hz) and TMS. The chemical shifts are reported in Hz relative to TMS as internal standard and the accuracy is estimated to be within  $\pm 1$  Hz.

The samples of androstane and of 1-, 2-, 3-, 4-, 6-, 7-, 11-, 12-, 15-, 16- and 17-keto-androstane were prepared by established methods. The physical constants (m.p. and  $[\alpha]_D$ ) agreed with the recorded values. In each case the low field NMR profile and the IR spectrum were in agreement with the accepted structures.

The preparation of the diterpenes has been described.<sup>27</sup>

The mathematical calculations used to process the experimental data were carried out on the Atlas computer of the University of London using CHLF<sub>3</sub> autocode language.

Measurements of the necessary parameters (angles and distances) for the calculations were made using Dreiding Stereomodels with the aid of special devices<sup>28</sup> which facilitated the measurements and increased their accuracy. Each value for any given angle or distance used in the calculations is the average of six different measurements; two being made on each of three different molecular models. Reproducibilities for distances were  $\pm 0.1$  Å and for angles were  $\pm 2^{\circ}$ .

The following new compounds were prepared during the synthesis of the keto-androstanes.

17β-Acetoxy-5α-androstan-3α-ol and -3β-ol. A soln of 17β-acetoxy-5α-androstan-3-one (1·2 g) in AcOH (40 ml) containing 64% perchloric acid (1 drop) and PtO<sub>2</sub> (0·2 g) was shaken in an atm of H<sub>2</sub> for 0·25 hr after which time absorption of H<sub>2</sub> (74 ml, 1 mole) had ceased. After isolation a soln of the crude product in benzene was adsorbed upon silica gel (50·0 g). Elution with benzene/EtOAc (15:1) afforded (a) 17β-acetoxy-5α-androstan-3α-ol (0·4 g) which formed needles from acetone, m.p. 186–187°, (Found: C, 75·2; H, 10·4. C<sub>21</sub>H<sub>34</sub>O<sub>3</sub> requires: C, 75·5; H, 10·2%);  $[\alpha]_D^{20^\circ} = +8^\circ$ , IR:  $v_{max} = 1730$  (acetate) and 3465 (alcohol) cm<sup>-1</sup> and (b) a mixture of 17β-acetoxy-5α-androstan-3α-ol and -3β-ol in which the 3β epimer predominated. The sample had m.p. 145–151°,  $[\alpha]_D = +4^\circ$  and was used without further purification for NMR measurements.

Hydrazone of androstan-17-one. A soln of androstan-17-one (5.9 g) in EtOH (70 ml) containing Et<sub>3</sub>N (12 ml) and 95% hydrazine hydrate (20 ml) was refluxed for 1.5 hr. Purification of the product from MeOH gave androstan-17-one hydrazone (5.5 g), in plates, m.p. 108–109°, (Found: N = 11.1;  $C_{19}H_{32}N_2$  requires: N, 11.1%,  $[\alpha]_D^{-1} = +26^\circ$ , IR:  $v_{max} = 1635$  (C=N), 3400 (NH<sub>2</sub>) cm<sup>-1</sup>.

17-lodoandrost-16-ene. This hydrazone (50 g) was dissolved in THF (100 ml) containing Et<sub>3</sub>N (20 ml) and treated in an atm of N<sub>2</sub> while vigorously stirring, with I<sub>2</sub> (20 g) dissolved in THF (50 ml). After the addition of I<sub>2</sub> was completed (approx 5 min) the mixture was stirred until evolution of the N<sub>2</sub> had ceased (5-10 min). Purification of the product from MeOH gave (17-iodoandros-16-ene (40 g) in plates, m.p. 111-113°, (Found: C, 59·3; H, 7·5; I, 33·4. C<sub>19</sub>H<sub>29</sub>I requires: C, 59·4; H, 7·6; I, 33·0%); [ $\alpha$ ]<sub>D</sub> = 21·8°, IR:  $\nu_{max} = 1580 \text{ cm}^{-1}$  (5-membered ring double bond), NMR: 48 Hz, 3H, s. (C-19); 43 Hz, 3H, s. (C-18); 365 Hz, 1H, t. (olefinic C(16) proton).

Androstan-17-one ethylene thioketal. To a soln of androstan-17-one (0-12 g), dissolved in ethane dithiol (0-2 ml) was added BF<sub>3</sub>-etherate (2 drops) while agitating the mixture with a glass rod. The mixture rapidly solidified to a white solid which was washed with cold MeOH and collected. Crystallization from n-hexane/acetone (3:1) gave androstan-17-one ethylene thioketal, (0-15 g) in colourless plates, m.p. 160–162°. (Found : C, 71-9; H, 9-6. C<sub>21</sub>H<sub>34</sub>S<sub>2</sub> requires : C, 71-9; H, 9-8%); [ $\alpha$ ]<sub>D</sub><sup>2</sup> =  $-34.5^{\circ}$ , IR : no CO absorption, NMR : 47 Hz, 3H, s. (C-19); 52 Hz, 3H, s. (C-18); 188 Hz, 4H, s. (4 protons  $\alpha$  to the S atoms in thioketal ring).

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#### REFERENCES

- 1 J. W. ApSimon, W. G. Craig, P. V. Demarco, D. W. Mathieson, L. Saunders and W. B. Whalley, Tetrahedron 23, 2339 (1967).
- <sup>2</sup> J. W. ApSimon, W. G. Craig, P. V. Demarco, D. W. Mathieson, L. Saunders and W. B. Whalley, *Ibid*, 23, 2357 (1967).
- <sup>3</sup> J. W. ApSimon, W. G. Craig, P. V. Demarco, D. W. Mathieson and W. B. Whalley, Ibid., 23, 2375 (1967).
- <sup>4</sup> J. W. ApSimon, W. G. Craig, P. V. Demarco, D. W. Mathieson, A. K. G. Nasser, L. Saunders and W. B. Whalley, *Chem. Comm.*, 754 (1966).
- <sup>5</sup> P. T. Narasimhan and M. T. Rogers, J. Chem. Phys. 63, 1388 (1958).
- <sup>6</sup> D. L. Hooper and R. Kaiser, Canad. J. Chem. 43, 2363 (1965).
- <sup>7</sup> H. M. McConnell, J. Chem. Phys. 27, 226 (1957).
- <sup>8</sup> J. R. Didry, F. Cabaret and J. Guy, J. Phys. Radium 23, 65 (1962).
- <sup>9</sup> R. F. Zürcher, Progress in N.M.R. Spectroscopy (Edited by J. W. Emsley, J. Feeney and L. H. Sutcliffe) Vol. II, p. 205. Pergamon Press, Oxford (1967).
- <sup>10</sup> A. D. Buckingham, Canad. J. Chem. 38, 300 (1960).
- <sup>11</sup> R. J. Abraham, Mol. Phys. 369 (1961).
- <sup>12</sup> J. E. Anderson, Tetrahedron Letters 4713 (1965); P. Laszlo, Bull. Soc. Chim. Fr, 85, 2658 (1964).
- <sup>13</sup> J. J. Schneider, P. Crabbe and N. S. Bhacca, J. Org. Chem. 33, 3118 (1968).
- <sup>14</sup> K. M. Wellman, E. Bunnenburg and C. Djerassi, J. Am. Chem. Soc. 85, 1870 (1963).
- <sup>15</sup> J. M. Lehn, J. Levisalles and G. Ourisson, Bull. Soc. Chim. Fr. 1096 (1963); A. L. McClellan Tables of Experimental Dipole Moments. San Francisco (1963).
- <sup>16</sup> A. Pacault, J. Horeau and A. Manchand, Advances in Chemical Physics Vol. III, p. 171. Interscience, New York (1961).
- <sup>17</sup> J. A. Pople, Proc. Roy. Soc. A239, 541 550 (1957).
- <sup>18</sup> K. Lonsdale, Ibid. A177, 272 (1944).
- <sup>19</sup> L. M. Jackman, Applications of Nuclear Magnetic Resonance in Organic Chemistry p. 129. Pergamon Press, Oxford (1962).
- <sup>20</sup> G. J. Karabatos, G. C. Sonnichsen, N. Hsi and D. J. Fenoglio, J. Am. Chem. Soc. 89, 5067 (1967).
- <sup>21</sup> J. D. Connolly and R. McCrindle, Chem. & Ind. 379 (1963).
- <sup>22</sup> K. Tori, Y. Hamashima and A. Takamizaura, Chem. Pharm. Bull. 12, 924 (1964).
- <sup>23</sup> Unpublished work from the Lilly Laboratories.
- <sup>24</sup> F. A. L. Anet and A. J. R. Bourn, J. Am. Chem. Soc. 87, 5250 (1965).
- <sup>25</sup> R. J. Stedman and L. D. Davis, Tetrahedron Letters 1871 (1968).
- <sup>26</sup> N. S. Bhacca and D. H. Williams, Applications of NMR Spectroscopy in Organic Chemistry Chapter 7. Holden Day, San Francisco (1964).
- <sup>27</sup> J. W. ApSimon, P. V. Demarco and J. Lenke, Canad. J. Chem. 43, 2793 (1965).
- <sup>28</sup> J. W. ApSimon, P. V. Demarco and A. Raffler, Chem. & Ind. 1792 (1966).