Fungal Metabolites. Part IV.[1] Solvent and Transition Metal Effects on Proton Chemical Shifts in Multifunctional Molecules

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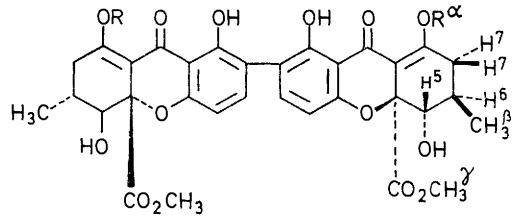
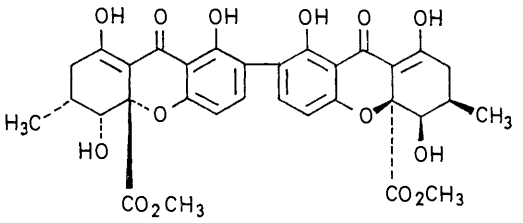
During attempts to define the stereochemistry of secalonic acids isolated from fungi, we made use of a europium shift reagent and were able to define the major complexing sites in these multifunctional compounds. However, we also observed changes in the chemical shifts of protons near hydroxy-groups in the secalonic acids simply on change of solvent. From an examination of the ^1H n.m.r. spectra of sterols, terpenols, other alcohols, and phenols, we have been able to propose a relationship between the amount by which the chemical shift of a proton moves on change of solvent and the distance of the proton from a hydroxy-group. The relationship can be used to determine the torsional angle between a methyl and a hydroxy-group situated in a 1,2-relationship. In multifunctional compounds, these solvent-induced changes can be influenced by other groups close to the proton considered.

THE use of transition metal shift reagents in n.m.r. spectroscopy is well established [2] and proves particularly useful when the site of complex formation between the metal and the compound under investigation is readily locatable. When the transition metal binds to more than one site in a molecule, the effects on proton chemical shifts are more difficult to interpret but a method for dealing with such cases has been proposed and used.[3] The secalonic acids isolated from *Phoma* species [1] contain methoxycarbonyl, carbonyl, and aliphatic and aromatic hydroxy-groups and offer a number of binding sites for the transition metal. The configuration at C-10a(10a') in the secalonic acids (I) is not easy to obtain because there is no proton at this position and inversion is easy under mildly basic conditions.[4] It was hoped that the transition metal shift reagent would bind to the secalonic acids in such a way that the orientation of the methoxycarbonyl group at C-10a(10a') could be inferred from shifts in the methyl proton resonance signals. In the event, this was possible indirectly but, during the experiments, other effects due to change of solvent were observed and investigated further.

The transition metal shift reagents are commonly used in deuteriochloroform as solvent, but the ^1H n.m.r. spectra of secalonic acids A (I) and E (II) were obtained in pyridine or hexadeuteriodimethyl sulphoxide in which they are more soluble. In comparing data from the n.m.r. spectra, it was observed that the chemical shift of the methyl group at C-6(6') in (I) changed markedly on changing solvent in the triad, pyridine, dimethyl sulphoxide, chloroform. Compared with the spectra in $CDCl_3$, the chemical shift of the methyl group moved downfield in pyridine and upfield in $(CD_3)_2SO$. Specific solvent induced changes in chemical shifts are known. The effect of changing solvent from $CDCl_3$ to benzene on the chemical shift of a methyl group adjacent to carbonyl has been investigated extensively [5] and two or three isolated instances have been reported [6] on the change in chemical shift of a methyl group near hydroxy when the solvent was changed from $CDCl_3$ to pyridine. Subsequent to a communication of ours [7] on these solvent-induced shifts of protons near hydroxy-groups, it was pointed out to us that we had overlooked two important earlier contributions in this field. The first of these concerns changes in chemical shifts of protons in methyl hydroxyhexadecanoates on changing solvent from carbon tetrachloride to pyridine.[8] These shift changes were used to identify the position of the hydroxy-group in the aliphatic chain of the hydroxyhexadecanoates. The second contribution reported the changes in chemical



(I)



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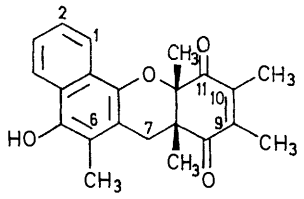

(III)

[1] Part III, C. C. Howard and R. A. W. Johnstone, *J.C.S. Perkin I*, 1973, 2440.
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[3] C. C. Hinkley, M. Klotz, and F. Patil, *J. Amer. Chem. Soc.*, 1971, **93**, 2417.
[4] J. W. ApSimon, J. A. Corran, N. G. Creasy, W. Marlow, W. B. Whalley, and K. Y. Sim, *J. Chem. Soc.*, 1965, 4144.
[5] N. S. Bhaca and D. H. Williams, 'Applications of N.M.R. Spectroscopy in Organic Chemistry,' Holden-Day, San Francisco, 1964, p. 165.
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[7] B. P. Hatton, C. C. Howard, and R. A. W. Johnstone, *J.C.S. Chem. Comm.*, 1973, 744.
[8] A. P. Tulloch, *J. Amer. Oil. Chem. Soc.*, 1966, **43**, 670.

shifts for protons in a wide variety of alcohols on changing solvent from deuteriochloroform to pyridine. Some of the alcohols discussed in the second contribution [9] are the same as some reported in this present one, but many are different and provide valuable additional data for the formula (III) relating the change in proton chemical shift on change of solvent with the distance of the proton from the hydroxy-group. We fully recognise the prior claims to novelty of the two earlier papers [8,9] with regard to changes in shift between chlorinated solvents and pyridine; the present contribution consolidates that work, extends it to other solvent systems, and provides a general relationship between the change in proton shift with change of solvent and the spatial arrangement of protons and hydroxy-groups. Because hydroxy and methyl groups frequently occur in close proximity in natural products, particularly those derived from fungi, and their relative orientations are important, we investigated the possibility that a simple relationship existed between the magnitude of the solvent-induced change in chemical shift of a methyl group and its orientation with respect to a neighbouring hydroxy-group.

TABLE 1

Shifts (δ) of methyl signals in pyridine, $CDCl_3$, and $(CD_3)_2SO$

Compound	Torsional angle (θ°)	Pyridine	$CDCl_3$	$(CD_3)_2SO$
o-Cresol	0	2·42	2·24	2·08
m-Cresol	0	2·33	2·29	2·22
p-Cresol	0	2·21	2·26	2·16
n-Hexanol	Free rotation	0·83	0·87	0·84
n-Propanol	Free rotation	1·63	1·55	1·38
endo-Camphenilol	0 (*endo*-CH_3)	1·07	0·86	0·77
	120 (*exo*-CH_3)	0·97	0·90	0·92
D-Borneol	90 (β-CH_3)	0·97	0·86	0·77
D-Fenchyl alcohol	0 (*endo*-CH_3)	1·05	0·83	0·72
	120 (*exo*-CH_3)	0·99	0·94	0·89
	90 (bridgehead-CH_3)	1·20	1·07	0·97
4-Terpineol	Free rotation	1·00	0·92	0·82
Loganin	90	1·00		0·82
4,4-Dimethylandrost-5-en-17β-ol	40	0·95	0·74	0·64
4,4-Dimethyl-13-epiandrost-8-en-17α-ol	15 (C-18)	1·11	0·96	0·82
4,4-Dimethyl-13-epiandrost-5-en-17β-ol	140	0·92	0·87	0·79
4,4-Dimethyl-13-epiandrost-5-en-17α-ol	30	1·11	0·86	0·76
17β-Hydroxy-4,4-dimethylandrost-5-en-13-one	40 (C-18)	0·87	0·78	0·66
4,4-Dimethylcholesterol	60 (C-4)	1·41	1·08	
	60 (C-4)	1·46	1·14	
4,4-Dimethyl-5,6α-epoxycholestan-3β-ol	60 (C-4)	1·33	1·06	
	60 (C-4)	1·15	0·82	
3β-Hydroxy-4,4-dimethylcholestan-6-one	60 (C-4)	1·62	1·21	1·02
	60 (C-4)	1·42	1·07	0·93
Cholestan-5α-ol	180 (C-19)	0·92	0·90	
Cholestan-5α-6β-diol	180 (C-19)	1·50	1·15	1·00
Compound (III)	0 (C-CH_3)	2·42	2·20	2·15
	0 (7a-CH_3)	1·35	1·31	1·22
	0 (11a-CH_3)	1·60	1·53	1·46
	0 (9,10-CH_3)	1·93	2·00 2·04	1·95

RESULTS AND DISCUSSION

(a) *Solvent-induced Changes.*—The n.m.r. spectrum of secalonic acid E in pyridine shows a signal for the 6-Me group centred at δ 1·06; in $(CD_3)_2SO$, this signal occurs at δ 1·02, and 8,8-di-*O*-methylsecalonic acid E gives the signal at δ 1·23. Thus, when the solvent is changed from $(CD_3)_2SO$ to $CDCl_3$ to pyridine, there is a strong downfield shift in the position of the methyl resonance. A similar shift is shown by the proton on C-5 but the other protons in acid (II) show only small changes in their resonance positions on change of solvent. Because this solvent-induced shift seemed to be a localised phenomenon, we supposed that it was induced by interaction of the 5-OH group with the solvent. The torsional angle (θ) between the C–Me and C–OH bonds of the 6-Me and 5-OH is *ca.* 80° in secalonic acid E.[1] In secalonic acid A (I), this torsional angle is *ca.* 165° and the shift in the position of the 6-Me resonance on changing solvents from $CDCl_3$ to pyridine is less than for acid E (II) whereas the shift in the position of the 5-H resonance is about the same as for acid (II). These observations suggested that the proximity of the 6-Me and 5-OH groups is critical in determining the magnitudes of the solvent-induced shifts. A search of the literature revealed references to similar solvent shifts which were used to help determine the *cis*- or *trans*-arrangement of 17-OH and 13-Me groups in some steroids.[6] At that time we were unaware that solvent effects between deuteriochloroform and pyridine had been reported [9] for a wide variety of alcohols. Accordingly, we examined the effects of solvent changes on the chemical shifts of protons in some 20 compounds (Table 1) for which geometries are known approximately and therefore Dreiding models can be used to measure approximate distances and torsional angles. Several of the compounds in Table 1 have more than one methyl group in the molecule and therefore yield more data. Mostly, only compounds with simple hydroxy-groups were examined to eliminate possible added effects of other functional groups.

[9] P. V. Demarco, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, *J. Amer. Chem. Soc.*, 1968, **90**, 5480.

If $\Delta\nu_1$ is the change in chemical shift of a methyl group β to hydroxy on changing solvent from $CDCl_3$ to pyridine, then $\Delta\nu_1$ can be related to the torsional angle (θ, Figure 1)

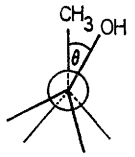

FIGURE 1 Torsional angle (θ) between OH and Me groups

by expression (1). Similarly, the corresponding change ($\Delta\nu_2$) on changing solvent from $(CD_3)_2SO$ to $CDCl_3$ is given by equation (2).[7]

$$100\Delta\nu_1 = 11 + 10\cos\theta\ (\pm 2) \qquad (1)$$

$$100\Delta\nu_2 = 17 + 15{\cdot}6\cos\theta\ (\pm 3) \qquad (2)$$

The nature of the solvent effects can be explained in terms of hydrogen-bonded complexes between solvent and solute. Hydrogen bonding from a hydroxy-group to pyridine is effected through the lone-pair electrons on nitrogen in the plane of the pyridine ring (Figure 2), *i.e.*

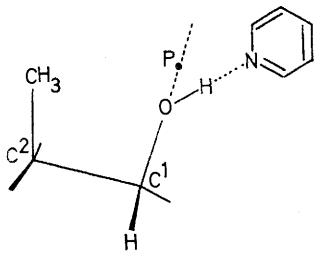

FIGURE 2 Orientation through hydrogen bonding of pyridine to OH group

the O, H, and N atoms lie along a straight line. In the absence of strong steric or electronic effects from the remainder of the molecule, either the OH–pyridine complex can be regarded as freely rotating or more probably, as the hydroxy-group rotates, pyridine molecules are orientated as in Figure 2.[9] In either case, the net solvent effect is anisotropic in the region of the OH group and a ' centre of anisotropy ' can be imagined to exist along the line of the C^1–O bond (Figure 2 and see later). The methyl group at C^2 can then lie in the deshielding region of the pyridine ring and suffer a downfield shift in its resonance signal compared to the $CDCl_3$ in which hydrogen bonding is less important. In $(CD_3)_2SO$ hydrogen bonding to the oxygen of the sulphoxide group will be at right angles to the S=O bond (lone-pair electrons on oxygen) and the methyl at C^2 will lie in the shielding region of the π-system.

It is possible that the observed effects could be explained in terms of a dipolar field set up by the solute–solvent complex and not in terms of simple shielding or deshielding by the π-systems in the solvents. This possibility was investigated by measuring n.m.r. spectra of alcohols in triethylamine in which strong hydrogen bonding between hydroxy and solvent should occur. Little or no change in the chemical shift for methyl was observed on changing solvent from $CDCl_3$ to triethylamine and this appears to eliminate the intermediacy of a simple dipole effect. On the other hand, with a more extended π-system in the solvent, as with quinoline, the change in chemical shift of methyl from its value in $CDCl_3$ was much greater than with pyridine. For example, in quinoline as solvent, the chemical shift of the bridgehead methyl in D-borneol was at δ 1·10 compared with δ 0·86 in $CDCl_3$.

In quinoline, the n.m.r. spectrum of *endo*-camphenilol was drawn out in the same manner as when a transition metal shift reagent is used, but less extensively. Unlike the transition metal shift reagents, little or no line broadening was observed and quinoline may be useful as a solvent for expanding portions of n.m.r. spectra.

It appears therefore that hydrogen bonding between solute and solvent leads to localised anisotropy and, as suggested above, a ' centre of anisotropy ' (P in Figure 2) may be defined. As shown in the Appendix, this point P can be calculated to lie *ca.* 0·7 Å from the oxygen atom along the line of the C^1–O bond. If the distance, p, from P to any proton in the molecule is measured, the change in the chemical shift of the proton on changing solvent from $CDCl_3$ to pyridine is given sufficiently accurately for the compounds studied here by equation (3). The distance p can be obtained from Dreiding models.

$$\log_{10}(100\Delta\nu_1) = 2{\cdot}84 - 0{\cdot}54p \qquad (3)$$

In 5α,6β-dihydroxycholestane, the chemical shift of the 10-Me group moves by 0·35 p.p.m. on changing solvent from $CDCl_3$ to pyridine. From Dreiding models, the distances of the two hydroxy-groups are 2·55 Å for 6β and 4·3 Å for 5α. Inserting these distances into equation (3) gives a predicted movement of 0·35 p.p.m. In 5α-hydroxycholestane, the predicted shift is 0·03 compared with 0·02 p.p.m. found. In 3β,5β,6α-trihydroxycholestane the predicted shift of 0·35 p.p.m. is observed.

For a proton on the C^1 atom (Figure 2), the predicted shift is 0·22 p.p.m. compared with an average of 0·20 p.p.m. for the compounds in Table 1 (see also ref. 6). For a proton on C^2, the change ($\Delta\nu_1$) observed is 0·11 p.p.m.; if this value is assumed to be the mean resulting from free rotation about the C^1–C^2 bond, then the value of $\Delta\nu_1$ predicted is 0·10 p.p.m. Similarly, from earlier reported data[9] the observed and predicted solvent-induced changes of chemical shifts of protons in a 1,3-diaxial relationship with a hydroxy-group are close.

Equation (3) appears to predict satisfactorily (to within *ca.* ±0·02 p.p.m.), the change of the chemical shift of a proton situated a distance p (Å) from the ' centre of anisotropy,' P, caused by a hydroxy-group on changing solvent from $CDCl_3$ to pyridine.

Many fungal metabolites contain aromatic rings substituted with phenolic and methyl groups and it is therefore of interest to find that where a methyl group is *ortho* to a phenolic hydroxy, a solvent-induced change in its chemical shift is observed. The magnitude of the change is about the same as for an aliphatic compound having a zero torsional angle between methyl and hydroxy. *meta*- and *para*-Methyl-substituted phenols show only

small solvent shifts common to all the other protons in these molecules. Thus, the solvent shift may prove useful for determining substitution patterns in phenols.[9]

Equations (1) and (2) gave erroneous results with 3β-hydroxy-4,4-dimethylcholestan-6-one. Although changes in the chemical shifts of the 4,4-dimethyl groups were large, as expected on changing solvent from $CDCl_3$ to pyridine, the actual changes did not fit equation (1). The effects of changing solvent from $CDCl_3$ to benzene on chemical shifts of methyl groups close to ketone functions have been reported,[5] and it seemed likely in this case that the 6-oxo-group was disturbing the predicted effect of the hydroxy. In 17β-hydroxy-4,4-dimethylandrost-5-en-3-one, the solvent shift, $\Delta\nu_1$, of the 3-Me group, which is well separated spatially from the 3-oxo-group, was correctly predicted by equation (1). However, of the two 4,4-dimethyl groups, the chemical shift of one changed by 0·13 and the other by −0·02 p.p.m. If these values are regarded as corrections for the effect of a ketone group and applied to the results for 3β-hydroxy-4,4-dimethylcholestan-6-one, then the predicted and observed movement of the chemical shift ($\Delta\nu_1$) for the 13-Me group are in agreement. Further work is in hand to investigate the effects of other functional groups on expressions (1)—(3).

(b) *Chemical Shift Reagent.*—Addition of portions of europium(fod)$_3$ to a solution of 8,8′-di-*O*-methylsecalonic acid A (or E) in $CDCl_3$ caused shifts in the n.m.r. signals as shown in Table 2. The shifts in the signals were

TABLE 2

Shifts ($\Delta\nu$) with Eu(fod)$_3$

	Secalonic acid A(I)		Secalonic acid E (II)	
Proton	$\Delta\nu$(Hz)	R(Å) *	$\Delta\nu$(Hz)	R(Å) *
5-H	22	6·0	8	7·3
7-H	29	5·0	25	5·0
7-H	33	5·0	28	5·0
α-H (8-OCH_3)	55	3·0	47	3·0
β-H (6-CH_3)	9	7·5	6	7·5
(10-CO_2CH_3)	−2	6·5	−5	6·5

* The formula for the observed shift, $\Delta\nu = c[3\cos^2\theta - 1]/R^3$, was used although strictly it applies only to axially symmetrical molecules. For 5-, 7-, α-, and β-H the angle θ is relatively small (*ca.* 20° at maximum) and was not quantitatively taken into account in Figure 3. However, for γ-H, the angle θ must be relatively large since upfield shifts are observed ($3\cos^2\theta < 1$); this observation also is in line with the Eu complexing mostly near the 8-OMe oxygen atom.

gradual and, for brevity, the results from only one spectrum for each of the acids are shown.

Examination of the spectrum of 8,8′-di-*O*-methylsecalonic acid A with the europium shift reagent shows that the shifts of the signals for 7-H (α and β) are approximately equal and suggests that the vector distances from these protons to the site of the bound europium are about equal. Although the shifts in the signals for protons α to an ether oxygen are only about half those for protons α to a hydroxy-group,[2] 5-H is shifted much less than γ-H. The major complexing site for europium in the multifunctional secalonic acids might have been expected to be 5-OH but this result indicates that the major binding site is near the 8-*O*-methyl ether. Such a conclusion is compatible with the 5-OH being strongly hydrogen-bonded to the 10a-methoxycarbonyl group.[1] Therefore, the europium atom was placed in the general plane of the molecule equidistant (2·4 Å) from the oxygen atom at C-8 and the carbonyl oxygen, and the distances (R, Table 2) were measured from the europium to each proton by using Dreiding models. Using the analytical method proposed by Hinkley *et al.*,[3] a reference line of slope −3 was drawn on the graph of log Δν plotted against log R (Figure 3). The protons 5-, 7α-, and 7β-H

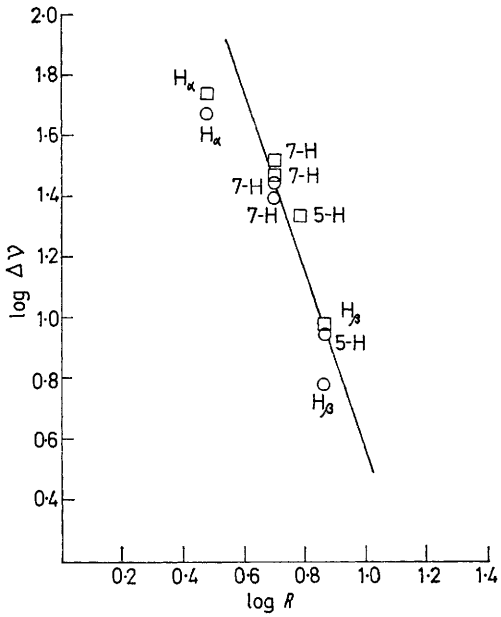

FIGURE 3 Shifts in proton resonances on addition of shift reagent to solutions of the secalonic acid; □ (I), ○ (II)

and α- and β-H lie along a line of slope −3 and only γ-H is off the line. The closeness with which the other protons lie to a line of slope −3 suggests that the major complexing site for europium is near the C-8 ether. The signals for γ-H on the methoxycarbonyl group moved only very slightly and upfield rather than downfield. As the methoxycarbonyl group projects below the plane of the molecule, the small upfield shift is in keeping with the relatively large distance of the protons from the complexing site and the large angle made by the Eu–O(C^8)–H(γ) atoms.

A similar analysis was made of the results of adding europium shift reagent to 8,8′-di-*O*-methylsecalonic acid E (Figure 3). Again, little shift of γ-H was observed. Although the shifts caused by the europium did not directly resolve the problem of the relative orientations of the 5-OH and 10a-CO_2Me groups in the secalonic acids, the analysis of the binding sites does show that the methoxycarbonyl group projects below the plane of the rings.

Conclusion.—The change in the chemical shift of a proton near a hydroxy-group on changing solvent from $CDCl_3$ to pyridine may be estimated from equation (3) although the possible effects of other functional groups in close proximity are unknown. Nevertheless, the tech-

nique promises to be useful for determining the relative orientations of hydroxy and methyl groups in alcohols and phenols.

Chemical shift reagents can resolve the problem of the relative configurations of hydroxy and methoxycarbonyl groups in secalonic acids.

EXPERIMENTAL

All the substances used were checked for purity. Solutions for n.m.r. contained *ca.* 100 mg ml^{-1} but were not made up accurately. The europium shift reagent was added in portions (0·6 mg) to a solution of the 8,8′-di-*O*-methylsecalonic acid (25 mg) in $CDCl_3$ (0·5 ml) and an n.m.r. spectrum was obtained after each addition until line broadening made this no longer possible. Because the 8,8′-di-*O*-methyl ethers are very acid labile, it was essential to remove all traces of HCl from the $CDCl_3$ by filtration of the solvent through alumina immediately before use.

APPENDIX

The ' centre of anisotropy ' was estimated as follows. Consider the atoms shown in Figure 4, in which A is the methyl group attached to C^2, O is the hydroxy-oxygen atom, C^2 and C^1 are carbon atoms, H is a proton attached to C^1 and A, C^2, C^1, and O all lie in the plane of the paper at the x, y co-ordinates shown. As mentioned above, on change of solvent the chemical shift of a proton on C^1 is affected to a similar extent to the protons on A. Although the effects are not equal, they are initially assumed to be so and allowance is made later for this assumption. If the solvent induced shifts ($\Delta\nu$) at A and H are equal, they may be considered to lie vectorially equidistant from the ' centre of anisotropy,' P. Simple vector analysis then shows that P (x,y,z) must lie along the line, $y = 1{\cdot}21x - 0{\cdot}65$ which is reasonably close to the direction of the C^1–O bond. As we assumed earlier that the solvent shift for H was equal to that at A, whereas in fact it is slightly less, it is now possible to argue that P does lie along the direction of the C^1–O bond, as outlined earlier (Figure 4a) from consideration of hydrogen-bonding effects between solute and solvent. Accordingly, we place P along the line of the C^1–O bond and it remains to find its position. For this purpose, we suppose that $\Delta\nu$ and the vector distance, p, of a proton from the ' centre of anisotropy,' P can be fitted to an equation of the form $\Delta\nu = a \exp(-bp)$ where a and b are constants. Such a general equation seems reasonable because the shift $\Delta\nu$ is likely to be affected by some sort of inverse power relationship with the distance, p. We write the exponential equation in the form (4).

$$\log(100\Delta\nu) = c - bp \qquad (4)$$

For the case shown in Figure 4, $100\Delta\nu = 21$ and the distance AP ($=p_{21}$) is determined by the position of P. When A is rotated through 180° about the C^2–C^1 bond, then experimentally, $100\Delta\nu = 1$ and AP $= p_1$. On inserting these values into equation (4) expression (5) is obtained.

$$\begin{aligned} \log 21 &= c - bp_{21} \\ \log 1 &= c - bp_1 \\ \therefore \log 21/1 &= +b(p_1 - p_{21}) \\ \therefore \log 21 &= +b(p_1 - p_{21}) \end{aligned} \qquad (5)$$

For the case of a 1,3-diaxial interaction between methyl and hydroxy in a six-membered ring (Figure 4b; 5α,6β-dihydroxycholestane; Table 1), then $100\Delta\nu = 33$ and AP $= p_{33}$. Inserting these values into equation (4) gives (6) and combining (5) and (6) yields equation (7). Thus, to

$$\log 33 = +b(p_1 - p_{33}) \qquad (6)$$

$$(\log 33)/(\log 21) = 1{\cdot}148 = (p_1 - p_{33})/(p_1 - p_{21}) \qquad (7)$$

find P, we need to know at which point equation (7) holds. By considering the movement of P along the line C^1–O, the expression $(p_1 - p_{33})/(p_1 - p_{21})$ can be calculated either graphically or trigonometrically and plotted against the distance, OP. At the value $(p_1 - p_{33})/(p_1 - p_{21}) = 1{\cdot}148$, the distance OP is found to be 0·7 Å. Hence, the ' centre of anisotropy,' P, can be placed 0·7 Å from oxygen along the

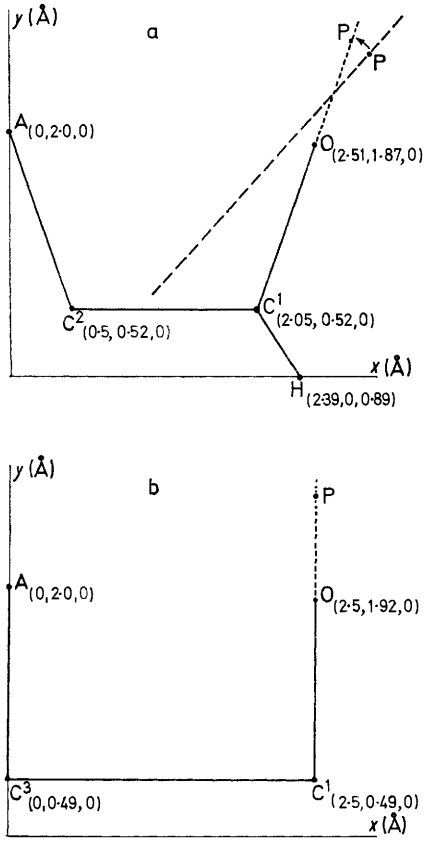

FIGURE 4 Disposition of atoms used to calculate formula (3) for a, methyl group β to hydroxy and b, 1,3-diaxial interaction between methyl and hydroxy-groups (see text for key). The dotted line in a was calculated to be $y = 1{\cdot}21x - 0{\cdot}65$

line of the C^1–O bond and equation (4) becomes equation (3) with $c = 2{\cdot}84$ and $b = 0{\cdot}54$.

Equation (3) was tested by obtaining the distances of A from P, as A is rotated about the line of the C^2–C^1 bond and calculating $\Delta\nu$ from (3). The predicted values for $\Delta\nu$ were close to those found experimentally for the various torsional angles (θ) and therefore equation (3) appears to hold to within ±0·02 p.p.m., at least for all distances (p) between 2·5 and 4·5 Å. As the solvent shifts, $\Delta\nu$, are very small for distances >4·5 Å, we consider that equation (3) is adequate for all distances >2·5 Å for protons situated behind a plane through the oxygen of the hydroxy-group and at right angles to the C–O bond the limits of our observations for alcohols and phenols.

Using equation (3), the shift $\Delta\nu$ for the proton H on C^1 is

predicted to be 0·23 p.p.m., close to the observed mean value of 0·20 p.p.m.

In n-propanol and n-hexanol, the protons on C^2 have the chemical shifts moved by 0·11 and 0·12 p.p.m. respectively on changing solvent from $CDCl_3$ to pyridine. These values are averages in these freely rotating systems at room temperatures, so we have calculated a mean value for $\Delta\nu$ for the torsional angles 0 and 180°. The calculated mean value is 0·11 p.p.m., very close to those observed.

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