Acid-Induced Broadening of ^{1}H N.M.R. Signals in the 6-Hydroxychroman and 5-Hydroxydihydrobenzofuran Series

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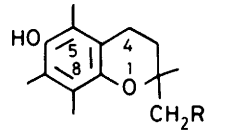
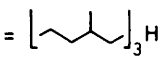
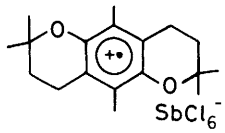
Acids at least as strong as trichloroacetic acid induce line broadening in the ^{1}H n.m.r. spectra of 6-hydroxychroman and 5-hydroxy-2,3-dihydrobenzofuran derivatives. The effect is specific for derivatives of hydroquinone although it is weak in the absence of the heterocyclic rings. The dihydrofuran ring confers greater sensitivity than the dihydropyran ring. A second heterocyclic ring increases the sensitivity greatly. Nuclear (aromatic) methyl groups increase the sensitivity but acyl groups remove it. The effect is attributed to the formation of traces of cation radicals and is destroyed by bases or water. It varies in the same way as hyperfine coupling constants where these are known for the cation radical species. It can be used to simplify complex spectra because only protons very close to the carbon or oxygen atoms of the hydroquinone nucleus are affected strongly; conversely, it can be used for diagnostic purposes. The syntheses of some oxygen heterocycles needed for the survey are discussed briefly.

We have noted that the ^{1}H n.m.r. signals from derivatives of 6-hydroxychroman including tocopherol (**1a**) are broad if the solutions contain acids.[1] Broad signals have been noticed occasionally by other workers but no significance seems to have been attached to them;[2] Figure 1 illustrates the effect for the tocopherol-model chroman (**1b**). Surmising that an unexpectedly easily formed cation radical[3] must be responsible, we were able to isolate the salt (**2**) from a benzodipyran derivative and to characterise it and show that in concentrations of *ca.* 10^{-4} mol l^{-1} it has the same effect on the spectra as adding acid.[1]



(1) a; R = 

b; R = H



(2)

Parallel studies of the e.s.r. spectra exhibited by 6-hydroxychroman derivatives in line-broadening conditions have confirmed the radical nature of the species present and have further shown that the spectra may be temperature-dependent and that conformational inversions of the dihydropyran rings can be important.[4] The effect has itself proved useful in making assignments in complex e.s.r. spectra,[4] and it has also been used in ^{1}H n.m.r. spectroscopy for detecting the 6-hydroxychroman nucleus in compounds of uncertain structure[5] and for the simplification of complex spectra where some lines could be broadened enough to 'remove' them from the trace.[6]

We now report the broadening effect in greater detail along with a survey of its scope, and limitations. The solvent must be non-basic and should not contain constitutional oxygen since this has an 'acid-levelling' effect with the stronger acids. Acetic acid is too weak, but some of its halogenated derivatives are satisfactory and we have used trifluoroacetic acid for general survey purposes with deuteriotrichloromethane as solvent. Acids are not really essential for the production of cation radicals since this can be done with oxidising agents alone but, as has often been noted, acids stabilise cation radicals[4,7-9] and so assist the studies. Occasionally we have used iodine, triphenylcarbenium salts, or tris-(4-bromophenyl)iminium salts[10] in neutral media. Many reagents useful for obtaining the high concentrations of cation radicals necessary for e.s.r. work (*e.g.* aluminium chloride in nitrobenzene[11]) are too powerful for the present purposes since they broaden the lines to vanishing point.

The assessment of relative broadening sometimes presents problems. The range of sensitivities is very wide, so that one band may be broadened beyond measurement before another is measurably affected. If a band is composed of two or more accidentally equivalent signals, the addition of acid (or other reagent) may induce chemical shifts that separate the signals or bring them closer together thus obscuring the true broadening; the effect is relatively small, but when measurements are made at low resolution a 'sharpening' can sometimes be observed before broadening overtakes it, as with 5,7,8-trimethylchroman-6-ol (**13**) (Table 1). Moreover, accidentally coincident signals may suffer different broadening effects thus giving abnormal line shapes.

Nevertheless, the broadening usually gives a meaningful though not very accurate indication of the distribution of spin density within individual cation radicals. It is less satisfactory for deciding which of two phenols is the more sensitive. This is because the broadening is determined not only by the spin distribution but also by how readily the acid attacks the phenol to produce a cation radical in the first place [equation (1)], and by how quickly the radical exchanges with unperturbed molecules in the second [equation (2)].

$$\text{phenol} \xrightarrow{H^+} [\text{phenol}]^{+\bullet} \quad (1)$$

$$[\text{phenol}]^{+\bullet} + \text{phenol} \rightleftharpoons \text{phenol} + [\text{phenol}]^{+\bullet} \quad (2)$$

The second circumstance is the one that makes the n.m.r. experiment a more sensitive test for radicals than the e.s.r. experiment, but if the exchange becomes slow on the n.m.r. time scale the substrate will seem unresponsive even when the sensitivity of the phenol to acid [equation (1)] remains high.

Ordinarily, the phenol (or derivative) was examined in neutral chloroform and re-examined after the addition of an aliquot of trifluoroacetic acid. When necessary, further runs

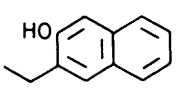
Table 1. Acid induced broadenings[a] in the ^1H n.m.r. spectra[b] of monoheterocyclic chroman and 2,3-dihydrobenzofuran derivatives.

Compd	Acid concn.[c] (%)	2-Me	4-Me	ArMe	ArCH	3-CH_2[d]	Ring O–CH	OMe	ArH
(**1b**)	1.3	0.26		3.6	2.3	0.64			
(**8**)	100	1.02			14	0.64			6.4
(**9**)	9.7	0.26			0.64	0.0	0.08	0.38	0.77
(**10**)	1.3	0.0		*ca.* 30	1.3	0.0			3.6
(**10**)	2.6	0.7		∞	*ca.* 23	2.6			∞
(**11**)	2.6	0.0		19	?	0.0		∞	10
(**13**)	1.3			−1.7	1.28	0.0	19.2		
(**13**)	2.6			9.0	*ca.*17	1.0	∞		
(**14**)	1.3		0.64	13; ∞?		4.2	20		
(**15**)	1.3	0.0		6.0	7.3	0.90			
					$(CH_2)_2$ 19				
(**16**)	10.4	0.0	0.0		9	0.0			8.0
(**16**)[e]	100	0.94; 2.8	0.47		∞	0; 6.6			*ca.* 55
(**17**)[e]	100	1.4; 1.9	0.47			1.9; 4.7		*ca.* 120	*ca.* 100
(**18**)	1.3	1.0		21	14	?	∞		
(**18**)	2.6	2.0		*ca.* 36	*ca.* 30	?	∞		
(**19**)	1.3			3.2	19		21		
(**20**)	2.0	0.26		0.90	7.9				

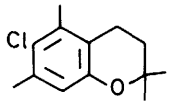
[a] Normally the difference (Hz) in half-height widths of bands in presence of, and absence, of acid. Bands broadened beyond measurement are recorded as ∞. Obscured bands are denoted by ? [b] At 60 MHz and *ca.* 29 °C with substrates at concentrations near 0.3M in $CDCl_3$ with $SiMe_4$ as internal standard. [c] Expressed as percentage by weight of trifluoroacetic acid in $CDCl_3$. [d] Refer to benzopyran derivatives only. [e] At 220 MHz and 18 °C.

were made after the addition of further aliquots. Finally, water or deuterium oxide was added and a last run made to ensure that the original spectrum had been restored. For the reasons detailed above we attached importance only to the larger differences between molecules and do not regard the smallest differences as having any significance.

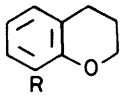
Monohydric phenols such as the naphthol (**3**) and the chroman[12] (**4**) were inert. Simple dihydric phenols may show small changes but never line broadening unless they are hydroquinone derivatives. Moreover, there was no broadening in the spectra of chroman itself (**5a**), 8-methoxychroman[13] (**5b**), 7-hydroxychroman (**6a**), 6-ethyl-7-hydroxychroman (**6b**), or the dipyran[14] (**7**). Acylated compounds, *i.e.* acetates of phenols or chromanones, are never sensitive even when the parent phenols respond. Although broadening is always observed in chromans possessing unhindered hydroquinone nuclei, acidities greater than the standard are needed to make it obvious in the simplest examples like 2,2-dimethylchroman-6-ol[15] (**8**) and its methyl ether (**9**) which have no nuclear methyl groups. When methyl groups are present, as in the chroman[16] (**10**) and its methyl ether (**11**), the broadening is marked under the standard conditions. Exceptionally the phenol (**1b**) is sensitive but its ether (**12**) is not; the methoxy group is prevented from residing in the plane of the benzene ring which therefore cannot behave as a hydroquinone derivative.[17,18]



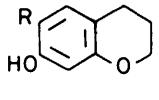
(**3**)



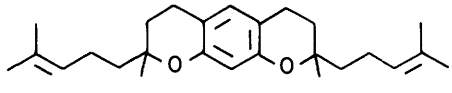
(**4**)



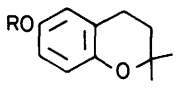
(**5**) **a**; R = H
b; R = OMe



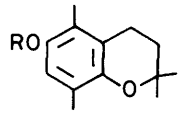
(**6**) **a**; R = H
b; R = Et



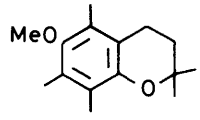
(**7**)



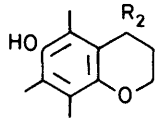
(**8**) R = H
(**9**) R = Me



(**10**) R = H
(**11**) R = Me



(**12**)



(**13**) R = H
(**14**) R = Me

In the model chromanol (**1b**) it is the aromatic methyl resonances that are most strongly affected, then the 4-methylene protons, and finally the 3-methylene protons (Figure 1), an order commonly observed in this series. The *gem*-dimethyl resonances are affected only very weakly; a methylene group at position 2, however, is always very strongly affected—often more so than any other, as in example (**13**). This important

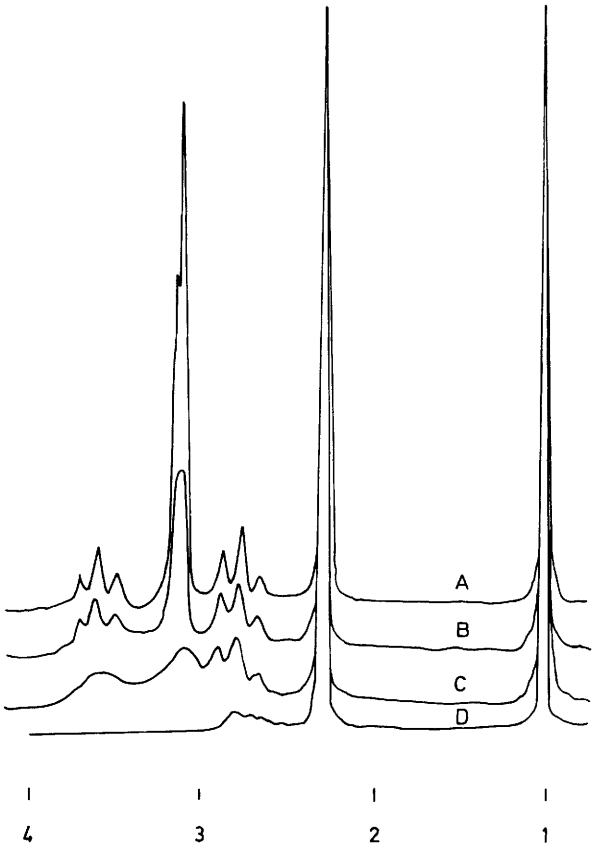


Figure 1. ^{1}H N.m.r. spectra (δ scale) for the chromanol (**1b**): (A) in $CDCl_3$ at 60 MHz; (B) in $CDCl_3$ containing 1.3% F_3CCO_2H; (C) in $CDCl_3$ containing 2.6% F_3CCO_2H; (D) sample (A) after addition of 2 drops of 70% perchloric acid.

result is illustrated in Figure 2, which also illustrates the virtual disappearance of an entire spectrum at high acid levels. Methoxy protons can also be strongly affected.

In the 4,4-dimethylchroman[19] (**14**) the aromatic methyl resonances happen to fall into two distinct sets with different responses to acid. A three-proton band at a rather low field is assigned to the 5-methyl group, since this will be deshielded by the *gem*-dimethyl groups, and it is this band which shows the greater broadening. It is also the 5-methyl group in (**1b**) that is selectively attacked by 'one-electron' oxidising agents.[20] To check the assignment we examined the ethylenebischroman[21] (**15**) which clearly suffers more broadening of the band from the linking methylene protons at position 5 than of bands from the aromatic methyl groups.

The 4-methylchroman[22] (**16**) and its ether (**17**) are of interest because the 3-methylene protons are differentiated geometrically and afforded separate sets of lines in the spectra with different broadenings; it is the 'more axial' proton that shows the lesser broadening. Unusually, the *gem*-dimethyl groups also differ in chemical shift and in the extent of broadening; furthermore, both their bands are moved downfield by about 0.05 p.p.m. at higher acid concentrations. The secondary methyl group is less affected. In the 2-methylchroman[23] (**18**), on the other hand, the 2-methyl group is affected more than any *gem*-dimethyl groups as if spin is transmitted better past a CH group than past a CMe group; however conformational effects may be interfering.

Originally we had thought benzofuran analogues to be less sensitive to acid than the chromans,[1] but now recognise that that is true only of the methyl signals; the effect is not simply

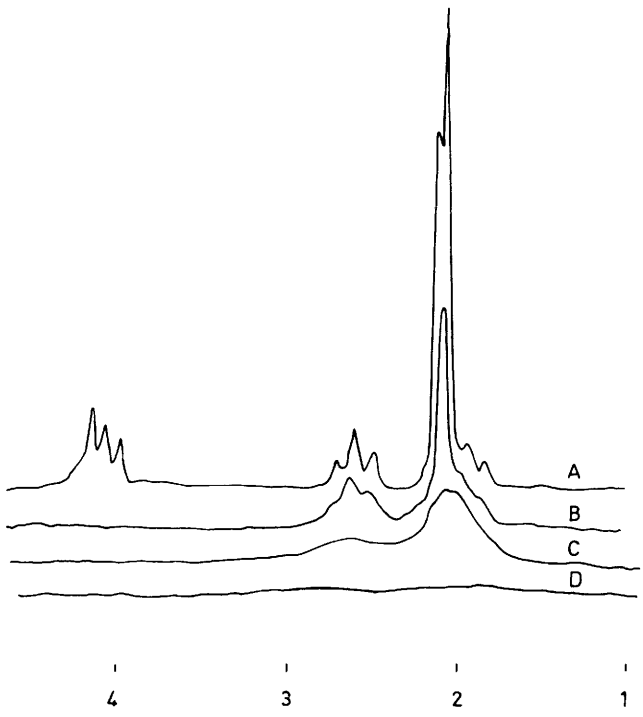
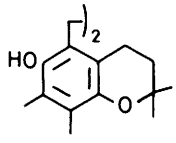
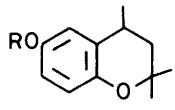


Figure 2. ^{1}H N.m.r. spectra of chromanol (**13**) at 60 MHz (δ scale): (A) in $CDCl_3$; (B) in $CDCl_3$ containing 1.3% F_3CCO_2H; (C) in $CDCl_3$ containing 2.6% F_3CCO_2H; (D) in $CDCl_3/F_3CCO_2H$ (2:1 v/v).

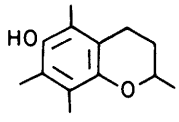


(**15**)

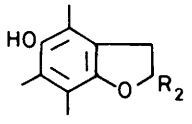


(**16**) R = H

(**17**) R = Me



(**18**)



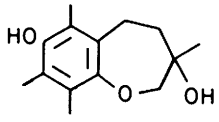
(**19**) R = H

(**20**) R = Me

one of absolute sensitivity, but includes a change in relative sensitivity. It is clear from details for the dihydrobenzofuranol[24] (**20**) that while the response from the aromatic methyl groups has dwindled, that from the ring aromatic methylene group has increased. As in the chroman series, the *gem*-dimethyl band is sharp and little affected by acid whereas a methylene group in the 2-position as in the dihydrobenzofuranol[24] (**19**) shows the greatest response. None of the aromatic methyl groups seem to be more sensitive than the others, which accords with the chemistry of 'one-electron' oxidation since the furanols are attacked at the methyl groups but with only a low selectivity that somewhat favours the 6-position.[6,25]

In contrast, enlarging the heterocyclic ring destroys the effect of acid completely as with the benzoxepin derivative[26] (**21**).

Molecular models show plainly that the larger ring can be fitted in only by twisting both the ether and the benzylic methylene group so that neither can interact with the benzylic π-system, a phenomenon examined by Mandolini and Masci using u.v. methods.[27]



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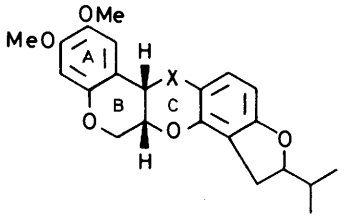
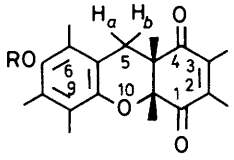


(22) X=CO

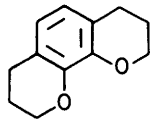
(23) X=CH_2

The lack of planarity in the ring ether group is also important for the rotenone derivatives (**22**) and (**23**), which do not respond to acid although rings A and B constitute a 6-oxychroman system. The ring fusion is known to be *cis* with a boat-like ring B and the ether links twisted out of plane. On the other hand, the xanthene derivative[29] (**24a**) provides an example of a *cis*-fused chroman that does respond normally (Table 2). Indeed the spectrum obtained from a solution in neat trifluoroacetic acid shows none of the bands associated with the chroman nucleus because these are broadened beyond detection while all the others remain almost unchanged. Being hindered, its methyl ether[30] (**24b**) exhibits all the expected lines without broadening.



(24) a; R=H

b; R=Me



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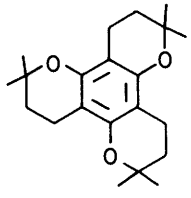


(26)

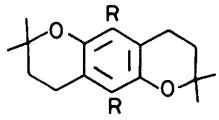
Because the presence of a heterocyclic ring of the right size appeared to be so important we examined some substrates containing two such rings. Again those not derived from hydroquinone, *i.e.* the dipyran (**7**) or dipyran[31] (**25**), were unaffected; even the tripyran[32] (**26**) showed only the slightest trace of broadening. In marked contrast, derivatives (**27**)—(**32**) of hydroquinone were highly susceptible (Table 3), much more so than equivalent monoheterocycles. These substrates were attractive because of their symmetry which made assignments easy and ruled out problems associated with accidental equivalence.

The linear benzodipyran[33] (**27**) has no nuclear methyl groups and requires fairly concentrated trifluoroacetic acid to provide easily measurable broadenings (Table 3). The inclusion of two methyl groups as in (**28**) increases the sensitivity markedly, but an even larger increase is found when the heterocyclic rings are diminished as in the benzodifuran derivative (**29**), for the study of which trifluoroacetic acid was too strong and was replaced by trichloroacetic acid. The angular series proved more or less the same, except that the methylated dipyran (**31**) was noticeably more sensitive than its linear counterpart (**30**); again, the difuran was yet more sensitive. A comparison with 9-methylanthracene (**33**) and 9,10-dimethylanthracene (**34**) (Table 3) shows that a dihydropyran ring imparts sensitivity equivalent to a benzene ring while a dihydrofuran ring is markedly better.

Table 2. Chemical shifts and broadenings for the fused chroman derivative[a] (**24**).

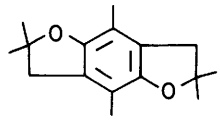
Proton	δ	*J*(Hz)	Broadening (Hz)
10a-Me	1.25		0.1 ± 0.2
4a-Me	1.43		0.2 ± 0.2
ArMe	*ca.* 2.00		1.9 ± 0.2
2(3)-Me	*ca.* 2.14		−0.2 ± 0.2
10-H_a	2.42	16	1.0 ± 0.4
10-H_b	2.98	16	1.8 ± 0.4

[a] At 60 MHz in $CDCl_3$. The acid used was trifluoroacetic acid in $CDCl_3$ at 0.43 × 10^{-2}M.



(27) R=H

(28) R=Me



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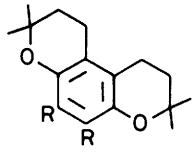
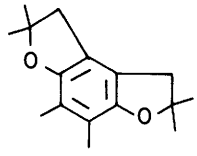
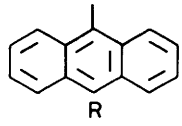


(30) R=H

(31) R=Me



(32)



(33) R=H

(34) R=Me

The tendency for the 5-position of a 6-hydroxychroman nucleus to be more affected than other aromatic sites can be seen again in the linear dipyrans (**27**) and (**28**) (Table 3) but not in the angular dipyrans (**30**) and (**31**), the benzylic methylene groups of which show no corresponding selective sensitivity. In neither the angular nor the linear dibenzofuran derivative is there any corresponding site difference.

In theory, the broadening bears a complex relationship to the splitting constant producing it, and Table 4 compares the

Table 3. Line broadenings[a] and hyperfine coupling constants[b] for benzodipyran, benzodifuran, and anthracene derivatives.[c]

Compd.	Proton	Acid induced broadening (Hz)	Acid and concn. (10^{-2}M)	Added cation radical induced broadening (Hz)	Concn. (10^{-5}M)	a_H(mT)
(27)	*gem*-Me	0.0 ± 0.2	CF_3CO_2H			
	$ArCH_2CH_2$	11.3 ± 0.4	(4.3)			
	$ArCH_2CH_2$	0.7 ± 0.4				
	ArH	16.4 ± 0.3				
(28)	*gem*-Me	0.0 ± 0.2	CF_3CO_2H	0	4.35	−0.002
	ArMe	17.8 ± 0.3	(0.43)	33		0.30
	$ArCH_2CH_2$	7.2 ± 0.3		35		0.13
	$ArCH_2CH_2$	0.6 ± 0.3		11		−0.017
(29)	*gem*-Me	0.2 ± 0.2	CCl_3CO_2H	0.3	0.57	−0.007
	ArMe	8.6 ± 0.2	(0.096)	15		0.1
	$ArCH_2$	12.7 ± 0.2		40		0.6
(30)	*gem*-Me	0.3 ± 0.2	CF_3CO_2H			
	$ArCH_2CH_2$	7.8 ± 0.4	(4.3)			
	$ArCH_2CH_2$	0.6 ± 0.3				
	ArH	9.2 ± 0.2				
(31)	*gem*-Me	0.0 ± 0.2	CCl_3CO_2H	0.0	0.62	
	ArMe	3.6 ± 0.2	(0.37)	19		
	$ArCH_2CH_2$	2.9 ± 0.4		23		
	$ArCH_2CH_2$	0.0 ± 0.2		0.0		
(32)	*gem*-Me	0.2 ± 0.2	CCl_3CO_2H			
	ArMe	16.7 ± 0.3	(0.096)			
	$ArCH_2$	17.8 ± 0.3				
(33)	ArMe	9.7 ± 0.2	CF_3CO_2H			0.78
	ArH-10	>30	(4.3)			0.71
(34)	ArMe	21.4 ± 0.3	CF_3CO_2H			0.80
	ArH_α	2.7 ± 0.3	(0.43)			0.24
	ArH_β	1.0 ± 0.3				0.146

[a] Values for added cation radical salt broadenings are adapted from ref. 4. [b] Motionally averaged values taken from ref. 4 for heterocycles; values for anthracene derivatives from ref. 34. [c] Concentrations *ca.* 0.1—0.5M in $CDCl_3$.

Table 4. Proton chemical shifts (δ) for monoheterocyclic compounds in $CDCl_3$ at 60 MHz.

Compd.	2-Me	2-H	3-H	4-H	4-Me	ArH	ArMe	OMe
(1b)	1.28		1.79	2.64			2.11; 2.15	
(8)	1.28		1.75	2.70		*ca.* 6.55		
(9)	1.29		1.78	2.75		*ca.* 6.7		3.74
(10)	1.28		1.79	2.63		6.49	2.09	
(11)	1.28		1.79	2.62		6.54	2.05; 2.08	3.72
(12)	1.30		1.80	2.64			2.11; 2.16; 2.20	3.65
(13)		4.13	2.03	2.66			2.11; 2.16	
(14)		4.13	1.81		1.45		2.12; 2.15; 2.36	
(15)	1.17		1.67	2.62			1.99; 2.12 $(CH_2)_2$ 2.62	
(16)[a]	1.21; 1.37		1.51[b] 1.82[c]	2.91	1.28	6.60; 6.68; 6.74		
(17)[a]	1.20; 1.37		1.52[b] 1.82[c]	2.91	1.30	6.69; 6.79		3.74
(18)	1.38	3.91	*ca.* 1.88	2.65			*ca.* 2.13	
(19)		4.52	3.09				*ca.* 2.14	
(20)	1.47		2.95				*ca.* 2.12	

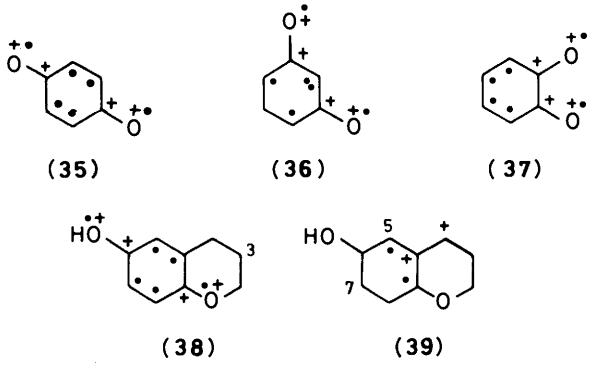
[a] At 200 MHz. [b] First-order analysis gave *J* 14, 13 Hz. [c] First-order analysis gave *J* 13, 7 Hz.

relevant values currently available.[4,34] There is general agreement in that very small splitting constants are associated with very limited or negligible broadenings, and large constants with extensive broadenings. In particular, the splitting constants mirror the change in relative susceptibilities to broadening, the constants for the methyl groups in the linear dipyran (**28**) being reduced in the angular isomer (**31**) and in the linear difuran (**29**).

Although the compounds discussed here have too little symmetry to permit interpretation by the simple HMO approach used by Vincow,[8] a VB approach allows some clarification. In a vinylic cation radical, the positive charge will be concentrated upon the carbon with an attached oxygen and on the oxygen itself and the alternative polarisation will be unimportant since radicals are not greatly stabilised by oxygen:

$$CH_2^{\bullet}\text{–}CH^{+}\text{–}OH \longleftrightarrow C\dot{H}_2\text{–}CH{=}\overset{+}{O} \longleftrightarrow CH_2{=}CH\text{–}\overset{+}{O}^{\bullet}$$

Applied to a hydroquinone nucleus, this consideration, along with symmetry considerations, leads to the distribution of charge and unpaired spin in (**35**). A resorcinol nucleus, (**36**)

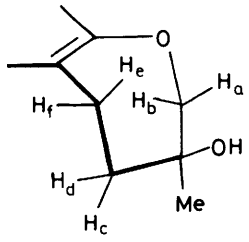


shows a much less even distribution of charge and spin, and for a catechol nucleus, (**37**), there is a one-sided distribution with strong charge repulsions. Thus the hydroquinone nucleus emerges as most favourable for cation radical formation. The ability of the ether oxygen atom to sustain the charge and spin distributions will depend on whether or not the ether grouping lies in-plane. Methoxy groups need not lie in-plane and their contribution is variable; chroman (pyran) ether links are nearly but not exactly in-plane, and dihydrofuran ether links are necessarily exactly planar.[35] We have here the reasons for the chief variations in sensitivity amongst the compounds discussed.

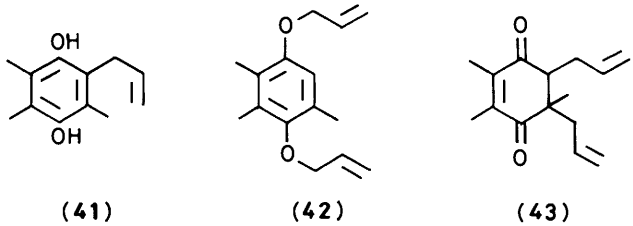
We believe the somewhat enhanced sensitivity of the 5-methyl group in a 6-hydroxychroman nucleus to be connected with the selective reactivity of the 5-position of this system towards electrophiles and some oxidising agents, a selectivity not found in the benzofuran analogue.[6,36] The earlier explanation can be adapted here. Thus the benzylic methylene group is considered to stabilise a positive charge rather well at the adjacent aromatic position as in (**39**). Of course, the effect is much smaller than that exerted by an oxygen atom, but the next position, position 5, will tend to be slightly more radical in character as a result. The effect cannot be transmitted to position 7 without upsetting major interactions already in existence (cross-conjugation), so only position 5 responds. This remains possible in the linear benzodipyran (**28**), where each chroman ring activates its own '5-methyl' group, but in the angular dipyran (**31**) it is the benzylic methylene groups that occupy the 5-positions in the chroman system relative to each oxygen. Hence the sensitivity of the aromatic methyl groups appears to fall while that of the benzylic methylene groups rises. In the dihydrobenzofuran series, a contribution like that in (**39**) would be small because rehybridisation is more difficult in the smaller ring, which therefore exerts no selectivity.

In examining the inhibition of oxidation by chromanols and similar phenols, Burton, Hughes, and Ingold[35] have noted that a dihydrofuran-5-ol was superior to the corresponding chroman-6-ol, which is what we would expect from our own work. However, these workers reject radical cation intermediates and argue that the planarity of the ether system will affect simple radical intermediates in the required sense. This is not our view, but the matter cannot be discussed further at this stage because our criteria involve quite different reactions aside from the initial oxidations; moreover, their criterion refers to the entire molecule and does not give specific information about individual parts, whereas the reverse is true for ours.

The new compounds required for this study are described in the next section and for most of them no discussion is necessary. The formation of the oxepin derivative (**21**) has been described briefly already;[37] the semi-rigid out-of-plane conformation (**40**) is indicated by the individual resonances of the methylene protons and the long-range couplings. The isomeric benzodipyrans (**27**) and (**29**) have been made previously by several



workers using various modifications of the condensation between hydroquinone and isoprene equivalents; none of these modifications have been satisfactory, and as the isomers have never been securely oriented, the literature contains uncertainties.[32,38] We have examined some of these and other condensations and conclude that the best method is based upon the use of phosphorus pentaoxide pre-treated with ether to give a cyclic polyphosphate as the active catalyst capable of inducing smooth condensation between hydroquinone and 2-methylbut-3-en-2-ol during a few hours at room temperature.[39] Both isomers are formed, and structures have been assigned by showing that only in the angular isomer (**29**) is there an upfield compression shift in the ^{13}C resonance from the benzylic methylene carbon atoms, and that only in the linear isomer (**27**) can long-range coupling (J 3 Hz) be detected between the aromatic methine carbon atoms and the benzylic methylene protons. The allyltrimethylhydroquinone (**41**) was made by conducting a Claisen rearrangement on the diallyl ether (**42**) under stringent conditions intended to eliminate one allyl group. Although this procedure succeeded, a small part of the material retained both allyl groups giving the cyclohexenedione derivative (**43**).



Experimental

Molecular weights were determined by mass spectrometry. N.m.r. spectra were recorded for solutions in trichlorodeuteriomethane, with tetramethylsilane as internal standard; coupling constants are from first order analysis only; Table 4 collates results for simple chromans.

Broadening Experiments.—The chromanol or other substrate (*ca.* 20 mg; *ca.* 10^{-4} mol) was normally dissolved in trichlorodeuteriomethane (0.60 ml) containing either tetramethylsilane or dichloromethane to provide reference and lock signals. The ^1H n.m.r. spectrum was determined (CW mode) at fields of 60 MHz and a temperature near to 29 °C or, if greater resolution was required, at 220 MHz and 19 °C. Wherever possible widths at half peak-height were determined on suitable expansions before and after broadening, but with some multiplets and some resonances lying close together widths of the bands were determined at a third peak-height.

Broadening was induced most commonly by adding to the initial solution a known amount of trifluoroacetic acid. For many substrates sufficient broadening resulted from adding 2

drops (*ca.* 0.0067 ml or 0.0045 g) of the acid from a syringe; a few needed less and some much more. The least responsive substrates were examined in the neat acid. Where the amount of acid used did not make the procedure impractical, the acid-treated solution was shaken with deuterium oxide in excess or with enough pyridine to neutralise the acid and the spectrum determined again.

In all cases the original spectrum was restored as regards sharpness though sometimes some resonances suffered small shifts consistent with a change in solvent composition.

2,3,5-*Trimethyl*-6-*prop*-2-*enylbenzene*-1,4-*diol* (**41**).—Trimethylhydroquinone (15.2 g) and allyl bromide (30 g) were heated together in acetone (400 ml) containing potassium carbonate (150 g) for 1 day; allyl bromide (10 g) was again added and heating continued for another 6 h. The filtered solution was concentrated giving an oil that was dissolved in ether and washed with saturated aqueous sodium metabisulphite (100 ml). Recovered from the ether, the oil was chromatographed from light petroleum on neutral alumina (200 g) to supply, as the main fraction, 2,3,5-*trimethyl*-1,4-*diprop*-2-*enyloxybenzene* (**42**) as an oil, $\nu_{max.}$(film) 2 820, 2 775, 1 488, 1 412, 1 213, 1 110, 1 095, 1 002, 935, and 848 cm^{-1}; δ 6.49 (1 H, s, ArH), 5.80—4.28 (2 H, mm, =CH–), 5.52—5.04 (4 H, mm, $=CH_2$), 4.43 (2 H, d, *J* 5 Hz, OCH_2), 4.19 (2 H, d, *J* 5 Hz, OCH_2), and 2.25, 2.20, and 2.16 (each 3 H, s, ArMe) (Found: C, 77.3; H, 8.5%; M^+, 232. $C_{15}H_{20}O_2$ requires C, 77.55; H, 8.7%; *M*, 232.

The ether (3.0 g) was heated under reflux with di-*N*-ethylaniline (50 ml) under nitrogen for 4 h, after which the solvent was removed by vacuum distillation and the brown residue taken into ether (100 ml) and washed with dilute hydrochloric acid, aqueous sodium metabisulphite, and water. Recovered in the usual way the product formed an oil that partly crystallised when left in contact with light petroleum; the solid then separated from ether–light petroleum giving the diol (**41**) as needles (1.13 g), m.p. 137 °C (lit.,[40] 137—138 °C), *m/z* 192. The part that remained oily was chromatographed on neutral alumina (3% water; 100 g) from light petroleum, the main yellow band furnishing 2,3,5-*trimethyl*-5,6-*diprop*-2-*enylcyclohex*-2-*ene*-1,4-*dione* (**43**) as a yellow oil (1.10 g), $\nu_{max.}$(film) 2 840, 1 679, 1 643, 1 450, 1 385, 1 306, 1 255, 1 011, and 935 cm^{-1}; δ 5.98—5.37 (2 H, mm, =CH–), 5.37—5.41 (4 H, mm, $=CH_2$), 3.00—2.12 (4 H, mm, $C-CH_2-C$), 1.97 (6 H, s, vinylic Me), 1.13 (3 H, s, angular Me), and *ca.* 1.23 (1 H, m, partially hidden, ring CH) (Found: M^+, 232.146 91. $C_{15}H_{20}O_2$ requires *M*, 232.146 32).

5,7,8-*Trimethylchroman*-6-*ol* (**13**).—To the benzenediol (**41**) (2.0 g) in ethanol (3 ml) was added iron(III) chloride (15 g) also in ethanol (40 ml) and the mixture was warmed for a few minutes to *ca.* 50 °C; it was then cooled and diluted with ether (150 ml). This solution was washed with water and the contents isolated in the usual manner leaving an oil that was purified on a column of silica (70 g) by elution with ether–light petroleum (1:15, v/v) giving 2,3,5-*trimethyl*-6-*prop*-2-*enyl*-1,4-*benzoquinone* as a yellow oil, $\nu_{max.}$(film) 2 940, 1 647, 1 438, 1 380, 1 302, 1 260, 1 007, 928, and 732 cm^{-1}; δ *ca.* 5.86 (1 H, m, vinyl CH), 5.16 and 4.91 (each 1 H, m, $=CH_2$), 3.26 (2 H, m, $=CCH_2C=$), and 2.03 (9 H, s, 3 Me) (Found: M^+, 190. $C_{12}H_{14}O_2$ requires *M*, 190). This compound seemed unstable and was used at once for the next preparation. The quinone (1.5 g) was heated in refluxing pyridine (distilled from calcium hydride immediately before use) (50 ml) under nitrogen for 3 h. The pyridine was removed by vacuum distillation and the residue was purified on silica (50 g) by elution with ether–light petroleum (1:4, v/v) which first removed residual quinone (0.35 g) and then gave a solid that crystallised from acetone–light petroleum to supply 5,7,8-*trimethyl*-2H-1-*benzopyran*-6-*ol* as needles (1.1 g), m.p. 127—128 °C $\nu_{max.}$(mull) 3 465, 1 610, 1 247, 1 130, 1 060, 790, and 707 cm^{-1}; 6.57 (1 H, d, *J* 8 Hz, ArCH=), 5.79 (1 H, m, $=CHCH_2$), 4.58 (2 H, m, OCH_2), 4.23 (1 H, s, removed by D_2O, OH), 2.09, 2.12, and 2.15 (each 3 H, 3 Me) (Found: C, 75.5; H, 7.4%; M^+, 190. $C_{12}H_{14}O_2$ requires C, 75.8; H, 7.4%; *M*, 190).

The benzopyranol (2.0 g) in ethyl acetate (200 ml) was shaken with palladium-on-carbon (10%; 1 g) under hydrogen (1 atm) until absorption ceased (*ca.* 1 h). Isolated as usual, the product crystallised from light petroleum giving 5,7,8-*trimethylchroman*-6-*ol* as needles (1.75 g) m.p. 140 °C, $\nu_{max.}$(mull) 3 320, 1 256, 1 124, 1 095, and 978 cm^{-1}; 4.20 (1 H, s, removed by D_2O, OH), 4.07 (2 H, rough t, OCH_2), 2.63 (2 H, rough t, $ArCH_2$), *ca.* 2.0 (2 H, m partly overlaid), 2.15 (3 H, s, ArMe), and 2.11 (6 H, s, 2 ArMe) (Found: C, 75.1; H, 8.4%; M^+, 192. $C_{12}H_{16}O_2$ requires C, 75.0; H, 8.4%; *M*, 192).

Methylations.—Several phenols already known were converted by the usual iodomethane–potassium carbonate–acetone method into their methyl ethers. In every case the reaction was allowed to continue until t.l.c. showed no further change and the products were all obtained in yields >85% after purification by chromatography on silica from ether–light petroleum. 2,2,5,8-Tetramethylchroman-6-ol[24] supplied 6-*methoxy*-2,2,5,8-*tetramethylchroman* (**11**) as an oil, $\nu_{max.}$(film) 1 572, 1 368, 1 265, 1 163, and 1 095 cm^{-1} (Found: *M*, 220.146 01. $C_{14}H_{20}O_2$ requires *M*, 220.146 32). 2,2,4-Trimethylchroman-6-ol[22] furnished 6-*methoxy*-2,2,4-*trimethylchroman* (**17**) as an oil, $\nu_{max.}$(film) 1 618, 1 582, 1 195, and 1 043 cm^{-1} (Found: *M*, 206.131 01. $C_{13}H_{18}O_2$ requires *M*, 206.130 67). 2,2-Dimethylchroman-6-ol[15] furnished 6-*methoxy*-2,2-*dimethylchroman* (**9**) as an oil, $\nu_{max.}$(film) 1 605, 1 252, 1 208, and 1 055 cm^{-1} (Found: M^+, 192.115 09. $C_{12}H_{16}O_2$ requires *M*, 192.115 02).

2,3,6,7-*Tetrahydro*-2,2,4,6,6,8-*hexamethylbenzo*[1,2-b;4,5-b′]-*difuran* (**29**).—2,5-Dimethylhydroquinone (10 g) was heated in formic acid (100 ml) containing sulphuric acid (0.2 ml) at 100 °C and 2-methylprop-3-en-2-ol (7 g) was added dropwise during 40 min. After further heating for 9 h the mixture was allowed to cool and poured onto crushed ice and the solid product (8.5 g) was collected and crystallised from a large volume of ethanol giving the *difuran* as needles, m.p. 189—190 °C, $\nu_{max.}$(KBr) 2 970, 2 920, 2 900, 2 850, 1 495, 1 485, 1 405, 1 375, 1 360, 1 310, 1 285, 1 275, 1 255, 1 198, 1 135, 1 115, 1 058, 968, 948, 935, 885, 840, 875, 640, and 633 cm^{-1}; δ 1.43 (s, 12 H, *gem*-Me), 2.03 (s, 6 H, ArMe), and 2.87 (s, 4 H, CH_2) (Found: C, 78.1; H, 9.1%; M^+, 246. $C_{16}H_{22}O_2$ requires C, 78.0; H, 9.0%; *M*, 246).

2,3,4,5-*Tetrahydro*-2,2,5,5,7,8-*hexamethylbenzo*[1,2-b;4,3-b′]-*difuran* (**32**).—2,3-Dimethylhydroquinone (10 g) was heated at 100 °C under reflux in formic acid (100 ml) containing sulphuric acid (0.2 ml) while 2-methylprop-3-en-2-ol (6 g) was added during 30 min. After a further 9 h at 100 °C the dark solution was poured onto ice (500 g) and the organic products isolated with ether from which formic acid was washed out by water and then aqueous sodium hydrogen carbonate. The ether was then removed and the residue heated with methanol (150 ml) and concentrated hydrochloric acid (2 ml) for 10 min.

The residue left after concentrating the reaction mixture was dissolved in diethyl ether and treated with light petroleum to precipitate unchanged dimethylhydroquinone which was filtered off. The filtrate was concentrated to a semi-solid mass which was then extracted with light petroleum. The less soluble part crystallised from diethyl ether–light petroleum giving 2,3-dihydro-2,2,6,7-tetramethylbenzofuran-5-ol[25] as tan needles (3 g), m.p. 107—108 °C. The more soluble part was chromatographed on silica from ether–light petroleum (1:10 v/v) to

supply a solid (1.5 g) that crystallised from ethanol giving the *difuran* as needles, m.p. 107—108 °C, $\nu_{max.}$(KBr) 2 970, 2 920, 2 850, 2 840, 1 617, 1 448, 1 407, 1 372, 1 365, 1 358, 1 293, 1 272, 1 250, 1 210, 1 155, 1 152, 1 100, 1 070, 970, 935, 900, 882, 850, 780, 640, and 620 cm^{-1}, δ 1.44 (s, 12 H, *gem*-Me), 2.06 (s, 6 H, ArMe), and 2.86 (s, 4 H, CH_2) (Found: C, 77.9; 8.9%; M^+, 246. $C_{16}H_{22}O_2$ requires C, 78.0; H, 9.0%; *M*, 246).

2,3,4,7,8,9-*Hexahydra*-2,2,7,7-*tetramethylbenzo*[1,2-b;4,5-b′]-*dipyran* (**27**) *and* 1,2,3,8,9,10-*Hexahydro*-3,3,8,8-*tetramethylbenzo*[1,2-b; 4,3-b′]*dipyran* (**30**).— The reagent cyclic polyphosphate ester was prepared by dissolving phosphorus pentaoxide (15 g) in a refluxing mixture of ether (15 ml) and chloroform (30 ml) during 8 h. Residual phosphorus pentaoxide was then filtered off and the filtrate was concentrated to a viscous brown oil which was taken up in chloroform to give a 10% solution (w/v). Benzene-1,4-diol (0.01 mol) was suspended in this solution (62.5 ml) under argon, 2-methylbut-3-en-2-ol (0.05 mol) was added, and the mixture was stirred for 7 h at room temperature, and then poured into iced water. The products were extracted into ether and washed with 2M-sodium hydroxide solution and then recovered in the usual way. The alkaline solution gave 6-hydroxy-2,2-dimethylchroman. The neutral products were separated by flash chromatography on silica with toluene as the eluant. The benzo[1,2-*b*; 4,5-*b*′]-dipyran (R_F 0.37) left the column in the first 500 ml, then mixtures were obtained until about 600 ml eluant had been collected. The benzo[1,2-*b*; 4,3-*b*′]dipyran (R_F 0.28) was eluted after a further 200 ml. The benzo[1,2-*b*; 4,5-*b*′]dipyran separated from hexane in prisms (0.58 g) m.p. 162—164 °C (lit.,[38] 157—158 °C, δ (^{1}H), 1.28 (12 H, s, *gem*-Me), 1.72 (4 H, t, *J* 7 Hz, $ArCH_2CH_2$), 2.67 (4 H, t, *J* 7 Hz, $ArCH_2$), and 6.48 (2 H, s, Ar*H*); δ_C (100 MHz), 22.28 (C-4, t, *J* 126.34, *J*′ 4.88 Hz), 26.74 (Me, q, *J* 125.73, *J*′ 3.66 Hz), 32.94 (C-3, t, *J* 128.18, *J*′ 3.66 Hz), 73.45 (C-2, d, *J*′ 3.66 Hz), 116.60 (C-5, d, *J* 156.25, *J*′ 3.66 Hz), 119.94 (C-4a, s), and 146.96 (C-10a, s).

The benzo[1,2-*b*; 4,3-*b*′]dipyran separated from hexane as needles (0.66 g), m.p. 141—146 °C (lit.,[38] 141—143 °C), δ_H 1.28 (12 H, s, *gem*-Me), 1.78 (4 H, t, *J* 7 Hz, $ArCH_2CH_2$), 2.55 (4 H, t, *J* 7 Hz, $ArCH_2$), 6.58 (2 H, s, Ar*H*), δ_C (100 MHz), 19.94 (C-1, t, *J* 128.20, *J*′ 3.71 Hz), 26.50 (Me, q, *J* 125.81, *J*′ 3.71 Hz), 32.65 (C-2, t, *J* 128.12, *J*′ 3.71 Hz), 72.65 (C-1, d, *J*′ 3.6 Hz), 115.93 (C-5, d, *J* 159.62 Hz), 118.93 (C-10b, d, *J*′ 2.44 Hz), 146.88 (C-4a, d, *J*′ 2.44 Hz).

2,3,4,5-*Tetrahydro*-3,6,8,9-*tetramethyl*-1-*benzoxepin*-3,7-*diol* (**21**).—Sodium hydride (0.194 g; washed with freshly redistilled tetrahydrofuran and dried *in vacuo*) was added to 2-hydroxy-2,5,7,8-tetramethylchroman-6-ol (0.6 g) and trimethylsulphonium iodide (0.6 g) in dimethyl sulphoxide (freshly distilled under reduced pressure; 25 ml) at 50 °C. After 24 h at this temperature the mixture was kept at 0 °C during neutralisation by ice-cold dilute hydrochloric acid (*ca.* 50 ml) and extraction by ether (3 × 100 ml). The combined extracts were dried (Na_2SO_4) and the volatile materials removed under reduced pressure and without heating. The residue in benzene was placed on a column of silica and eluted with benzene–ethyl acetate (4:1 v/v). The main fraction provided the diol which crystallised from benzene as prisms (0.32 g), m.p. 159—160 °C (lit.,[26] 160—161 °C) (Found: C, 71.0; H, 8.6%; M^+, 236. Calc. for $C_{14}H_{20}O_3$: C, 71.2; H, 8.5%; *M*, 236).

The ^{1}H n.m.r. results agreed with those of earlier workers, who recorded only the chemical shifts.[26] We have assigned shifts to specific oxepin protons and analysed the coupling constants (first order only) to support the conformation depicted in diagram (**40**), thus: 3.40 (H_b), 3.98 (H_a), 1.50(H_d), 1.90 (H_c), 2.74 (H_e), and 2.92 (H_f). The relatively high fields for H_b and H_d within their methylenic pairs reflect their position pointing over the benzene ring. The small chemical shift difference between the methylenic protons H_e and H_f agrees with the fact that this methylene group is so twisted that its protons are *both* very nearly in the plane of the benzene ring. The main coupling constants are J_{ab} 12.5; J_{cf} 12; J_{ef} 14; J_{cf} 5; J_{de} 13 Hz. There is a long range (W path) coupling between J_a and J_c of 2.5 Hz. There are two torsion angles approaching zero, one of which leads to J_{df} 0 and the other to J_{ee} *ca.* 1.5 Hz.

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