The Acid-sensitive ^{1}H Nuclear Magnetic Resonance Spectra of Tocopherols and Other Derivatives of 6-Hydroxychroman

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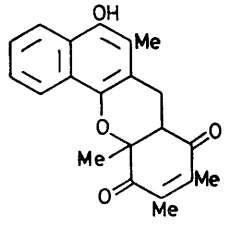
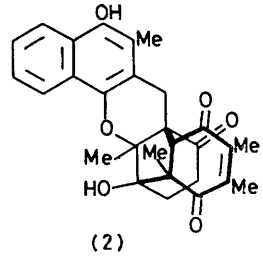
Summary Acids selectively cause the collapse of n.m r. signals originating from protons attached to, or closely associated with, the 6-hydroxychroman nucleus; the signals are restored by base and it is thought that the effect is produced by an aromatic nucleus that is very easily oxidisable to the cation radical state.

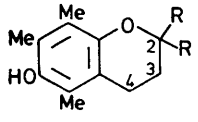
DURING earlier work on the phenols (**1**) and (**2**) their n.m.r. spectra could not be studied because solubilities in acceptable solvents were too low.[1] The better instrumentation now available has allowed us to study these phenols in deuteriochloroform, and to note considerable variations from run to run. The bands affected are those associated with the naphthalene nucleus, *i.e.* the aromatic protons, the aromatic methyl group, and the ring methylene group, which tend to give low, broad peaks, while the aliphatic methyl and methine peaks from the rest of the molecule remain sharp. The effect has been traced to the presence of acid in the solvents employed. In neat trifluoroacetic acid the phenols (**1**) and (**2**) show sharp alicyclic peaks still, but show no peaks for the other protons.



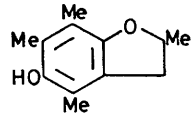
(1)



(2)



(3) R = Me
(4) R = H



(5)

A survey of phenols immediately available suggests that the effect is characteristic of, though not strictly confined to, derivatives of 6-hydroxychroman. Tocopherol and its relatives show it; indeed, some of the spectra already published[2] show the early stages of this broadening. The details are more readily observed in the simpler chroman (**3**); as trifluoroacetic acid is added to the solution in deuteriochloroform, the peaks from the aromatic methyl groups collapse first, followed by those from the benzylic methylene groups (Figure 1). The band from the remaining methylene group is rather resistent to trifluoroacetic acid but collapses when a little perchloric acid is added (Figure 2). In general the stronger acids have the more marked effect whereas acetic acid has none, though the chloroacetic acids have some effect. No acid affects the band from the *gem* dimethyl group in any way.

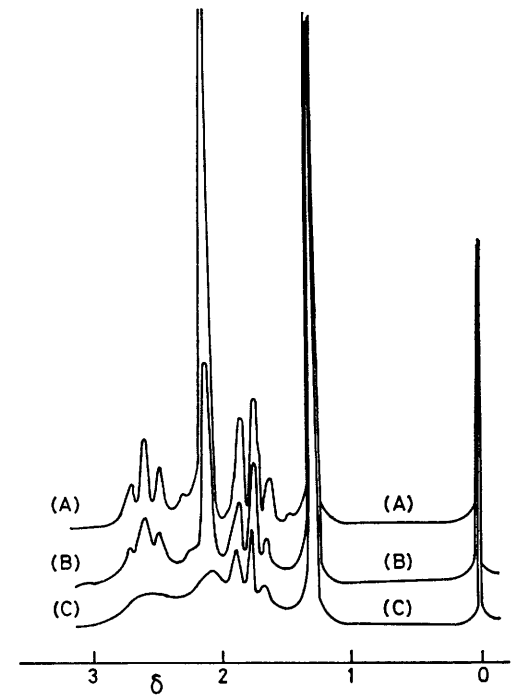


FIGURE 1. ^{1}H N.m.r. spectra (δ scale) for the chroman (**3**) in a 5 mm tube at 60 MHz: (A) in $CDCl_3$; (B), (A) with addition of trifluoroacetic acid (2 drops); (C), (B) with further addition (2 drops) of trifluoroacetic acid.

The phenomenon is essentially a broadening; peak heights fall, but multiplicities are not affected and spectra in partial collapse may exhibit 'impossible' splitting patterns (see Figure 1). There is no shift in band positions, no coalescence until broadening obscures the fine structure, and no change in integrated intensity while the band is well clear of the noise level. Finally, the band becomes so wide that the instrument (Varian HA-100) fails to register it.

The chroman (**4**) has a methylene group at position 2 that is yet more sensitive to acids. Indeed, all the peaks in the spectrum of this compound broaden: the 2-methylene first followed by the methyl groups, the benzylic methylene, and (lastly) the central methylene group. At the limit the spectrum cannot be distinguished from a base line modified only by bands from the solvent, acid, and reference compound (tetramethylsilane).

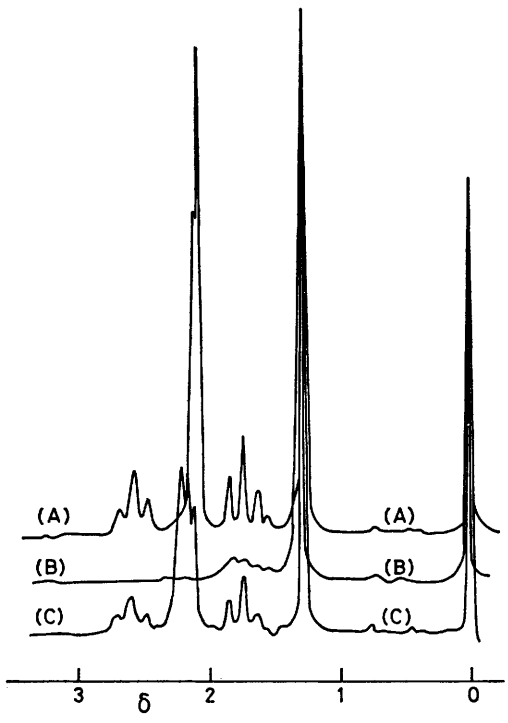


FIGURE 2. ^{1}H N.m.r. spectra (δ scale) for the chroman (**3**) in a 5 mm tube at 60 MHz: (A) in $CDCl_3$; (B), (A) after addition of 70% perchloric acid (2 drops); (C), (B) after addition of pyridine (the aromatic methyl band shows solvent shifts typical of this solvent).

At any stage in the broadening the original bands may be recovered immediately by the addition of pyridine (Figure 2) or by washing away the acid with water. There is no loss of intensity except by dilution with reagents, and the original chromans can be recovered nearly quantitatively even after several hours in contact with acid.

The behaviour of the phenols immediately available to us suggests that the phenomenon depends upon the presence of an aromatic nucleus from which an electron is very easily removed leaving a cation radical. The broadening is associated with the development of e.s.r. signals that are very complex and are being separately studied by Dr. L. H. Sutcliffe and his colleagues. It is common knowledge that hydroquinone (1,4-dihydroxybenzene) derivatives are very readily oxidised; we have not found such broadening amongst 1,3-dihydroxybenzene or 1,3,5-trihydroxybenzene derivatives and not with certainty amongst 1,2-dihydroxybenzene derivatives. The aromatic nucleus need not be fully substituted, though methyl substituents enhance the effect. Acetylation of the hydroxy group in a 6-hydroxychroman destroys the effect and alkylation sometimes does so; for example, the methyl ether of the phenol (**1**) is not sensitive. The one chromen examined (kindly given us by Professor L. Crombie) was decomposed by acid too quickly to allow any observations.

The six-membered heterocyclic ring is not absolutely necessary even though it is required for the phenomenon to appear dramatic. Some broadening can be induced in the methyl bands of trimethylhydroquinone. The 2,3-dihydrofuran derivative (**5**) has an intermediate sensitivity. Elsewhere[3] we have discussed the special character of the 6-hydroxychroman nucleus in connection with its anomalous behaviour in electrophilic substitution (Mills–Nixon effect) and pointed out that, for the six-membered oxygen ring, and only for that sized ring, can the C–H σ-bonds of the methylene groups be precisely aligned with the p-π system for hyperconjugation.

If this analysis is correct the phenomenon will be found in other areas, *e.g.* amongst 1,2,3,4-tetrahydroquinoline and pyrrole derivatives. For this reason the practice of using trifluoroacetic acid and other acids as solvents for rather insoluble materials needs particular caution. On the other hand, the deliberate use of acid solvents in conjunction with others can be used for structural diagnosis or just to simplify a region of a spectrum containing many peaks. Finally, the possible roles of tocopherols in cell chemistry need reconsideration, acid-dependent redox phenomena being in mind instead of oxidation to quinonoid species.

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[1] F. M. Dean and L. E. Houghton, *J. Chem. Soc.* (*C*), 1968, 2060; F. M. Dean, K. B. Hindley, and L. E. Houghton, *ibid.*, 1971, 1171.
[2] C. Cassagne and J. Rabaud, *Bull. Soc. chim. France*, 1968, 1470.
[3] J. M. Behan, F. M. Dean, and R. A. W. Johnstone, *Tetrahedron*, 1976, **32**, 167.