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SOLVENT EFFECTS IN NMR SPECTROSCOPY

SOLVENT SHIFTS OF METHOXYL RESONANCES IN FLAVONES INDUCED BY BENZENE; AN AID TO STRUCTURE ELUCIDATION

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Abstract—The position and relative orientation of OMe groups in methoxyflavones can be inferred from benzene-induced solvent shifts of the OMe resonances. OMe groups at C-5, C-7, C-10 and C-12 exhibit large positive Δ values ($\Delta = \delta_{CDCl_3} - \delta_{C_6H_6} \simeq 0{\cdot}5$ to 0·8 ppm) in the absence of OMe or OH substituents *ortho* to these groups. In contrast, OMe groups at C-3, or those flanked by two *ortho*-OMe functions (or one *ortho*-OH and one *ortho*-OMe function) show small positive or negative Δ values. An OMe at C-5 suffers a drastic algebraic decrease in solvent shift upon the introduction of an OMe group at C-6. Electronic and conformational factors which may account for these differences are considered.

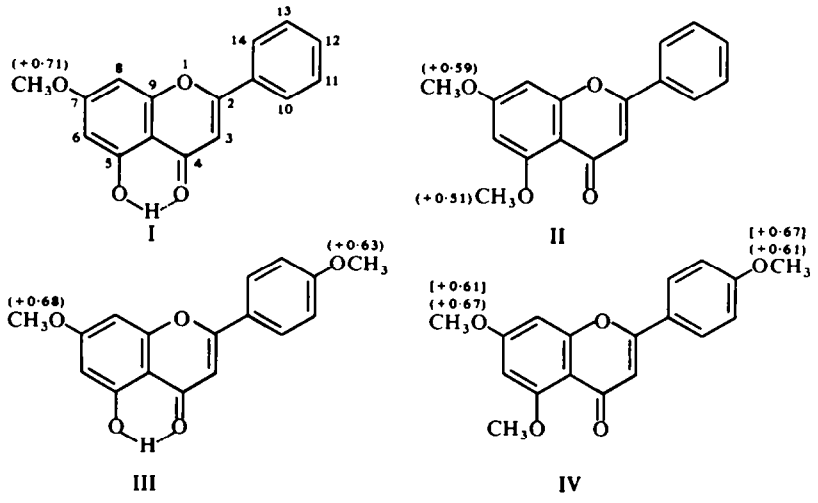
THE dependence of solvent shifts of OMe resonances induced by benzene (relative to a comparatively "inert" solvent, such as CCl_4 or $CDCl_3$) upon electronic, steric and conformational factors have been noted,[2–4] and the potential of such solvent shifts for structure elucidation in the coumarin field has been emphasized.[5] The present paper points out the utility of benzene-induced shifts in the NMR spectra of methoxyflavones.

The solvent shifts ($\Delta = \delta_{CDCl_3} - \delta_{C_6H_6}$ ppm) which are observed for the simple mono-, di-, and tri-methoxyflavones (I–IV) can be assigned without much ambiguity, and are given with the structural formulae; where ambiguities exist, alternative assignments are given in square brackets. In flavones which are more highly substituted (V–XVI), the assignments are frequently not unambiguous, and the shifts of the OMe resonances are therefore most conveniently pictured by means of line spectra of the OMe region of each compound in the two solvents. Where lines representing OMe resonances are bracketed together, unambiguous assignments are not possible even when using the criteria which are enumerated below. The numbering system of the flavone nucleus which is employed is given with structure I; conventionally the phenyl substituent ring is numbered 1′ through 6′, but to avoid possible confusion in the diagrams a continuous series of numbers is used for our present purposes.

It is possible to follow the shifts of OMe resonances in multi-substituted flavones by using the following guides.

1. The data available from model compounds, e.g. the Δ value of the C-1 and C-3 OMe resonances of 1,2,3-trimethoxybenzene is +0·38 ppm, while that of the C-2 OMe resonance is −0·11 ppm.[2]

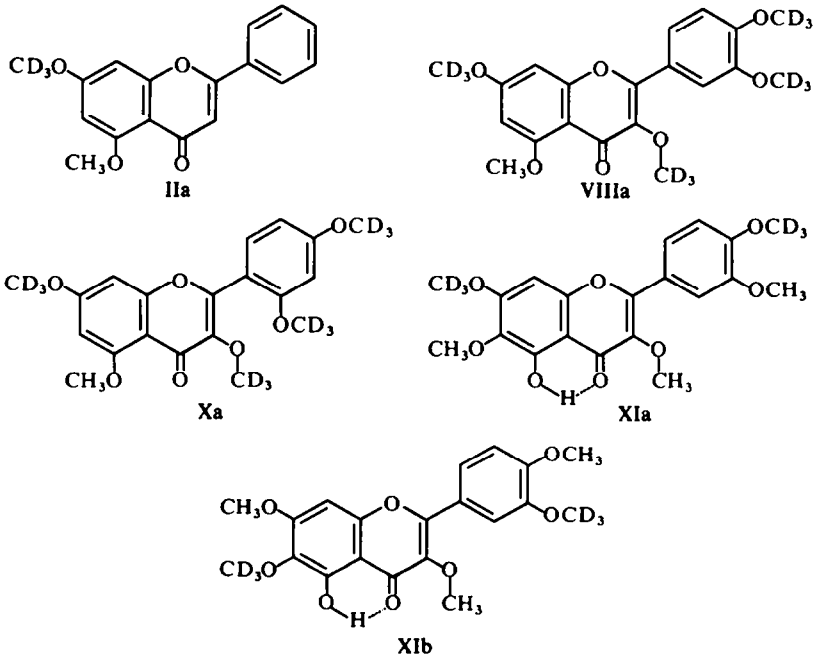
2. By making sensibly self-consistent assignments for flavones with similar structures, e.g. the OMe resonances of III are coincident at $\delta = 3{\cdot}84$ ppm in $CDCl_3$, but occur at 3·21 and 3·16 ppm in benzene. Since the corresponding figures for the



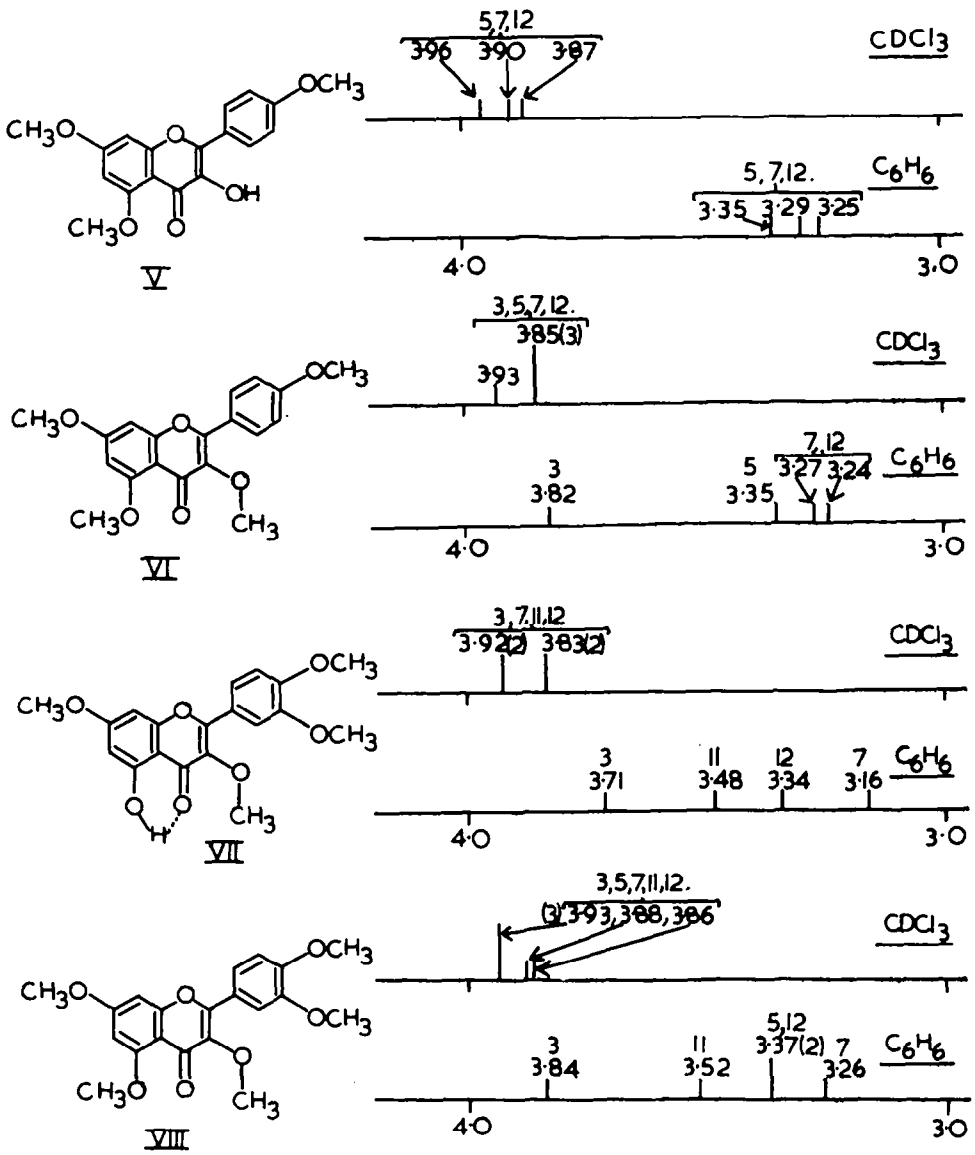
I II III IV

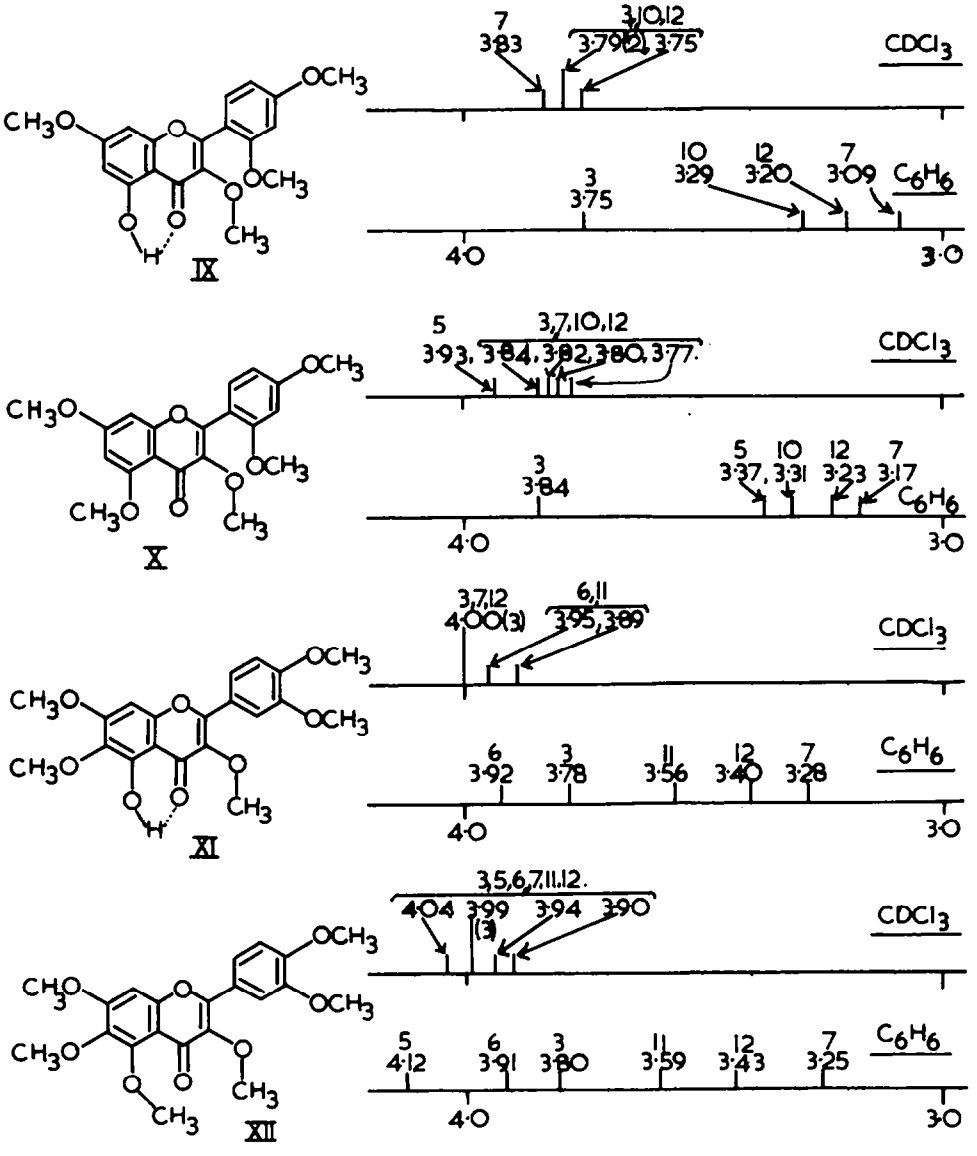
7-OMe of I in the two solvents are 3·86 and 3·15 ppm (in $CDCl_3$ and C_6H_6, respectively), the larger solvent shift in III is assigned to the 7-OMe group.

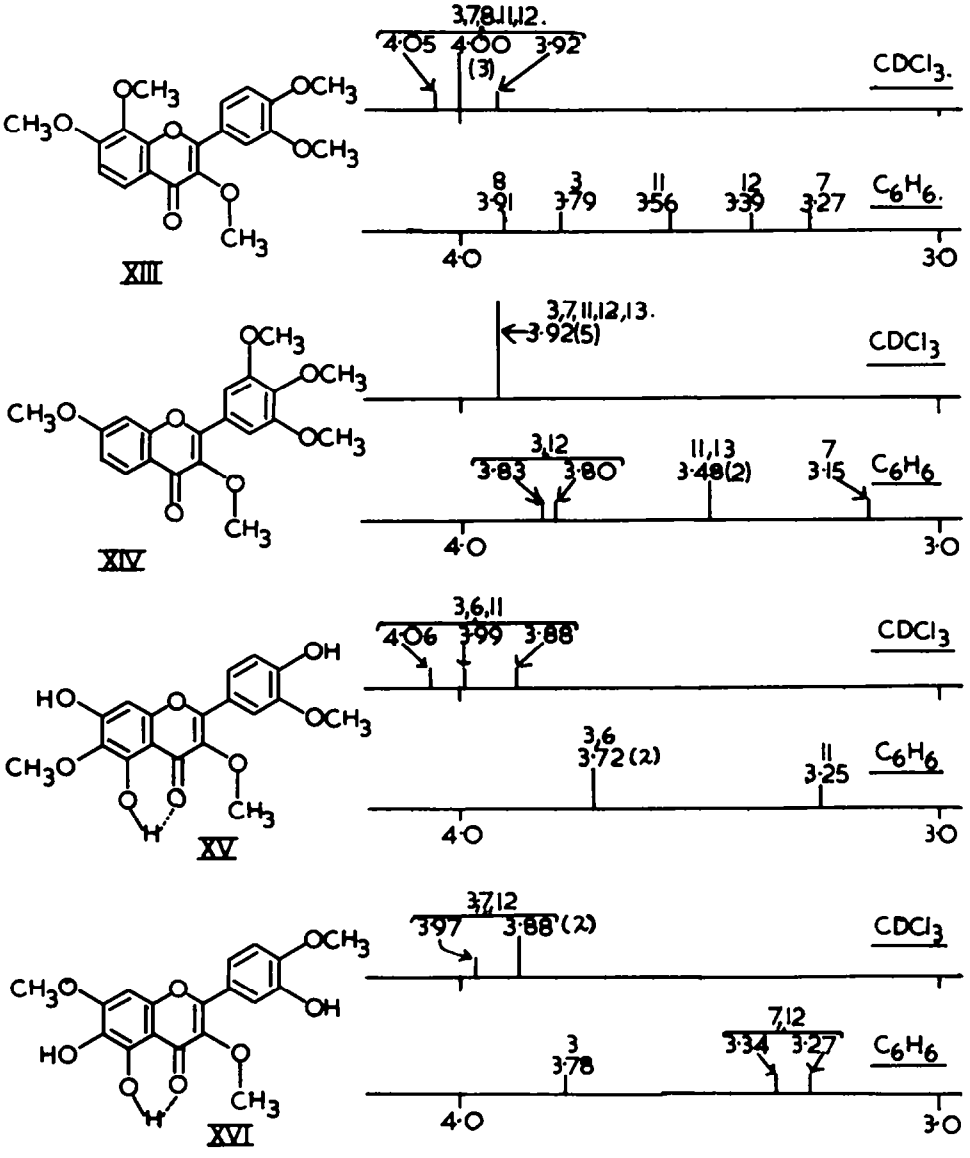
3. Specific deuteration of certain OMe groups by deuteromethylation of the corresponding phenol. For deuteromethylation, the method of Van der Merwe *et al.*[6] was employed (treatment of the phenol with diazomethane in the presence of a dioxan–deuterium oxide mixture). The following specifically deuterated flavones were prepared by this method and have been utilized in assigning the OMe resonances. In the syntheses of IIa, VIIIa and Xa, the inert nature of the hydrogen-bonded 5-OH group towards diazomethane was utilized, this group being methylated subsequently by treatment with dimethyl sulphate and alkali.



IIa VIIIa Xa XIa XIb


5,7,12
3·96 3·90 3·87
CDCl3
5, 7, 12.
C6H6
3·35 3·29 3·25
4·0
3·0
V
3,5,7,12.
3·85(3)
3·93
CDCl3
7,12
3
3·82
5
3·27 3·24
C6H6
3·35
4·0
3·0
VI
3,7,11,12
3·92(2) 3·83(2)
CDCl3
3
3·71
11
3·48
12
3·34
7
3·16
C6H6
4·0
3·0
VII
3,5,7,11,12.
(3) 3·93, 3·88, 3·86
CDCl3
5,12
3
3·84
11
3·52
3·37(2)
7
3·26
C6H6
4·0
3·0
VIII


IX
7
3·83
3,10,12
3·79(2), 3·75
CDCl3
10
3·29
12
3·20
7
3·09
C6H6
3
3·75
4·0
3·0
X
5
3·93, 3·84, 3·82, 3·80, 3·77
CDCl3
3
3·84
5
3·37, 3·31
10
12
3·23
7
3·17
C6H6
4·0
3·0
XI
3,7,12
4·00(3)
6,11
3·95, 3·89
CDCl3
6
3·92
3
3·78
11
3·56
12
3·40
7
3·28
C6H6
4·0
3·0
XII
3,5,6,7,11,12.
4·04
3·99
(3)
3·94
3·90
CDCl3
5
4·12
6
3·91
3
3·80
11
3·59
12
3·43
7
3·25
C6H6
4·0
3·0


3,7,8,11,12.
4·05 4·00 3·92
(3)
CDCl3.
8 3 11 12 7
3·91 3·79 3·56 3·39 3·27
C6H6.
4·0
3·0
XIII
3,7,11,12,13.
←3·92(5)
CDCl3
3,12
3·83 3·80
11,13
3·48(2)
7
3·15
C6H6
4·0
3·0
XIV
3,6,11
4·06 3·99 3·88
CDCl3
3,6
3·72(2)
11
3·25
C6H6
4·0
3·0
XV
3,7,12
3·97 3·88(2)
CDCl3
7,12
3·34 3·27
3
3·78
C6H6
4·0
3·0
XVI

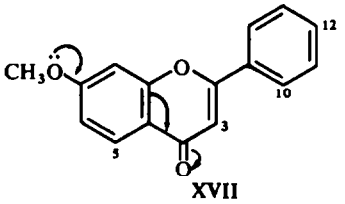
From a consideration of the results *in toto*, it is apparent that if the local environment (mainly with regard to immediately adjacent substituents) of an OMe group is defined, the solvent shifts are characteristic of that local environment, and frequently also characteristic of the position of substitution. In Table 1, the ranges of values for OMe groups at C-5, C-7, C-10 and C-12, in the absence of *o*-OMe or *o*-OH

TABLE 1. Δ VALUES ($\delta_{CDCl_3} - \delta_{C_6H_6}$ ppm) for C-3, C-5, C-7, C-10 AND C-12 OMe RESONANCES IN THE ABSENCE OF *ortho*-SUBSTITUENTS

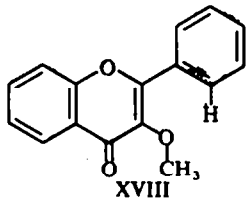
Position of OMe	Range of Δ values
C-3	−0·07 to +0·34
C-5	+0·43 to +0·58
C-7	+0·54 to +0·76
C-10	+0·46 to +0·53
C-12	+0·54 to +0·71

neighbours are given. Since the environment of the C-3 OMe group cannot be altered by substitution on an adjacent carbon atom, the range of solvent shifts for this OMe group is also included. It is apparent that OMe groups at C-5, C-7, C-10 and C-12 can in the absence of *ortho*-neighbours be differentiated from a C-3 OMe group. For "isolated" OMe groups at C-5, C-7, C-10 and C-12, the shifts are always larger than that (0·46 ppm) of the OMe resonance of anisole. This observation is consistent with the formal ability of all these OMe groups to conjugate with the electron-withdrawing carbonyl group (see, for example, XVII). This conjugation can lead to a decrease in π-electron density at oxygen atoms of the OMe groups in question, and so enhance an association with benzene at these electron-deficient sites with a resultant increased shielding effect.[2,3] The C-3 OMe resonances are in contrast deshielded or only slightly shielded in benzene (Table 1). This observation strongly suggests that the C-3 OMe group in general prefers the conformation indicated in XVIII. In this conformation, phase independent associations of benzene with the carbonyl group will have a deshielding influence on the C-3 OMe group.[7,8] Since the Δ values of the C-5 OMe group are only slightly smaller in magnitude than those for the C-7, C-10 and C-12 OMe groups, it is concluded that in the absence of a C-6 substituent, the preferred conformation for the C-5 OMe is as shown in XIX (i.e., as distant as possible from the negative end of the carbonyl dipole).

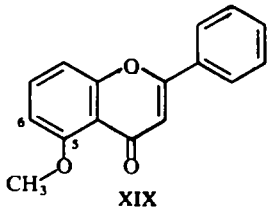
In the compounds studied, the central OMe of three OMe groups suffers a small positive or negative solvent shift (widest possible range is +0·13 to −0·12 ppm), as can be seen from the data for XII and XIV. This behaviour is analogous to the case of 1,2,3-trimethoxybenzene[2,3] which was cited earlier, and if used cautiously (i.e. by taking account of the presence of additional polar substituents) should be generally useful in indicating the presence of three adjacent OMe groups in natural products. The reason for the small positive or negative shift is probably due to some combination of (i) steric inhibition of benzene solvation of the central OMe group,[4] (ii) reduction in solvation of the central OMe (relative to the anisole case) due to the presence of two *ortho* electron-donating substituents,[2,3] and (iii) solvation of the



XVII



XVIII



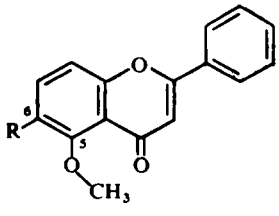
XIX

outer OMe groups, the stereochemistry of benzene association being such as to place the central OMe in a region of deshielding. It is emphasized that the steric factor cannot be the major influence, since an electron-withdrawing substituent *ortho* to an OMe function increases the upfield shift which is observed in benzene.[3]

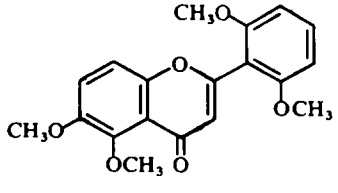
Since the heterocyclic oxygen atom attached to C-9 should have an effect similar to a hypothetical OMe substituent at the position, it might be anticipated that in 7,8-dimethoxyflavones (e.g. XIII), the C-8 OMe resonance would suffer only a small solvent shift. This supposition is confirmed by the data for XIII.

In a similar manner, an OMe group which is situated such that one neighbouring carbon atom carries an OH group and the other an OMe group, both of which can formally conjugate with the carbonyl group, has a very small positive or negative solvent shift [the C-6 OMe of XI exhibits $\Delta = +0{\cdot}03$ ppm (or $\Delta = -0{\cdot}03$ ppm as an alternative assignment); the possible assignments have been reduced with the aid of the deuterated derivatives XIa and XIb].

The solvent shift of an OMe group at C-5 suffers a drastic change in magnitude from a relatively large positive value (see Table 1) to a small or negative value (see data for XII) in the presence of an OMe at C-6. Such a change is in accord with expectations, since the introduction of an *ortho*-OMe group generally causes an algebraic decrease in Δ, and in addition a C-6 substituent should lead to a higher population of the conformer XX in which the Me of the C-5 functionality lies in close proximity to the negative end of the carbonyl dipole (which is a region of strong deshielding due to benzene association at the carbonyl group[7]). This characteristic solvent shift has proved useful in the structure elucidation of zapotin (XXI).[9]



XX



XXI

EXPERIMENTAL

NMR spectra were obtained either on a Perkin–Elmer 60 Mc instrument or a Varian Associates HA 100 Mc instrument. In all cases the concentration of the flavones in benzene or $CDCl_3$ solns was not greater than 2% w/v. The spectra were (with one exception, see below) obtained at normal probe temps (30–33°), using TMS as internal reference. Due to solubility problems, the spectra of XVI were recorded in $CDCl_3$ soln at 60° and benzene soln at 110° (sealed tube). The recorded shifts therefore differ from the values to be expected at room temp, but the trends are clear for the purposes of empirical correlation.

The preparation of specifically deuterated flavones may be exemplified by the preparation of IIa.

Chrysin 5-methyl-7-trideuteromethyl ether (IIa). Deuterium oxide (3 ml) was added to a soln of diazomethane in dry dioxan,[6] followed by slow dropwise addition of a dioxan–D_2O soln of chrysin (250 mg). After the mixture had been allowed to stand overnight, the solvents were removed and the residue recrystallized from EtOH to give chrysin 7-trideuteromethyl ether (144 mg, m.p. 160–164°; lit.[10] m.p. for chrysin 7-methyl ether is 163°). The 7-trideuteromethyl ether (100 mg) in acetone (5 ml) was treated with Me_2SO_4 (0·3 ml) and 20% NaOHaq (1·3 ml) and the reaction mixture heated on a water bath for 1 hr, after standing at room temp for 1 hr. Water (3 ml) and conc NH_4OH (3 ml) were then added to the cooled reaction mixture, and the yellow crystals which formed were isolated by filtration. Recrystallization from aqueous EtOH gave IIa (m.p. 144–146°; lit.[10] m.p. for chrysin 5,7-dimethyl ether is 143°).

Other deuterated flavones were prepared by unexceptional variations of this technique (see also Ref. 11).

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