Benzopyrones. Part 18. Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Chromones

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The carbon n.m.r. spectra of 29 substituted chromones have been measured and assigned. The data for these and 10 other chromone derivatives show that the chemical shifts of the six benzenoid carbon nuclei are affected to a relatively small extent (< ±2 p.p.m.) by changes in the substituents on the pyrone ring. Similarly the pyrone ring carbons (C-2, C-3, and C-4) are relatively insensitive to changes in substituents at C-6 and C-7 of the benzene ring. Carbon n.m.r. data can be used to identify isomeric chromone derivatives which are otherwise difficult to differentiate.

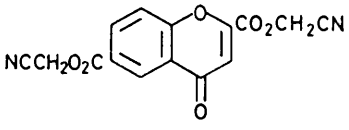
CHROMONE derivatives occur widely in nature [1] and many natural and synthetic chromones have biological activities which render them of considerable pharmaceutical interest.[2]

In connection with the problems of differentiating between isomeric chromone derivatives, we have measured and assigned the carbon n.m.r. spectra of 29 substituted chromones.

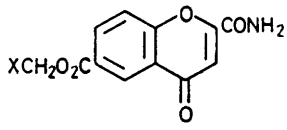
The spectrum of chromone itself (1) was first reported [3] in 1975, and the spectra of a few substituted chromones have since been assigned.[4,5] The assignments reported in this paper were made by comparison with chromone itself and using the known substituent effects.[6-8] In addition, specific decoupling was used when practicable to confirm some assignments, and a few spectra were measured without proton decoupling. The shielding of hydroxy-bearing carbon atoms that results when D_2O exchange is effected was used to confirm the assignment for C-7 and differentiate it from the ester carbonyl carbon atom in ester (28). A similar shielding (0.15 p.p.m.) after D_2O exchange in ester (27) was observed for C-6 to which an amino-substituent was attached; this enabled C-6 to be differentiated from C-8a.

The carbon chemical shifts of the chromone derivatives (1)—(9), in which the benzenoid ring (A) is unsubstituted are listed in Table 1. Data for compounds (10)—(15) are taken from the literature.[4,5] For compounds that were insufficiently soluble in $CDCl_3$, $(CD_3)_2SO$ was used as solvent; we have found that changing the solvent from $CDCl_3$ to $(CD_3)_2SO$ causes only small chemical shifts (between 0 and 1.3 p.p.m.). Similarly a four-fold change in concentration of the ester (8) in $CDCl_3$ solution caused shifts of between 0 and 0.4 p.p.m. The data in Table 1 show that in derivatives with a variety of substituents on the pyrone ring (B) the chemical shifts of the ring A carbon atoms fall within the following ranges: 117.3—119.2 p.p.m. for C-8, 154.9—156.4 p.p.m. for C-8a, 132.7—135.8 p.p.m. for C-7, 121.5—125.4 p.p.m. for C-4a. For many compounds the shifts of C-5 and C-6 were very similar and were not assigned; the shift range for these two carbons taken together was 124.2—127.1 p.p.m. The relatively small effect that changing the substituents in ring B has on the chemical shifts of ring A carbons is further illustrated by comparison of the following pairs of compounds (in Table 2); (20) and (22) (26) and (31), (25) and (30), and (28) and (34). Similar but narrower chemical-shift ranges have been reported for the ring A carbons of isoflavone derivatives, though the variations in structure that were studied were mainly in the substituents on the phenyl ring attached to the pyrone ring.[9]

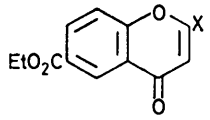
The data in Table 2 show that for derivatives (21)—(29) of ethyl 4-oxochromen-2-carboxylate with varying substituents in ring A, the chemical shifts of the pyrone ring carbons C-2, C-3, and C-4 fall within the following ranges: 151.3—152.9 p.p.m. for C-2, 112.2—115.3 p.p.m. for C-3, and 176.1—178.1 p.p.m. for C-4. Comparison of the pairs of compounds (14) and (30), (14) and (31), (30) and (31), (34) and (35), and (36) and (37) also shows the relatively small shift variations of the ring B carbons C-2, C-3, and C-4 with substituent changes in ring A. These shift ranges are small enough to be useful in assigning the spectra of compounds of related structure.



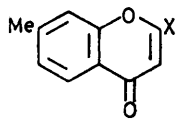
(32)



(33)



(36)



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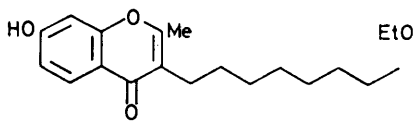

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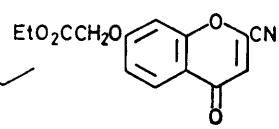
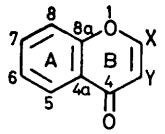


(39)

X = 1H-tetrazol-5-yl

TABLE 1 [1]



(1) X = Y = H
(2) X = Y = Me
(3) X = H, Y = NO_2
(4) X = H, Y = CHO
(5) X = Ph, Y = OH
(6) X = CH=CHPh, Y = CH_2OAc
(7) X = $CONH_2$, Y = H
(8) X = CO_2Et, Y = H
(9) X = H, Y = Ac
(10) X = CH_2OH, Y = H
(11) X = CHO, Y = H
(12) X = Ph, Y = H
(13) X = H, Y = Ph
(14) X = Me, Y = H
(15) X = H, Y = Me
(16) X = Me, Y = CHO
(17) X = Me, Y = CO_2Et
(18) X = CH=CHPh, Y = CHO
(19) X = $CHBr_2$, Y = Me

Compd.	C-8	C-7	C-6	C-5	C-4a	C-8a	C-4	C-3	C-2	Other
(1)	118.2	133.7	125.6 *	125.2 *	124.8	156.4	177.4	112.9	155.9	
(2)	117.5	132.8	125.6 *	124.3 *	122.5	155.7	177.5	116.7	161.8	18.4 and 9.9 (Me)
(3) [2]	118.9	135.5	127.1 *	125.9 *	124.5	154.9	167.2	136.6	160.3	
(4)	118.6	134.8	126.6	126.1 ‡	125.3	156.2	175.8	120.3	160.7	188.5 (CHO)
(5) [2]	118.2	133.4	125.0 *	124.2 *	121.5	154.9	173.1	139.3	145.1	131.5, 129.6, 128.3, and 127.7 (Ph)
(6)	117.7 *	133.9	125.0	126.0 ‡	123.2	155.5	177.1	115.7	161.0	138.6, 135.2, 130.1, 129.0, 127.9, and 117.3 * (CH=CHPh)
(7) [2]	118.8	134.9	125.9 *	124.8 *	123.5	155.1 †	177.4	110.5	155.8 †	160.7 (CO)
(8)	118.7	134.7	125.8 *	125.6 *	124.4	155.9	178.1	114.6	152.3	160.4 (CO), 62.9, and 14.1 (CH_2CH_3)
(9)	118.3	134.3	126.2 *	126.4 *	125.4	155.8	175.1	122.9	161.6	196.4 and 31.4 ($COCH_3$)
(10) [2,3]	118.1	134.1	124.9	125.3	123.3	155.7	176.8	107.2	169.7	59.8 (CH_2)
(11) [2,3]	119.2	135.8	125.3	126.4	124.4	155.3	178.3	117.8	156.7	187.7 (CHO)
(12) [4]	118.6	134.2	125.7	126.2	124.5	156.8	178.9	108.1	163.7	132.0, 129.5, and 126.8 (Ph)
(13) [4]	118.1	133.6	125.3	126.4	125.4 *	156.2	176.1	124.7 *	153.1	132.0, 129.0, 128.5, and 128.2 (Ph)
(14) [4]	117.4	132.9	124.4	125.0	123.1	155.9	177.3	110.0	165.8	20.0 (Me)
(15) [4]	117.4	132.7	124.2	125.0	123.0	156.0	177.2	120.0	151.3	10.5 (Me)
(16)	118.1	134.6	126.1	125.7 ‡	124.1	155.7	177.3	117.2	174.0	190.9 (CHO)
(17)	117.7	134.0	126.1 *	125.5 *	123.4	155.6	174.3	118.2	166.6	165.1 (CO) and 19.5 (Me)
(18)	117.9	134.7	125.8	125.8	124.2	155.3	178.1	114.2	165.6	191.3 (CHO), 143.6, 134.8, 131.0, 129.1, 128.7, and 117.9 (CH=CHPh)
(19)	118.0	134.2	125.5 *	125.3 *	121.9	155.5 †	177.4	114.2	156.6 †	32.4 ($CHBr_2$) and 9.2 (Me)

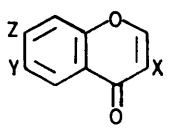
[1] Chemical shifts, in p.p.m. from $SiMe_4$, refer to solutions in $CDCl_3$ unless otherwise stated. [2] Solvent: $(CD_3)_2SO$. [3] Data from ref. 4. [4] Data from ref. 5.

* and †: Assignments may be reversed. ‡ Assignment confirmed by specific irradiation of ^1H signal.

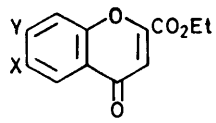
The use of carbon chemical shifts to differentiate isomeric structures is illustrated by the ester amide (33). This synthetic compound [10] had either structure (33) or that of its isomer with the ester and amide groups interchanged. To differentiate these amides, use was made of the decreased shielding (3.5 or 2.8 p.p.m.) of C-2 and the increased shielding (4.1 p.p.m.) of C-3 in the 2-carboxamide (7) compared with the 2-carboxylic ester (8). A similar deshielding and shielding is observed when amide and ester groups are attached to benzene and furan rings.[11] The chemical shift of the tetrazole ring carbon was assigned the value 153.1 p.p.m. by comparison with the shift for the corresponding carbon in tetrazol-5-ylmethyl benzoate (153.2 p.p.m.). The shift of 156.1 p.p.m. was thus assigned to C-2, and this, together with the shift of 111.0 p.p.m. for C-3, established that the synthetic compound was the 2-carboxamide (33).

It may also be noted that the carbonyl carbons of carboxylic esters and carboxamides are *ca.* 4 p.p.m. more shielded when attached to C-2 than when attached to C-6, the chemical shift ranges being 163.3—165.8 p.p.m. for C-6-carbonyl carbons and 158.9—160.7 p.p.m. for C-2-carbonyl carbons. This difference is presumably a reflection of the reduced polarisation of the carbonyl π orbital caused by electron withdrawal by C-2, which has a relatively low electron density.[12] There is also a small difference in shielding for C-1′ of the alkyl groups of carboxylic esters, the substituent at C-2 being more shielded (by *ca.* 1 p.p.m.) than the C-6 substituent. Thus in one slightly impure sample of the monoester (24), it was possible to identify the contaminant as the isomeric 6-ethoxycarbonyl derivative from the ethyl methylene carbon signal at 61.3 p.p.m. The presence of an isomeric impurity would not be detected by elemental analysis. In a similar manner the structure of the diester (29) was deduced from the chemical shift

TABLE 2 [1]

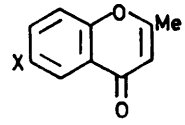


(20) X = Y = H, Z = Me
(34) X = cyclopentyl, Y = H, Z = OH
(35) X = cyclopentyl, Y = OH, Z = H



(21) X = Me, Y = H
(22) X = H, Y = Me
(23) X = Br, Y = H
(24) X = CO_2H, Y = H
(25) X = CO_2Et, Y = H

(26) X = CN, Y = H
(27) X = NH_2, Y = H
(28) X = H, Y = OH
(29) X = CO_2CH_2CN, Y = H



(30) X = CO_2Et
(31) X = CN

Compd.	C-8	C-7	C-6	C-5	C-4a	C-8a	C-4	C-3	C-2	C-2/C=O	C-6/C=O	Other
(20)	117.4	144.5	126.1	124.7	122.0	156.0	176.7	112.2	154.9			21.1 (Me)
(21)	118.5	135.9	135.9	124.9	124.1	154.2	178.1	114.4	152.1	160.5		62.9, 14.0 (CH_2CH_3), and 20.9 (Me)
(22)	118.4	146.2	127.3	125.3 †	122.1	156.0	177.9	114.5	152.0	160.4		62.9, 14.1 (CH_2CH_3), and 21.8 (Me)
(23)	120.7	137.7	119.5	128.4 †	125.7	154.7	176.9	114.7	152.5	160.2		63.1 and 14.1 (CH_2CH_3)
(24) [2]	119.5	135.1	128.4 *	126.6	123.4 *	157.6	176.9	114.1	152.4	159.7	165.8	62.8 and 13.8 (CH_2CH_3)
(25)	119.2	135.3	128.4	128.1	124.1	158.4	177.8	115.2	152.5	160.2	165.0	63.2, 61.6, 14.3, and 14.1 (CH_2CH_3)
(26)	120.6	136.9	110.3	131.4	124.8	157.7	176.5	115.3	152.9	159.9		63.3 and 14.1 (CH_2CH_3)
(27) [2]	122.8	119.4 †	147.3	104.3	124.8	147.5	177.1	122.2 †	151.3	160.2		62.4 and 13.8 (CH_2CH_3)
(28) [2]	102.5	163.7	115.9	126.7 †	116.7	157.3	176.1	113.8	151.6	160.0		62.5 and 13.9 (CH_2CH_3)
(29)	120.2	135.1	125.5 *	127.2	123.7 *	158.2	176.8	114.2	152.6	159.6	163.4	62.9, 13.8 (CH_2CH_3), 115.8, and 50.2 (CH_2CN)
(30)	118.2	134.2	127.5 *	128.1	123.3 *	158.9	177.6	111.0	166.4		165.4	61.4, 14.4 (CH_2CH_3), and 20.5 (Me)
(31)	119.6	135.8	109.2	131.4 †	124.1	158.2	176.1	111.3	166.9			117.6 (CN) and 20.6 (Me)
(32) [2]	120.1	135.3	125.7 *	127.2	123.7 *	158.2	176.6	115.0	151.4	158.9	163.3	115.7, 115.1 (CN), 51.1, and 50.2 (CH_2)
(33) [2]	119.9	135.0	126.0 *	127.2	123.4 *	157.9	177.0	111.0	156.1	160.4	163.9	153.1 (tetrazole C), and 56.3 (CH_2)
(34) [3,5]	102.0	162.4	114.7	126.7	116.4	157.6	176.1	126.4	150.7			36.6, 31.0, and 24.8 (cyclopentyl)
(35) [4,5]	123.4	120.2	151.2	109.0	125.6	155.4	177.4	127.1	152.3			38.0, 32.0, and 25.8 (cyclopentyl)
(36) [2]	119.2 †	134.6	127.1	126.3	123.2	157.6	175.6	110.4	151.8		164.0	61.3 and 14.0 (CH_2CH_3)
(37) [2]	118.0	146.1	127.4	124.5	121.5	155.5	176.1	110.4	151.5			153.0 (tetrazole C), and 21.2 (Me)
(38)	102.5	163.1 *	115.7	127.3	115.7	158.1	178.4	120.8	163.0 *			31.9, 29.8, 29.5, 29.3, 29.0, 25.0, 22.7, 14.1 (octyl), and 18.4 (Me)
(39)	101.7 †	163.3	116.0	127.7	119.0	157.7	174.7	120.3 †	137.6			167.5 (CO), 111.8 (CN), 65.5 † (CH_2), 61.9, and 14.2 (CH_2CH_3)

[1] Chemical shifts. in p.p.m. from $SiMe_4$ refer to solutions in $CDCl_3$ unless otherwise stated. [2] Solvent: $(CD_3)_2SO$. [3] Solvent: $CDCl_3$–$(CD_3)_2SO$ 1 : 1. [4] Solvent: $(CD_3)_2CO$. [5] Data from ref. 9.

* Assignments may be reversed. † Assignment confirmed by specific irradiation of ^1H signal.

of the ethyl methylene carbon atom (62.9 p.p.m.) In eight derivatives of known structure with an ethoxycarbonyl group at C-2, the chemical shifts of the ethyl methylene carbons were in the range 62.4—63.4 p.p.m. The corresponding range for the ethoxycarbonyl group at C-6 in (25), (30), (36) and the isomeric impurity in (24) was 61.3—61.4 p.p.m.

EXPERIMENTAL

The ^{13}C n.m.r. spectra were measured using a Varian XL-100 spectrometer interfaced with a 620L-100 computer and disc. For routine measurements a 33° pulse was used with a repetition time of 1.6 s. Under these conditions quaternary carbons gave weaker signals than protonated carbons, but their identification was confirmed using off-resonance ^1H-decoupled spectra. The digital resolution for the plotted spectrum was 1 data point per Hz; chemical shifts (p.p.m. downfield from internal Me_4Si) are therefore rounded to the nearest 0.1 p.p.m. For spectra measured without proton decoupling, 32K data points were used for a sweep width of 5 400 Hz; the digital resolution in the frequency domain was thus 3 points per Hz.

The undecoupled spectrum of compound (17) was required to assign the signals for C-2 and the ester carbonyl carbon. The latter gave a triplet (^3J 3 Hz) due to coupling with the methylene protons; C-2 gave a quartet (^2J 6.5 Hz). Other undecoupled spectra supported the assignments listed.

The signal of the tetrazole ring carbon could not be seen in the spectra of compound (36), which was suspected to contain a trace of paramagnetic impurity because the relative peak intensities were unusual. Such a carbon nucleus in the related tetrazole derivative (37) gave signals which were much less intense than those of other quaternary carbons.

The chemical shifts cited by Huckerby and Sunman [5] were relative to the solvent ($CDCl_3$) whose shift was not given. Since our chemical shifts for chromone differed by 0.5 p.p.m. from published values,[5] the shifts reported for compounds (12)—(15) were increased by 0.5 p.p.m. for consistency. The $CDCl_3$ shift in most of our measurements was 77.4 ± 0.2

p.p.m.; it usually increased with increasing solute concentration and for some dilute solutions (concentration *ca.* 0.2M) it was 77.1 p.p.m.

^{1}H N.m.r. spectra were measured on Perkin-Elmer R32 and Varian HA 100 spectrometers.

The chromone derivatives were synthesised by literature procedures, and one reference compound was synthesised as follows.

Tetrazol-5-ylmethyl Benzoate.—Benzoyl chloride (0.91 g, 6.5 mmol) was added to a solution of tetrazol-5-ylmethanol (0.5 g, 5.0 mmol) in dry pyridine (4 ml) at 0 °C. The mixture was stirred at room temperature for 10 min, and then poured into water (20 ml) and acidified with 5M-hydrochloric acid to pH 5. Extraction with dichloromethane gave (after drying and removal of the solvent) the *benzoate* (0.29 g, 28%), m.p. 120—121 °C (from dichloromethane) (Found: C, 53.1; H, 4.0; N, 27.8. $C_9H_8N_4O_2$ requires C, 52.9; H, 3.9; N, 27.5) $\nu_{max.}$ 1 740, 1 600, and 1 572 cm^{-1}; δ [$(CD_3)_2CO$] 12.87 (1 H, s, NH), 8.01—7.35 (5 H, m, ArH), and 5.70 (2 H, s, CH_2).

The authors are indebted to Mr. P. S. Bevan for the preparation of tetrazol-5-ylmethyl benzoate. Most of the n.m.r. spectra were measured by Messrs. W. M. Nettle, G. Llewellyn, and J. C. Weeks.

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REFERENCES

1 G. P. Ellis, ' Chromenes, Chromanones and Chromones,' Wiley, New York, 1977, Ch. VII.
2 A. Nohara in ' Drugs Affecting the Respiratory System,' ed. D. L. Temple, American Chemical Society, Washington, 1980. Ch. 7.
3 C. A. Kingsbury and J. H. Looker, *J. Org. Chem.*, 1975, **40**, 1120.
4 M. Payard and J. Couquelet, *Synthesis*, 1979, 889.
5 T. N. Huckerby and G. Sunman, *J. Mol. Struct.*, 1979, **56**, 87.
6 J. B. Stothers, ' Carbon-13 N.M.R. Spectroscopy,' Academic Press, New York, 1972, p. 196.
7 G. C. Levy and G. L. Nelson, ' Carbon-13 Nuclear Magnetic Resonance for Organic Chemists,' Wiley Interscience, New York, 1972, p. 80.
8 E. Breitmaier and W. Voelter, ' ^{13}C N.M.R. Spectroscopy,' 2nd edition, Verlag Chemie, Weinheim, 1978, p. 205.
9 A. Pelter, R. S. Ward, and R. J. Bass, *J. Chem. Soc. Perkin Trans. 1*, 1978, 666.
10 See preceding paper.
11 J. M. Williams, unpublished observations.
12 G. P. Ellis, ' Chromones. Chromanones and Chromones,' Wiley, New York, 1977, p. 560.