Tetrahedron Vol. 34, pp. 1837–1840
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0040–4020/78/0615–1837/$02.00/0

^{13}C NMR-SPECTROSCOPY OF POLYMETHOXYXANTHONES

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(*Received in the UK* 13 *October* 1977; *Accepted for publication* 9 *December* 1977)

Abstract—The ^{13}C NMR chemical shifts of eight methoxy-xanthones are reported. Methoxy substituent effects depending on substituent position as well as on shielded ring carbon position have been evaluated. Methoxy substituent increments for xanthones are proposed.

Polyoxygenated xanthones, often found as glycosides or substituted with alkyl groups and fused oxygen heterocyclic rings, are yellow plant pigments or mould metabolites. They have been found in higher plants in a limited number of families.[1,2] In the last few years xanthones have been well studied[1,3] and the growing interest in these compounds is easily explained by their pharmacological[4,5] and microbiological activities.[6,7]

Proton magnetic resonance spectroscopy is the most useful method for structure determination of xanthones.[8] However, there has yet been no systematic study of the use of ^{13}C NMR as a tool in structure elucidation for this class of compounds, although such data promise to be at least equally valuable. Recently ^{13}C NMR data of a few xanthones of fungal origin have been reported.[9]

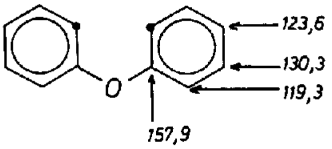
In this first paper we report ^{13}C NMR spectra of a range of methoxyxanthones,† with the object of providing background data and conclusions for use in future structural studies of naturally occuring xanthones. All investigated compounds except **4** are identically substituted in ring C, while methoxy groups in ring A change number and position (Table 1).

The ^{13}C-chemical shift values of xanthone‡ and the methoxyxanthones are given in Table 2. ^{13}C-Resonances of xanthone **3** are assigned on the basis of shift correlation in the incorporated partial-structures of the diphenylether **1**[10] and the benzophenone **2**[11] in combination with the chemical shift increments for *ortho* substitution (0, X)[11,12] in the fused system. The carbon-shifts of **1–3** are portrayed on the structure formulae:

In **3** C-8b (C-8a) and C-4a (C-4b) are 3 and 6 ppm, respectively, more shielded than expected from calculation, and the carbonyl-carbon by 20 ppm, owing to the non bonded electron pairs at oxygen, which are delocalized achieving a higher measure of aromaticity in ring B. Steric fixation in the plane of the carbonyl group of benzophenone in xanthone causes high field shift of C-1 (C-8) in contrast to the expected low field shift from the additive principle ($\Delta\delta \sim 5$ ppm). C-2, C-3 and C-4 shifts are in good agreement with calculated values ($\Delta\delta \pm$ 1 ppm).

With the help of qualitative Substituent Chemical Shift (SCS) effect of methoxy groups upon the ^{13}C-resonances of *ortho*, *meta* and *para* carbon atoms, all line frequencies of the methoxyxanthones have been correlated to specific carbons in proton noise decoupled spectra. Subsequently these assignments were supported by multiplicity and coupling constant information from off-resonance decoupled and coupled nuclear Overhauser enhanced spectra (gated decoupled).[13]

The effect of methoxy-groups on ^{13}C NMR shifts of aromatic carbons has been studied previously.[14–16] The evaluated shift increments for *ortho*, *meta* and *para* carbons however cannot be applied to methoxylated xanthones, since the increments are dependent on the position of the methoxy groups and on the position of the shifted *ortho*, *meta* and *para* carbons in the ring system, due to the special mesomeric interaction in the xanthone system. From measured chemical shifts for aryl carbon nuclei (Table 2) we have derived particular shift increments for non-*ortho*-methoxylated xanthones, which may be applied as additive increments to the shifts of the corresponding carbons of xanthones. The shift increments are given in Table 3. Accordingly the



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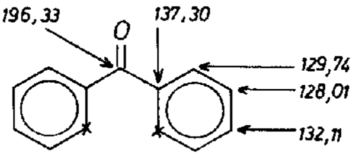

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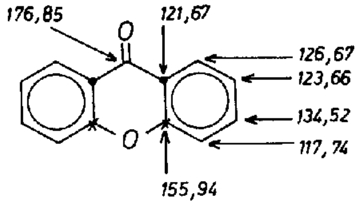

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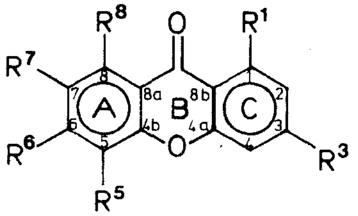
†Papers on ^{13}C NMR of hydroxyxanthones are under preparation.

‡Since the completion of our work, the ^{13}C data of xanthone have been published (see Ref. 24).

Table 1. Substitution pattern of methoxyxanthones



R = H or $-OCH_3$

Compound	R^1	R^3	R^5	R^6	R^7	R^8
4	H	OMe	H	H	H	H
5	OMe	OMe	H	H	H	H
6	OMe	OMe	OMe	H	H	H
7	OMe	OMe	H	OMe	H	H
8	OMe	OMe	H	H	OMe	H
9	OMe	OMe	H	H	H	OMe
10	OMe	OMe	OMe	OMe	H	H
11	OMe	OMe	H	OMe	OMe	H

Table 2. ^{13}C NMR-Chemical shifts of polymethoxyxanthones.

Compd.	C-1	C-2	C-3	C-4	C-4a	C-4b	C-5	C-6	C-7	C-8	C-8a	C-8b	C=O
3	126.49 Dd	123.66 Dd(d)	134.52 Dd	117.74 Dd	155.94 Sddd	155.94 Sddd	117.74 Dd	134.52 Dd	123.66 Dd(d)	126.49 Dd	121.67 St(dd)^{c}	121.67 St(dd)^{c}	176.85 Sm^{b}
4	128.06 D	113.03 Dd	164.93 Sdq	100.07 Dd	157.89 Sdd	156.04 Std	117.50 Dd	134.04 Dd^{e}	123.66 Dd	126.45 Dd^{e}	121.82 Sm^{b,c}	115.66 Sdd	176.01 Sm^{b}
5	161.75 Sq	94.85 Dd	164.64 Sq	92.56 Dd	159.50 Sd	154.07 St(dd)	116.64 Dd	133.34 Dd	123.45 Dd	126.42 Dd	122.84 Sdd^{c}	107.03 St(dd)	174.99 Sdd^{b}
6	161.78 Sq	95.33 Dd	164.73 Sq(dq)	92.80 Dd	159.45 Sd	145.08 Sm^{b}	147.82 Sm^{b}	114.38^{+} Ddd	123.07 D	117.61^{+} Dd	123.94 Sd	107.22 Sdd	175.03 Sm^{b}
7	161.70 Sq	94.83 Dd	164.26‡ Sm^{e}	92.60 Dd	159.56 Sd	156.36 Sdd	99.35 Dd	163.93‡ Sm^{e}	112.31 Ddd	127.91 Dd	116.72 St(dd)^{c}	106.94 St(dd)	174.78 Sm^{b}
8	161.75 Sq	94.85 Dd	164.56 Sq^{f}	92.45 Dd	159.62 Sd	149.45 St(dd)	118.06 D	122.94 Dd	155.79 Sm^{b}	106.40 Ddd	123.26 Sm^{b}	106.77 Sdd	174.95 Sd
9	161.41 Sq	94.82 Dd	163.91 Sq	91.84 Dd	158.24 Sd	156.63 Sdd	108.76 Dd	133.13 D	105.58 Dd	160.15 Sm^{b}	113.48 Sdd^{c}	108.19 St(dd)	174.89 Sd
10	161.81 Sqn(dq)	95.15 Dd	164.58 Sq	92.91 Dd	159.66 Sd	149.10 Sdd	135.69 Sm^{b}	156.46 Sm^{b}	108.20 Dd	121.97 Dd	117.86 Sd	106.69 Sdd	174.70 Sd
11	161.75 Sq	94.93 Dd	164.93 Sq	92.53 Dd	159.61 Sd	150.68 Sdd	98.83 D	154.29 Sm^{b}	146.43 Sm^{b}	105.81 D	115.94 Sdd	106.88 Sdd	174.41 Sd

a) Capital letters refer to $^{1}J_{^{13}C^{1}H}$- and small letters to $^{2-LR}J_{^{13}C^{1}H}$-splitting pattern.

S = Singlet, D and d = Doublet, t(dd) = double Doublet, q = Quartet, qn = Quintet, m = Multiplet.

b) not resolved;

c) partly overlapped by bigger signals;

d) undecoupled pattern are overlapping;

e) with further unresolved splitting.

+ Further confirmation under study.

‡ Signals may be interchanged in horizontal lines.

following shift rules can be established for *ipso*-, *ortho*-, *meta*- and *para*-carbon nuclei:

Carbon relative to methoxy group	Carbon in ring position	Increment [ppm]
C-*ipso*:	1–8	+32.0 ± 2.5
C-*ortho*:	1, 4, 5, 8	−19.0 ± 1.5
	8b, 4a, 4b, 8a	−9.5 ± 1.5
	2, 3, 6, 7	
	by *ortho*-methoxy at C-1, 4, 5, 8	−19.0 ± 1.5
	at C-3, 2, 7, 6	−11.0 ± 1.0
C-*meta*:	1, 4, 5, 8	
	8b, 4a, 4b, 8a	+1.5 ± 1.0
	2, 3, 6, 7	−1.0 ± 1.0
C-*para*:	1, 4, 5, 8	−8.0 ± 1.0
	8b, 4a, 4b, 8a	−5.5 ± 1.0

Highfield shifts of *ortho* carbons, facing the incorporated γ-pyrone ring, are nearly twice as large as those of carbons in the opposite direction. This indicates a preferred electron release by the methoxy oxygen towards the γ-pyrone system. For *ortho* and vicinally methoxylated xanthones failure of additivity with the given *ortho* increments is observed. However, good agreement between measured and calculated shift values is achieved if increments for *ortho* carbons, which are methoxylated as well, are levelled to −9.5 ± 1.5 ppm.[17,18] This "downfield" shift is caused by the *ortho* steric effect of two methoxy groups with steric hindrance to resonance interaction of the methoxy oxygen with the methoxylated *ortho* carbon.

It is also noteworthy, that number and position of substitution in one ring (C or A) has very little or no effect on the chemical shifts of the otherone (A or C), except when there is substitution in 1 and/or 8 position. The corresponding shift increments for A- and C-ring carbons are shown in Table 4. Methoxy substitution in position 1 (8) keeps positions 7 and 8 (1 and 2) nearly unaffected.

The CO carbon may be easily identified by its characteristic chemical shift at low field, 174.7 ppm, which is confined to an extremly narrow range (±0.3 ppm) for all 1- and/or 8-methoxy compounds[19] showing an apparent lack of sensitivity towards number and position of additional methoxy groups in ring A.[20] The high field shift of carbonyl carbons in these compounds in comparison with xanthone amounts to ~2 ppm.

Methoxyl carbons in ring positions 1, 2,† 3, 5, 6, 7, 8 show resonances between 55.3 and 56.3 ppm[19] (Table 5) and are in general of no diagnostic value. The shift values of methoxyl carbons in position 1, 5, 8 are ≥56 ppm, in position 2,† 3, 6, 7 around 55.5 ppm, increasing to >56 ppm, in the case of an *ortho* methoxy group.

The δ-values for methoxyl carbons surrounded by two *ortho* substituents[21] (OCH$_3$, O–Aryl, $\underset{\underset{\text{O}}{\|}}{\text{C}}$–Aryl[22]) are shifted downfield to 60–62 ppm, due to *ortho* steric

Table 3. ^{13}C-Shift increments for methoxyxanthones

Substituent in position	Shift Increments (in ppm) for carbon in position C-1(8)	C-2(7)	C-3(6)	C-4(5)	C-4a(4b)	C-8b(8a)
1(8)	+33.7	-18.1	-0.9	-8.3	+1.2	-8.8
2(7)	-20.1	+32.1	-11.6	+0.4	-6.5	+1.6
3(6)	+1.5	-11.0	+30.0	-18.0	+1.2	-5.0
4(5)	-8.9	-0.6	-20.1	+30.1	-10.6	+2.3

Table 4. ^{13}C-Shift increments for methoxyxanthones. Influence of 1-methoxysubstituent on ring A and/or 8-methoxysubstituent on ring C

Substituent A-Ring-Carbon	1-OCH$_3$ - shift	8-OCH$_3$ and increment (ppm) -	1-OCH$_3$ C-Ring-Carbon
4b	-1.3	-1.3	4a
5	-1.1	-0.7	4
6	-1.2	-0.7	3
8a	+1.2	+1.1	8b

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†Unpublished result of 2-methoxyxanthone: δ_{OCH_3} = 55.81 ppm.

Table 5. ^{13}C NMR Chemical shifts of methoxyl carbons in xanthones

Compound	^{13}C-Chemical Shifts of OCH_3 Groups in position					
	1	3	5	6	7	8
4	-	55,61	-	-	-	-
5	56,04	55,43	-	-	-	-
6	56,27	55,67	56,27	-	-	-
7	56,05	55,43	-	55,43	-	-
8	56,13	55,50‡	-	-	55,62‡	-
9	55,98‡	55,29	-	-	-	55,92‡
10	56,13	55,56	61,32	56,13	-	-
11	56,16	55,51	-	56,16	56,16	-

‡ interchangeable in horizontal line

hindrance. This effect on the methoxy group is known for other substituents (alkyl,[18] hydroxy[23,24]).

Methoxy groups in position 1, 4, 5 or 8 may also be identified by the relative intensities of the *ortho* positioned quarternary C-atoms C-8b, −4a, −4b or −8a, which are equal in xanthone. The intensity decreases by up to 50% (under specified measurement conditions), if the respective *ortho* position is substituted.

In conclusion, the following procedures for evaluation of the methoxy substitution pattern of xanthones emerge:

(1) Correlation of line frequencies of specific xanthone carbons with the help of the proposed substituent increments,

(2) correlation of line frequencies of methoxyl carbons. Differentiation between *ortho* and vicinally substituted methoxyxanthones;

(3) identification of 1- and/or 8-methoxy groups by $\delta_{C=O}$;

(4) identification of methoxy groups in 1, 4, 5, 8 position by comparing signal intensities of geminal quarternary C-atoms 8b, 4a, 4b and 8a with those of the unsubstituted analogue.

EXPERIMENTAL

Materials. All compounds were synthesized by published procedures.

^{13}C NMR spectra were obtained at 20.0 MHz in Fourier transform mode using a Varian Associates CFT-20 spectrometer and were run in deuteriochloroform solutions (saturated), which also provided the deuterium locksignal. δ-Values are given in ppm downfield from TMS ($\delta_{TMS} = 0$), measured from internal $CDCl_3$ and corrected by using the equation $\delta_{TMS} = \delta_{CDCl_3} - 76.89$.

Measurement conditions were as follows: PULSE WIDTH: 5 sec (approx. 21°); pulse delay: none; acquisition time: 1.023 sec; data points: 8192 (8 K); spectra width: 4 kHz; effective resolution: 0.05 ppm; probe temperature: 35°C; sample tubes: ϕ 10 mm. Accumulation of FID: (a) in ^1H-broad band noise decoupled mode: 1–6.5 × 10^4 times; (b) in coupled nuclear Overhauser enhanced mode: 4–24.5 × 10^4 times.

Acknowledgements—We wish to thank Frau B. Schley for carefully recording the ^{13}C NMR-spectra. One of us (R.K.C.) thanks Alexander von Humboldt foundation and Deutsche Forschungsgemeinschaft, respectively, for the awards of a postdoctoral fellowship (1975–76) and a postdoctoral research associateship (1977).

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