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Reference Data

^{1}H and ^{13}C NMR Spectroscopy of Mono-, Di-, Tri- and Tetrasubstituted Xanthones

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ABSTRACT: The structural elucidation of 24 xanthones with different substitution patterns was performed by spectroscopic methods, namely 2D NMR techniques, such as correlation spectroscopy (COSY), nuclear Overhauser effect (NOE), heteronuclear correlation (HETCOR) and a 1D NMR technique, selective insensitive nuclei enhanced by polarization transfer (INEPT). © 1997 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ^{1}H NMR; ^{13}C NMR; xanthones; structural elucidation

INTRODUCTION

Xanthones are a group of heterocyclic compounds having a dibenzo-γ-pyrone carbon skeleton (Fig. 1). Most of them have been isolated from two families of higher plants, *Guttiferae* and *Gentianaceae*,[1,2] and also from lichens, fungi and ferns.[3] They differ from each other mainly in the extent and pattern of oxidation. The growing interest in these natural and synthetic compounds is due to their pharmacological and biological activities and their importance in chemotaxonomy.[3–6]

The spectral assignments of xanthones by modern NMR methods is important not only to increase our knowledge of this class of compounds but also to supplement some of the data already obtained, mainly for naturally occurring xanthones.[7]

The 1D and 2D NMR spectroscopic techniques applied in this study allow an unambiguous assignment for all the proton and carbon resonances. The xanthonic compounds examined in this study included natural (**1**, **3**, **7**, **10**, **20**) and synthetic derivatives (**2**, **4**–**6**, **8**, **9**, **11**–**19**, **21**–**24**) (Fig. 2).

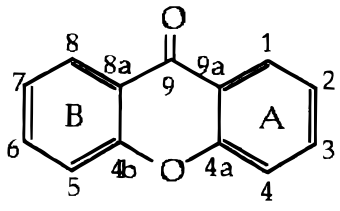

Figure 1. Structure of xanthone.

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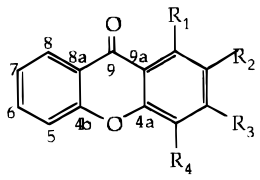
RESULTS AND DISCUSSION

^{1}H and ^{13}C NMR chemical shifts and proton coupling constants for xanthones **1**–**24** are given in Tables 1 and 2.

The common structural feature of **1**–**24** is that ring B is unsubstituted. The assignment of the ABCD system corresponding to H-5, H-6, H-7 and H-8 protons was carried out using COSY experiments. The following coupling paths were found corresponding to $^3J_{ortho}$ couplings: δ (ppm) 7.57–7.78; 7.78–7.93; 7.42–7.54; 8.09–8.20.

This experiment does not allow one to determine the sequence order, *i.e.* the distinction between the H-5 and H-8 resonances. However, this problem can be solved by taking into account that the H-8 are deshielded by mesomeric and anisotropic effects of the carbonyl group. In this way, the signals at higher frequency are assigned to the H-8 resonances. These assignments have also been performed in an indirect and unambiguous way using one-dimensional selective INEPT.[8] These experiments give the connectivity of a selected proton, by irradiation of the corresponding resonance, to the carbon atoms to which it is coupled, and can be optimized for different long-range J_{CH} coupling. The irradiation of the signals at δ 8.09–8.20, assigned to H-8, with a long-range J_{CH} coupling of 7 Hz, produces enhancement of the signals of C-9, whereas irradiation of the signals at δ 7.57–7.78, assigned to H-5, has no effect on the signals of C-9 (δ 174.7–181.8) (Table 2).

In the ^{1}H NMR spectra of **1**–**24**, the resonances of H-6 (δ 7.78–7.93) appear at higher frequencies than those corresponding to H-5 and H-7 resonances. This is also due to the mesomeric deshielding effect of the carbonyl group.



1) $R_1 = R_2 = R_3 = H$; $R_4 = OH$
2) $R_1 = R_2 = R_4 = H$; $R_3 = OH$
3) $R_1 = R_3 = R_4 = H$; $R_2 = OH$
4) $R_2 = R_3 = R_4 = H$; $R_1 = OH$
5) $R_1 = R_2 = R_3 = H$; $R_4 = OCH_3$
6) $R_1 = R_2 = R_4 = H$; $R_3 = OCH_3$
7) $R_1 = R_3 = R_4 = H$; $R_2 = OCH_3$
8) $R_2 = R_3 = R_4 = H$; $R_1 = OCH_3$
9) $R_1 = R_2 = H$; $R_3 = R_4 = OCH_3$
10) $R_1 = R_2 = H$; $R_3 = OH$; $R_4 = OCH_3$
11) $R_1 = R_2 = H$; $R_3 = OCH_3$; $R_4 = OH$
12) $R_1 = R_2 = H$; $R_3 = OH$; $R_4 = OCH_2CH_3$
13) $R_1 = CHO$; $R_2 = H$; $R_3 = OCH_3$; $R_4 = OH$
14) $R_1 = CHO$; $R_2 = H$; $R_3 = OCH_3$; $R_4 = OCH_2C_6H_5$
15) $R_1 = H$; $R_2 = CHO$; $R_3 = OH$; $R_4 = OCH_3$
16) $R_1 = H$; $R_2 = CHO$; $R_3 = OH$; $R_4 = OCH_2CH_3$
17) $R_1 = H$; $R_2 = CHO$; $R_3 = OCH_2C_6H_5$; $R_4 = OCH_3$
18) $R_1 = H$; $R_2 = R_3 = OH$; $R_4 = OCH_3$
19) $R_1 = H$; $R_2 = OH$; $R_3 = OCH_2C_6H_5$; $R_4 = OCH_3$
20) $R_1 = H$; $R_2 = R_3 = R_4 = OCH_3$
21) $R_1 = H$; $R_2 = CO_2H$; $R_3 = OH$; $R_4 = OCH_3$
22) $R_1 = OH$; $R_2 = CH_3$; $R_3 = OH$; $R_4 = H$
23) $R_1 = OH$; $R_2 = CH_3$; $R_3 = OH$; $R_4 = Cl$
24) $R_1 = OH$; $R_2 = CH_3$; $R_3 = OH$; $R_4 = Br$

Figure 2. Structures of xanthones **1**–**24**.

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Table 1. ^{1}H chemical shifts of xanthones 1–24

Compound	H-1	H-2	H-3	H-4	H-5	H-6	H-7	H-8
1	7.61 (dd; 7.8 and 1.8)	7.26 (t; 7.8)	7.34 (dd; 7.8 and 1.8)	10.51 [O*H*, s]	7.73 (dd; 8.0 and 0.8)	7.88 (ddd; 8.0, 7.6 and 1.6)	7.48 (ddd; 7.8, 7.6 and 0.8)	8.19 (dd; 7.8 and 1.6)
2	8.04 (d; 8.6)	6.91 (dd; 8.6 and 2.2)	11.01 [O*H*, s]	6.88 (d; 2.2)	7.61 (d; 8.2)	7.82 (ddd; 8.2, 7.6 and 1.7)	7.44 (dd; 7.9 and 7.6)	8.15 (dd; 7.9 and 1.7)
3	7.48 (d; 3.0)	10.00 [O*H*, s]	7.32 (dd; 9.0 and 3.0)	7.56 (d; 9.0)	7.63 (dd; 8.2 and 0.9)	7.85 (ddd; 8.2, 7.6 and 1.7)	7.45 (ddd; 8.0, 7.6 and 0.9)	8.19 (dd; 8.0 and 1.7)
4	12.56 [O*H*, s]	6.83 (dd; 8.3 and 0.6)	7.74 (dd; 8.3 and 8.2)	7.09 (dd; 8.2 and 0.6)	7.67 (d; 8.1)	7.92 (ddd; 8.1, 7.6 and 1.7)	7.51 (dd; 8.2 and 7.6)	8.18 (dd; 8.2 and 1.7)
5	7.73 (dd; 7.9 and 1.4)	7.40 (t; 7.9)	7.52 (dd; 7.9 and 1.4)	3.99 [OCH_3, s]	7.72 (d; 8.1)	7.88 (dt; 8.1 and 1.6)	7.49 (dd; 8.0 and 7.8)	8.20 (dd; 8.2 and 1.7)
6	8.10 (d; 8.9)	7.05 (dd; 8.9 and 2.4)	3.93 [OCH_3, s]	7.16 (d; 2.4)	7.63 (d; 8.0)	7.85 (ddd; 8.0, 7.6 and 1.7)	7.47 (dd; 7.7, 7.6)	8.17 (dd; 7.7 and 1.7)
7	7.54 (d; 3.2)	3.87 [OCH_3, s]	7.47 (dd; 9.1 and 3.2)	7.63 (d; 9.1)	7.64 (dd; 8.2 and 1.0)	7.86 (ddd; 8.2, 7.4 and 1.7)	7.46 (ddd; 7.7, 7.4 and 1.0)	8.18 (dd; 7.7 and 1.7)
8	3.91 [OCH_3, s]	7.00 (d; 8.3)	7.74 (dd; 8.4 and 8.3)	7.15 (d; 8.4)	7.57 (dd; 7.8 and 0.7)	7.80 (ddd; 7.8, 7.6 and 1.6)	7.42 (ddd; 7.7, 7.6 and 0.7)	8.09 (dd; 7.7 and 1.6)
9	7.94 (d; 9.0)	7.26 (d; 9.0)	3.97 [OCH_3, s]	3.92 [OCH_3, s]	7.69 (d; 8.1)	7.85 (ddd, 8.1, 7.5 and 1.7)	7.47 (dd; 7.9 and 7.5)	8.16 (dd; 7.9 and 1.7)
10	7.80 (d; 8.9)	7.00 (d; 8.9)	10.79 [O*H*, s]	3.92 [OCH_3, s]	7.69 (dd; 8.1 and 1.0)	7.84 (ddd; 8.1, 7.6 and 1.7)	7.46 (ddd; 7.7, 7.6 and 1.0)	8.16 (dd; 7.7 and 1.7)
11	7.68 (d; 9.0)	7.19 (d; 9.0)	3.96 [OCH_3, s]	9.66 [O*H*, s]	7.65 (dd; 8.3 and 1.0)	7.84 (ddd; 8.3, 7.6 and 1.7)	7.44 (ddd; 7.8, 7.6 and 1.0)	8.16 (dd; 7.8 and 1.7)
12	7.79 (d; 8.9)	6.99 (d; 8.9)	10.78 [O*H*, s]	4.16 and 1.37 [CH_2, q; CH_3, t; 7.0]	7.66 (dd; 8.2, and 1.0)	7.83 (ddd; 8.2, 7.4 and 1.7)	7.46 (ddd; 7.7, 7.4 and 1.0)	8.15 (dd; 7.7 and 1.7)
13	10.98 [C*H*O, s]	7.47 (s)	3.96 [OCH_3, s]	—	7.65 (d; 8.1)	7.85 (ddd; 8.1, 7.6 and 1.7)	7.46 (dd; 7.8 and 7.6)	8.15 (dd; 7.8 and 1.7)
14	10.88 [C*H*O, s]	7.40 (s)	4.03 [OCH_3, s]	5.24 [OCH_2, s]	7.64 (d; 8.0)	7.89 (ddd; 8.0, 7.9 and 1.6)	7.49 (t; 7.9)	8.14 (dd; 7.9 and 1.6)
15	8.30 (s)	10.30 [C*H*O, s]	10.51 [O*H*, s]	3.99 [OCH_3, s]	7.73 (d; 8.2)	7.89 (ddd; 8.2, 7.4 and 1.5)	7.50 (dd; 7.8 and 7.4)	8.16 (dd; 7.8 and 1.5)
16	8.25 (s)	10.25 [C*H*O, s]	11.41 [O*H*, s]	4.22 and 1.41 [CH_2, q; CH_3, t; 7.2]	7.66 (d; 8.1)	7.85 (ddd; 8.1, 7.8 and 1.4)	7.47 (dd; 7.8 and 7.5)	8.12 (dd; 7.5 and 1.4)
17	8.24 (s)	10.15 [C*H*O, s]	5.42 [OCH_2, s]	4.12 [OCH_3, s]	7.78 (dd; 8.1 and 0.8)	7.93 (ddd; 8.1, 7.3 and 1.6)	7.54 (ddd; 7.7, 7.3 and 0.8)	8.18 (dd; 7.7 and 1.6)
18	7.27 (s)	—	—	3.92 [OCH_3, s]	7.66 (d; 7.9)	7.80 (ddd; 7.9, 7.6 and 1.6)	7.43 (dd; 7.7 and 7.6)	8.14 (dd; 7.7 and 1.6)
19	7.35 (s)	10.32 [O*H*, s]	5.24 [OCH_2, s]	3.93 [OCH_3, s]	7.66 (d; 7.9)	7.83 (ddd; 7.9, 7.4 and 1.7)	7.44 (dd; 8.0 and 7.4)	8.13 (dd; 8.0 and 1.7)
20	7.35 (s)	3.92 [OCH_3, s]	3.85 [OCH_3, s]	3.97 [OCH_3, s]	7.66 (d; 8.2)	7.83 (ddd; 8.2, 7.7 and 1.7)	7.46 (dd; 7.8 and 7.7)	8.15 (dd; 7.8 and 1.7)
21	8.39 (s)	—	—	3.96 [OCH_3, s]	7.67 (d; 7.9)	7.86 (ddd; 7.9, 7.6 and 1.6)	7.48 (dd; 7.7 and 7.6)	8.15 (dd; 7.7 and 1.6)
22	13.07 [OH, s]	11.11 [OH,s]	1.99 [CH_3, s]	6.48 (s)	7.58 (d; 7.9)	7.83 (ddd; 7.9, 7.7 and 1.7)	7.45 (t; 7.7)	8.12 (dd; 7.7 and 1.7)
23	13.16 [OH, s]	10.70 [OH, s]	2.10 [CH_3, s]	—	7.68 (d; 8.2)	7.90 (ddd; 8.2, 7.8 and 1.5)	7.52 (dd; 7.9 and 7.8)	8.17 (dd; 7.9 and 1.5)
24	13.11 [OH, s]	10.90 [OH, s]	2.10 [CH_3, s]	—	7.63 (d; 8.1)	7.78 (ddd; 8.1, 7.7 and 1.6)	7.49 (t; 7.7)	8.13 (dd; 7.7 and 1.6)

Table 2. ^{13}C chemical shifts[a] of xanthones 1–24

Compound	C-1	C-2	C-3	C-4	C-4a	C-4b	C-5	C-6	C-7	C-8	C-8a	C-9a	C-9
1	115.2	124.1	120.2	146.7	145.2	155.4	118.3	135.4	124.3	126.0	120.9	122.2	176.2
2	128.0	114.2	164.0	102.1	157.6	155.6	117.9	134.9	124.2	125.9	121.2	114.0	174.8
3	108.5	153.9	124.6	119.5	149.2	155.6	118.2	135.2	124.0	125.9	120.4	121.7	175.9
4	161.0	110.2	137.6	107.3	155.8	155.7	118.1	136.5	124.7	125.5	119.9	108.4	181.8
5	116.4	124.0	116.4	148.4	145.8	155.4	118.4	135.5	124.5	125.9	121.9	121.0	176.0
6	127.6	113.7	165.0	100.6	157.6	155.6	117.9	135.1	124.4	125.9	121.2	114.9	174.9
7	105.7	155.7	124.7	119.8	150.3	155.5	118.2	135.4	124.2	126.0	120.5	121.5	175.8
8	160.2	106.4	135.7	109.6	157.4	154.4	117.5	134.8	124.2	125.9	122.4	111.6	174.7
9	121.7	109.7	157.5	135.9	149.9	155.6	118.2	135.2	124.4	125.9	120.8	115.9	175.2
10	121.6	114.1	156.3	134.6	150.7	155.5	118.2	135.0	124.3	125.9	120.9	114.8	175.0
11	116.3	109.0	152.5	134.1	145.5	155.7	118.1	135.1	124.1	126.0	120.8	115.9	175.6
12	121.5	114.1	151.0	133.4	156.7	155.5	118.2	135.1	124.4	125.9	121.0	114.9	175.2
13	127.9	108.1	151.0	140.1	145.7	155.2	118.1	135.9	124.5	126.2	115.8	121.4	177.7
14	133.6	108.5	156.7	138.4	150.4	155.0	118.1	135.9	124.9	126.0	115.2	121.2	177.0
15	123.3	120.6	157.7	135.4	153.7	155.4	118.4	135.7	125.0	126.0	120.8	114.9	175.1
16	123.7	120.5	158.1	134.2	154.0	155.4	118.4	135.8	125.1	126.1	120.8	115.0	175.3
17	120.9	125.8	157.4	141.2	154.3	155.5	118.6	136.1	125.3	126.1	120.9	118.1	175.5
18	103.4	144.1	144.9	135.3	144.9	155.4	118.2	134.5	124.0	125.8	120.7	113.9	174.8
19	104.5	144.3	146.6	142.0	148.3	155.7	118.6	135.4	124.5	126.1	120.7	117.4	175.6
20	101.3	142.0	149.0	150.7	146.3	156.2	119.1	136.4	125.5	126.6	121.1	117.3	176.7
21	123.7	112.4	159.6	135.2	152.9	155.6	118.4	135.7	124.9	126.1	120.9	113.9	175.2
22	159.9	106.0	163.9	93.1	155.0	155.3	117.7	135.5	124.2	125.2	119.8	101.9	179.7
23	158.0	107.4	159.3	98.0	150.2	155.1	117.9	136.0	124.9	125.4	119.6	102.7	178.9
24	158.8	107.4	160.1	87.8	151.2	155.1	117.2	135.9	124.8	125.4	119.5	103.0	179.9

[a] ^{13}C chemical shifts of the substituents of the xanthones: **5**, 56.2 (OCH_3); **6**, 59.2 (OCH_3); **7**, 55.8 (OCH_3); **8**, 56.2 (OCH_3); **9**, 56.1 (3-OCH_3), 60.9 (4-OCH_3); **10**, 60.9 (OCH_3); **11**, 56.4 (OCH_3); **13**, 56.7 (OCH_3), 192.4 (CHO); **14**, 56.8 (OCH_3), 75.2 (OCH_2), 192.7 (CHO); **15**, 61.5 (OCH_3), 190.8 (CHO); **16**, 69.7 (OCH_2), 191.4 (CHO), 15.4 (CH_3); **17**, 61.9 (OCH_3), 76.3 (OCH_2), 188.6 (CHO); **18**, 61.0 (OCH_3); **19**, 61.9 (OCH_3), 74.6 (OCH_2); **20**, 62.7 (2-OCH_3), 56.9 (3-OCH_3), 62.1 (OCH_3); **21** 60.9 (OCH_3), 171.2 (CO_2H); **22**, 7.3 (CH_3); **23**, 8.2 (CH_3); **24**, 8.4 (CH_3).

The assignments for ring A protons of mono- and disubstituted xanthones **1**–**12** were made by COSY experiments.

The assignment of the H-2 resonance of **8** was carried out via NOE experiments. A NOE effect was observed for the signal of H-2 (6%) on irradiation of the OCH_3-proton resonance.

Even though **15**–**21** have the same substitution pattern, the singlets due to the H-1 resonances appeared at different ranges of frequencies. This proton in **15**–**17** and **21** suffered a mesomeric deshielding effect of the carbonyl group of the CHO and COOH substituents. In contrast, the H-1 in **18**–**20** experienced a mesomeric shielding effect caused by the 2-OR substituents (R = H, CH_3).

In the ^{13}C NMR spectra of **1**–**24** the resonances of C-5–C-8 and all of the other protonated carbons were assigned using HETCOR experiments, which correlate directly bonded ^{1}H and ^{13}C chemical shifts (Table 2). The resonances of C-6 (δ 134.5–136.5) appear at higher frequencies than those corresponding to C-5, C-7 and C-8. This NMR feature is due to the mesomeric deshielding effect of the carbonyl group.

The assignments of quaternary carbon resonances of ring B of **1**–**24** were performed by one-dimensional selective INEPT optimized for 7 Hz long-range J_{CH} coupling (Table 3).

As can be seen from Table 3, irradiation of H-8 resonances of **1**, **3**–**5**, **7**–**22** and **24**, gave enhancements of the signals of C-4b and C-9 and, in some cases, of the signals of C-6. In the case of **2**, **6** and **23**, the irradiation was on the signals of H-6, and enhancements of the signals of C-4b and C-8 were observed. For the assignment of C-8a, the irradiations were carried out on different protons as shown below:

(a) **1**, **2**, **4**, **8**, **10**–**13**, **15**, **16**, **18**, **20**, **21** and **22**–**24**: irradiation of the signals of H-7 gave enhancements of the C-8a signals;

(b) **6** and **9**: irradiation of the signals of H-5 gave enhancements of the C-8a signals;

(c) **3**, **7**, **14**, **17** and **19**: irradiation of the signal of H-6, long-range J_{CH} coupling optimized for 2 Hz, gave enhancements of the C-8a signals.

The assignments of the ring A quaternary carbons of all the xanthones were also carried out using one-dimensional selective INEPT measurements (Table 3).

Although some of the quaternary carbon resonances of **1**–**24** have been unequivocally assigned, in some cases one or two of these carbons were identified by elimination, i.e. only after the assignments of other carbon atom resonances.

The main feature of the ^{13}C NMR spectra of halogenated xanthones **23** and **24** is that the introduction of halo substituents on C-4 affected the resonance of this carbon. In **23** (R_4 = Cl), C-4 suffered a higher frequency shift (+ 4.9 ppm) whereas in **24** (R_4 = Br), C-4 showed a lower frequency shift (− 5.3 ppm) when compared with the resonance of the same carbon in **22**.

EXPERIMENTAL

Melting points were obtained in a Köfler microscope and are uncorrected.

^{1}H and ^{13}C NMR spectra were taken at ambient temperature on a Bruker AMX 300 instrument operating at 300.13 and 75.47 MHz, respectively. Chemical shifts are expressed as δ (ppm) values relative to tetramethylsilane (TMS) as internal reference. In a typical measurement of a ^{1}H NMR spectrum, the spectral width was 5.55 kHz, acquisition time 2.95 s and pulse width 4.13 μs (33.3°). In the broadband decoupled ^{13}C NMR spectra, the spectral width was 18.5 kHz, acquisition time 0.885 s and pulse width 1.5 μs (33.3°). Samples contained 10–30 mg of a specific compound dissolved in *ca.* 0.5 ml of DMSO-d_6.

COSY, HETCOR and one-dimensional selective INEPT[8] experiments were carried out using Bruker microprograms. Typical COSY acquisition parameters were 2400 Hz for f_1 and f_2, 1024 data points and 256 increments (both zero-filled to 1024), 0.8 s relaxation delay and

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Table 3. ^{1}H–^{13}C long-range correlations of the substituted ring (and some of their substituents) of xanthones 1–24, determined by one-dimensional selective INEPT

Compound	Protons	Carbon atoms
1	H-1	C-4a, C-8a and C-9
2	H-2 and H-4	C-4a and C-9a
	H-1	C-4a and C-9
3	H-3	C-4a
	H-3[a]	C-9a and minor effects on C-2 and C-4
4	OH	C-1, C-2 and C-9a
5	OCH_3	C-4
	H-2	C-9a
6	OCH_3	C-3
	H-4	C-2, C-3, C-4a and C-9a
7	OCH_3	C-2
8	OCH_3	C-1
	H-2	C-4 and C-9a
9	H-1	C-3 and C-4a
	H-2	C-4 and C-9a
10	H-2	C-4 and C-9a
11	OCH_3	C-3
	H-2	C-4, C-9a and minor effects on C-3
12	H-1	C-3 and C-4a
	H-2	C-4 and C-9a
13	OCH_3	C-3
	H-2 and H-7	C-4, C-8a, C-9a and CHO
14	OCH_3	C-3
	OCH_2	C-4 and C-1,2,6 of the benzyl group
15	H-1 and H-8	C-3, C-4a, C-4b, C-9 and CHO
	OCH_3	C-4
	CHO	C-2
16	H-1	C-3, C-4a and C-9
	H-1[a]	C-3, C-4 and C-4a
	OCH_2	C-4
	CHO	C-1 and C-2
17	OCH_3	C-4
	OCH_2	C-3 and C-1,2,6 of the benzyl group
	H-1 and H-8	C-4a, C-4b, C-6 and C-9
18	H-1	C-3, C-4a
	OCH_3	C-4
19	OCH_3	C-4
	OCH_2	C-3 and C-1,2,6 of the benzyl group
20	OCH_3	C-2, C-3 and C-4
	H-1	C-3 and C-4a
21	H-1	C-3, C-4a, C-9 and CO_2H
	OCH_3	C-4
22	OH-1 (δ 13.07 ppm)	C-1, C-2 and C-9a
	CH_3	C-1, C-2 and C-3
	H-4	C-2, C-3, C-9a and C-9
23	OH-1 (δ 13.11 ppm)	C-1, C-2 and C-9a
	CH_3	C-1, C-2 and C-3
24	OH-1 (δ 13.16 ppm)	C-1, C-2 and C-9a
	CH_3	C-1, C-2 and C-3

[a] J_{CH} Long-range couplings optimized for 2 Hz.

64 transients per increment. HETCOR experiments used ^{1}H and ^{13}C spectral windows of 2400 and 4000 Hz, respectively, $^{1}J_{CH} = 160$ Hz, 2048 ^{13}C data points (sinusoidal multiplication without zero-filling), 256 time increments (zero-filled to 512) and 1.5 s relaxation delay. In the one-dimensional selective INEPT experiments, the spectral width was 18.5 kHz, acquisition time 0.885 s, relaxation delay 1.5 s and the d_3 and d_4 were optimized for 2 or 7 Hz long-range J_{CH} coupling constants, depending upon the situation (see text). NOE experiments were determined by means of the NOE-difference technique, using a spectral width of 5.55 kHz, acquisition time 2.95 s, irradiation time 2 s and relaxation delay 3 s.

Purification of compounds was performed by column chromatography using Merck silica gel 60 (0.50–0.20 mm).

The following compounds were synthesized and purified by described procedures: 4-hydroxyxanthone (**1**);[9] 3-hydroxyxanthone (**2**);[10] 2-hydroxyxanthone (**3**);[9] 1-hydroxyxanthone (**4**);[11] 4-methoxyxanthone (**5**);[9,12,13] 3-methoxyxanthone (**6**);[10,14] 2-methoxyxanthone (**7**);[10] 1-methoxyxanthone (**8**);[15] 2,3,4-trimethoxyxanthone (**20**);[10] 1,3-dihydroxy-2-methylxanthone (**22**);[16] 4-chloro-1,3-dihydroxy-2-methylxanthone (**23**);[6] and 4-bromo-1,3-dihydroxy-2-methylxanthone (**24**).[6]

3,4-dimethoxyxanthone (9), 3-hydroxy-4-methoxyxanthone (10), 4-hydroxy-3-methoxyxanthone (11) and 4-ethoxy-3-hydroxyxanthone (12)

2-Methoxybenzoyl chloride (9.2 g, 54 mmol), 1,2,3-trimethoxybenzene (10.0 g, 60 mmol) and sublimed $AlCl_3$ (29.0 g, 219 mmol) in dry diethyl ether (435 ml) were stirred at room temperature for 22 h. The solvent was evaporated to dryness under reduced pressure and the viscous residue, after cooling, poured on to ice. The aqueous suspension was acidified with 10% HCl and extracted with benzene. The organic layer was collected and dried ($MgSO_4$) and the solvent was evaporated to dryness. The crude product was used without further purification.

The crude product (5.3 g, 18 mmol) in piperidine (64 ml, 65 mmol) and water (53 ml) was heated under reflux for 47 h. After this period, the mixture was cooled and poured into 4 M HCl (300 ml). The mixture was extracted with dichloromethane and dried ($MgSO_4$). The solvent was evaporated to dryness, yielding a granular solid. The product was purified by column chromatography [light petroleum (b.p. 40–60 °C)–ethyl acetate] yielding 3,4-dimethoxyxanthone (**9**) (300 mg, 8%), m.p. 156–158 °C (lit.,[17,18] 158–159 °C), 3-hydroxy-4-methoxyxanthone (**10**) (2.1 g, 48%), m.p. 221–222 °C (lit.,[17] 220–221 °C; lit.,[18] 218–220 °C), 4-hydroxy-3-methoxyxanthone (**11**) (1.7 g, 38%), m.p. 194–196 °C and 4-ethoxy-3-hydroxyxanthone (**12**) (50 mg), m.p. 164–166 °C.

2-Formyl-3-hydroxy-4-methoxyxanthone (15)

A mixture of 3-hydroxy-4-methoxyxanthone (**10**) (703.2 mg, 3 mmol) and hexamethylenetetramine (2.8 g, 20 mmol) in acetic acid (62 ml) was stirred at 90–100 °C for 33 h. After cooling, 15% HCl (41 ml) was added and the mixture was heated under reflux for 15 min. After this period, the mixture was cooled, poured on to ice and kept for 8 h. The solid obtained was separated by filtration and purified by column chromatography [light petroleum (b.p. 40–60 °C)–ethyl acetate (1:1)]. The solvent was evaporated to dryness and the solid was crystallized from ethyl acetate, yielding 2-formyl-3-hydroxy-4-methoxyxanthone (**15**) as colourless crystals (223.3 mg, 28%), m.p. 215–218 °C.

1-Formyl-4-hydroxy-3-methoxyxanthone (13)

4-Hydroxy-3-methoxyxanthone (**11**) (500.1 mg, 2 mmol) and hexamethylenetetramine (2.0 g, 14 mmol) were dissolved in acetic acid (45 ml). After work-up as described above for **15**, 1-formyl-4-hydroxy-3-methoxyxanthone (**13**) was obtained as yellow crystals (201.1 mg, 36%), m.p. 245–247 °C.

4-Ethoxy-2-formyl-3-hydroxyxanthone (16)

4-Ethoxy-3-hydroxyxanthone (**12**) (50.1 mg, 0.2 mmol) and hexamethylenetetramine (0.2 g, 1.4 mmol) were dissolved in acetic acid (15 ml). After work-up as described above for **15**, 4-ethoxy-2-formyl-3-hydroxyxanthone (**16**) was obtained as colourless crystals (19.5 mg, 35%), m.p. 197–200 °C.

Reference Data

2-Carboxy-3-hydroxy-4-methoxyxanthone (21)

2-Formyl-3-hydroxy-4-methoxyxanthone (**15**) (400.1 mg, 1.5 mmol), 10% tetramethylammonium hydroxide (70 ml) and 6% H_2O_2 (8 ml, 14 mmol) were heated at 50 °C for 2 h. After cooling, the reaction mixture was acidified with 20% H_2SO_4. The precipitate was removed by filtration, washed with water and crystallized from methanol, yielding 2-carboxy-3-hydroxy-4-methoxyxanthone (**21**) as colourless crystals (265.0 mg, 63%), m.p. 245–250 °C.

3-Benzyloxy-2-formyl-4-methoxyxanthone (17)

A mixture of 2-formyl-3-hydroxy-4-methoxyxanthone (**15**) (1.6 g, 6 mmol), benzyl chloride (1.3 ml, 11 mmol) and anhydrous potassium carbonate (2.9 g, 21 mmol) in dry dimethylformamide (60 ml) was heated at 140 °C for 5 h. After cooling, the reaction mixture was poured on to ice and extracted with chloroform. The organic layer was washed with water, dried (Na_2SO_4) and evaporated to dryness. The crude solid was crystallized from methanol–chloroform, yielding 3-benzyloxy-2-formyl-4-methoxyxanthone (**17**) as colourless needles (1.2 g, 55%), m.p. 165–168 °C.

4-Benzyloxy-1-formyl-3-methoxyxanthone (14)

1-Formyl-4-hydroxy-3-methoxyxanthone (**13**) (100.3 mg, 0.4 mmol), benzyl chloride (0.08 ml, 0.7 mmol) and anhydrous potassium carbonate (180 mg, 1.3 mmol) in dry dimethylformamide (20 ml) were heated at 140 °C for 5 h. After work-up as described above for **17** 4-benzyloxy-1-formyl-3-methoxyxanthone (**14**) was obtained as yellow crystals (92.3 mg, 69%), m.p. 171–174 °C.

3-Benzyloxy-2-hydroxy-4-methoxyxanthone (19)

A mixture of 3-benzyloxy-2-formyl-4-methoxyxanthone (**17**) (314.2 mg, 0.9 mmol) and *m*-chloroperbenzoic acid (226.1 mg, 1.3 mmol) in dichloromethane (19 ml) was refluxed, under a nitrogen atmosphere, for 6 h. After cooling, the solvent was removed and the residue was dissolved in ethyl acetate (40 ml). This solution was washed with 5% $NaHCO_3$, water and brine and evaporated to dryness. The residue was dissolved in a mixture of 10% KOH (2 ml), methanol (38 ml) and chloroform (10 ml). This mixture was heated at 90 °C for a few minutes and, after cooling, was poured on to ice. The reaction mixture was neutralized with HCl and extracted with ethyl acetate. The organic layer was washed with water, dried (Na_2SO_4) and evaporated to dryness. The crude solid was crystallized from chloroform–light petroleum (b.p. 60–80 °C), yielding 3-benzyloxy-2-hydroxy-4-methoxyxanthone (**19**) as colourless crystals (352.1 mg, 83%), m.p. 152–155 °C.

2,3-Dihydroxy-4-methoxyxanthone (18)

A mixture of 3-benzyloxy-2-hydroxy-4-methoxyxanthone (**19**) (115.1 mg, 0.33 mmol) and 10% Pd–C (20.3 mg) in methanol (41 ml) was stirred, under a hydrogen atmosphere, at room temperature for 24 h. The catalyst was removed by filtration and the filtrate evaporated to dryness. The residue was crystallized from chloroform–light petroleum (b.p. 40–60 °C), yielding 2,3-dihydroxy-4-methoxyxanthone (**18**) as colourless crystals (63.1 mg, 74%), m.p. 218–220 °C.

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