Complete assignment of the ^{13}C NMR spectra of 4,4-dimethylanthracene-1,9,10(4*H*)-trione and the regioisomeric monomethyl derivatives

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ABSTRACT: The ^{1}H and ^{13}C NMR spectra of a set of structurally related tricyclic quinones consisting of 4,4-dimethylanthracene-1,9,10(4*H*)-trione **(1)**, 4,4,6,7-tetramethylanthracene-1,9,10(4*H*)-trione **(2)** and the regioisomers 4,4,5- **(3)**, 4,4,6- **(4)**, 4,4,7- **(5)** and 4,4,8-trimethylanthracene-1,9,10(4*H*)-trione **(6)** were assigned completely using two-dimensional techniques. Copyright © 2000 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ^{1}H NMR; ^{13}C NMR; HMBC; HMQC; anthracene-1,9,10-triones

INTRODUCTION

The anthraquinone derivatives are the largest group of natural quinones.[1] Some derivatives of anthracene-9,10-diones show antiparasitic activity and appear to act by a number of mechanisms, such as interaction with the enzyme trypanothione reductase[2] or by disrupting mitochondrial electron transport.[3,4] A few such compounds have been shown to exhibit cytotoxicity towards cancer cells.[5] The aromatic ring-unsubstituted 4,4-dimethylanthracene-1,9,10(4*H*)-trione exhibits potent lytic activity *in vitro* against *T. cruzi* and several *Leishmania* species.[6]

We have previously reported the synthesis[7,8] and the complete assignment of the ^{13}C NMR spectra of a series of 5,8-disubstituted-4,4-dimethylanthracene-1,9,10(4*H*)-triones[9] and this paper reports the complete assignment of the ^{13}C NMR spectra of a further series of compounds.

EXPERIMENTAL

Compounds

The quinones **1–6** were prepared according to methods described earlier.[7,8]

Spectra

Proton and ^{13}C NMR spectra were acquired using a Bruker AVANCE DRX 300 spectrometer operating at 300.13 MHz (^{1}H) or 75.47 MHz (^{13}C). All measurements were carried out at a probe temperature of 300 K, using solutions of **1–6** (20–60 mg ml^{-1}) in $CDCl_3$ containing tetramethylsilane (TMS) as an internal standard. All two-dimensional spectra were acquired with a Bruker inverse 5 mm Z gradient probe. HMQC spectra were recorded using standard Bruker software (inv4gstp). These spectra were collected with 512 × 512 data points, with eight scans acquired for each of 256 increments in t_1. Spectral widths of 3000 Hz and 18 000 Hz were used in the F_2 (^{1}H) and F_1 (^{13}C) domains, respectively. HMBC spectra were obtained using the inv4gslplrnd pulse sequence from the Bruker software. The spectral widths were 3000 Hz (F_2) and 18 000 Hz (F_1) and the delays Δ_1 and Δ_2 were set to 3.45 and 65 ms, respectively. Data were processed using an exponential window in F_2 with lb = 5 Hz and Qsine window in F_1.

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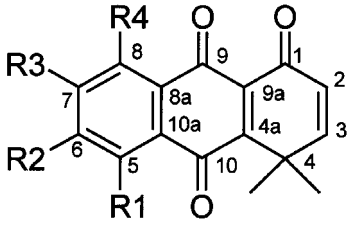

Compound	R_1	R_2	R_3	R_4
1	H	H	H	H
2	H	Me	Me	H
3	Me	H	H	H
4	H	Me	H	H
5	H	H	Me	H
6	H	H	H	Me

RESULTS AND DISCUSSION

In the conventional one-dimensional 300 MHz ^{1}H NMR spectra of this series of compounds, the olefinic resonances can be assigned with certainty on the basis of the appearance of their two doublets at about 6.4 and 6.8 ppm forming an AB spin system with a vicinal coupling of 10.1 Hz corresponding to the enone moiety. These signals correspond to H-2 and H-3 and serves as the entry point for spectral interpretation.[9] In the aromatic region, H-5 and H-8 can be easily differentiated from H-6 and H-7 on the basis of their chemical shifts. The former appears at lower field owing to the deshielding effect of the quinonic nucleus. Additionally, two singlets may be observed at about 1.6 and 2.6 ppm corresponding to the two equivalent 4-methyl and the Ar-methyl groups, respectively. The ^{1}H NMR chemical shifts assignments for **1–6** are given in Table 1.

The ^{1}H NMR spectra of the pairs of compounds **3**, **6** and **4**, **5** are almost identical, and it is possible to differentiate between them only through their ^{13}C NMR spectra. The assignment of these spectra is not straightforward, because the central region of these linear chemical structures consists only of quaternary and carbonyl carbon atoms whose resonances must be correlated via long-range J(C,H). In this study we differentiated the position of the methyl group on the aromatic ring by the concerted use of ^{1}H-detected one-bond (C—H) heteronuclear multiple quantum coherence (HMQC)[10] and long-range C—H heteronuclear multiple bond connectivity (HMBC)[11–15] and we also

Table 1. ^{1}H NMR chemical shift assignments (ppm, TMS) for quinones **1–6**

Atom	**1**	**2**	**3**	**4**	**5**	**6**
H-2	6.39	6.29	6.29	6.38	6.36	6.37
H-3	6.83	6.71	6.72	6.80	6.78	6.80
H-5	8.05–8.30 (H-5 and 8)	7.73 (H-5 and 8)	—	7.86	7.95	7.95
H-6	7.72–7.81 (H-6 and 7)	—	7.45	—	7.45	7.58
H-7	Same to H-7	—	7.54	7.57	—	7.54
H-8	Same to H-5	Same to H-5	7.90	7.98	7.85	—
(Me-4) × 2	1.65 (s)	1.55 (s)	1.56	1.63	1.56	1.61
Me-Ar	—	2.53 (s)	2.66	2.51	2.66	2.73

Table 2. ^{13}C NMR chemical shift assignments (ppm, TMS) for quinones **1–6**

Atom	**1**	**2**	**3**	**4**	**5**	**6**
C-1	183.42	184.08	183.32	183.60	183.28	183.32
C-2	127.49	127.88	127.28	127.54	127.21	127.50
C-3	157.72	158.02	157.91	157.64	157.53	157.70
C-4	38.92	39.26	39.07	38.89	38.71	38.49
C-4a	156.81	157.17	158.02	156.70	157.21	154.85
C-5	126.38	127.61	140.82	126.63	126.37	125.06
C-6	133.75	144.01	137.50	144.88	134.34	132.66
C-7	134.55	145.05	133.57	135.35	145.65	138.00
C-8	126.38	127.67	125.08	126.63	126.29	140.32
C-8a	132.32	130.79	133.74	129.92	131.82	130.63
C-9	182.70	183.32	183.28	182.61	182.75	184.85
C-9a	133.25	133.48	132.64	133.20	132.92	135.45
C-10	185.45	185.94	187.47	185.80	184.96	186.02
C-10a	132.11	130.52	130.55	132.28	129.95	133.76
Me-4	26.41	26.79	26.46	26.41	26.19	26.21
Me-Ar	—	20.56 20.67	22.69	21.86	21.76	21.69

compared the carbonyl resonances with those of the 5,8-disubstituted-4,4-dimethylanthracene-1,9,10(4*H*)-triones described previously.[9]

The ^1H NMR spectrum of **3** shows an AMX spin system corresponding to the aromatic ring protons appearing at 7.45, 7.54 and 7.90 ppm with an *ortho* coupling constant of 7.6 Hz and a *meta* coupling of 0.8 Hz. The proton resonating at 7.90 ppm is bonded at C-8, as it lies closer to the quinonic ring. The HMBC method allowed the observation of a ^4J(CH) coupling from the methyl group linked to the aromatic ring to the C-10 carbonyl carbon and a ^4J(CH) coupling from this nucleus to H-3. This method also allows the observation of the ^3J(CH) couplings from C-1 to H-3 and from C-9 to H-8. Unlike the 5- or 8-acetyloxymethyl-4,4,8-trimethylanthracene-1,9,10(4*H*)-trione, we were unable to observe the H-3–C-9 ^5J(C,H) correlations. The assignments of the carbon resonances obtained from the analysis of long-range correlations are presented in Table 2.

The ^1H NMR spectrum of **6** is almost identical with that of **3**. In this case the HMBC method also allows the observation of ^3J(C,H) couplings from C-1 to H-3 and a ^4J(C,H) from the latter to C-10. The 8-methyl–C-9 ^4J(C,H) and H-5–C-10 ^3J(C,H) couplings are also observed.

The ^1H NMR spectra of **4** and **5** show the usual enone AB spin system, aside from the *gem*-dimethyl, the aromatic ring methyl and the aromatic resonances. In these cases, unlike **3** and **6**, a ^4J(C,H) coupling between C-10 and H-3 is not seen. In **4**, the carbonyl resonances were assigned on the basis of ^3J(C,H) between H-3 and C-1, between H-8 and C-9 and between H-5 and C-10. In **5**, the ^3J(C,H) between H-3 and C-1, between H-5 and C-10 and between H-8 and C-9 were also key features that allowed the assignment of the carbonyl resonances.

The 300 MHz ^1H NMR spectrum of the unsubstituted parent compound **1** does not allow one to discriminate between the H-5 and H-8 or the H-6 and H-7 resonances. One observes two multiplets at 7.72–7.81 and 8.05–8.30 ppm corresponding to pairs of protons H-6 and H-7 and H-5 and H-8, respectively. As for the 6- or 7-monomethylsubstituted-4,4,8-trimethylanthracene-1,9,10(4*H*)-triones the HMBC spectrum allows to observe the strong ^3J(C,H) interactions between C-1 and H-3 and a ^4J(C,H) interaction between C-10 and H-3. In this case also ^5J(C,H) couplings between H-3 and C-10a and between C-9 and 3-H are observed.

The ^1H NMR spectrum of **2** show the *gem*-dimethyl, the two methyl groups linked to aromatic ring and the H-5 and H-8 resonances as singlets at 1.55, 2.53 and 7.73 ppm, respectively.

The HMBC method allowed the observation of a ^3J(C,H) couplings from C-1 to H-3 and a ^4J(C,H) coupling to C-10 and this allowed the carbonyl resonances to be assigned.

Assignments of C-6 and C-7 for **1** and **2** were made through a chemical shift correlation in this series of molecules, considering the additivity of substituent effects of methyl groups.[16] The assignment for C-8a and C-10a was made by a comparison with 5-acetyloxymethyl-4,4,8-trimethylanthracene-1,9,10(4*H*)-trione and 8-acetyloxymethyl-4,4,5-trimethylanthracene-1,9,10(4*H*)-trione.[9] The spectra of these compounds show the C-8a resonance at a lower field than C-10a.

Similarly to the 5,8-disubstituted 4,4-dimethylanthracene-1,9,10(4*H*)-triones,[9] in all compounds of the present series C-10 resonates several ppm downfield from C-9, regardless of the arrangement of the aromatic substituents. However, the analysis of both series seems to indicate that the long-range correlations show a dependence on the nature and position of the aromatic substituents.

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