Carbon-13 NMR of Quinone Methides

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The ^{13}C NMR spectra of four *ortho*- and seven *para*-quinone methides were assigned using chemical shift and long-range carbon–proton coupling information. The carbonyl shifts are compared with those in *ortho*- and *para*-benzoquinones. The chemical shifts of the carbonyls of the *p*-quinone methides are observed at δ 186.2–186.4 for the three *ortho*-di-*tert*-butyl-substituted compounds and at δ 180.7–181.5 for the four *ortho*-oxy-substituted compounds. In the three *o*-quinone methides with *meta,para*-dioxy substituents, the carbonyl signals are at δ 184.2–185.4. The carbonyl signal of the one *o*-quinone methide with no oxygen substitution is shifted downfield to δ 200.9, apparently as a result of hydrogen bonding to the nearby hydroxyl.

INTRODUCTION

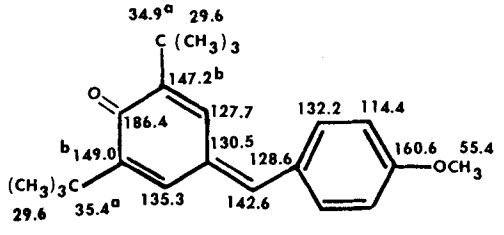
Quinone methides are suspected to be the reactive intermediates in many chemical and biochemical phenol oxidation and elimination reactions.[1] More recently it has been suggested that the toxicological[2] and antineoplastic[3] properties of substituted benzoquinones, as well as the insect-sterilizing action of some benzylphenols and benzyl-1,3-benzodioxoles,[4,5] may be due to the *in vivo* conversion of these compounds to bioactive quinone methide alkylating agents.

o-Quinone methides are particularly unstable, so that until a few years ago none of these compounds had actually been isolated or crystallized.[6] *p*-Quinone methides, however, are generally more stable and a number of these compounds have been synthesized or isolated from natural sources, e.g. the potent fish poison obtusaquinone (**6**).[7] During the course of our work on the development of insect sterilant and growth regulators, several crystalline *p*-quinone methides (compounds **1–7**) and *o*-quinone methides (compounds **8–11**) were either synthesized or isolated from plant sources, and their structures determined by x-ray analysis.[4,6–8] ^{13}C NMR data for only a few quinone methides have been reported.[9] In view of their biochemical significance, we have investigated the ^{13}C NMR of a series of these quinonoid compounds.

RESULTS AND DISCUSSION

para-Quinone methides

For compounds **1** and **2** the assignments of the carbon signals generally follow from their shifts, multiplicities and long-range carbon–proton couplings. In **1** the methine carbon signal at δ 142.6, which is replaced in **2** by a new quaternary carbon signal at δ 153.3, is assigned to the carbon connecting the two rings. The methines of unit intensity absorbing in **1** and **2** at δ 127.7 and 128.4 and at δ 135.3 and 131.5 are the protonated quinone methide ring carbons. The peak at δ 135.3 in **1** and at δ 131.5 in **2** is assigned to the carbon *trans* to the phenyl ring, as this carbon shows a larger signal shift on methylation of the double bond. This 3.8 ppm upfield shift on methylation is comparable to the upfield shift between buta-1,3-diene and (*Z*)-penta-1,3-diene, where the C-2 signal shifts 4.7 ppm upfield from δ 136.9 to 132.2.[10] The quaternary carbons at δ 128–134 can be assigned by examining their long-range carbon–proton coupling. In the proton coupled spectra of both **1** and **2** these peaks are obscured by other resonances. Examination of these peaks using single-frequency excitation[11] shows in **1** that the carbon absorbing at δ 128.6 exhibits long-range coupling to two protons with $J = 6$ Hz, typical of three-bond coupling, while the carbon signal at δ 130.5 does not show three-bond coupling. The peak at δ 128.6 is therefore assigned to the carbon in



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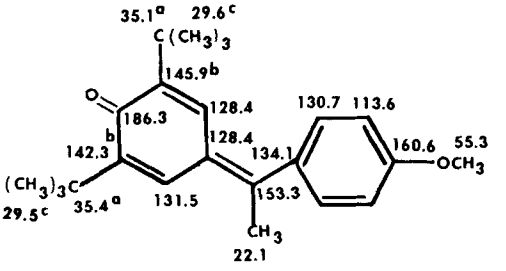

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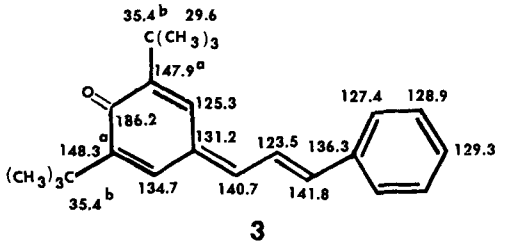
a,b,c Assignments with the same letter may be interchanged.

CCC-0030-4921/84/0022-0086$02.00

the phenyl ring with two *meta* protons. Methyl substitution should shift the δ 128.6 peak in **1** downfield (compare the chemical shift of C-1 in toluene at δ 137.4 to that in ethylbenzene at δ 144.2)[10] and the δ 130.5 peak upfield (compare the chemical shift of C-1 in ethylene at δ 122 to that of C-1 in propene at δ 114).[10] Thus, the δ 134.1 peak in **2** is assigned to the carbon in the phenyl ring and the δ 128.4 peak to that in the quinone methide ring. Examination of the proton coupling of these peaks shows that the δ 134.1 peak is much broader than the δ 128.4 peak. This is expected if the phenyl ring carbon shows three-bond coupling to three methyl protons as well as to the two *meta* protons, while the quinone methide carbon has three bond coupling to only the three methyl protons.

In the series **3–7** the ring carbons are assigned on the basis of their chemical shifts, comparison with **1**, **2** and styrene,[10] and on examination of the long-range couplings. In **5** the peak at δ 125.3 shows long-range coupling (q, $^3J = 5$ Hz) to the adjacent methyl, confirming its assignment. In **6** and **7** the methines at δ 100.8–103.1 can be distinguished by examination of their long-range coupling. In each compound one of the peaks (δ 100.8 for **6** and δ 103.1 for **7**) shows no long-range coupling and is thus due to the carbon *ortho* to the carbonyl, while the other peak (δ 102.8 in **6** and δ 102.3 in **7**) shows long range coupling (d, $J \approx 7$ Hz) and is the carbon *meta* to the carbonyl with three-bond coupling to the methine proton of the connecting chain. Of the peaks on the propenylidene connecting chains at δ 136.3–141.6, 122.9–124.8 and 141.8–144.4, the upfield peaks at δ 122.9–124.8 are those β to the quinone methide ring, reflecting the increased electron density at these carbons of the conjugated carbonyl system.[12] The peaks at δ 141.8–144.4 are assigned to the carbons adjacent to the benzene ring, as they shift least with changes in substitution in the quinone methide ring.



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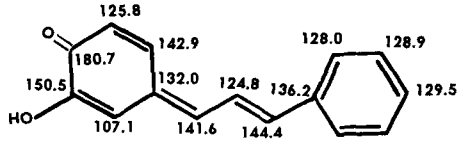

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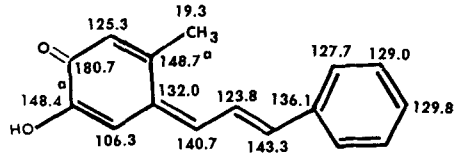

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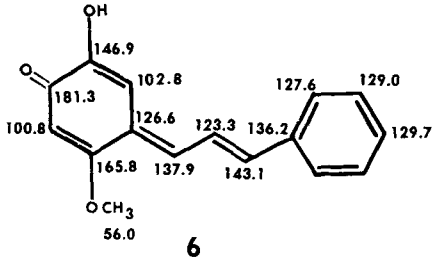

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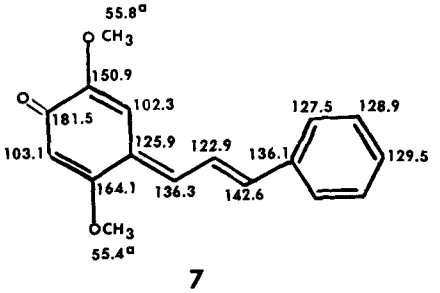

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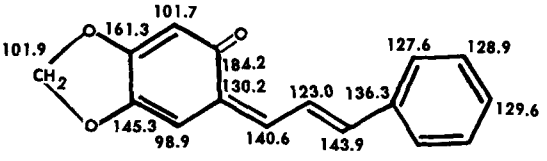
ortho-Quinone methides

In compounds **8–10** the carbons are assigned by their chemical shifts, comparison with the *para*-quinone methides, and for **8** by their long-range couplings. In **8** the protonated quinone methide ring



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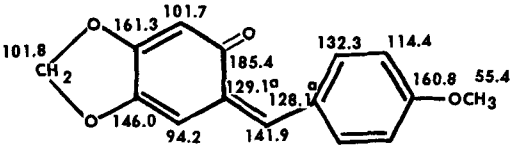

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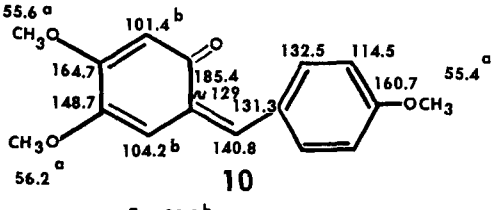

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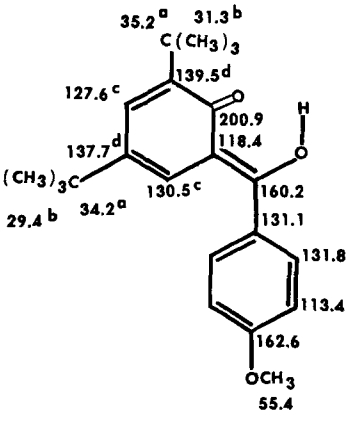

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carbons can be distinguished because the peak at δ 98.9 shows long-range coupling (d, $^3J = 9$ Hz) to the connecting chain. Because **9** and **10** dimerized so readily, fully proton-coupled spectra could not be obtained before dimerization occurred and the assignments of the peaks at δ 101.4 and 104.2 and δ 129–131.3 could not be confirmed. In **11**, observation of long-range coupling (t, $^3J = 8$ Hz) by selective irradiation[11] of the peak at δ 131.1 allowed its assignment. The long-range coupling observed for the peaks at δ 118.4 (d, $^3J = 4$ Hz) and at δ 160.2 (m) disappeared or changed after D_2O exchange, indicating coupling of these carbons to the hydroxyl and, therefore, permitting their assignment. Long-range coupling was not observed between either of the *tert*-butyl-substituted carbons and the hydroxyl, although *anti* three-bond couplings of 7–8 Hz have been observed between the hydroxyl and the ring carbon C-3 in 2-hydroxybenzaldehyde and similar compounds.[13] It was concluded[14] that the structure for **11** was the form shown and not its tautomer, a substituted *o*-hydroxydiphenyl ketone.

The chemical shifts of the carbonyl carbons in the quinone methides **1–3** are similar to those in *p*-benzoquinone (δ 187) and in 2,6-di-*tert*-butylbenzoquinone (δ 187 and 188).[15] No upfield shift of the carbonyl resonance due to increased conjugation, seen in aliphatic systems,[16] is observed. In compounds **4–7** the chemical shift of the carbonyl is shifted upfield by about 5 ppm to δ 180–181 due to the *ortho*-oxy-substituent. No hydrogen bonding occurs between the carbonyl and the adjacent hydroxyl because the carbonyl position is nearly identical in obtusaquinone (**6**) and *O*-methylobtusaquinone (**7**). Earlier work[16] has shown that hydrogen bonding of carbonyls leads to increased polarization of the C=O bond and to downfield shifts of about 7 ppm of the ^{13}C signal. Just such a shift is observed for **11** (see below). In comparing the carbonyl chemical shifts in **4** and **5**, the carbonyl position appers to be insensitive to β-methyl substitution. A small (about 1 ppm) upfield shift due to β-methyl substitution had been previously observed in cyclic α,β-unsaturated ketones.[16] In spite of the *para*-oxy substituent, which should cause upfield shifts of 6–9 ppm of the carbonyls (cf. substituent effects in benzene),[17] the carbonyl positions in the *ortho*-quinone methides **8–10** are at lower fields than those in *o*-benzoquinone (δ 179, 182).[10] Perhaps this difference is due to anisotropy differences between C=O and C=C. The carbonyl in **11** absorbs considerably downfield at δ 200.9. Allowing for downfield shifts of about 6–9 ppm for the lack of a *para* oxygen, and about 7 ppm for hydrogen bonding to the adjacent hydroxyl,[16] this position is not unreasonable.

EXPERIMENTAL

The ^{13}C NMR spectra were obtained on a Jeol PFT-100 spectrometer operating in the FT mode at 25.03 MHz at ambient temperature (about 29 °C). Spectra were pulsed with a flip angle of 45° at a rate of 2 s. Sixteen thousand data points were used to cover a spectral width of 6.25 kHz to give a digital resolution of 0.76 Hz. ^1H NMR spectra were run at 100 MHz on a Varian HR-100 spectrometer modified with a field-frequency lock to be equivalent to an HA-100 spectrometer. All compounds were run in $CDCl_3$ except for **3**, which was insoluble; this was recorded in DMSO-d_6. TMS was used as an internal standard.

The preparation and isolation of 2,6-bis(1,1-dimethylethyl)-4-(4-methoxyphenylmethylidene)cyclohexa-2,5-dien-1-one (**1**),[4] 2,6-bis(1,1-dimethylethyl)-4-[1-(4 methoxyphenyl)ethylidene]cyclohexa-2,5-dien-1-one (**2**),[4] 2,6-bis(1,1-dimethylethyl)-4-(3-phenyl-2-propenylidene)cyclohexa-2,5-dien-1-one (**3**),[4] 2-hydroxy-5-methoxy-4-(3-phenyl-2-propenylidene)cyclohexa-2,5-dien-1-one (obtusaquinone) (**6**),[7] 2,5-dimethoxy-4-(3-phenyl-2-propenylidene)cyclohexa-2,5-dien-1-one (*O*-methylobtusaquinone) (**7**),[7] 3,4-methylenedioxy-6-(3-phenyl-2-propenylidene)cyclohexa-2,4-dien-1-one (**8**),[6] 3,4-methylenedioxy-6-(4-methoxyphenylmethylidene)cyclohexa-2,4-dien-1-one (**9**),[6] 3,4-dimethoxy-6-(4-methoxyphenylmethylidene)cyclohexa-2,4-dien-1-one (**10**)[6] and 2,4-bis(1,1-dimethylethyl)-6-[hydroxy)4-methoxyphenyl)methylidene]cyclohexa-2,4-dien-1-one (**11**)[14] are described elsewhere. 2-Hydroxy-5-methyl-4-(3-phenyl-2-propenylidene)cyclohexa-2,5-dien-1-one (**5**) was prepared by the acid-catalysed reaction of cinnamyl alcohol with 4-methyl-1,2-dihydroxybenzene to give 4-cinnamyl-5-methyl-1,2-dihydroxybenzene. Oxidation of this with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone gave **5**. 2-Hydroxy-4-(3-phenyl-2-propenylidene)cyclohexa-2,5-dien-1-one (**4**) was prepared similarly by reaction of cinnamyl alcohol with catechol to give 4-cinnamyl-1,2-dihydroxybenzene, and oxidation of this compound to **4**.

4-Cinnamyl-5-methyl-1,2-dihydroxybenzene. A mixture of 1,2-dihydroxy-5-methylbenzene (124 g) and cinnamyl alcohol (134 g) in 2% aqueous citric acid (1500 ml) containing ascorbic acid (10 g) was boiled under reflux for 20 h. After cooling, the bottom oily layer was separated and distilled to give the product as a colorless oil, b.p. 205–230 °C (1.0 mmHg) (119 g). This was crystallized from benzene–Skelly Solve F to give 4-cinnamyl-5-methyl-1,2-dihydroxybenzene as colorless needles, m.p. 85 °C (Found C, 79.9; H, 6.68. Calc. for $C_{16}H_{16}O$: C, 80.0; H, 6.71%). 100 MHz ^1H NMR spectrum in $CDCl_3$: 3H, s, δ 2.07; 2H, d, δ 3.37, $J = 5.0$; 2H (OH), s, δ 5.02; 2H, m, δ 6.23–6.31; 1H, s, δ 6.65; 1H, s, δ 6.68; 5H, m, δ 7.10–7.38. On warming with acetic anhydride and pyridine, the phenol formed 4-cinnamyl-5-methyl-1,2-diacetoxybenzene, which crystallized from methanol as colourless needles, m.p. 87–88 °C (Found: C, 74.0; H, 6.18. Calc. for $C_{20}H_{20}O_4$: C, 74.0; H, 6.22%).

2-Hydroxy-5-methyl-4-(3-phenylpropenylidene)cyclohexa-2,5-dien-1-one (5). A solution of 4-cinnamyl-5-methyl-1,2-dihydroxybenzene (12.0 g) in warm benzene (50 ml) was added to a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (16.0 g) in boiling benzene (150 ml), and the mixture was boiled under reflux for 5 min. The warm mixture was filtered and the filtrate was treated with Skelly Solve F (30 ml). On

cooling, the product crystallized (8.6 g). Recrystallization from benzene gave 2-hydroxy-5-methyl-4-(3-phenylpropenylidene)cyclohexa-2,5-dien-1-one as orange needles, m.p. 164–165 °C. (Found: C, 80.4; H, 5.95. $C_{16}H_{14}O_2$ requires C, 80.6; H, 5.92%). 100 MHz NMR spectrum in $CDCl_3$: 3H, d, δ 2.32, $J = 1.0$; 1H, s, δ 6.41; 10 H, m, δ 6.86–7.60.

4-Cinnamyl-1,2-dihydroxybenzene. A mixture of catechol (110 g), cinnamyl alcohol (134 g) and ascorbic acid (5 g) in 2% aqueous citric acid (1500 ml) was boiled under reflux for 17 h. After cooling the oily product was collected and distilled to give a colourless oil, b.p. 205–210 °C (0.5 mmHg) (111 g). The oil crystallized from benzene–Skelly Solve F to give 4-cinnamyl-1,2-dihydroxybenzene as slightly yellow needles, m.p. 99–100 °C (Found: C, 79.6; H, 6.29. $C_{15}H_{14}O$ requires C, 79.6; H, 6.24%).

2-Hydroxy-4-(3-phenyl-2-propenylidene)cyclohexa-2,5-dien-1-one (4). Oxidation of 4-cinnamyl-1,2-dihydroxybenzene with an equivalent amount of dichlorodicyano-1,4-benzoquinone as described above gave **4**, which crystallized from acetone–benzene as orange–red brittle prisms, m.p. 154 °C (Found: C, 80.1; H, 5.42. $C_{15}H_{12}O_2$ requires C, 80.3; H, 5.39%).

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Received 3 December 1982; accepted (revised) 20 June 1983