Applications of High-potential Quinones. Part 14.[1] Oxidation of 4-Hydroxy-3-methoxyphenylpropan-2-one and Related Compounds by Dichlorodicyanobenzoquinone

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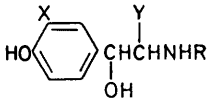
Oxidation of guaiacylacetone (3) by dichlorodicyanobenzoquinone in the inert solvent dioxan gives a polymer (7)' together with small amounts of a dimer (5). In methanol, benzylic monomethoxy- and dimethoxy-derivatives (20) and (23) are formed. Evidence for the involvement of radical and quinone methide intermediates in the formation of these products is discussed. In the mass spectra of the monoalkoxy adducts, the characteristic fragmentation is loss of an acetyl group from the side-chain.

QUINONE methides have been suggested as intermediates in the mediation of adrenergic responses to catecholamines.[2] Structure–activity studies [3-5] directed towards the elucidation of the mode of action of the adrenergic agonists adrenaline and noradrenaline (and their synthetic analogues) have revealed that the general structure (1), with various restrictions on the nature of



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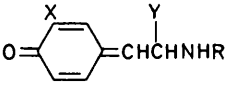

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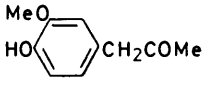

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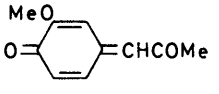

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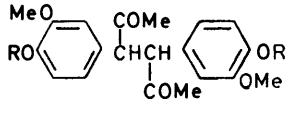


(5) R = H
(6) R = Ac

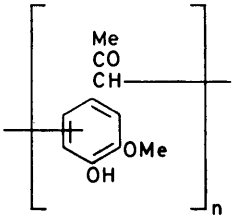
substituents R, X, and Y, and on the stereochemistry, is associated with adrenergic activity. Larsen [2] elegantly summarised this information in a mechanism involving the quinone methides (2) as key intermediates, although his hypothesis is only one of several which have been proposed,[6] and has met with some criticism.[6] We now report studies on the oxidation of 4-hydroxy-3-methoxypropan-2-one [guaiacylacetone (3)], the dehydrogenation product (4) of which is formally related to the quinone methides invoked by Larsen.

RESULTS

Oxidation of guaiacylacetone (3) by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) can, depending on the reaction conditions, give dimer (5), polymer (7), or alkoxy adducts, *e.g.* (20).

Reaction of the ketone (3) with an equimolar amount of DDQ took place readily at room temperature in dioxan solution, as shown by the rapid precipitation of dichlorodicyanohydroquinone ($DDQH_2$). The latter was isolated in 87% yield, but work-up by percolation through alumina gave only a very poor yield (<5%) of a solid whose i.r. and u.v. spectra closely resembled those of the starting ketone (a liquid). The n.m.r. spectrum of the product showed the signal for the benzylic protons to be halved in intensity, and deshielded (δ 3.65 ⟶ 4.47), allowing the product to be identified as the dimer (5) which was characterised as its acetate (6). Attempts to improve the yield of this dimer by running the reaction in more dilute solution failed, although a marginal increase in the amount of material was noted. Clearly the bulk of the product was being retained on the alumina, and when the use of alumina was avoided during the work-up, an amorphous solid was obtained in 70% yield. The product could not be crystallised or sublimed, and, although readily soluble in most organic solvents, was immobile on t.l.c. Its i.r. and u.v. spectra were very similar to those of guaiacylacetone, but the n.m.r. spectrum contained only broad, unresolved peaks. The mass spectrum showed peaks up to *m/e* 550, but the molecular weight was measured (by osmometry) as 1 278. These findings are consistent with a polymeric structure (7) containing, on average, seven guaiacylacetone units. The polymer could be acetylated, but the acetate was equally intractable. However, in the i.r. spectrum of the polyacetate, the ester carbonyl stretching frequency was of similar intensity to that of the ketonic carbonyl, suggesting that the phenolic oxygens were not involved in the linking of the monomer units. This was supported by the strong O–H stretch in the i.r. spectrum of the unacetylated material (absent in the i.r. spectrum of the acetate) and the fact that the molecular weight of the acetate was found to be 1 496 ± 45, corresponding to a degree of polymerisation of 6.6—7.0, assuming the monomer to be $C_{12}H_{12}O_4$. Examination of the polymer (7) by pyrolysis g.c. and pyrolysis g.c.–m.s. showed the main product of pyrolysis to be guaiacylacetone [*m/e* 180 ⟶ 137 (100%)], together with a minor product [*m/e* 194 ⟶ 151 (100%)], in the ratio 3 : 1. The former probably arises by cleavage of a terminal unit to give the benzyl radical, followed by hydrogen transfer, but the origin of the latter is not clear.

Pyrolysis of the acetylated polymer gave guaiacylacetone and its acetate [*m/e* 222 ⟶ *m/e* 180 (20%) ⟶ *m/e* 137 (100%)] in the ratio 1 : 2. Guaiacyl derivatives have previously been identified by gas chromatography from lignin pyrolyses, and the method has been used for the rapid identification of lignins.[7]



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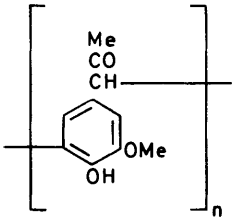

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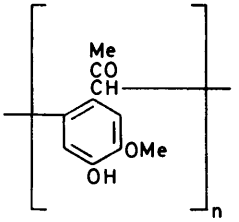

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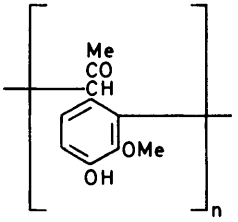
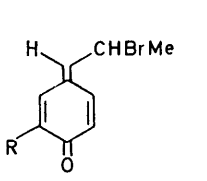


(10)

The increase in molecular weight upon acetylation of the polymer indicated that most of the phenolic hydroxy groups were free, so that the likeliest form of linkage is as in (8). Support for this was forthcoming from the integration of the aromatic and benzylic proton signals in the n.m.r. spectra of both the acetylated and unacetylated material. Coupling through the other free positions in the aromatic nucleus, as in (9) and (10), is less probable, owing to steric hindrance. The signals for the methyl ketone, methoxy, and acetoxy protons all appeared as pairs of singlets, which could be interpreted as evidence for a mixture of (8) and (9), but an alternative explanation could be the occurrence of ' head-to-tail ' and ' tail-to-tail ' linkages, and, in the absence of degradative data, no firm conclusion can be drawn.

The nature of the polymer was further investigated by ^{13}C n.m.r. spectroscopy, since it appeared likely that the compound was a linear rather than a network polymer. The spectrum of guaiacylacetone (3) showed no overlapping signals, with the carbon resonances falling into three well-defined regions: (i) δ 207.12 (carbonyl), (ii) 146.81, 144.93, and 126.02 (quaternary aromatics) and 122.31, 114.71, and 111.91 (unsubstituted aromatics), and (iii) 55.96 (side-chain methyl), 50.63 (benzylic), and 28.99 (methoxy). The polymer gave a less well resolved spectrum containing signals in these same three regions. The position of the terminal methyl absorption was unchanged at δ 56.02 in the polymer, and only slight changes were apparent for the methoxy (δ 30.35) and the carbonyl signals (δ 206.41). The benzylic carbon appeared well downfield at δ 60.57, but it was not possible to discern the changes in the aromatic region. The degree of polymerisation is the most likely cause of this loss of resolution, since two end-groups were present for only six or seven condensed units in each chain.

Freudenberg [8] studied the polymerisation of quinone methides (11; R = H or Br), but found that the polymer [*e.g.* (12)] contained benzyl aryl ether linkages, regardless of whether or not the positions *ortho* to the quinonoid carbonyl group were blocked. However, when the benzyl chloride precursor (13) was stored at room temperature, evolution of hydrogen chloride occurred and a polymer was formed which consisted predominantly of the units (14) and (15). The difference in behaviour between the quinone methides (4) and (16) could be due to the conditions under which polymerisation takes place. Freudenberg's polymerisations of (11) and (16) were induced thermally, or by homogeneous catalysis with tertiary amines, or with hydrated inorganic salts under conditions of heterogeneous catalysis.[8] Since polymerization of (4) occurred at room temperature, it is likely to have been catalysed by the acidic $DDQH_2$ present in the reaction mixture. Assuming that the benzyl chloride (13) polymerised *via* quinone methide (16), then the formation of polymers (14) and (15) instead of (12) can be ascribed to the acidic environment created by the hydrogen chloride which is eliminated in the process. [Volod'kin [9] describes the polymerization



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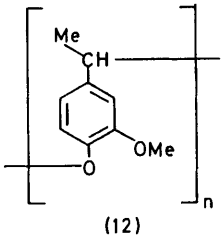

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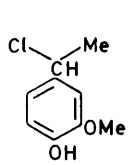

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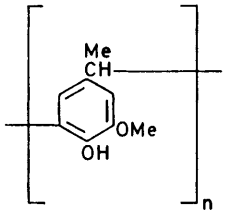

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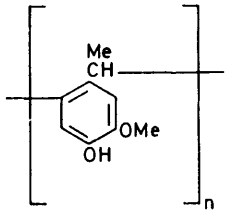

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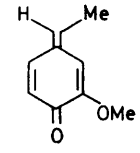
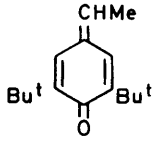


(16)

of the quinone methide (17) when treated with dry hydrogen chloride, although the detailed structure of the polymer is not discussed.] It thus appears that base catalysis leads to benzyl aryl ether coupling, while acid catalysis leads to coupling *via* the aromatic nucleus. Sheppard [10] has studied the polymerization of the quinone methide (18) and found that free radical polymerization led only to low molecular weight material, whereas crystalline high molecular weight polymers were obtained by treatment with sodium iodide or tetraethylammonium chloride. These had the benzyl aryl ether structure (19), as might be expected from the presence of the bulky t-butyl groups in the ring.

When the reaction was repeated in methanol, the major product was the benzylic methoxy-derivative

(20), which was isolated as its acetate (21). The structure of the acetate was clear from its n.m.r. spectrum, which showed four different methyl resonances, with a new methoxy signal at δ 3.40 in addition to the



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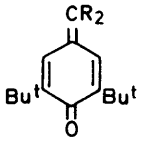
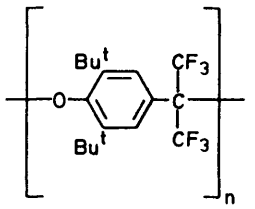


(18) R = CF_3
(28) R = H



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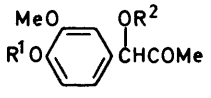
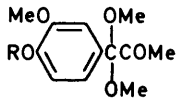


(20) R^1 = H, R^2 = Me
(21) R^1 = Ac, R^2 = Me
(29) R^1 = R^2 = H
(30) R^1 = H, R^2 = Et



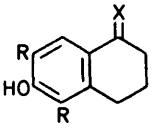
(22) R = Ac
(23) R = H

aromatic methoxy, methyl ketone, and acetate signals. The peak for the benzylic proton was again halved in intensity and deshielded, appearing at δ 4.60. The structure (21) was confirmed by mass spectrometry (see later discussion) and microanalysis. Use of 5% methanolic dioxan as solvent gave similar results, g.l.c. analysis revealing the presence of a single volatile product (20). The acetylated mixture consisted again mainly of the acetate (21), together with a trace of the dimeric diacetate (6), which was isolated in 3% yield. The monomethoxy compound (20) is considered to arise by addition of methanol to the extended quinone (4).

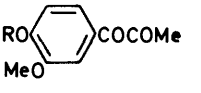
Guaiacylacetone (3) also reacted with two equivalents of DDQ in methanolic dioxan at reflux temperature to give, after acetylation, the acetal (22) in 24% yield. The benzylic proton signal was absent from the n.m.r. spectrum and there was now a singlet at δ 3.24 integrating for six protons.

Possible Mechanisms of Reactions Studied.—The results obtained from the DDQ oxidation of the phenol (3) in various solvents provide strong evidence for the involvement of the quinone methide (4). In the presence of methanol, nucleophilic attack by the alcohol gives the adduct (20) as described earlier for *p*-alkylphenols [11a] and 6-hydroxytetralins.[11b] Apparently the carbonyl group in the side-chain exerts no directing influence, presumably because such influence does not lead to direct reformation of the aromatic ring in the addition process. Unusual features of the reaction are the resistance of the mono-adduct (20) to further oxidation, and the stability of the bis-adduct (23). Whereas analogous ketals, such as 1,1-dimethoxy-6-hydroxytetralin, are very unstable and hydrolyse [11b] spontaneously under the reaction conditions to the corresponding tetralones (25), the acetal (23) survived these conditions, and was also recovered from refluxing methanolic dioxan. No trace of the diketone (26) could be detected. This could be attributed to steric hindrance at the benzylic carbon atom but a more likely explanation involves destabilization of the oxocarbonium ion intermediate by the adjacent carbonyl group. Oxocarbonium ion intermediates have recently been trapped by sulphite dianion during acetophenone dimethyl acetal hydrolysis.[12] The fact that formation of the acetal (23) from the mono-adduct (20) requires a two-hour reflux, while the oxidation of guaiacylacetone (3) to the monoadduct (20) proceeds rapidly at ambient temperature, sheds some light on the detailed mechanism of the initial oxidation (see below).

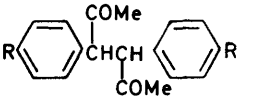
The isolation of the benzylic dimer (5) from the oxidation of guaiacylacetone (3) by DDQ is also of mechanistic interest. The analogous dimers (27) have been obtained [13-15] by oxidation of the appropriate phenylacetone derivatives with diacetyl peroxide, potassium persulphate, and di-t-butyl peroxide, respectively; the product being formed in each case by dimerisation of the benzylic radical. Dimer (5) could arise by a similar hydrogen atom abstraction from guaiacylacetone, followed by coupling of the resulting benzyl radical, but its formation more probably involves disproportionation of the quinone methide (4). Bauer and Coppinger [16] describe the disproportionation of quinone methide (28) to the corresponding diphenylethane and stilbenequinone. Although a stilbenequinone analogous to this



(24) X = H_2
(25) X = O



(26) R = H
(42) R = Me

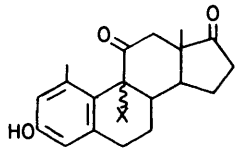


(27) R = H, OAc, or OMe

was not isolated in the present work, all the DDQ oxidations (and in particular those carried out in the absence of nucleophiles) yielded varying amounts of an intractable mixture of polar, highly coloured products.

In view of the stability and ease of formation of the methoxy compound (20), attempts were made to prepare the analogous hydroxy compound (29) by oxidation of guaiacylacetone (3) with DDQ in 2% aqueous dioxan. Only a poor yield of $DDQH_2$ was obtained, but, after evaporation of the solvent and dissolution of the residue in ethanol, g.l.c. revealed only one major volatile product, having a retention time different from that of the ketol (29).[17] The product was isolated by preparative t.l.c. and identified, on the basis of n.m.r. and mass spectrometry, as the ethanol adduct

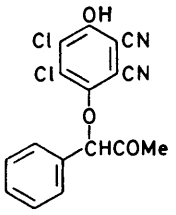
(30). Its formation could be explained either by the presence, in the residue left after evaporation of the solvent, of quinone methide (4) (or another species capable of reaction with ethanol to generate the adduct), or by the presence in the residue of substantial amounts of DDQ and the substrate (3) before it was dissolved in ethanol. The low yield (34%) of $DDQH_2$ supports the latter explanation, although it is not clear why the reaction should be so much slower in aqueous dioxan than in pure or methanolic dioxan. When the reaction was repeated at reflux temperature in 10% aqueous dioxan, the hydroquinone was obtained in 88% yield, but g.l.c. analysis of the tarry product revealed traces of starting material to be the only volatile constituent. These findings contrast with results in the 6-hydroxytetralin series,[11b] where smooth oxidation to the tetralones was observed, the intermediate benzyl alcohol being too reactive for isolation. The findings of Volod'kin and his co-workers [9] suggest that the electron-withdrawing effect of the carbonyl group would activate the quinone methide (4) towards nucleophilic attack, but not by alcohols any more than by water, since both Volod'kin [9] and Freudenberg [8] found that water and simple alcohols were comparable in their rates of addition to quinone methides. In the case of the 11-oxoestrone (31), oxidation with DDQ in aqueous dioxan gives the



(31) X = 9α-H
(32) X = 9β-OH

9-hydroxy-derivative (32), whereas the corresponding methanol adduct could not be prepared using methanol or methanolic dioxan.[18] This behaviour is the exact opposite to that of the phenol (3).

As far as the mechanism of the initial oxidation is concerned, there are three positions on the guaiacylacetone molecule at which the high-potential quinone can attack, namely at the phenolic hydroxy group, the benzylic position, and the enolic form of the ketone. Oxidation of the enol could explain the appearance of the benzylic dimer,[19] but can be discounted since phenylacetone was found to be quite unreactive towards DDQ at room temperature. Furthermore, reaction did occur after 24 h at reflux temperature, to give an unstable adduct (33) containing $DDQH_2$. In this adduct, the benzylic proton appeared at δ 5.94, showing a downfield shift of 2.27 p.p.m. from that of the benzylic protons of benzyl methyl ketone (δ 3.67). Its i.r. spectrum showed saturated carbonyl and cyanide stretching frequencies. Attempts to purify the adduct led to decomposition, with the formation of $DDQH_2$. This confirms the possibility of one-electron oxidation of the enol at elevated temperatures, and suggests that one electron oxidation is followed by coupling of the benzyl radical with the semiquinone, a reaction which does not appear to occur in the oxidation of guaiacylacetone with DDQ.



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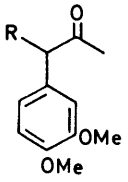
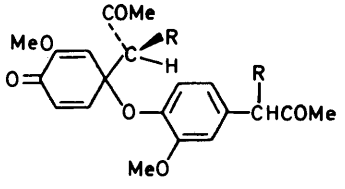
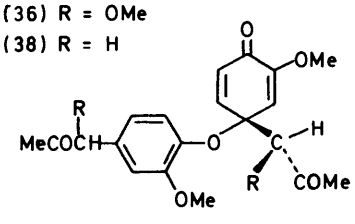


(34) R = H
(35) R = OMe

An indication of the likelihood of hydride abstraction from the benzylic position being the preferred mechanism can be obtained from the behaviour of 3,4-dimethoxyphenylacetone (34). This reacted more slowly with DDQ than the phenol (3); complete formation of the adduct (35) took several days in methanol at room temperature, whereas the phenol (3) reacted in 2 h under the same conditions. The greater reactivity of the phenol (3) reveals the deactivating influence of the side-chain carbonyl group upon the benzylic position and indicates that it is oxidised to the quinone methide by attack of DDQ at the phenolic hydroxy group. The possibilities here are (i) hydrogen atom abstraction to form the phenoxyl radical, followed by dimerisation and disproportionation as in Becker's mechanism,[11a] (ii) formation of the phenoxonium ion, followed by loss of a proton from the benzylic carbon, or (iii) concerted transfer of two hydrogen atoms to DDQ giving the quinone methide directly.[1] The resistance of the methanol adduct (20) to further oxidation provides some support for the free radical mechanism (i). Space-filling models did not reveal any steric impediment to



(36) R = OMe
(38) R = H



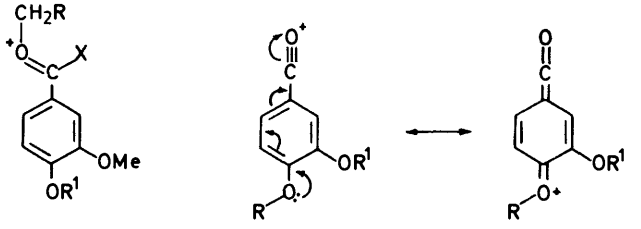
(37) R = OMe
(39) R = H

the oxidation of the adduct (20) by either the phenoxonium ion route (ii) or the concerted process (iii). However, in the radical mechanism (i) the key intermediate should [11a] be the dimer (36), but it can be clearly seen

from Catalin models that the ' open ' structure (36) is impossible owing to steric crowding between the benzylic and aromatic methoxy groups, and the molecule is forced towards the ' folded ' structure (37). In the oxidation of guaiacylacetone itself, the corresponding dimer is free to adopt the whole range of conformations between (38) and (39).

We have assumed in the foregoing discussion that guaiacylacetone (3) and its methoxy derivative (20) are oxidised by the same mechanism. Becker [20] has recently published evidence that the oxidation by DDQ of *para*-hydroxybenzyl alcohols need not involve quinone methides at all, since the *meta*-hydroxy derivatives were converted to the corresponding benzaldehydes as easily as the *para*-hydroxy compounds. Thus uncertainty still exists as to the precise mechanism of the DDQ oxidation of guaiacylacetone and its derivatives, but most of the available data can be rationalised by the free radical mechanism.

Mass Spectra.—Interesting trends were noted in the mass spectra of the adducts (21), (22), (30), and (35). In each case, the initial cleavage of an acetyl radical from the side-chain, followed by loss of ketene in the case of the two acetates, gave ions of type (40) as the base peak.

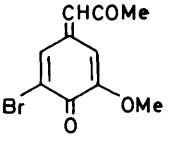


(40) (41)

Thereafter the trend was towards the formation of the system (41), which could occur by a number of routes. Although quinone methides do not appear to be formed directly by elimination of methanol or ethanol, as has been observed previously [9] in analogous systems, most of the stable fragments involved can be represented as hybrids of the extreme aromatic and quinonoid forms depicted in (41). The mass spectrum of guaiacylacetone also showed loss of acetyl to give the base peak: *m/e* 180 (M^+, 8%) ⟶ *m/e* 137 ($M - CH_3CO$, 100%) ⟶ *m/e* 122 (4%).

Alternative Routes to the Extended Quinone (4).—The oxidation of 3,4-dimethoxyphenylacetone (34) with silver(II) oxide was investigated, following a report [21] that this reagent cleaves catechol and hydroquinone methyl ethers to *ortho*- and *para*-benzoquinones. In fact the only product isolated was the α-diketone (42), previously obtained [22] by selenium dioxide oxidation of the phenylacetone (34).

Attempts were also made at benzylic bromination of guaiacylacetone (3), since elimination of hydrogen bromide by treatment with base would give the quinone methide.[23] However, bromination of the ketone (3) under a variety of conditions led only to oils, except in one instance when treatment of an ethereal solution with an equimolar amount of bromine, followed by washing with water, resulted in the precipitation of a yellow powder. The yield was very low, and many attempts to repeat the preparation failed, as did attempts to purify the material by crystallisation, sublimation, and chromatography. However, the product was already of sufficient purity to allow identification as the quinone methide (43). The mass spectrum showed the presence



(43)

of one bromine atom, and established the molecular weight as 257, while the n.m.r. spectrum contained three one-proton singlets at δ 7.65, 7.40, and 6.40, in addition to the methoxy and methyl ketone signals. Absorption at 345 nm in the u.v.[24] and two carbonyl absorptions at 1 690 and 1 655 cm^{-1} in the i.r. spectrum were also in accord with the proposed structure. Satisfactory elemental analyses were obtained for carbon and hydrogen. From the data available it was not possible to fix the position of the bromine atom in the ring with certainty, but the position adjacent to the carbonyl group seems the most likely, particularly if ring bromination takes place before benzylic bromination. The compound was reasonably stable, discolouring over a period of a few months at room temperature.

EXPERIMENTAL

^{13}C N.m.r. were recorded in deuteriochloroform with a tetramethylsilane as internal standard on a Bruker HX 90E spectrometer at 22.63 MHz.

Pyrolysis g.c.[25] and g.c.–m.s. was carried out on a Pye 104 instrument fitted with a Curie point pyrolyser,[26] consisting of a control unit and a pyrolysis head. An iron wire having a Curie point of 770 °C was used with a timing period of 12.5 sec. Subsequent analytical g.c. and g.c.–m.s. was performed on 3% E-301 or 3% OV-225 on Chromosorb W glass columns (2 m × 2 mm i.d.) at 150 °C using an N_2 flow rate of 25 ml min^{-1}.

Preparative g.c. was conducted on a Perkin-Elmer F 21 instrument using a stainless steel column (2 m × 9 mm i.d.) packed with 15% Apiezon L on Chromosorb P (30—60 mesh) at 210 °C using an N_2 flow rate of 330 ml min^{-1}. For other general directions see ref. 1.

DDQ Oxidation of Guaiacylacetone (3).—*In dioxan.* (*a*) A stirred solution of guaiacylacetone [27] (127 mg; t_R 3.8) in dioxan (2.5 ml) was treated dropwise with a solution of DDQ (160 mg) in dioxan (4 ml). As each drop of the quinone solution was added a transient deep green colour developed, and faded rapidly to yellow, with precipitation of $DDQH_2$ after a few minutes. After 2 h at 20 °C, the $DDQH_2$ was collected (140 mg, 87%) and the solvent was evaporated. The residue was taken up in ethyl acetate and filtered through a short column of neutral alumina to give a grey solid (10 mg), $\lambda_{max.}$ 222, 239sh, and 287 nm, $\nu_{max.}$ 3 420, 2 960, 1 710, and 1 620 cm^{-1}, δ 7.35 (s, 2-ArH),

6.86 (s, 1-ArH), 5.56 (s, 1 H, exchangeable), 4.47 (s, benzylic H), 3.92 (s, OMe), and 1.92 (s, COMe).

(*b*) A solution of guaiacylacetone (476 mg) in dioxan (5 ml) was similarly treated with DDQ (605 mg) in dioxan (10 ml). After 6 h at 20 °C $DDQH_2$ (565 mg, 93%) was removed and the solvent was evaporated off. The residue was dissolved in benzene (10 ml), then evaporated, and this process was repeated several times until a glass was obtained. Trituration with ether left the polymer (8) as a buff, amorphous powder (330 mg, 70%), m.p. 137—140°, $\lambda_{max.}$ 216, 241sh, and 285 nm, $\nu_{max.}$ 3 420, 2 930, 1 710, and 1 600 cm^{-1}, *M* 1 278 (osmometric, in benzene). Pyrolysis g.c.–m.s. gave components of t_R 7.6 [*m/e* 180 (15%), 137 (100), and 122 (5)] and 9.4 [*m/e* 194 (1%), 151 (100), and 137 (10)] in the ratio 3 : 1.

Acetylation of the polymer (100 mg) with acetic anhydride (0.5 ml) in pyridine (1 ml) gave the acetate (94 mg) as a buff, amorphous solid, $\nu_{max.}$ 1 765, 1 710, and 1 595 cm^{-1}, *M* 1 496. Pyrolysis g.c.–m.s. gave components t_R 7.6 [*m/e* 180 (9%), 137 (100), and 122 (3)] and t_R 13.6 [*m/e* 222 (0.6%), 180 (20), and 137 (100)] in the ratio 1 : 2.

In methanol. A solution of guaiacylacetone (491 mg) in methanol (3 ml) was treated with DDQ (616 mg) in methanol (6 ml). After 1.5 h at 20 °C, the solvent was evaporated and the residue was triturated with benzene. The insoluble $DDQH_2$ (544 mg, 88%) was collected and the filtrate was evaporated to dryness. The residue was acetylated by overnight treatment at 20 °C with pyridine (10 ml) and acetic anhydride (5 ml). The mixture was poured into water (100 ml) and extracted with ethyl acetate (3 × 30 ml), and the combined extracts were washed successively with 2N-sodium hydroxide (20 ml), 2N-hydrochloric acid (20 ml), and water (20 ml). Evaporation of the dried ($MgSO_4$) extracts gave a dark oil (749 mg) which was purified by p.l.c. [ethyl acetate–light petroleum (b.p. 60—80 °C) 1 : 1] to give 1-(4-*acetoxy*-3-*methoxyphenyl*)-1-*methoxypropan*-2-*one* (21) (200 mg, 29%) as an oil (Found: C, 61.8; H, 6.6%; $M^+ - 43$, 209.081 2. $C_{13}H_{16}O_5$ requires C, 61.9; H, 6.4%; *M* − 43, 209.081 3), t_R 10.4, $\nu_{max.}$ 2 940, 1 770, 1 725, and 1 605 cm^{-1}, δ 7.00 (s, ArH), 4.60 (s, benzylic H), 3.82 (s, OMe), 3.40 (s, OMe), 2.30 (s, OCOMe), and 2.12 (s, COMe), *m/e* 252 (M^+, 0.3%), 209 (18), 168 (11), 167 (100), 152 (16), 151 (18), and 137 (10).

In methanolic dioxan. (*a*) A solution of guaiacylacetone (369 mg) in dioxan (9 ml) and methanol (1 ml) was treated with DDQ (464 mg) in dioxan (5 ml) as above. $DDQH_2$ (339 mg, 73%) was isolated and the acetylated products were dissolved in ethanol. G.l.c. analysis showed the major product to be the above adduct (8), t_R 10.4. After several days, the ethanolic solution deposited 3,4-*bis*-(4-*acetoxy*-3-*methoxyphenyl*)*hexane*-2,5-*dione* (6) as crystals (12 mg), subliming at 190° and 0.05 mmHg, m.p. 192—196° (Found: M^+, 442.162 7. $C_{24}H_{26}O_8$ requires *M*, 442.162 7), δ ([$^2H_6$]DMSO) 7.14 (s, 1-ArH), 7.03 (s, 2-ArH), 4.84 (s, benzylic H), 3.80 (s, OMe), 2.24 (s, OCOMe), and 1.95 (s, COMe), *m/e* 442 (7%), 222 (32), 180 (100), 179 (50), 147 (71), and 137 (32).

(*b*) A solution of guaiacylacetone (561 mg) in dioxan (5 ml) and methanol (2 ml) was treated with DDQ (1 416 mg; 2 equiv.) in dioxan (20 ml) and the mixture was left for 18 h at 20 °C. $DDQH_2$ (652 mg, 46%) was removed by filtration, and the filtrate was heated under reflux for 2 h. On cooling, more $DDQH_2$ (713 mg, 50%) crystallised out (total yield 96%). The residue after evaporation was acetylated as before, giving a dark oil (720 mg). G.c. showed two volatile components (t_R 5.2 and 6.1 at 175 °C) in the ratio 1 : 2. The minor one corresponded to the mono-adduct (8). A solution of this material in ethyl acetate was filtered through a short column of neutral alumina to give a dark yellow oil (540 mg) which was further purified by p.l.c. [ether–light petroleum (b.p. 60—80 °C) 2 : 1] to give 1-(4-*acetoxy*-3-*methoxyphenyl*)-1,1-*dimethoxypropan*-2-*one* (212 mg; 24%) as a viscous oil (Found: C, 59.6; H, 6.5; OCH_3, 32.7. $C_{14}H_{18}O_6$ requires C, 59.6; H, 6.4; OCH_3, 33.0%), t_R 6.1 at 175 °C, $\nu_{max.}$ 1 770, 1 730, 1 610, 1 270, and 1 200 cm^{-1}, δ 7.14—6.98, (m, 3-ArH), 3.82 (s, ArOMe), 3.23 (s, *gem* di-OMe), 2.29 (s, OCOMe), and 2.08 (s, COMe), *m/e* 282 (<0.3%), 239 (56), 197 (100), 181 (14), and 151 (16).

In aqueous dioxan. To a solution of guaiacylacetone (99 mg) in dioxan (1.9 ml) and water (0.1 ml) was added DDQ (125 mg) in dioxan (4 ml) and the mixture was left overnight at room temperature. The precipitated $DDQH_2$ (43 mg; 34%) was removed, and the filtrate was evaporated *in vacuo*. The residue was purified by p.l.c. [ethyl acetate–light petroleum (b.p. 60—80 °C) 1 : 1] to give 1-*ethoxy*-1-(4-*hydroxy*-3-*methoxyphenyl*)*propan*-2-*one* (30) as a pale yellow oil (86 mg; 69%) (Found: M^+, 224.105 0. $C_{12}H_{16}O_4$ requires *M*, 224.104 8), t_R 5.0, $\nu_{max.}$ 3 380, 2 980, 1 720, and 1 610 cm^{-1}, δ 6.91 (m, 3-ArH), 5.85 (s, OH), 4.70 (s, benzylic H), 3.88 (s, OMe), 2.11 (s, COMe), and 3.51 and 1.28 (q and t, *J* 7 Hz, OEt), *m/e* 224 (0.6%), 181 (100), 153 (35), 152 (11), 151 (25), 125 (10), and 93 (50).

1-*Methoxy*-1-(3,4-*dimethoxyphenyl*)*propan*-2-*one* (35).—(i) A solution of 3,4-dimethoxyphenylacetone [27] (450 mg, t_R 5.5) in methanol (2 ml) was treated with DDQ (525 mg) in methanol (4 ml). After 7 days at room temperature, the solvent was evaporated *in vacuo* and the residue was triturated with dioxan. The insoluble $DDQH_2$ (420 mg; 80%) was collected and the filtrate was allowed to percolate through a short column of neutral alumina, eluting with ethyl acetate, to give a brown oil (389 mg). This was purified by p.l.c. (benzene–ethyl acetate 1 : 1) and further purified by preparative g.c. to furnish the *ketone* (35) as a pale yellow oil (163 mg, 32%) (Found: C, 63.9; H, 6.8. $C_{12}H_{16}O_4$ requires C, 64.3; H, 7.1%), t_R 7.3, $\nu_{max.}$ 1 720, 1 595, 1 510, 1 260, 1 135, 1 020, 805, and 760 cm^{-1}, δ 6.90 (m, 3-ArH), 4.58 (s, benzylic H), 3.85 (s, 2-ArOMe), 3.35 (s, benzylic OMe), and 2.09 (s, COMe), *m/e* 224 (M^+, 4%), 181 (100), 166 (66), 165 (35), and 151 (20).

(ii) A solution of DDQ (186 mg) in dioxan (3 ml) was added to a solution of 3,4-dimethoxyphenylacetone (156 mg) in dioxan (1.5 ml) and methanol (0.5 ml) and the mixture was heated under reflux for 2.5 h. On cooling, $DDQH_2$ (93 mg; 50%) was obtained, and g.l.c. of the reaction mixture showed that it contained approximately equal amounts of starting material (34) and the methanol adduct (35), t_R 5.3 and 7.3, respectively (2.5% E-301 at 170 °C). The reaction mixture was heated under reflux for a further 5 h when g.l.c. showed that the ratio of (34) to (35) had changed to 1 : 4. The product was isolated as before and shown (i.r.) to be identical to material previously characterised.

Oxidation of 3,4-*Dimethoxyphenylacetone with Silver*(II) *Oxide*.[21]—Silver(II) oxide [28] (992 mg) was added to a solution of 3,4-dimethoxyphenylacetone (388 mg) in dioxan (2 ml) and reaction was initiated by addition of 50% nitric acid (0.4 ml). The mixture was stirred for 3 min before being poured into ether (8 ml) containing water (2 ml). The organic layer was separated and washed with water (2 ml) and the combined aqueous layers and unchanged

oxide were re-extracted with ether (5 ml). Evaporation of the dried ($MgSO_4$) extracts gave a yellow oil from which 3,4-dimethoxyphenylpropane-1,2-dione (42) was isolated by p.l.c. [ethyl acetate–light petroleum (b.p. 60—80 °C) 1 : 1] as needles (38 mg, 10%), m.p. 59—62° (from aq. ethanol) (lit.,[22] 67—68°), δ 7.60—6.85 (m, 3-ArH), 3.96 (s, OMe), 3.94 (s, OMe), and 2.50 (s, COMe).

4-*Acetonylidene*-2-*bromo*-6-*methoxycyclohexa*-2,5-*dien*-1-*one* (43).—Bromine (2.55 g) in ether (10 ml) was added dropwise to a vigorously stirred solution of guaiacylacetone (2.88 g) in ether (35 ml) at −10 °C. The solution was washed with iced water (2 × 10 ml), whereupon the *quinone methide* (118 mg; 3%) separated from the ethereal layer as a yellow solid, m.p. 150° (decomp.) (Found: C, 46.7; H, 3.2%; M.Wt. 254 (in benzene); M^+, 255.972 3 and 257.970 9. $C_{10}H_9BrO_3$ requires C, 46.7; H, 3.5%; M.Wt. 257; *M*, 255.973 6 and 257.971 6), $\lambda_{max.}$ 345 nm (log ε 4.15), $\nu_{max.}$ 3 055, 2 940, 1 690, 1 650, 1 625, and 1 570 cm^{-1}, δ 7.65, 7.40, and 6.40 (all s, olefinic H), 3.82 (s, OMe), and 2.38 (s, COMe), *m/e* 258/256 (M^+, 100%), 243/241 (34), 231/229 (30), 215/213 (48), and 177 (81).

Oxidation of Phenylacetone.—Phenylpropan-2-one (463 mg) in dioxan (5 ml) was treated with DDQ (780 mg) in dioxan (5 ml). The solution was heated under reflux for 7 h, after which time there was no trace of starting material [R_F 0.4 (ethanol–hexane 1 : 9)]. Evaporation of the dioxan *in vacuo* gave a brown gum, $\nu_{max.}$ 2 230, 1 720, 1 115, 870, and 695 cm^{-1}, δ 7.30 (m, ArH), 5.94 (s, benzylic H), and 2.22 (s, COMe).

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REFERENCES

[1] Part 13, A. B. Turner and S. Kerr, preceding paper.
[2] A. A. Larsen, *Nature*, 1969, **224**, 25.
[3] R. P. Ahlquist, *Amer. J. Physiol.*, 1948, **153**, 586.
[4] P. Pratesi and E. Grana, *Adv. Drug Research*, 1965, **2**, 127.
[5] E. J. Ariëns, *Ann. N.Y. Acad. Sci.*, 1967, **139**, 606; C. Kaiser, D. F. Colella, M. S. Schwartz, E. Garvey, and J. R. Wardell, *J. Med. Chem.*, 1974, **17**, 49.
[6] R. T. Brittain, D. Jack, and A. C. Ritchie, *Adv. Drug Research*, 1970, **5**, 197.
[7] K. Kratze, H. Czepal, and J. Gratzl, *Holz als Roh und Werkstoff*, 1965, **23**, 237.
[8] K. Freudenberg and H. K. Werner, *Chem. Ber.*, 1964, **97**, 579; K. Freudenberg and A. C. Neish, 'Constitution and Biosynthesis of Lignin,' Springer, Berlin, 1968, p. 93.
[9] A. A. Volod'kin, V. V. Ershov, and G. D. Ostapets-Sveshnikova, *Bull. Acad. Sci., U.S.S.R.*, 1969, 580.
[10] W. A. Sheppard, *J. Org. Chem.*, 1968, **33**, 3297.
[11] (*a*) H-D. Becker, *J. Org. Chem.*, 1965, **30**, 982; (*b*) J. W. A. Findlay and A. B. Turner, *J. Chem. Soc.* (*C*), 1971, 23.
[12] P. R. Young and W. P. Jencks, *J. Amer. Chem. Soc.*, 1977, **99**, 8238.
[13] M. S. Kharasch, H. C. McBay, and W. H. Urry, *J. Amer. Chem. Soc.*, 1948, **70**, 1269.
[14] H. Bretschneider and R. Lutz, *Monatsh.*, 1964, **95**, 1702.
[15] R. L. Huang and L. Kum-Tatt, *J. Chem. Soc.*, 1955, 4229.
[16] R. H. Bauer and G. M. Coppinger, *Tetrahedron*, 1963, **19**, 1201.
[17] K. Lundquist and K. Hedlund, *Acta Chem. Scand.*, 1967, **21**, 1750.
[18] G. M. Buchan, J. W. A. Findlay, and A. B. Turner, *J.C.S. Chem. Comm.*, 1975, 126.
[19] H-D. Becker, *J. Org. Chem.*, 1965, **30**, 989.
[20] H-D. Becker in 'Chemistry of the Quinonoid Compounds,' ed. S. Patai, Wiley, 1974, p. 335.
[21] C. D. Snyder and H. Rapoport, *J. Amer. Chem. Soc.*, 1972, **94**, 227.
[22] J. M. Pepper and M. Saha, *Canad. J. Chem.*, 1964, **42**, 113.
[23] T. Zincke and O. Hahn, *Annalen*, 1903, **329**, 1.
[24] E. Adler and B. Stenemur, *Chem. Ber.*, 1956, **89**, 291.
[25] R. W. McKinney, in 'Ancillary Techniques of Gas Chromatography,' eds. L. S. Ettre and W. H. McFadden, Wiley, 1969, p. 55.
[26] W. Simón, P. Kriemler, J. A. Voellmin, and H. Steiner, *J. Gas Chromatog.*, 1967, **5**, 53; C. Buehler and W. Simon, *J. Chromat. Sci.*, 1970, **8**, 323.
[27] I. A. Pearl and D. L. Beyer, *J. Org. Chem.*, 1951, **16**, 221.
[28] R. N. Hammer and J. Kleinberg, *Inorg. Synth.*, 1953, **4**, 12.