

## Applications of High-potential Quinones. Part VIII.<sup>1</sup> Mechanism of Oxidation of 2-Benzylphenol to Benzylbenzoquinones

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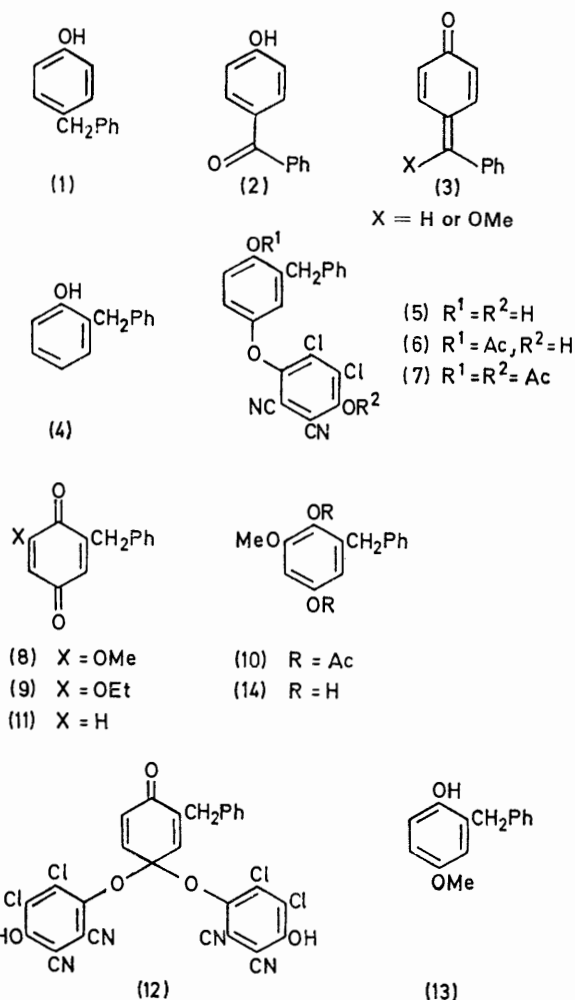
One-electron oxidation of 2-benzylphenol by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in alcoholic solvents leads to the coupled adduct (5), together with 2-alkoxy-6-benzyl-1,4-benzoquinones. The alkoxyquinones (8) and (9) are formed from the adduct (5) *via* 2-benzyl-1,4-benzoquinone (11), which undergoes DDQ-catalysed addition of the alcohol at C-6. The regioselectivity of nucleophilic attack in this latter reaction is explained by steric inhibition to co-ordination of the catalyst at the C-1 carbonyl oxygen atom.

OXIDATION of 4-benzylphenol (1) with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in methanol at room temperature is reported to give 4-hydroxybenzophenone (2) in 91% yield.<sup>2</sup> The postulated mechanism involves introduction of a methoxy-group at the benzylic position by nucleophilic attack of the solvent upon the *para*-quinone methide intermediates (3). The present work was undertaken with the object of exploring the possible intermediacy of the more energetic *ortho*-quinone methides in the analogous oxidation of 2-benzylphenol (4) by DDQ.

Oxidation of 2-benzylphenol (4) by an equimolar amount of DDQ occurred readily in methanol at room temperature. The reaction mixture was initially blue-black, but had lightened to brown after 1 h. After 12 h the solution was pale yellow-brown, and thereafter a reddish tinge developed, which progressively deepened. When the mixture was worked up after 12 h, the benzene-insoluble hydroquinone was obtained in only 40% yield. However, hydrogen transfer was complete, as shown by the absence of DDQ from the mixture, and the major product (55% yield) was a crystalline adduct, which was soluble in benzene and dioxan, and which was conveniently recrystallised from benzene. Its structure (5) was clear from its spectral data, and those of the derived mono- and di-acetates (6) and (7), which showed that coupling had occurred at the *para*-position of the phenol (4). Adducts of this type are well known, being formed by one-electron oxidation of phenols by DDQ, followed by nuclear coupling of the resulting phenoxy radical with the DDQ semiquinone radical. The only remarkable feature of the present reaction is the complete absence of attack at the highly activated benzylic methylene group. An alternative structure for the adduct, formed by addition of the hydroquinone to the *o*-quinone methide, was incompatible with the n.m.r. spectrum, which showed an intact benzylic methylene group, together with the replacement of one aromatic proton.

A second product, obtained in 20% yield by preparative t.l.c., was a methoxy-derivative of 2-benzyl-1,4-benzoquinone. Its n.m.r. spectrum suggested that the methoxy-group was at C-6, as the coupling constant of the nuclear protons was 2.5 Hz. Double-resonance experiments confirmed that the nuclear protons were coupled. Irradiation at  $\tau$  6.25 eliminated the benzylic

coupling and caused the multiplet at  $\tau$  3.70 to collapse to a doublet ( $J$  2.5 Hz). Irradiation at  $\tau$  3.70 caused the doublet at  $\tau$  4.13 to collapse to a singlet. The



structure (8) was confirmed by reductive acetylation to the hydroquinone diacetate (10), which showed *meta*-coupled aromatic protons ( $J$  2.5 Hz). This  $J$  value lies outside the range for *para*-oriented protons.

A red band was also evident on the t.l.c. plates, and the n.m.r. spectrum of the material isolated from this zone suggested that it was a mixture of the starting phenol (4) and 2-benzyl-1,4-benzoquinone (11), which were of similar mobility in the solvent systems employed. Acetylation of the mixture confirmed this conclusion, by

<sup>1</sup> Part VII, W. Brown and A. B. Turner, *J. Chem. Soc. (C)*, 1971, 2566.

<sup>2</sup> H. D. Becker, *J. Org. Chem.*, 1965, **39**, 982.

allowing separation of the yellow quinone (11) from the slightly more mobile acetate. The red colour originally observed was presumably due to  $\pi$ -complex formation between the phenol (4) and the quinone (11), both of which had the same  $R_F$  value.

The adduct (5) was subsequently shown to be oxidised by methanolic DDQ to the quinone (8), thereby establishing the following pathway for the DDQ oxidation of the phenol (4) in methanol: (4)  $\longrightarrow$  (5)  $\longrightarrow$  (11)  $\longrightarrow$  (8).

The mechanism of oxidation of the adduct (5) to the quinone (11) is obscure. It seems likely that one-electron oxidation to the bis-adduct (12), followed by hydrolysis, is involved. This mechanism is supported by the oxidation of 2-benzyl-4-methoxyphenol (13) to the quinone (8) by DDQ in methanol. The methoxy-benzylquinone (8) was obtained in 25% yield.

The final steps in this sequence, namely conjugate addition of methanol to 2-benzyl-1,4-benzoquinone (11), followed by oxidation of the resulting methoxy-hydroquinone (14) by DDQ to give the quinone (8), was substantiated by an independent investigation of the behaviour of the benzylbenzoquinone (11). This quinone has been prepared by oxidation with chromic acid of 2-benzylhydroquinone, obtained by condensation of benzaldehyde with cyclohexane-1,4-dione.<sup>3</sup> Attempts to repeat this sequence resulted only in a low yield of the benzyl-quinone, so the 2-benzylhydroquinone was prepared by 2-benzoylation of hydroquinone, followed by reduction with zinc amalgam. It was conveniently oxidised to 2-benzyl-1,4-benzoquinone (11) with DDQ in benzene (in 76% yield). The quinone (11) was also readily obtained by oxidation of 2-benzylphenol with Fremy's salt (50% yield). Oxidation of the phenol by this stable radical probably involves an overall sequence closely similar to that of the DDQ oxidation.

2-Benzyl-1,4-benzoquinone (11) did not react significantly with methanol during 24 h at room temperature, and there was also no reaction upon addition of the acidic 2,3-dichloro-5,6-dicyanohydroquinone. However, in the presence of DDQ, the 6-methoxy-derivative (8) was obtained. Thus DDQ functions as a Lewis acid catalyst for the addition of alcohol to the benzylbenzoquinone, as well as bringing about the final reoxidation of the hydroquinone. Zinc chloride, the traditional catalyst for the addition of alcohols to quinones,<sup>4</sup> also promotes formation of the 6-methoxy-quinone (8). Toluquinone in fact reacts with methanol in the presence of zinc chloride<sup>4</sup> to give 5-methoxy-2-methyl-1,4-benzoquinone, and not the 6-isomer, so that an explanation is required for the different site of alcohol attack in the case of 2-benzylbenzoquinone. We suggest that this is solely a steric effect, since 2-*t*-butylbenzoquinone has been found<sup>5</sup> to give the 6-methoxy-derivative in the presence of zinc chloride, whereas the 5-methoxy-derivative is obtained in the uncatalysed reaction, which takes place in refluxing methanol. Thus, in the re-

actions which are catalysed by the Lewis acids, the site of nucleophilic attack by the solvent is determined by co-ordination of the catalyst at the unhindered carbonyl oxygen atom, and the normal inductive effect (+*I*) of the substituent, which directs attack towards C-5, is overruled.

An unusual feature of the mass spectra of the alkoxy-benzylbenzoquinones described here was the ready loss of alcohol. Further investigation of this phenomenon will be described elsewhere.

## EXPERIMENTAL

For general directions see ref. 1.

*Oxidation of 2-Benzylphenol by DDQ in Methanol.*—DDQ (650 mg) in methanol (10 ml) was added to a stirred solution of 2-benzylphenol (500 mg) in methanol (10 ml) at room temperature. A blue-black colour developed instantaneously and this had turned to brown after 1 h. Stirring was continued for a further 12 h and the pale yellow-brown solution was evaporated to dryness. Treatment of the residue with benzene (25 ml) left the insoluble hydroquinone (260 mg), which was collected and washed with a little benzene. After concentration and refrigeration the benzene solution afforded 2-benzyl-4-(2,3-dichloro-5,6-dicyano-4-hydroxyphenoxy)phenol (5) (600 mg, 55%) as needles, m.p. 209—210° (decomp.) (from aqueous ethanol) (Found: C, 61.3; H, 2.9.  $C_{21}H_{12}Cl_2N_2O_3$  requires C, 61.3; H, 2.9%),  $\lambda_{max}$  254 and 390 nm (log  $\epsilon$  4.45 and 3.89),  $\nu_{max}$  3150, 3420, and 2245  $cm^{-1}$ ,  $\tau$  (CD<sub>3</sub>OD) 6.12 (s, PhCH<sub>2</sub>), 3.30—3.55 (m, 3-, 5- and 6-H), and 2.85 (s, Ph). Overnight acetylation of the adduct (5) (200 mg) in pyridine (5 ml) and acetic anhydride (5 ml) followed by addition of water (10 ml) and work-up after a further 12 h gave the *monoacetate* (6) (150 mg), m.p. 94—95° (from ethanol) (Found: C, 61.2; H, 3.6.  $C_{23}H_{14}Cl_2N_2O_4$  requires C, 60.9; H, 3.1%),  $\lambda_{max}$  253 and 390 nm (log  $\epsilon$  4.55 and 3.83),  $\nu_{max}$  3400, 2240, and 1760  $cm^{-1}$ ;  $\tau$  (CD<sub>3</sub>)<sub>2</sub>CO] 7.44 (s, OAc), 6.10 (s, PhCH<sub>2</sub>), and 2.76—3.50 (m, ArH). When the acetylation was repeated and hydrolysis of the excess of acetic anhydride was allowed to proceed only for 1 h, the *diacetate* (7) (160 mg) was obtained, m.p. 152—154° (from methanol) (Found: C, 60.9; H, 3.5.  $C_{25}H_{16}Cl_2N_2O_5$  requires C, 60.6; H, 3.2%),  $\lambda_{max}$  256 and 320 nm (log  $\epsilon$  4.18 and 3.40),  $\nu_{max}$  1800 and 1770  $cm^{-1}$ ;  $\tau$  (CDCl<sub>3</sub>) 7.82 (s, 4'-OAc), 7.72 (s, 1-OAc), 6.10 (s, PhCH<sub>2</sub>), and 3.34—3.26 and 2.99—2.74 (m, ArH).

Evaporation of the benzene mother liquor *in vacuo* gave a black residue which on t.l.c. [silica gel; benzene-ethyl acetate (4 : 1)] yielded the starting 2-benzylphenol (25 mg) and 2-benzyl-6-methoxy-1,4-benzoquinone (125 mg, 20%), which was purified by sublimation, m.p. 130° (Found:  $M^+$ , 228.0785.  $C_{14}H_{12}O_3$  requires  $M$ , 228.0786),  $\lambda_{max}$  265 and 370 nm (log  $\epsilon$  4.11 and 3.07),  $\nu_{max}$  1680 and 1650  $cm^{-1}$ ,  $\tau$  (CDCl<sub>3</sub>) 6.25 (s, PhCH<sub>2</sub>), 6.20 (s, OMe), 4.13 (d,  $J$  2.5 Hz, 5-H), 3.70 (m, 3-H), and 2.75 (m, ArH), *m/e* 228 (100%,  $M^+$ ), 213 (90), 196 (80,  $M - MeOH$ ), 185 (30), 157 (30), 143 (60), 115 (80), and 68 (90).

*Reductive Acetylation of 2-Benzyl-6-methoxy-1,4-benzoquinone.*—A mixture of the quinone (100 mg), zinc dust (200 mg), sodium acetate (200 mg), and acetic anhydride (50 ml) was stirred overnight at room temperature. It was poured into water (50 ml) and extracted with ether.

<sup>3</sup> R. Stolle and W. Möring, *Ber.*, 1904, **37**, 3486.

<sup>4</sup> J. N. Ashley, *J. Chem. Soc.*, 1937, 1471.

<sup>5</sup> F. R. Hewgill, B. R. Kennedy, and D. Kilpin, *J. Chem. Soc.*, 1965, 2904.

The extract was washed with saturated sodium hydrogen carbonate solution, then with water, dried ( $\text{MgSO}_4$ ), and evaporated. The residue (80 mg) gave 2-benzyl-6-methoxyhydroquinone diacetate (70 mg, 51%), m.p. 84—85° (from aqueous ethanol) (Found: C, 68.7; H, 6.0.  $\text{C}_{18}\text{H}_{18}\text{O}_5$  requires C, 68.7; H, 5.7%),  $\lambda_{\text{max}}$  275 nm ( $\log \epsilon$  3.24),  $\nu_{\text{max}}$  1770  $\text{cm}^{-1}$ ,  $\tau$  ( $\text{CDCl}_3$ ) 7.80 (s,  $2 \times \text{OAc}$ ), 6.24 (s, OMe), 6.16 (s,  $\text{PhCH}_2$ ), 3.55 (m, 3-H), 3.40 (d,  $J$  2.5 Hz, 5-H), and 2.80—2.84 (m, ArH).

*Oxidation by DDQ of 2-Benzyl-4-(2,3-dichloro-5,6-dicyano-4-hydroxyphenoxy)phenol* (5).—To a stirred solution of the adduct (5) (500 mg) in methanol (15 ml) was added DDQ (270 mg), and the solution was kept at room temperature for 24 h. Evaporation left a dark oil, which partially dissolved in benzene, leaving the insoluble hydroquinone (200 mg). The residue left after evaporation of the benzene solution was separated by t.l.c. [benzene–ethyl acetate (3:1)] into unchanged starting material (125 mg) and 2-benzyl-6-methoxy-1,4-benzoquinone (100 mg, 37%), m.p. 130°, identical (mixed m.p., i.r. spectrum) with the material from oxidation of 2-benzylphenol.

*Oxidation by DDQ of 2-Benzyl-4-methoxyphenol*.<sup>6</sup>—DDQ (227 mg) was added in 20 mg portions to a stirred solution of the phenol (13) (214 mg) in methanol (10 ml). The resulting solution was left for 24 h at room temperature, then evaporated to dryness *in vacuo*. Benzene (20 ml) was added to the residue, the insoluble hydroquinone (198 mg) was removed, and the filtrate was evaporated. T.l.c. [benzene–ethyl acetate (4:1)] of the residual dark oil gave the starting phenol (50 mg) and 2-benzyl-6-methoxy-1,4-benzoquinone (55 mg, 25%), m.p. 130°, identical (mixed m.p., i.r. and n.m.r. spectra) with material already described.

*Oxidation of 2-Benzylphenol by DDQ in Ethanol*.—DDQ (2.27 g) was added in small portions to a stirred solution of 2-benzylphenol (1.84 g) in ethanol (50 ml), the quinone being allowed to dissolve each time before the next addition was made. Colour changes similar to those observed with methanol as solvent were noted, and the same work-up procedure after 12 h at room temperature gave dichlorodicyanohydroquinone (0.80 g, 35%), the adduct (5), m.p. 209—210° (2.20 g, 55%), identical (i.r. spectrum, mixed m.p.) with material already described, unchanged starting material (0.02 g), and 2-benzyl-6-ethoxy-1,4-benzoquinone (0.36 g, 20%), as yellow needles (from chloroform), m.p. 135° (Found:  $M^+$ , 242.0946.  $\text{C}_{15}\text{H}_{14}\text{O}_3$  requires  $M$ , 242.0943),  $\lambda_{\text{max}}$  265 and 370 nm ( $\log \epsilon$  4.25 and 3.16),  $\nu_{\text{max}}$  1685 and 1650  $\text{cm}^{-1}$ ,  $\tau$  ( $\text{CDCl}_3$ ) 8.52 (t,  $J$  7 Hz,  $\text{O-CH}_2\text{-CH}_3$ ), 6.25 (s,  $\text{PhCH}_2$ ), 6.01 (q,  $J$  7 Hz,  $\text{O-CH}_2\text{-CH}_3$ ), 4.18 (d,  $J$  2 Hz, 5-H), 3.70 (m, 3-H), and 2.75 (m, ArH),  $m/e$  242(100%,  $M^+$ ), 213(90), 196(33,  $M - \text{EtOH}$ ), 185(20), 157(15), 143(30), 115(45), and 68(45).

*2-Benzylhydroquinone*.—2-Benzylhydroquinone<sup>7</sup> (0.50 g) was heated with amalgamated zinc (2.5 g) and hydrochloric acid (10 ml) under reflux for 8 h. The cooled mixture was extracted with ether ( $2 \times 50$  ml). The residue left on evaporation of the combined extracts was extracted with water to give 2-benzylhydroquinone (0.16 g, 30%), m.p. 104° (from water) (lit.,<sup>3,8</sup> 105°, 101—103°).

*2-Benzyl-1,4-benzoquinone*.—(a) *By oxidation of 2-benzylhydroquinone with DDQ*. A solution of 2-benzylhydroquinone

(200 mg) and DDQ (227 mg) in benzene (20 ml) was left at room temperature for 2 h. The precipitated hydroquinone (198 mg, 98%) was filtered off and the residual oil left after evaporation of the benzene was separated by t.l.c. [benzene–chloroform (4:1)] into the starting phenol (5 mg) and 2-benzyl-1,4-benzoquinone (150 mg, 76%), m.p. 44—45° (lit.,<sup>3</sup> 43°) (Found: C, 78.9; H, 5.1. Calc. for  $\text{C}_{13}\text{H}_{10}\text{O}_2$ : C, 78.7; H, 5.05%),  $\tau$  ( $\text{CDCl}_3$ ) 6.28 (s,  $\text{PhCH}_2$ ), 3.64 (m, 3-H), 3.30 (m, 4- and 5-H), and 2.75 (m, ArH), identical (i.r. spectrum) with an authentic sample,<sup>3</sup> m.p. 40—42°.

(b) *By oxidation of 2-benzylphenol with Fremy's salt*. A solution of 2-benzylphenol (0.50 g) in methanol (50 ml) was added to a solution of potassium nitrosodisulphonate (2.0 g) and potassium dihydrogen phosphate (1.3 g) in water (125 ml), and the mixture was stirred at room temperature for 2 h before being extracted with ether ( $3 \times 25$  ml). The combined extracts were washed with water ( $2 \times 25$  ml), followed by saturated aqueous sodium chloride (50 ml), and dried ( $\text{MgSO}_4$ ). Evaporation of the ether, filtration of a solution of the brown residue in benzene through Woelm polyamide (5 g), followed by elution with benzene and evaporation of the eluate gave a yellow residue, which yielded 2-benzylbenzoquinone (0.26 g, 50%), m.p. 45° (from light petroleum), identical with material prepared by method (a).

*Action of Methanol on 2-Benzyl-1,4-benzoquinone at Room Temperature*.—(a) *Alone*. A solution of 2-benzyl-1,4-benzoquinone (100 mg) in methanol (5 ml) was kept at room temperature for 24 h. Evaporation of the solvent *in vacuo* left unchanged starting material (100 mg), m.p. 44—45°.

(b) *With dichlorodicyanohydroquinone*. A solution of 2-benzyl-1,4-benzoquinone (100 mg) and the hydroquinone (100 mg) in methanol (5 ml) was stored for 24 h. Removal of the solvent *in vacuo*, followed by addition of benzene (10 ml) allowed separation of unchanged 2-benzylbenzoquinone (100 mg), m.p. 44—45°, from the insoluble hydroquinone.

(c) *With DDQ*. A solution of 2-benzylbenzoquinone (100 mg) and DDQ (100 mg) in methanol (5 ml) was left for 24 h, then evaporated *in vacuo*. The reddish-brown residue was separated by t.l.c. [benzene–ethyl acetate (4:1)] into starting material (65 mg) and 2-benzyl-6-methoxybenzoquinone (30 mg, 25%), m.p. 130° (from chloroform), identical with material already described.

(d) *With zinc chloride*. Anhydrous zinc chloride (100 mg) was added to a solution of 2-benzylbenzoquinone (100 mg) in methanol (5 ml) and the mixture was stirred for 24 h. It was then poured into water (30 ml) and extracted with ether (50 ml). The organic layer was washed with water and dried ( $\text{MgSO}_4$ ). Evaporation left a residue which on separation by t.l.c. [benzene–hexane–ethyl acetate (6:4:1)] gave the starting quinone (70 mg) and 2-benzyl-6-methoxybenzoquinone (20 mg, 19%) as yellow needles, m.p. 130° (from chloroform), identical with material already described.

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<sup>6</sup> W. F. Short and M. L. Stewart, *J. Chem. Soc.*, 1929, 553.

<sup>7</sup> D. B. Bruce and R. H. Thomson, *J. Chem. Soc.*, 1953, 2403.

<sup>8</sup> M. F. Fredrick, *J. Amer. Chem. Soc.*, 1965, 87, 4585.