Directive Effects in the Addition of Alcohols to Benzoquinones

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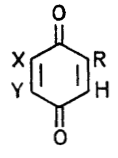
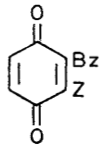
2-Alkyl-1,4-benzoquinones react with alcohols to give 5- and 6-alkoxy-derivatives, with the former predominating, in both uncatalysed and Lewis-acid-catalysed reactions. Exclusive formation of the 6-isomer was observed only in the catalysed reactions of 2-benzyl- and 2-t-butyl-1,4-benzoquinones. 2-Benzoyl-1,4-benzoquinone is attacked by methanol at C-3.

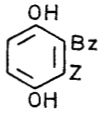
REGIOSPECIFIC addition of alcohols to 2-t-butyl- and 2-benzyl-1,4-benzoquinone occurs at the 6-position in the presence of Lewis acid catalysts.[1,2] Zinc-chloride-catalysed reaction of methanol with 2-methyl-1,4-benzoquinone was originally reported [3] to give only the 5-methoxy-derivative, but more recent work [4] has shown



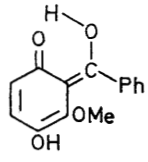
(1) R = CH_2Ph, X = Y = H
(2) R = CH_2Ph, X = H, Y = OMe
(3) R = CH_2Ph, X = OMe, Y = H
(4) R = Bu^t, X = Y = H
(5) R = Bu^t, X = H, Y = OMe
(6) R = Bu^t, X = OMe, Y = H



(7) Z = H
(10) Z = OMe



(8) Z = OMe
(11) Z = H



(9)

that the 6-isomer is also formed. During an investigation of the reaction of 2-benzyl-1,4-benzoquinone (1) in boiling methanol we obtained a methoxy-quinone fraction consisting of two monomethoxy-derivatives (ratio 5 : 4) which were separated by multiple-development t.l.c. The predominant isomer, which was slightly the more mobile, was shown by n.m.r. to be 2-benzyl-5-methoxy-1,4-benzoquinone (2), as there was no appreciable coupling between its nuclear protons. The other product was the 6-methoxy-isomer (3), previously characterised,[2] in which the nuclear protons are coupled (J 2·5 Hz). The uncatalysed reactions of a series of alkylquinones with alcohols were analysed by the same method; similar mixtures of 5- and 6-alkoxy-derivatives were obtained (Table 1). In each case the two isomers

TABLE 1

Uncatalysed reactions of quinones with methanol

2-Substituent	% Product 5-OMe	% Product 6-OMe	% Starting material recovered
Me	25	20	5
	(OEt, 21)	(OEt, 25)	(4)
Et	21	12	5
Bu^s	25	20	
Bu^t	12	10	20
CH_2Ph	20	16	12

were readily distinguished by degree of coupling of their nuclear protons. Several of these quinones had previously been prepared by other methods.

The reaction involves addition of the alcohol to the

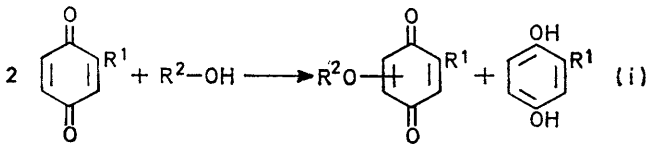
[1] (*a*) F. R. Hewgill, B. R. Kennedy, and D. Kilpin, *J. Chem. Soc.*, 1965, 2904; (*b*) F. R. Hewgill and L. R. Mullings, *J. Chem. Soc.* (*B*), 1969, 1155.

[2] J. M. Singh and A. B. Turner, *J.C.S. Perkin I*, 1972, 2294.

[3] J. N. Ashley, *J. Chem. Soc.*, 1937, 1471.

[4] S. Heitz, *Compt. rend.*, 1965, **261**, 3158.

quinone to give an alkoxy-hydroquinone, which is then oxidised by the excess of starting quinone, as this has a higher oxidation potential than the resulting alkoxy-quinone. The overall reaction is as shown in equation



(i). The combined yield of alkoxy-quinones approaches 50% when the reaction is complete.

The only substrate which initially appeared to depart from the general pattern was t-butylbenzoquinone (4). This gave mainly 6-alkoxy-derivatives (6) in both catalysed [dichlorodicyanobenzoquinone (DDQ) and zinc chloride] and uncatalysed reactions. However, as our t-butyl quinone was originally prepared by oxidation of t-butylhydroquinone with DDQ, it was thought desirable to prepare it by a route in which there was no possibility of contamination with a known catalyst for 6-alkoxy-derivative formation. Other oxidants used included silver oxide,[5] which gave a quantitative yield of the quinone, and the quinone was also prepared by oxidation of 2-butylphenol with Fremy's salt. From the quinone (4) prepared by these methods, the reaction with methanol gave the 5-methoxy-derivative (5) as major product, in accord with the results of Hewgill and his co-workers,[1] although the reaction was not always reproducible. When the reaction with methanol was carried out with t-butyl quinone prepared by oxidation of t-butyl-hydroquinone with DDQ in homogeneous solution, or with cerium(IV) ammonium nitrate in the two-phase water–acetonitrile system, the major product was the 6-methoxy-derivative (6). The corresponding 6-ethoxy-2-t-butylquinone was formed in ethanol. We assume that formation of these 6-alkoxy-derivatives was due to catalysis by traces of DDQ in the former case, and to traces of acid derived from the cerium salt in the latter. Erratic results and poor yields in the reactions of the quinone (4) could be ascribed to the formation of rearranged products *via* diradical intermediates (*cf.* ref. 5).

Similar results were obtained for the same series of quinones in reactions catalysed by zinc chloride (Table 2), with the 5-alkoxy-derivative being the major product, except in the case of the t-butyl quinone. This yielded only the 6-isomer. Since this is the only quinone in which approach to both sides of the ring is hindered, the regiospecificity is best explained by steric hindrance to co-ordination of the catalyst at the 1-carbonyl group, in keeping with the usual type of π-complex formation with this grouping. More difficult to explain is the similar regiospecificity which has been noted in the oxidation of the t-butyl quinone to its 6-hydroxy-derivative in alkaline solution.[6] When this oxidation was run in methanolic or ethanolic alkali the 6-alkoxy-2-t-butyl semiquinone radical anions were identified as intermediates by e.s.r. spectroscopy.

Specific formation of the 6-methoxy-derivative (3) from benzylbenzoquinone (1) in the presence of zinc chloride, previously observed at room temperature,[2] has now been confirmed at reflux temperature (Table 2).

TABLE 2

Zinc-chloride-catalysed reactions of quinones with methanol

2-Substituent	% Product 5-OMe	% Product 6-OMe	Starting material recovered
Me	26 (OEt, 21)	21 (OEt, 18)	12 (9)
Et	15	10	8
Bu^s	20	15	15
Bu^t		22	10
CH_2Ph		20	60

1,4-Benzoquinone itself reacts with alcohols in the presence of zinc chloride to give 2,5-dialkoxybenzoquinones,[7] and in this case addition of the second alcohol molecule to the intermediate monoalkoxy-quinone occurs exclusively at C-5, in keeping with the more powerful electron-releasing effect of the alkoxy-group.

One example of a quinone containing an electron-withdrawing substituent was studied. Benzoylbenzoquinone (7) yielded 2-benzoyl-3-methoxyhydroquinone (8) in both catalysed and uncatalysed reactions with methanol. Here C-3 is the most electrophilic carbon atom, being conjugated with the 1-carbonyl group and the side-chain carbonyl group. It is unusual for the initial hydroquinone to survive in the presence of the higher-potential starting quinone, and the isolation of the hydroquinone from this reaction may be due to the additional stability derived from its hydrogen-bonded *o*-hydroxy-ketone system. This type of hydroquinone may exist predominantly in the tautomeric quinone methide form (9) [both it and 2-benzoylhydroquinone are yellow] and hence may resist oxidation by 2-benzoylbenzoquinone. However, it is smoothly oxidised by the higher-potential quinone, DDQ, to give 2-benzoyl-3-methoxy-1,4-benzoquinone (10).

Farina and Valderrama [8] have reported similar results with 2-acetyl-1,4-benzoquinone. This is attacked at C-3 by a variety of alcohols, and poor yields of the initial hydroquinone adduct were obtained when the alcohol was used as solvent. These workers obtained good yields of the corresponding alkoxy-acetyl quinone when equimolar amounts of reactants were used in dry benzene. When these conditions were applied to benzoylbenzoquinone an orange oil was obtained which appeared from its n.m.r. spectrum to consist mainly of benzoylhydroquinone, together with the quinone (10). However, attempts to isolate this quinone from the mixture were not successful: only the hydroquinones (8) and (11) were obtained.

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[6] J. Pilar, I. Buben, and J. Pospisil, *Coll. Czech. Chem. Comm.*, 1970, **35**, 489.

[7] E. Knoevenagel and C. Buckel, *Ber.*, 1901, **34**, 3993.

[8] F. Farina and J. Valderrama, *Synthesis*, 1971, 315.

EXPERIMENTAL

For general directions see ref. 9.

General Procedures.—(a) *Uncatalysed reactions* (Table 1). A 0·2M-solution of the quinone in the alcohol was heated under reflux for 48 h. The alcohol was removed *in vacuo* and the residue was separated by t.l.c. on silica gel [Merck GF 254; five developments in benzene–ethyl acetate (10 : 1)]. The alkoxy-quinone was eluted with benzene.

(b) *Zinc-chloride-catalysed reactions* (Table 2). Alcoholic 0·1M-solutions of the quinone and anhydrous zinc chloride were mixed and heated under reflux for 2 h. The mixture was poured into water and extracted with ether. The extracts were washed with water, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by t.l.c. as in (a).

2-*Methoxy*-5-*methyl*-1,4-*benzoquinone* had m.p. 170—171° (from MeOH) (lit.,[3] 172—173°), τ 7·95 (d, *J* 2 Hz, 5-Me), 6·20 (s, 2-OMe), 4·09 (s, 3-H), and 3·45 (d, *J* 2 Hz, 6-H); 2-*methoxy*-6-*methyl*-1,4-*benzoquinone* had m.p. 146—147° (from MeOH) (lit.,[10] 148—150°), τ 7·90 (d, *J* 2 Hz), 6·15 (s, 2-OMe), 4·09 (d, *J* 3 Hz, 3-H), and 3·45 (m, 5-H); 2-*ethoxy*-5-*methyl*-1,4-*benzoquinone* had m.p. 96—97° (from EtOH) (lit.,[11] 101°), τ 8·51 (t, *J* 8 Hz, 2-O·CH_2·CH_3), 7·92 (d, *J* 2 Hz, 5-Me), 5·99 (q, *J* 8 Hz, 2-O·CH_2·CH_3), 4·08 (s, 3-H), and 3·44 (q, *J* 2 Hz, 6-H); 2-*ethoxy*-6-*methyl*-1,4-*benzoquinone* had m.p. 54—55° (from EtOH) (lit.,[12] 56—58°), τ 8·51 (t, *J* 8 Hz, 2-O·CH_2·CH_3) 7·94 (d, *J* 2 Hz, 6-Me), 6·00 (q, *J* 8 Hz, 2-O·CH_2·CH_3), 4·15 (d, *J* 2 Hz, 3-H), and 3·47 (m, 5-H).

2-*Ethyl*-1,4-*benzoquinone*.—A solution of 2-ethylphenol (2·0 g) in methanol (60 ml) was added dropwise to a stirred solution of potassium nitrosodisulphonate (12·0 g) in water (500 ml) and the mixture was stirred for 1 h at room temperature. It was extracted with ether (3 × 100 ml) and the combined extracts were washed with water, then with saturated aqueous sodium chloride, and dried ($MgSO_4$). The residue left after evaporation of the ether was dissolved in benzene, and the solution was filtered through polyamide (10 g), and eluted with benzene. The yellow product was purified by t.l.c. [benzene–ethyl acetate (6 : 1)] to give the quinone (1·1 g, 50%) as a yellow oil (lit.,[13] 36·8—37·6°) (Found: C, 70·4; H, 5·3. Calc. for $C_8H_8O_2$: C, 70·5; H, 5·8%), $\lambda_{max.}$ 250 and 315 nm (log ε 4·13 and 3·09), $\nu_{max.}$ 1650 cm^{-1}, τ 8·90 (t, *J* 8 Hz, 2-CH_2·CH_3), 7·55 (q, *J* 8 Hz, 2-CH_2·CH_3), 3·45 (m, 3-H), and 3·33 (s, 5- and 6-H).

2-*Ethyl*-5-*methoxy*-1,4-*benzoquinone* had m.p. 149—152° (from ether–light petroleum) (Found: C, 65·4; H, 6·4. $C_9H_{10}O_3$ requires C, 65·1; H, 6·0%), $\lambda_{max.}$ 265 and 370 nm (log ε 4·14 and 2·65), $\nu_{max.}$ 1675 and 1650 cm^{-1}, τ 8·88 (t, *J* 7 Hz, 2-CH_2·CH_3), 7·50 (q, *J* 7 Hz, 2-CH_2·CH_3), 6·20 (s, 5-OMe), 4·10 (s, 6-H), and 3·52 (m, 3-H); 2-*ethyl*-6-*methoxy*-1,4-*benzoquinone* had m.p. 160—162° (from ether–light petroleum) (Found: C, 64·9; H, 5·7%), $\lambda_{max.}$ 265 and 370 nm (log ε 4·06 and 2·74), $\nu_{max.}$ 1675 and 1650 cm^{-1}, τ 8·85 (t, *J* 7 Hz, 2-CH_2·CH_3), 7·50 (dq, *J* 7 and 2 Hz, 2-CH_2·CH_3), 6·20 (s, 6-OMe), 4·13 (d, *J* 2 Hz, 5-H), and 3·50 (m, 3-H).

2-*s*-*Butyl*-1,4-*benzoquinone*.—Potassium nitrosodisulphonate (17·0 g) in water (500 ml) was added to a stirred solution of 2-s-butylphenyl (3·0 g) in methanol (60 ml), and stirring was continued for 1 h. Isolation and purification as above gave the quinone (1·7 g, 51%), m.p. 65—66° (from light petroleum) (lit.,[14] 66°) (Found: C, 73·4; H, 7·5. Calc. for $C_{10}H_{12}O_2$: C, 73·1; H, 7·3%), $\lambda_{max.}$ 250 and 310 nm (log ε 4·01 and 2·75), $\nu_{max.}$ 1650 cm^{-1}, τ 9·15 (t, *J* 7 Hz, CHMe·CH_2*Me*), 8·87 (d, *J* 7 Hz, CH*Me*·CH_2Me), 8·60 (m, CHMe·CH_2Me), 7·15 (m, C*H*Me·CH_2Me), 3·40 (m, 3-H), and 3·20 (m, 5- and 6-H).

2-*Methoxy*-5-*s*-*butyl*-1,4-*benzoquinone* was isolated by t.l.c. as a yellow oil (Found: C, 68·3; H, 7·8. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·3%), $\lambda_{max.}$ 267 and 365 nm (log ε 4·02 and 2·85), $\nu_{max.}$ 1670 and 1650 cm^{-1}, τ 9·10 (t, *J* 7 Hz, CHMe·CH_2*Me*), 8·99 (d, *J* 7 Hz, CH*Me*·CH_2Me), 8·55 (m, CHMe·*C*H_2Me), 7·09 (m, C*H*Me·CH_2Me), 6·19 (s, OMe), 4·09 (s, 3-H), and 3·55 (m, 6-H); 2-*methoxy*-6-*s*-*butyl*-1,4-*benzoquinone* was isolated by t.l.c. as a yellow oil (Found: C, 68·0; H, 7·3%), τ 9·11 (t, *J* 7 Hz, CHMe·CH_2*Me*), 8·88 (d, *J* 7 Hz, CH*Me*·CH_2Me), 8·55 (m, CHMe·*C*H_2Me), 7·09 (m, C*H*Me·CH_2Me), 6·17 (s, OMe), 4·10 (m, 3-H), and 3·52 (m, 5-H).

2-*t*-*Butyl*-1,4-*benzoquinone*.—Oxidation of 2-t-butylphenol with potassium nitrosodisulphonate as described above gave the quinone, m.p. 59°, in 46% yield. Oxidation of t-butylhydroquinone by DDQ in dioxan at room temperature gave the quinone in 85% yield; use of cerium(IV) ammonium nitrate [15] in aqueous acetonitrile gave the quinone in 80% yield.

M.p.s and spectral data of the methoxy- and ethoxy-derivatives of this quinone corresponded to literature values.[1]

2-*Benzyl*-5-*methoxy*-1,4-*benzoquinone* had m.p. 128—130° [from petroleum–ether (1 : 1)] (Found: M^+, 228·0781. $C_{14}H_{12}O_3$ requires *M*, 228·0786), $\nu_{max.}$ 1660 and 1640 cm^{-1}; τ 6·24 (s, $PhCH_2$), 6·19 (s, OMe), 4·06 (s, 6-H), and 3·72 (m, 3-H); 2-benzyl-6-methoxy-1,4-benzoquinone had m.p. 130—131° (lit.,[2] 130°), and was identical (mixed m.p. and i.r.) with an authentic sample.

Action of Methanol upon 2-*Benzoyl*-1,4-*benzoquinone*.[16]—(a) *Uncatalysed.* A solution of the quinone (100 mg) in methanol (10 ml) was heated under reflux for 48 h, then evaporated. The residue was separated by t.l.c. [benzene–ethyl acetate (5 : 1)] to give starting quinone (10 mg) and 2-*benzoyl*-3-*methoxyhydroquinone* (30 mg, 26%), m.p. 141—143° (from ethyl acetate–hexane) (Found: C, 68·3; H, 5·0. $C_{14}H_{12}O_4$ requires C, 68·8; H, 4·9%), $\lambda_{max.}$ 249, 281sh, and 325sh nm (log ε 4·14, 3·71, and 2·98), $\nu_{max.}$ 3390 and 1650 cm^{-1}, τ 6·67 (s, OMe), 3·24 and 2·88 (ABq, *J* 9 Hz, 5- and 6-H), and 2·60—2·20 (m, Bz).

(b) *Catalysed by zinc chloride.* A solution of 2-benzoyl-1,4-benzoquinone (150 mg) in methanol (20 ml) containing zinc chloride (200 mg) was refluxed for 12 h, cooled, poured into water, and extracted with ethyl acetate. The extracts were evaporated and the residue was separated by t.l.c. into starting quinone (25 mg) and 2-benzoyl-3-methoxyhydroquinone (40 mg, 23%), m.p. 140—142°, identical with material prepared by method (a).

Acetylation of this hydroquinone (40 mg) with acetic anhydride (3 ml) in pyridine (5 ml) for 12 h at room temperature gave 1,4-*diacetoxy*-2-*benzoyl*-3-*methoxybenzene* (20 mg) as an oil (Found: C, 66·0; H, 5·2. $C_{18}H_{16}O_6$ requires C, 65·8; H, 4·8%), $\lambda_{max.}$ 254 nm (log ε 3·44), $\nu_{max.}$ 1770 and 1670 cm^{-1}, τ 8·08 (s, 4-OAc), 7·68 (s, 1-OAc), 6·32 (s, OMe), 3·02 and 2·80 (Abq, *J* 9 Hz, 5- and 6-H), and 2·16—2·58 (m, Bz).

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2-*Benzoyl*-3-*methoxy*-1,4-*benzoquinone*.—A solution of DDQ (84 mg) in benzene (5 ml) was added dropwise during 10 min to a stirred solution of 2-benzoyl-3-methoxyhydroquinone (90 mg) in benzene (10 ml). Stirring was continued for 2 h. The precipitated dichlorodicyanohydroquinone (80 mg) was filtered off and the filtrate was evaporated. The residual oil was purified by t.l.c. [benzene–ethyl acetate (4 : 1)] to give 2-*benzoyl*-3-*methoxy*-1,4-*benzoquinone* (60 mg, 67%) as an oil (Found: C, 69·1; H, 4·3. $C_{14}H_{10}O_4$ requires C, 69·4; H, 4·1%), $\lambda_{max.}$ 254 and 370 nm (log ε 4·02 and 3·17), $\nu_{max.}$ 1675 and 1640 cm^{-1}, τ 6·14 (s, OMe), 3·24 (s, 5- and 6-H), and 2·08—2·54 (m, Bz).

Reductive Acetylation of 2-*Benzoyl*-3-*methoxy*-1,4-*benzoquinone*.—A mixture of the quinone (40 mg), zinc dust (40 mg), sodium acetate (40 mg), and acetic anhydride (10 ml) was stirred overnight at room temperature, poured into water, and extracted with ether. The extracts were washed with aqueous sodium hydrogen carbonate, then water, dried ($MgSO_4$), and evaporated. The residue was purified by t.l.c. to give 2-benzoyl-3-methoxyhydroquinone diacetate (30 mg, 55%) as an oil, identical with material described above.

We thank L. Hamill for assistance with some of the experimental work and the Cancer Research Campaign for financial support.

[4/1471 *Received*, 18*th July*, 1974]