Reactions of 4-Bromo-4-(1-hydroxypropyl)-2,6-di-t-butylcyclohexa-2,5-dienone in Methanolic Sulphuric Acid

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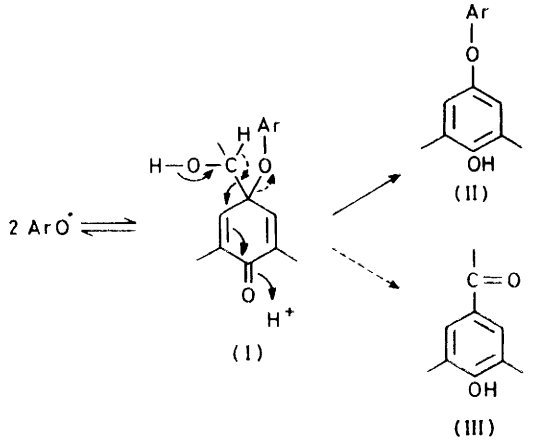
Reactions of the title compound (1) in methanolic sulphuric acid are described. At high acid concentrations the main reaction is the cleavage of the side chain as propionic aldehyde. At low acid concentrations the products are mainly formed by hydrolysis of (1) and subsequent reduction and oxidation reactions involving the bromide ion and bromine.

In phenol oxidations the quinol ethers of type (I) can be intermediates for the formation of both diphenyl ethers (II) and ketones (III),[1] although the ketones may also arise by direct disproportionation of the phenoxy-radicals. Following our earlier work on the mechanism of phenol oxidation [2] we have now examined the acid



hydrolysis of the bromocyclohexadienone (1) to gain more information on the cleavage of the 1-alkoxy-side chain and the possible disproportionation of cyclohexadienones. Previously, (1) has been reported to afford the ketone (4) in ethanol at 60 °C.[3]

Hydrolysis of the bromocyclohexadienone (1) in 5% methanolic sulphuric acid at room temperature led to an unexpectedly complex mixture of four phenolic compounds (2)—(5) and the *p*-quinone (6). To elucidate the mechanism involved in the formation of the products the bromocyclohexadienone was hydrolysed in six different concentrations of methanolic sulphuric acid. In each case the rate of the reaction was roughly estimated by following the disappearance of the starting material by t.l.c., and the isolated mixture of products was analysed by ^{1}H n.m.r. The results (Table 1) can be explained as follows.

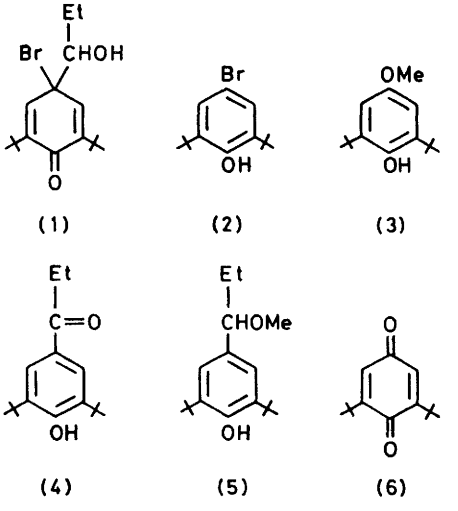
Table 1

Reactions of the bromocyclohexadienone (1) in methanolic sulphuric acid

Expt. no.	% H_2SO_4 (v/v)	Reaction time (min)	Products and % yield (2)	(3)	(4)	(5)	(6)
1	0	300	5	46	9	26	14
2	1	260	17	26	7	32	18
3	5	210	33	17	4	29	17
4	10	120	43	7	3	30	17
5	20	30	69	5	3	16	7
6 [a]	30	20	80	2	4	3	3
7	5	1080	36	33	10	14	7

[a] Reaction mixture was a suspension.

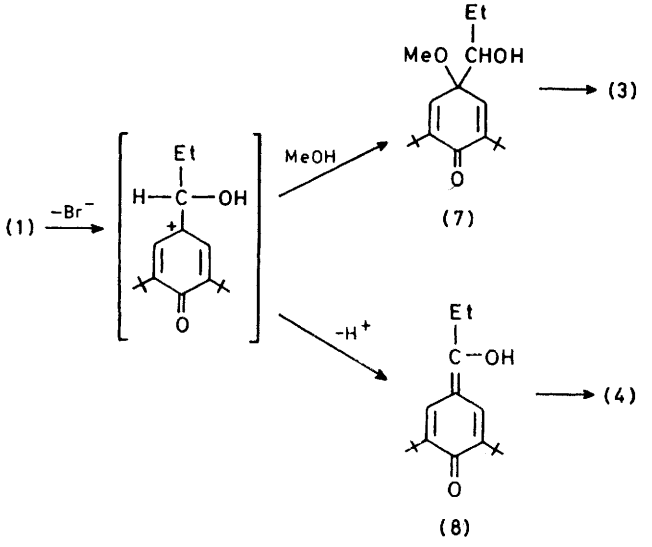
At high acid concentrations the main reaction is the formation of the *p*-bromophenol (2) by cleavage of the side chain as propionic aldehyde. In methanol and 1% methanolic sulphuric acid, on the other hand, the main product is the *p*-methoxyphenol (3), evidently due to the high reactivity of (1), as a tertiary allylic bromide, towards alcoholysis.[4] At low acid concentrations the solvolysis of the bromocyclohexadienone, leading to the *p*-methoxyphenol *via* the quinol ether (7) (Scheme 1), is faster than the direct cleavage of the side chain.



The ketone (4) is formed in a competing reaction. This reaction can be formulated as a deprotonation of the intermediate cation formed in the solvolysis,[5] or as an acid-catalysed elimination of (7) to give the quinone methide (8) which is tautomerized to the ketone (4).

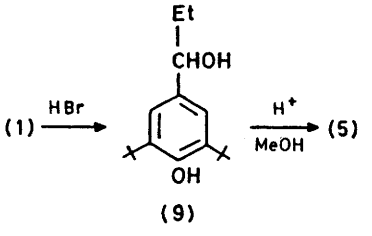
When water (25% v/v) in methanol was used in experiment 3 (Table 1) only the *p*-methoxyphenol (3), the ketone (4), and 2,6-di-t-butylhydroquinone were formed, in 73, 14, and 13% yields, respectively. As expected, the hydrolysis of (1) is facilitated by increasing solvent polarity to give higher amounts of (3) and (4) although in the same relative proportions.

The formation of the benzyl ether (5) cannot be explained in terms of homolytic dissociation of the C–Br bond followed by disproportionation of the phenoxy-radical to the quinone methide (8) and the phenol (9), since then roughly 1 : 1 ratios of (4) and (5) should be



SCHEME 1

obtained. We suggest Scheme 2 to account for the formation of (5). The bromide ion, formed in the hydrolysis of (1), liberates bromine from the starting material [6] to afford the phenol (9). Under the present reaction conditions (9) rapidly reacts with methanol to



SCHEME 2

give the benzyl ether (5) (see Experimental section). At high acid concentrations, where the bromide ion concentration is low owing to the formation of (2), considerably less (5) is formed.

Further evidence illustrating the action of the bromide ion in the formation of the benzyl ether (5) is summarized in Table 2. When allylic alcohol was added to scavenge the hydrogen bromide formed in the hydrolysis, the amount of the benzyl ether formed was diminished. No benzyl ether was obtained when 1 mol equiv. of silver nitrate was used to precipitate the bromide ion. Increasing the bromide ion concentration by addition of hydrogen bromide, in turn, gave a higher yield of the benzyl ether. Finally, addition of iodide ion, a better nucleophile than bromide ion, caused almost exclusive formation of the benzyl ether.

The reaction of bromide ion with the starting material to give bromine also explains the rather surprising formation of considerable amounts of the *p*-quinone (6). Bromine is capable of oxidizing the t-butyl-substituted *p*-bromophenol (2) and *p*-methoxyphenol (3) to the cyclohexadienones (10) and (11) [7] (Scheme 3) which give the *p*-quinone (6) through the readily hydrolysable acetal (12).[8] Experimental evidence for Scheme 3 was

TABLE 2

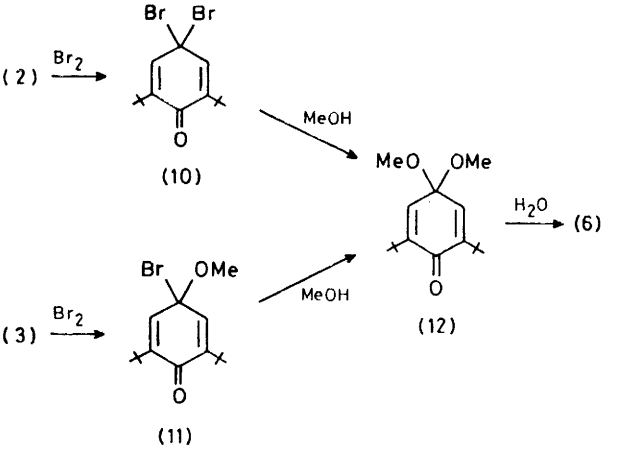
Reactions of the bromocyclohexadienone (1) in 5% methanolic sulphuric acid

		Products and % yield				
Reagent (mol. equiv.)		(2)	(3)	(4)	(5)	(6)
Allylic alcohol	(30.0)	31	42	10	15	2
$AgNO_3$[a]	(1.0)		66	19		15
HBr	(6.0)	9		4	62	25
LiI	(3.0)			7	93	
Br_2	(0.5)	15		8	9	68

[a] Water (25%) was used to dissolve the silver nitrate.

provided by addition of 0.5 mol equiv. of bromine to the reaction mixture to afford the *p*-quinone as the main product (Table 2). The faster oxidation of the *p*-methoxyphenol than the *p*-bromophenol is in accordance with the redox potentials of these compounds.[9]

The effect of reaction time on product distribution was examined by allowing the reaction mixture (5% H_2SO_4) to stand for 18 h at room temperature. Compared with the reaction which was stopped immediately after the disappearance of the starting material, significantly less



SCHEME 3

of the *p*-quinone (6) and the benzyl ether (5) was now formed, in favour of (3) and (4) (expt. 7, Table 1).

It appears that in acidic methanol the sequence of reactions (11) ⟶ (12) ⟶ (6) (Scheme 3) is reversible, giving the dienone (11) which reacts with the bromide ion to afford the *p*-methoxyphenol (3). This was verified by treatment of (6) with 5% methanolic sulphuric acid containing 1 mol equiv. hydrogen bromide to afford 9% of (3) and 91% of unchanged (6). As for the reaction in 5% methanolic sulphuric acid, the n.m.r. spectrum revealed traces of a few other unidentified compounds containing methoxy-groups.

The disappearance of the benzyl ether (5) is obviously caused by its oxidation. The bromine liberated in the

formation of (3) from (11) reacts with the benzyl ether to give the bromocyclohexadienone (1) *via* the corresponding benzyl alcohol (9) existing in equilibrium with (5) in methanolic sulphuric acid. The bromocyclohexadienone then reacts according to Scheme 1, enriching the *p*-methoxyphenol (3) and the ketone (4) in the reaction mixture. Higher amounts of the *p*-bromophenol (2) should also be obtained in the recycling of (5). However, the level of (2) is kept nearly constant by the oxidation in Scheme 3.

Both the benzyl alcohol (9) and the benzyl ether (5) gave, by oxidation with 0.2 mol equiv. of bromine, the products (3), (4), and (6), together with unchanged (5) in 8, 6, 8, and 78% yields, respectively.

EXPERIMENTAL

M.p.s were determined with a m.p. microscope (Zeiss). I.r. spectra were determined on a Perkin-Elmer 125 spectrophotometer. N.m.r. spectra were recorded with a JEOL JMN-PMX60 spectrometer for solutions in deuteriochloroform, using tetramethylsilane as internal standard. Precoated 2 mm-thick plates (Merck Kieselgel 60 F_{254}) were used for preparative t.l.c. Light petroleum refers to the fraction of b.p. 40—60 °C. A stock solution, prepared from analytical grade methanol (70 ml) and sulphuric acid (30 ml) without eliminating water, was diluted to the appropriate concentrations for reactions of the dienone (1).

Starting Material and Reference Compounds.—4-(1-hydroxypropyl)-2,6-di-t-butylphenol (5 g) was oxidized with bromine (1 ml) to the bromocyclohexadienone (1) by the method described earlier.[3] Since the isolated product proved to be unstable, the washed ($NaHCO_3$ and water) and dried ($MgSO_4$) light petroleum extracts (210 ml) were concentrated to *ca.* 20 ml under vacuum at room temperature. On standing in a freezer the dienone formed yellow crystals, m.p. 63—64.5 °C (lit.,[3] 51 °C), $\nu_{max.}$ (KBr) 1 630, 1 637, and 1 657 cm^{-1}; δ 6.90 and 6.67 [1 H, d (W long-range coupling), *J* 2.5 Hz, 'dienone' H],* 3.82 (1 H, m, C*H*OH), 2.57 (1 H, s, OH), 1.25 (18 H, s, CMe_3), and 1.30—0.80 (5 H, m, CH_2CH_3). According to n.m.r. the dienone contained *ca.* 2% of the ketone (4). When stored in a freezer under light petroleum only a slight deterioration of the product was observed after several months. A freshly prepared sample was used for reactions.

4-Bromo-2,6-di-t-butylphenol (2), m.p. 82—83 °C (lit.,[10] 80—81 °C), 4-methoxy-2,6-di-t-butylphenol (3), m.p. 105.5—106.5 °C (lit.,[11] 105—106 °C) 4-hydroxy-3,5-di-t-butylpropiophenone (4), m.p. 136—137 °C (lit.,[3] 137 °C), and 2,6-di-t-butyl-*p*-benzoquinone (6), m.p. 65—66 °C (lit.,[12] 65—66 °C), were prepared by reported methods.

Acid-catalysed etherification of 4-(1-hydroxypropyl)-2,6-di-t-butylphenol in 1% methanolic sulphuric acid at room temperature (5 min) afforded, according to t.l.c. [cyclohexane–ethyl acetate (8 : 1)], quantitatively 4-(1-methoxypropyl)-2,6-di-t-butylphenol (5), m.p. 44—45 °C (from ethanol) (lit.,[13] 45 °C).

General Procedure for Reaction of the Dienone (1) *in Methanolic Sulphuric Acid.*—The dienone (1) (0.4 g, 1.2 mmol) was dissolved with stirring in methanolic sulphuric acid (20 ml). The stirring was continued in a stoppered flask at room temperature until t.l.c. [cyclohexane–ethyl acetate (15:1)] showed no starting material. The reaction mixture was then poured into ice–water (50 ml) and extracted with light petroleum (3 × 25 ml). The combined extracts were washed with saturated sodium hydrogencarbonate solution (2 × 20 ml) and water (2 × 20 ml). Evaporation of the dried ($MgSO_4$) solution under vacuum at 40 °C gave a yellow oil.

For the reactions in Table 2 the appropriate reagent was added to the 5% methanolic sulphuric acid before the dienone.

Yields and Identification of Products.—The yields of (2), (3), (4), (5), and (6) in the crude products were evaluated by integrating the ^1H n.m.r. absorption signals of the aromatic protons at δ 7.22, 6.77, 7.87, 7.04, and 6.50, respectively (average of four integrations).

Two recrystallisations of the *p*-bromophenol (2) (expt. 6, Table 1) from ethanol afforded colourless crystals (120 mg), m.p. 82—83 °C, δ 7.22 (2 H, s, ArH), 5.12 (1 H, s, OH), and 1.43 (18 H, s, CMe_3), mixed m.p. 82—83 °C. The crude product from the reaction mixture containing 25% of water in 5% methanolic sulphuric acid was recrystallised twice from light petroleum to give the *p*-methoxyphenol (3) (64 mg), m.p. 105.5—106.5 °C, δ 6.77 (2 H, s, ArH), 4.75 (1 H, s, OH), 3.77 (3 H, s, OMe), and 1.43 (18 H, s, CMe_3), mixed m.p. 105.5—106.5 °C. Preparative t.l.c. [cyclohexane–ethyl acetate–benzene (14 : 2 : 1)] of the crude product from the reaction mixture containing lithium iodide gave the ketone (4) (27 mg), m.p. 136—137 °C (from light petroleum), δ 7.87 (2 H, s, ArH), 5.72 (1 H, s, OH), 2.97 (2 H, q, *J* 7 Hz, CH_2CH_3), 1.47 (18 H, s, CMe_3), and 1.23 (3 H, t, *J* 7 Hz, CH_2CH_3), mixed m.p. 136—137 °C, and the benzyl ether (5) (185 mg), m.p. 44—45 °C (from ethanol), δ 7.04 (2 H, s, ArH), 5.12 (1 H, s, OH), 3.95 (1 H, t, *J* 7 Hz, C*H*OH), 3.22 (3 H, s, OMe), 1.90—1.55 (2 H, m, CH_2CH_3), 1.48 (18 H, s, CMe_3), and 0.88 (3 H, t, *J* 7 Hz, CH_2CH_3), mixed m.p. 44—45 °C. Preparative t.l.c. [cyclohexane–ethyl acetate–benzene (16 : 1 : 1)] of the crude product from experiment 1 (Table 1) afforded the *p*-quinone (6) (22 mg) m.p. 64—65 °C (from ethanol), δ 6.50 (2 H, s, 'dienone' H) and 1.28 (18 H, s, CMe_3), mixed m.p. 65—66 °C.

All compounds had identical n.m.r. spectra with those of authentic samples.

Reaction of the p-*Quinone* (6) *with Hydrogen Bromide in Methanolic Sulphuric Acid.*—To a mixture of 2,6-di-t-butyl-*p*-benzoquinone (220 mg, 1 mmol) in 5% methanolic sulphuric acid (17.5 ml) was added a solution of hydrogen bromide (1 mmol) in methanol (2.5 ml). The reaction mixture was allowed to stand at room temperature for 18 h. Isolation and analyses of the products are described above.

Oxidation of the Benzyl Ether (5) *and Benzyl Alcohol* (9) *with Bromine.*—To a mixture of 4-(1-methoxypropyl)-2,6-di-t-butylphenol (220 mg, 0.75 mmol) or 4-(1-hydroxypropyl)-2,6-di-t-butylphenol (200 mg, 0.75 mmol) in methanol (16 ml) was added a solution of hydrogen bromide (0.8 mmol) in methanol (2 ml) and a solution of bromine (0.15 mmol) in methanol (2 ml). The products were isolated and analysed as above after 18 h at room temperature.

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* Owing to the asymmetric centre in the side chain the dienone ring protons are non-equivalent.

REFERENCES

[1] W. J. Connors, J. S. Ayers, K. V. Sarkanen, and J. S. Gratzl, *Tappi*, 1971, **54**, 1284 (*Chem. Abs.*, 1971, **75**, 130930n.

[2] M. Karhu, *J.C.S. Perkin I*, 1979, 1661.
[3] J. Hamada and T. Fujisaki, *Nippon Kagaku Zasshi*, 1961, **82**, 898 (*Chem. Abs.*, 1963, **59**, 496h).
[4] C. A. Vernon, *J. Chem. Soc.*, 1954, 423.
[5] J. G. Traynham and J. Schneller, *J. Amer. Chem. Soc.*, 1965, **87**, 2398.
[6] V. V. Ershov and A. A. Volod'kin, *Izvest. Akad. Nauk S.S.S.R., Odt. Khim. Nauk*, 1962, 2026 (*Chem. Abs.*, 1963, **58**, 11250h).
[7] V. V. Ershov and A. A. Volod'kin, *Izvest. Akad Nauk S.S.S.R., Odt. Khim. Nauk*, 1963, 893 (*Chem. Abs.*, 1963, **59**, 7385e); C. D. Cook, N. G. Nash, and H. R. Flanagan, *J. Amer. Chem., Soc.*, 1955, **77**, 1783.
[8] H.-D. Becker, *J. Org. Chem.*, 1962, **80**, 982.
[9] L. R. Mahoney and M. A. DaRooge, *J. Amer. Chem. Soc.*, 1970, **92**, 890.
[10] K. Ley, E. Müller, E. Mayer, and K. Scheffer, *Chem. Ber.*, 1958, **91**, 2670.
[11] C. D. Cook, R. G. Inskeep, A. S. Rosenberg, and E. C. Curtis, jun., *J. Amer. Chem. Soc.*, 1955, **77**, 1672.
[12] C. R. H. I. DeJonge, H. J. Hageman, G. Hoentjen, and W. J. Mijs, *Org. Synth.*, 1977, **57**, 78.
[13] J. Hamada and T. Fujisaki, *Nippon Kagaku Zasshi*, 1961, **82**, 902 (*Chem. Abs.*, 1963, **58**, 11256e).