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The Formation of Orthoquinones in the Dimethyldioxirane Oxidation of Phenols

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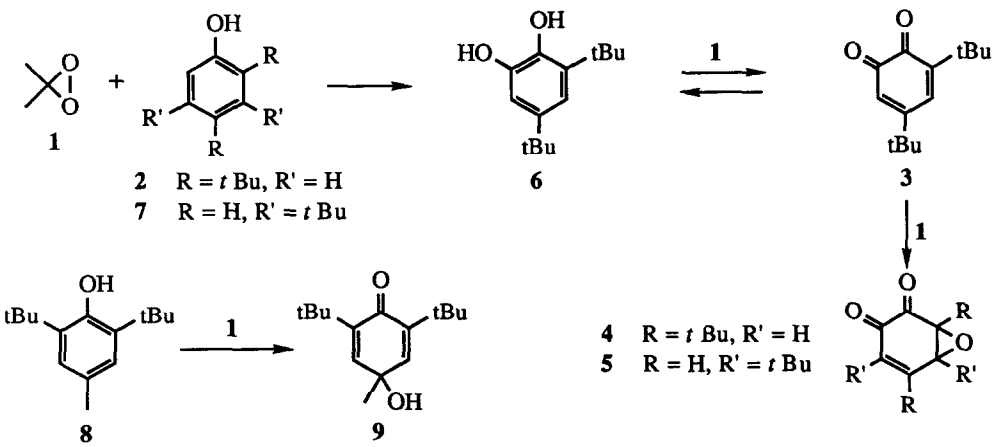
Abstract: The dimethyldioxirane oxidation of selected phenols provides the corresponding orthoquinones. This conversion proceeds *via* the related arenediols, which are cleanly oxidized to the quinones by this oxidant.

In the course of our studies on the dimethyldioxirane (**1**) oxidations of allenes,[1] we encountered problems associated with the competitive attack of an oxygenated aromatic ring by this reagent.[2] The present work was initiated to explore the nature of these unexpected complications. While it was readily shown that simple phenols and anisoles react with oxidant **1**, the product mixtures obtained were too complex to warrant detailed study. As a consequence, attention was turned to hindered phenols where oxidation was expected to proceed in a more controlled manner. This report describes those studies.[3]

Our observations are summarized in the Table. Thus, the reaction of 2,4-di-*tert*-butylphenol (**2**) with 4 equiv of a solution of dimethyldioxirane (**1**) in acetone[4] (Method A) gave orthoquinone **3** in 55% yield along with recovered starting material (30%). This transformation could be run more conveniently on a larger scale by an *in situ* procedure in which the phenol was incorporated into the buffered aqueous acetone solution of Oxone normally used to generate **1** (Method B; acetone was required for reaction). Under these conditions a 72% isolated yield of **3** was obtained. A mixture of epoxides **4** and **5** was also isolated in minor amounts in this case.[5] These by-products could be produced in reasonable yield by further reaction of orthoquinone **3** with a solution of **1**. Simple reduction of **3** by treatment with aqueous $NaHSO_3$ produced the corresponding



catechol **6** in good yield. Diol **6** was quantitatively re-oxidized to **3** by **1**. Conclusive proof for the intermediacy of catechol **6** in the oxidation of **2** was provided by an experiment in which the reaction mixture was monitored by gas chromatography as a function of time and added oxidant. This showed that diol **6** appeared first and increased in concentration to a maximum of 3% of the product mixture, before eventually being converted completely to quinone **3**. The isomeric 3,5-di-*tert*-butylphenol (7) was also oxidized to **3** in a comparable fashion using either oxidation method. Interestingly, 2,6-di-*tert*-butyl-4-methylphenol (**8**), which cannot give a quinone product, was converted to cyclohexadienone **9** under similar conditions, albeit relatively inefficiently.[6]

Several fused-ring phenols behaved in an analogous manner. Thus, 9-phenanthrol was transformed in good yield by either oxidation protocol to the stable 9,10-phenanthroquinone. 2-Naphthol gave a 60:40 mixture of starting material and 1,2-naphthoquinone in good crude yield, but this quinone decomposed during silica gel chromatography. The isomeric 1-naphthol was also oxidized by the *in situ* method to give a mixture of 1,2- and 1,4-naphthoquinone, although once again with low yields of purified products.

The problems associated with oxidations to these more fragile quinones prompted the development of a two-step oxidation-reduction protocol for the preparation of the corresponding dihydroxy compounds. This involved the direct aqueous $NaHSO_3$ reduction of the crude product mixture from either the oxidation of the phenol with preformed **1** (Method C), or the *in situ* oxidation (Method D). Subsequent chromatographic separation easily resolved oxidized products from starting phenol. In this fashion, phenol **2** was transformed into catechol **6**, and 2-naphthol as converted into 1,2-dihydroxynaphthalene in modest isolated yields. 1-Naphthol generated a mixture of the 1,2 diol and 1,4-naphthoquinone, the latter not being reduced by $NaHSO_3$ under these reaction conditions. Interestingly, 1,2-naphthoquinone could be produced quantitatively from 1,2-dihydroxynaphthalene by oxidation with **1** using Method A. Given the facile separation of diols, a multi-step procedure (oxidation, reduction, separation and re-oxidation) provides a viable route to pure 1,2-naphthoquinone. A similar sequence should be preparatively useful for more complicated analogs.

With this background in hand, examination of the oxidation of thymol (**10**), a more representative phenol, was judged to be feasible. Either oxidation method produced a mixture of products from which orthoquinone **11**[7], paraquinone **12**[8], and the interesting cyclohexene-1,4-diones **13** and **14**[9] were isolated. In addition, a significant amount of hydroxyquinone **15**[10] is formed with the *in situ* method.[11] The hypothesis that hydroquinone **16** might be the precursor of **13** and **14**, was contraindicated by the observation

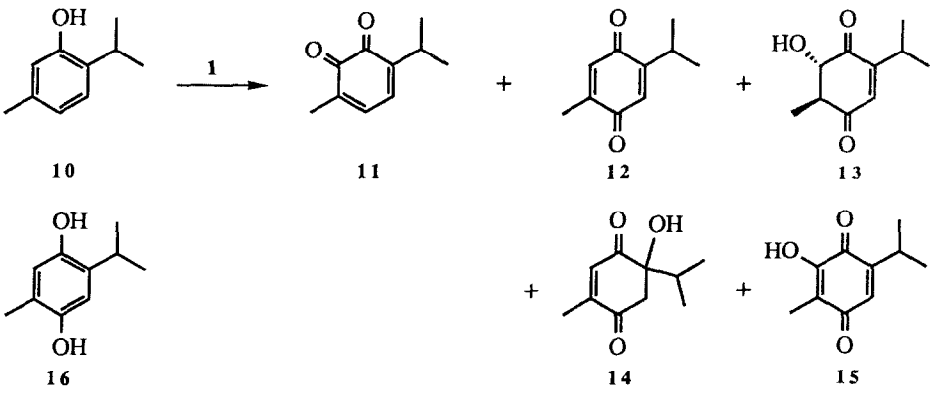


Table: Oxidation Reactions

Starting material	Method	Recovered St. Matl.	Ortho quinone	Ortho diol	Para quinone	Other products
2	A[a]	30%	55%	trace	-	
	B	6%	72%	-	-	9% **4,5** (2:1)
	C	(42%)[b]	-	(40%)[b]	-	
	D	-	-	72%	-	
3	A	-	-	-	-	52% **4,5** (1:20)
6	A		100%	-	-	
7	A	10%	46%	-	-	20% **5**
	B	(7%)[b]	(85%)[b]	-	-	(8%) **5**
8	A	45%	-	-	-	13% **9**
9-phenanthrol	A	20%	77%	-	-	
	B	-	100%	-	-	
1-naphthol	A	23%	14%	-	17%	
	C	22%	-	32%	16%	
2-naphthol	A	(57%)[b]	(38%)[b]	-	-	
	B	-	10%	-	-	
	C	52%	-	48%	-	
1,2-dihydroxy-naphthalene	A	-	100%	-	-	
thymol (**10**)	A	50%	5%	(15%)[b]	10	5% **13**, 5%**14**
	B	-	9%	-	23%	12%**13**,18%**14**, 9% **15**
16	A	-	-	-	77%	
	B	-	-	-	(81%)[c]	

[a] Method A: reaction with 4 equiv of **1** in acetone. Method B: reaction of 0.5 mmol of phenol and 6 g of $NaHCO_3$ in 25 mL of acetone, 25 mL of CH_2Cl_2 and 50 mL of water with 10-18 equiv of Oxone added in small portions. Method C: Method A followed by reaction with 3 mL of satd $NaHSO_3$ solution for 10 min. Method D: Method B followed by separation of CH_2Cl_2 layer, concentration, and reaction with 10 mL of satd $NaHSO_3$ solution for 2 hr. [b] NMR yield. [c] GC percentage.

that **16** was cleanly oxidized to **12** by **1** using either oxidation method. Further study of this complex oxidation will obviously be required to unravel the details of the processes involved, especially the intriguing formation of diketones **13** and **14**.

Thus, in suitable cases, phenols can be converted directly to orthoquinones by **1**. The corresponding orthodiols are very efficiently oxidized by **1** to the same products. Paraquinones can also be produced by this oxidant, where this is possible.[3] Although a variety of oxidation methods are available for such transformations,[12] the convenience of using **1** suggests that this complementary methodology will find important applications.

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9. *trans*-2-Hydroxy-6-isopropyl-3-methylcyclohex-5-ene-1,4-dione (**13**) is a pale yellow solid: mp 97-98°C; IR 3495, 1685, 1613, 1223 cm^{-1}; ^{1}H NMR δ 6.58 (d, 1, J=1.2 Hz), 4.17 (dd, 1, J=10.8, 2.4 Hz), 3.76 (d, 1, J=2.4 Hz), 3.04 (sept of d, 1, J=6.9, 1.2 Hz), 2.76 (qd, 1, J=10.8, 6.5 Hz), 1.38 (d, 3, J=6.5 Hz), 1.16 (d, 3, J=6.8 Hz), 1.09 (d, 3, J=6.8 Hz); ^{13}C NMR δ 199.5, 197.6, 157.5, 136.2, 77.5, 51.3, 27.6, 21.2, 20.6, 11.7; MS (EI) *m/z* (rel intensity) 182 (3), 151 (5), 139 (6), 124 (100), 96 (47); exact mass 182.094, calcd for $C_{10}H_{14}O_3$ 182.0943. 2-Hydroxy-2-isopropyl-5-methylcyclohex-5-ene-1,4-dione (**14**) is a pale yellow solid: mp 81-84°C; IR 3500, 1690, 1619 cm^{-1}; ^{1}H NMR δ 6.67 (d, 1, J=1.5 Hz), 3.61 (s, 1), 3.30 (d, 1, J=16 Hz), 2.75 (d, 1, J=16 Hz), 2.00 (d, 3, J=1.5 Hz), 1.81 (sept, 1, J=6.7 Hz), 0.98 (d, 3, J=6.7 Hz), 0.72 (d, 3, J=6.7 Hz); ^{13}C NMR δ 202.2, 196.3, 152.4, 134.4, 80.2, 49.3, 35.7, 17.0, 16.1 (2); MS (EI) *m/z* (rel intensity) 183 (85), 182 (43), 165 (78), 140 (24), 123 (19), 111 (100), 96 (48); exact mass 182.095, calcd for $C_{10}H_{14}O_3$ 182.0943.
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