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# BASE CATALYZED OXYGENATION OF HINDERED PHENOLS. SYNTHESIS OF 4-HYDROXY-5,6-EPOXY-2-CYCLOHEXENONES (EPOXY-p-QUINOLS)

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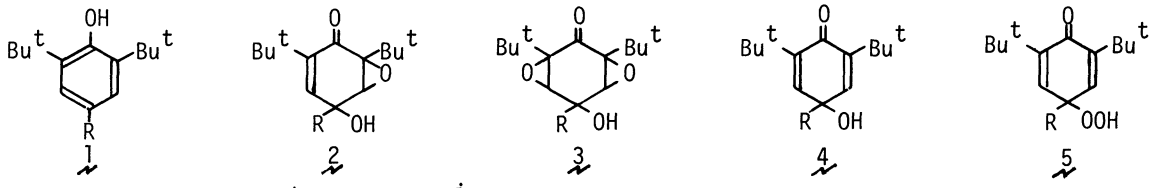
Oxygenation of 2,6-di-t-butyl-4-alkylphenols catalyzed by $Bu^tOK$ in aprotic solvents has been found newly to form 4-hydroxy-5,6-epoxy-2-cyclohexenones (2) in excellent yield. A mechanism by which 2 is formed envisaging intramolecular participation of the π-system in the degradation of 4-oxo-2,5-cyclohexadienyl peroxide ion (11) primarily formed as transient intermediate is discussed. 2,4-Di-t-butylphenols also gave epoxy-p-quinols in the same system.

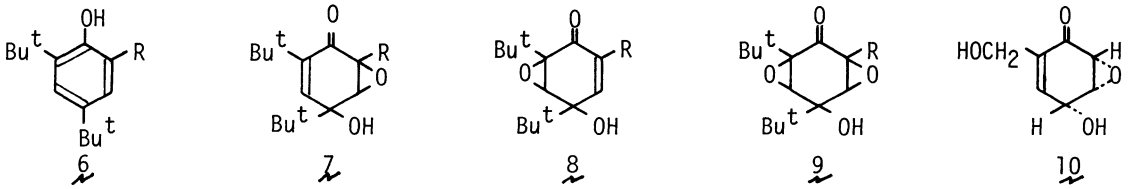
Autoxidation of monohydric hindered phenols in aqueous and alcoholic alkaline solutions has been investigated in some detail, where main products are hydroperoxides, quinols, and quinones.[1] We now find newly that the oxygenation of 2,6-di-t-butylphenols 1a~d in aprotic solvent such as DMF, DMSO, and HMPA containing $Bu^tOK$ gives 4-hydroxy-5,6-epoxy-2-cyclohexenones (epoxy-p-quinols) 2a~d.[2] This finding is of particular interest in connection with existence of naturally occurring epoxy-p-quinols, e.g. epoxidone (10), a fungal metabolite.[3]

The oxygenation was carried out by bubbling $O_2$ through a solution of 1a~d in the aprotic solvent containing $Bu^tOK$ at ambient temperature. The reaction was completed within 1 hr in DMF and DMSO, but required much longer time in HMPA. The products were isolated by silica gel chromatography. The results are summarized in Table 1. The structures of 2a~d were confirmed by examination of their spectral data (Table 2) and elemental analyses. The oxidation of 2a~d with t-butylhydroperoxide in the DMF-$Bu^tOK$ system quantitatively gave diepoxides (3a~d) providing an additional evidence for the structures of 2a~d. Yield of 2 in HMPA is independent with size of 4-alkyl group R, but that in DMF decreases with decreasing size of R being accompanied by the oxidation of side chain (Table 1). For the oxygenation of 1d, use of large excess amount of the base leads to the formation of 1(R=CHO) as a main product. Time course of the oxygenation of 1a showed that the reaction rate is faster at 35°C than at 0°C, and rate of the conversion of 1a is equal to that of the formation of 2a, as was to be expected (Figure 1). Total



1 2 3 4 5

a; R=Bu$^t$ b; R=Pr$^i$ c; R=Et d; R=Me



6 7 8 9 10

a; R=Me b; R=H

Table 1. Oxygenation of 1a~d catalyzed by Bu$^t$OK in aprotic solvent.

| Phenol | Base/Phenol (mol/mol) | Solvent | Product (%) 2 | 3 | 4 | Others |
|---|---|---|---|---|---|---|
| 1a | 4.5 | DMF | 100 | — | — | — |
| | 4.5 | DMSO | 100 | — | — | — |
| | 4.5 | HMPA | 100 | — | — | — |
| 1b | 4.5 | DMF | 87 | — | — | 1(R=$COCH_3$), trace |
| 1c | 4.5 | DMF | 59 | — | — | 1(R=CHO), 10 |
| | 4.5 | HMPA | 94 | — | — | — |
| 1d | 2 | DMF | 22 | 18 | 30 | 1(R=CHO), 4 |
| | 4.5 | DMF | 9 | 6 | 9 | 1(R=CHO), 58 |
| | 2 | DMSO | 67 | — | — | |
| | 10 | HMPA | 91 | — | — | |

Table 2. Spectral data for epoxy-p-quinols (2a~d) and their epoxidized products (3a~d)

| | mp (°C) | nmr τ($CDCl_3$), (ppm)  |  | Bu$^t$ | ir $cm^{-1}$ (Nujol) $\nu_{OH}$ | $\nu_{C=O}$ |
|---|---|---|---|---|---|---|
| 2a | 133-134 | 4.02(d; J=3 Hz) | 6.35(d; J=3 Hz) | 8.84, 8.88 9.02 | 3520 | 1690 |
| 2b | 62-63 | 4.02(d; J=3 Hz) | 6.48(J=3 Hz) | 8.83, 8.89 | 3520 | 1690 |
| 2c | 86-87 | 4.02(d; J=3 Hz) | 6.52(J=3 Hz) | 8.83, 8.89 | 3350 | 1690 |
| 2d | 102-103 | 3.95(d; J=3 Hz) | 6.47(J=3 Hz) | 8.85, 8.89 | 3350 | 1690 |
| 3a | 87-88 | — | 6.40(s) | 8.87, 8.94 | 3530 3480 3440 | 1710 |
| 3b | 75-76 | — | 6.62(s) | 8.93 | 3530 3450 | 1710 |
| 3c | 109-110 | — | 6.65(s) | 8.95 | 3300 | 1710 |
| 3d | 141-142 | — | 6.59(s) | 8.96 | 3520 | 1710 |

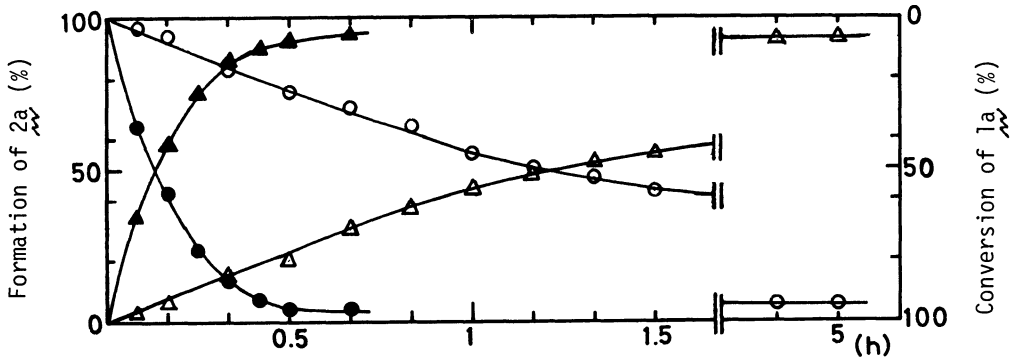
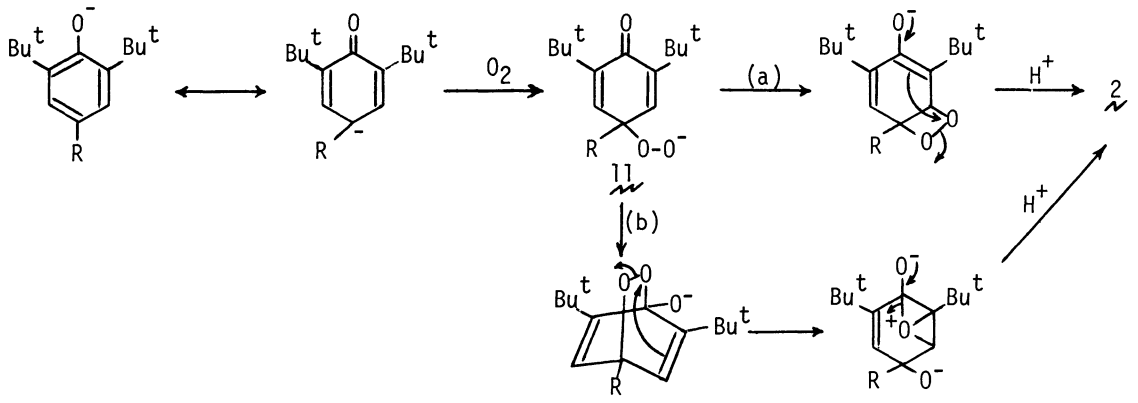



Figure 1. Time course of the oxygenation of 1a in DMF-Bu$^t$OK system. Conversion of 1a; ○ at 0°C and ● at 35°C. Formation of 2a; △ at 0°C and ▲ at 35°C.

uptake of $O_2$ was one mol/mol of the starting phenol. No p-quinol (4a) gave 2a under the reaction conditions.[4] These observations suggest that the formation of 2a is caused by the incorporation of two atoms of molecular oxygen into 1a. When hydroperoxide 5a was dissolved in the DMF-Bu$^t$OK system, a major part (ca. 90 %) of the compound instantaneously reverted to 1a with liberation of $O_2$ and the remainder was quantitatively converted to 2a suggesting that peroxide anion (11) is the intermediate in the oxygenation. As the hydroperoxides (5) are considerably stable in methanol containing MeONa or MeOK, it is thought that 11 can be stabilized by solvation or hydrogen-bonding, but otherwise easily decompose with intramolecular participation of the π-system to give 2 under oxygen atmosphere in the aprotic solvents. The mechanism of the following scheme is suggested for the oxygenation of 1 giving 2, where path (a) or (b) is possible for the degradation of the intermediate 11.




The oxygenation of 2,4-di-t-butylphenols (6) in the DMF-Bu$^t$OK system also gave epoxy-p-quinols together with further epoxidized products. Thus, 7a (20 %), 8a (20 %), and 9a (20 %) were obtained from 6a, while 6b gave 7b (40 %) and 9b (20 %). Formation of 9 (R=OMe) from 6 (R=OMe) has been reported.[2]

It is known that the autoxidation of 2,6-di-t-butylphenol in alcoholic alkaline solutions quantitatively gives tetra-t-butyldiphenoquinone,[1a] but we now find that the oxygenation of this phenol in DMF-Bu$^t$OK nearly quantitatively yields 2,6-di-t-butyl-p-benzoquinone and in DMSO-Bu$^t$OK an unidentified product, $C_{14}H_{22}O_3$, mp 74-76°C, besides the p-benzoquinone.

References and Notes

(1) H. R. Gersmann and A. F. Bickel, J. Chem. Soc., 2711 (1959); 2356 (1962); G. R. Yohe, J. E. Dunbar, M. W. Lansford, R. L. Pedrotti, F. M. Scheidt, F. G. Lee, and E. C. Smith, J. Org. Chem., 24, 1251 (1959), and references therein; A. Fairbourn and E. A. C. Lecken, Proc. Chem. Soc., 67 (1960); J. J. Conradi and G. A. McLarew, J. Amer. Chem. Soc., 82, 4745 (1960).

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(2) Formation of epoxy compounds in autoxidation has been reported for alkoxyphenols: F. R. Hewgill and S. L. Lee, J. Chem. Soc. (C), 2080 (1969); 1549 (1968).

(3) A. Closse, R. Mauli, and H. P. Sigg, Helv. Chim. Acta, 49, 204 (1966); G. Read and L. C. Vining, Chem. & Ind., 1239 (1963); S. Marumo, K. Sasaki, and S. Suzuki, J. Amer. Chem. Soc., 86, 4507 (1964).

(4) The oxidation of 4a with t-butylhydroperoxide in DMF containing Bu$^t$OK led to the migration of t-butyl group followed by epoxidation, which will be published elsewhere.

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