[Contribution from the Chemistry Department, University of Missouri]

# PHENOXYQUINONES. I. 2-PHENOXY-*p*-BENZOQUINONE AND 2-PHENOXY-5-METHYL-*p*-BENZOQUINONE

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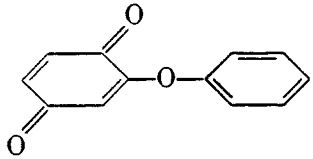
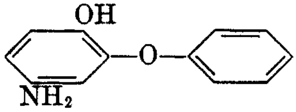
While complex aryloxy-*p*-benzoquinones have been described previously as oxidative degradation products of depsidones (1), the parent substance, 2-phenoxy-*p*-benzoquinone (I) has not been prepared before. The present investigation is concerned with the synthesis and the properties of this compound and one of its homologs.

An amino group is introduced in the 5-position of 2-hydroxyphenyl ether by coupling with diazotized sulfanilic acid and reduction of the resulting azo compound with sodium hydrosulfite according to the method perfected by Smith (1a). The quinone (I) is obtained by oxidizing the hydrochloride of the aminophenol (II) with chromic acid. Its structure has been confirmed by an independent synthesis of the corresponding hydroquinone from authentic 2,5-dimethoxyphenyl ether.



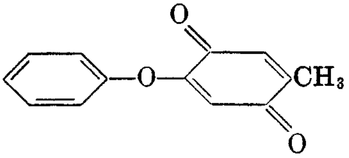
I



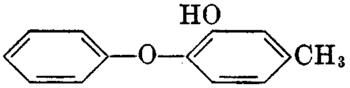
II

The yellow phenoxyquinone (I), m.p. 70–71.8°, is easily reduced with zinc and acetic acid to the colorless hydroquinone, m.p. 156–157°, with which it forms a purple quinhydrone, m.p. 118–120°.

The normal potential of the quinone-hydroquinone system in aqueous alcohol is 0.584 v., corresponding to a potential lowering of 0.131 v. for the phenoxyl group. A potential lowering of about the same magnitude is arrived at from the normal potential of 2-phenoxy-5-methyl-*p*-benzoquinone (III), m.p. 120–121° (2), which has been prepared from 3-hydroxy-4-phenoxytoluene (IV) by a sequence of reactions analogous to (I).



III



IV

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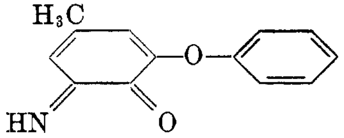
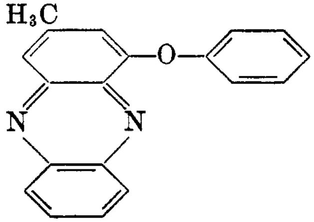
2-Phenoxybenzoquinone forms a dioxime and undergoes the Thiele reaction (3). Preliminary tests indicate that it does not possess any appreciable *in vitro* bacteriostatic activity in the very dilute aqueous solutions necessitated by its small solubility.

Phenoxy-*o*-benzoquinones are unknown in the literature and exploratory work has shown that they are difficult to obtain. The silver oxide oxidation of 2-phenoxy-4-methyl-6-aminophenol yields an intensely red solution. Although attempts to isolate a crystalline product have failed, it is believed that the solution contains some 3-phenoxy-5-methyl-*o*-benzoquinone imine (V) because it was possible to convert it to the phenazine (VI) of the corresponding quinone in small yield.



V



VI

## EXPERIMENTAL

All temperatures uncorrected.

*2-Hydroxyphenyl ether.* Demethylation of 2-methoxyphenyl ether (4) with hydriodic acid in acetic acid (5) gave a nearly quantitative yield of the hydroxyphenyl ether. For preparative purposes the substance was obtained by demethylation of the methyl ether (45 g.) with sodium hydroxide (180 g.) in diethylene glycol (900 cc.) by refluxing for 18 hours in a copper flask. The mixture was poured still warm into 4 l. of water and was acidified with hydrochloric acid. The precipitate was filtered and dried. It weighed 40.1 g. and melted at 103–105°. Recrystallization from petroleum ether (b.p. 60–70°) gave 37 g. (91%) of product melting at 104–105°.

*2-Hydroxy-5-aminophenyl ether.* A cold diazonium solution prepared from 10.5 g. of sulfanilic acid was added slowly with stirring to a cold solution of 7 g. of 2-hydroxyphenyl ether dissolved in a solution of 11 g. of sodium hydroxide in 60 cc. of water. The mixture was allowed to stand for at least two hours, preferably overnight. Then it was heated to 40–50° and treated with 23 g. of sodium hydrosulfite. The mixture was stirred for two hours. The precipitate was filtered and recrystallized from aqueous hydrochloric acid containing stannous chloride (6). An additional crystallization of the product (5.5 g.) from the same mixture yielded 4.8 g. (53.7%) of 2-hydroxy-5-aminophenyl ether hydrochloride. On heating this substance decomposed gradually with darkening.

*Anal.* Calc'd for $C_{12}H_{12}ClNO_2$: C, 60.63; H, 5.08; N, 5.89.
Found: C, 60.59; H, 5.21; N, 5.89.

*Acetyl derivative.* Acetylation of the hydrochloride (1 g.) with acetic anhydride and aqueous sodium hydroxide (7) gave 0.48 g. of acetyl compound, m.p. 125.6–126.7° (from aqueous ethanol).

*Anal.* Calc'd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.38; N, 5.76.
Found: C, 69.20; H, 5.32; N, 5.48.

*2-Phenoxy-p-benzoquinone.* Attempts to oxidize the above amine hydrochloride with ferric chloride (8) gave only 18% yield of quinone. A far better yield was obtained as follows. A solution of the hydrochloride (1.4 g.) in water (21 cc.) was treated with 2 cc. of concentrated sulfuric acid and the mixture was heated. The boiling solution was added with stirring to a mixture of 80 cc. of benzene and 1.4 g. of potassium dichromate dissolved in 20 cc. of water. Stirring was continued for ½ hour. The benzene layer was separated, washed with water, and distilled under reduced pressure. The residual quinone crystallized on scratching. It melted at 70–71.8°, yield 0.42 g.

*Anal.* Calc'd for $C_{12}H_8O_3$: C, 71.99; H, 4.02.
Found: C, 72.04; H, 4.11.

*Dioxime.* A mixture of 2-phenoxy-*p*-benzoquinone (0.5 g.), hydroxylamine hydrochloride (0.5 g.), pyridine (2.5 cc.), and absolute ethyl alcohol (2.5 cc.) was refluxed for two hours on a steam-bath. The solvents were removed by evaporation and the residual material was stirred with water. The remaining solid dioxime was crystallized from aqueous alcohol. The tan solid decomposed at 160°, yield 0.32 g.

*Anal.* Calc'd for $C_{12}H_{10}N_2O_3$: C, 62.00; H, 4.31; N, 12.05.
Found: C, 62.13; H, 4.39; N, 12.35.

*2-Phenoxyhydroquinone.*[3] The above quinone (0.75 g.) dissolved in 0.7 cc. of glacial acetic acid and 0.52 cc. of water was reduced with 0.175 g. of 20-mesh granulated zinc. The mixture was refluxed for 30 minutes. Boiling water (0.7 cc.) was added and the liquid was decanted from the metal. The hydroquinone crystallized when this liquid was cooled to 0°. The first crop (0.11 g.) melted at 152.7–154.7°. Recrystallization from acetic acid and from petroleum ether (b.p. 60–70°) raised the melting point to 156–157°.

*Anal.* Calc'd for $C_{12}H_{10}O_3$: C, 71.22; H, 4.98; Mol. wt., 202.2.
Found: C, 71.18; H, 4.97; Mol. wt., 199.3 (Rast).

The substance was also obtained by starting with 2-bromohydroquinone dimethyl ether (9).

*2,5-Dimethoxyphenyl ether.* The Ullmann reaction of 2-bromohydroquinone dimethyl ether (69 g.), potassium hydroxide (25.5 g.), a slight excess of phenol, and 0.3 g. of copper powder at 200° as described previously for an analogous compound (9) gave 29 g. of pure dimethoxyphenyl ether which melted at 46–47° after crystallization from petroleum ether (b.p. 60–70°).

*Anal.* Calc'd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13; Mol. wt., 230.
Found: C, 73.01; H, 6.01; Mol. wt., 229 (Rast).

*Demethylation.* A mixture of 2,5-dimethoxyphenyl ether (1 g.), acetic acid (5 cc.), hydriodic acid (5 cc., *d.* 1.5), and acetic anhydride (2.5 cc.), was refluxed for 45 minutes and poured still warm into water. The solution was brought to boiling and cooled in an ice-bath. The dihydroxy compound crystallized on scratching. The product melting at 149–151° weighed 0.75 g. Recrystallization from petroleum ether (60–70°) raised the melting point to 153–155°. The mixed melting point with the reduction product of 2-phenoxy-*p*-benzoquinone was 155–157°.

*Quinhydrone.* Equal amounts (0.095 g.) of 2-phenoxy-*p*-benzoquinone and 2-phenoxyhydroquinone, dissolved in benzene, were mixed and heated to remove the solvent. The residual dark purple crystals were recrystallized from benzene, yield 0.15 g., m.p. 118–120°.

*Anal.* Calc'd for $C_{24}H_{18}O_6$: C, 71.11; H, 4.50.
Found: C, 71.00; H, 4.63.

*2,4,5-Triacetoxyphenyl ether.* 2-Phenoxy-*p*-benzoquinone (1 g.) was added in small portions with stirring to a solution of 1.2 g. of concentrated sulfuric acid and 1.8 g. of acetic anhydride maintained at 40–50°. The mixture was allowed to stand for four hours. A colorless precipitate separated when it was poured into 20 cc. of cold water. The mixture was cooled to 10° and filtered. After crystallization from 5 cc. of 95% ethanol the product melted at 80–82°, yield 0.2 g.

*Anal.* Calc'd for $C_{18}H_{16}O_7$: C, 62.78; H, 4.68.
Found: C, 62.63; H, 4.79.

*Normal potential.* EMF values were determined in a series of buffer solutions each containing 50% ethyl alcohol and sufficient phenoxyquinhydrone (m.p. 118–120°) to give a

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[3] The senior author is indebted to Dr. L. I. Smith for this procedure.

saturated solution in a cell containing a platinum electrode, a standard calomel electrode (3.5 *N* KCl), and a stirrer. The EMF values (Table I) were interpolated to *p*H 0.

*3-Methoxy-4-phenoxytoluene.* The Ullmann reaction with 3-methoxy-4-hydroxytoluene (10 g.), potassium hydroxide (4.05 g.), and bromobenzene (11.4 g.) (4) at 230–240° (four hours) gave 4 g. of pure methyl ether, m.p. 74–75° (from aqueous methanol) (10).

*3-Hydroxy-4-phenoxytoluene.* Demethylation of the material (0.5 g.) in 3 cc. of acetic acid with 3 cc. of hydriodic acid (*d.* 1.5) and 1.5 cc. of acetic anhydride yielded 0.42 g. of pure hydroxy compound, m.p. 78–79° (from aqueous methanol).

*Anal.* Calc'd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04.
Found: C, 77.80; H, 6.16.

*3-Hydroxy-4-phenoxy-6-aminotoluene.* The diazonium solution prepared from 0.85 g. of sulfanilic acid was mixed with 12 g. of ice and added to a cold solution of 3-hydroxy-4-phenoxytoluene (1 g.) in 6 cc. of 14% aqueous sodium hydroxide. The azo dye was reduced by addition of sodium hydrosulfite. The precipitated amine was dissolved in methanol and reprecipitated with 1% aqueous sodium hydrosulfite. The dry substance weighed 0.3 g., m.p. 171–172.5°.

*Anal.* Calc'd for $C_{13}H_{13}NO_2$: C, 57.62; H, 6.08.
Found: C, 57.76; H, 6.24.

TABLE I

OXIDATION POTENTIALS

| *p*H[a] | EMF (in volts) |
|---|---|
| 3.28 | 0.450 |
| 3.51 | .443 |
| 5.49 | .367 |
| 6.31 | .329 |
| 7.49 | .288 |

[a] The precise *p*H values of the solutions were determined potentiometrically.

*2-Methyl-5-phenoxy-p-benzoquinone.* Concentrated nitric acid (2 cc.) was added with stirring at 25° to a solution of 3-hydroxy-4-phenoxy-6-aminotoluene (0.3 g.) dissolved in 10 cc. of glacial acetic acid. The dark red solution was diluted with cold water and extracted with two 25-cc. portions of ether. The combined ether extracts yielded a solid yellow residue which was crystallized from Skellysolve B. The pure quinone, m.p. 120–121°, weighed 0.26 g.

*Anal.* Calc'd for $C_{13}H_{10}O_3$: C, 72.89; H, 4.70.
Found: C, 72.80; H, 4.84.

*Absorption spectra.*[4] Ultraviolet absorption spectra of the two quinones were determined in dioxane solution in concentrations of 0.0018 g. per 25 cc. in the range of 240–430 m$\mu$. 2-Phenoxybenzoquinone showed maxima at 250 m$\mu$ (log $\epsilon$, 3.90) and 355 m$\mu$ (log $\epsilon$, 2.90). The 5-methyl homolog had $\lambda$ max 260 m$\mu$ (log $\epsilon$, 4.22) and 360 m$\mu$ (log $\epsilon$, 2.86).

*2-Phenoxy-4-methyl-6-aminophenol hydrochloride.* 3-Bromo-4-hydroxytoluene (11) was methylated with methyl sulfate (yield 75%). The Ullmann reaction with the methyl ether and potassium phenoxide gave 42.6% of 2-methoxy-5-methylphenyl ether, m.p. 68–69° (12). Demethylation of this substance with hydriodic acid yielded 98.4% of 2-hydroxy-5-methylphenyl ether, m.p. 65.7–66.5°. Coupling of this material (6 g.) with diazotized sulfanilic acid furnished a solution of the hydroxyazo compound which was immediately reduced with sodium hydrosulfite in the usual way (13). The recrystallized amine hydrochloride weighed 2.7 g. (36.2%). It decomposed on heating.

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[4] Ultraviolet absorption spectra by Dr. E. E. Pickett, University of Missouri.

*Anal.* Calc'd for $C_{13}H_{14}ClNO_2$: C, 62.02; H, 5.60; N, 5.56.
Found: C, 62.22; H, 5.70; N, 5.28.

*3-Phenoxy-5-methyl-o-benzoquinone imine.* The amine hydrochloride (0.8 g.) dissolved in anhydrous ether (75 cc.) was shaken for one hour with 6 g. of dry silver oxide and 2 g. of anhydrous sodium sulfate. Filtration of the reaction mitxure gave a bright red filtrate.

*Phenazine.* The above ether solution was mixed with *o*-phenylene diamine dissolved in very little acetic acid and the mixture was allowed to stand for two days. A brown oil remained after removal of the ether. This was redissolved in 20 cc. of ether. The solution was washed repeatedly with water, dried, and evaporated. The residue (0.16 g.) was taken up in benzene and adsorbed on aluminum oxide. The zones which fluoresced under ultraviolet light were eluted with the same solvent and the solutions were evaporated. The residual light tan crystals were recrystallized from benzene-ligroin giving the pure phenazine, m.p. 100.5–101.8° (yield 0.12 g.).

*Anal.* Calc'd for $C_{19}H_{14}N_2O$: C, 79.33; H, 4.93; N, 9.78.
Found: C, 79.15; H, 4.80; N, 9.38.

## SUMMARY

2-Phenoxy-*p*-benzoquinone and its 5-methyl homolog have been prepared. The structure of the former has been established by an independent synthesis of the corresponding hydroquinone. The compounds have been characterized by physical properties and chemical reactions.

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