p,p'-Biphenols

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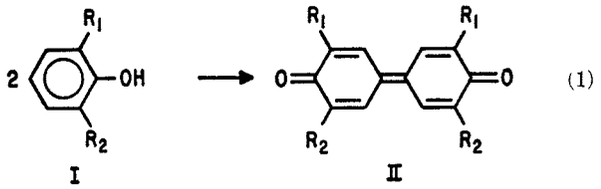
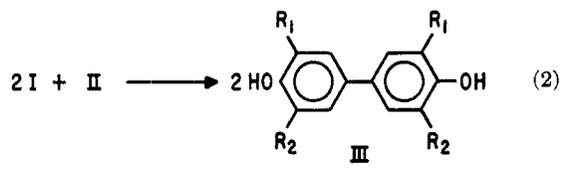
Oxidative coupling of 2,6-disubstituted phenols to diphenoquinones is particularly facile if at least one of the substituents is a bulky group such as *t*-butyl (eq 1).[1,2] However, less hindered 2,6-disubstituted



(1)

I II

phenols can also be oxidatively coupled to diphenoquinones in high yield with oxygen using copper complexes as catalysts.[2,3] From diphenoquinones, *p,p'*-biphenols are readily prepared by direct reduction or by reaction with 2 mol of the phenol (eq 2).[4]

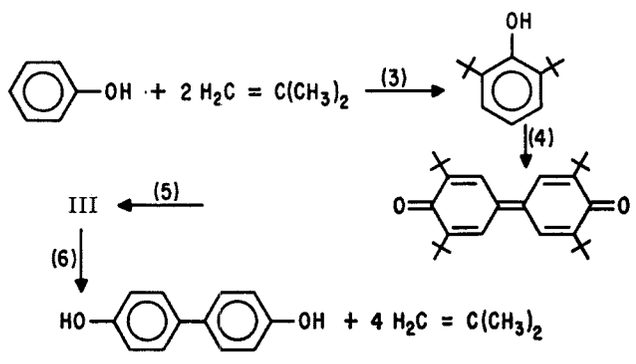


(2)

III

Phenols with *o*-*t*-butyl substituents are readily accessible by alkylation of phenols with isobutylene using aluminum phenoxide as catalyst.[5,6] The *ortho*-substituted phenols so prepared are readily dealkylated with the same catalyst at higher temperatures.[5]

We have found that *p,p'*-biphenols with *t*-butyl substituents can also be dealkylated in high yield at about 200° with an aluminum phenoxide catalyst in *p*-cresol or *p*-*t*-butylphenol as solvent. The solvent facilitates the preparation of the catalyst and prevents the formation of insoluble aluminum salts. Thus, by the following sequence of reactions *p,p'*-biphenol can be prepared in high yield from phenol. Reactions 4 and 5,[1,2] as well as 6, are almost quantitative and the *p,p'*-biphenol obtained is of very high purity and free from isomers.



The reaction has been extended to the preparation of mono- and disubstituted *p,p'*-biphenols. The same sequence of reactions applied to 2-*t*-butyl-6-phenylphenol gives as product 2,2'-diphenyl-*p,p'*-biphenol (III, $R_1 = C_6H_5$; $R_2 = H$).

Cooxidation of 2,6-di-*t*-butylphenol and 2-*t*-butyl-6-phenylphenol gives after reduction and dealkylation a mixture of three biphenols, *i.e.*, *p,p'*-biphenol, 2-phenyl-p,p'-biphenol, and 2,2'-diphenyl-*p,p'*-biphenol. Similarly, cooxidation of 2,6-di-*t*-butylphenol and 2,6-diisopropylphenol yields *p,p'*-biphenol, 2,6-diisopropyl-p,p'-biphenol, and 2,2',6,6'-tetraisopropyl-*p,p'*-biphenol.

Previously the best synthesis for *p,p'*-biphenol involved tetrazotization of benzidine, conversion into the biphenol and purification through the diacetate which gave an over-all yield of about 60%.[7] The present synthesis makes *p,p'*-biphenol as well as many substituted *p,p'*-biphenols for the first time readily accessible.

Experimental Section

***p,p'*-Biphenol.**—To a 100-ml round-bottom flask stirred with a magnetic stirrer and equipped with an air condenser was added 25 g of *p*-cresol and 0.017 g (0.00063 g-atom) of aluminum foil. The mixture was heated to reflux temperature until the aluminum had dissolved. After this had cooled below 150°, there was added 25 g (0.061 mol) of 2,2',6,6'-tetra-*t*-butyl-*p,p'*-biphenol. On top of the air condenser there was also added a Dean–Stark trap and a Dry Ice condenser to trap and measure the isobutylene as it was formed. The reaction mixture was then gradually heated with stirring. At about 180° isobutylene began to evolve. Over a 45-min period, the temperature was gradually raised to 194° and a total of 20 ml of isobutylene was collected. The reaction mixture was then cooled and diluted with 50 ml of toluene, filtered, and then washed with a small amount of toluene. The colorless *p,p'*-biphenol (III, $R_1 = R_2 = H$) was dried *in vacuo* at 110° for 4 hr. There was obtained 10.7 g (0.0575 mol, 94% yield), mp 286°, identical with that of an authentic sample.

2-*t*-Butyl-6-phenylphenol.[8]—To 170 g (1.0 mol) of *o*-phenylphenol was added 1 g of aluminum foil and the aluminum was dissolved by heating the reaction to 250°. The reaction mixture was cooled and the reaction flask was equipped with a Dry Ice condenser, thermometer, and gas inlet tube. The reaction was maintained at 60° for 4 hr during which time 56 g (0.96 mol) of isobutylene were slowly introduced. The reaction mixture was dissolved in ether and washed with 5% aqueous hydrochloric acid solution which was followed by a water wash. The ether solution was then washed three times with 5% aqueous sodium hydroxide solution which was followed by a water wash. After drying and distilling there was obtained 184.7 g (0.82 mol, 82% yield) of 2-*t*-butyl-6-phenylphenol, bp 129° (0.5 mm).

3,3'-Di-*t*-butyl-5,5'-diphenyldiphenoquinone.—Oxygen was passed through a vigorously stirred solution consisting of 1 g of copper(I) chloride, 2.3 g of N,N,N',N'-tetramethylethylenediamine, and 100 g (0.44 mol) of 2-*t*-butyl-6-phenylphenol in 500 ml of 95% ethanol. After 2 hr, the reaction was filtered and there was obtained 85.5 g (0.19 mol, 86% yield) of the diphenoquinone, mp 213–214°. Recrystallization from acetic acid gave red crystals, mp 214°.

Anal. Calcd for $C_{32}H_{32}O_2$: C, 85.68; H, 7.19. Found: C, 85.78, 85.58; H, 7.32, 7.21.

2,2'-Di-*t*-butyl-6,6'-diphenyl-*p,p'*-biphenol.—To a 100-ml three-necked flask equipped with a reflux condenser, stirrer, and thermometer was added 30 g (0.67 mol) of 3,3'-di-*t*-butyl-

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(3) G. F. Endres, A. S. Hay, and J. W. Eustance, *ibid.*, **28**, 1300 (1963).
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(5) A. J. Kolka, J. P. Napolitano, A. H. Filbey, and G. G. Ecke, *J. Org. Chem.* **22**, 642 (1957).
(6) R. Stroh, R. Seydel, and W. Hahn, *Angew. Chem. Intern. Ed. Engl.*, **69**, 699 (1957).
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(8) The author is indebted to Dr. J. R. Ladd who performed this experiment.

5,5′-diphenyldiphenoquinone, 31 g (0.137 mol) of 2-*t*-butyl-6-phenylphenol, and 10 g of pyridine under a nitrogen atmosphere. The reaction was slowly heated to 200° over a 55-min period and then heated for an additional 65 min at 220°. The initially deep red solution was now a light brown color. The reaction mixture was cooled to about 100° and diluted with 200 ml of acetic acid. When this mixture cooling to room temperature there was deposited 57 g (0.126 mol, 94% yield) of 2,2′-di-*t*-butyl-6,6′-diphenyl-*p,p*′-biphenol. After one recrystallization from aqueous alcohol, colorless crystals, mp 161°, were obtained.

Anal. Calcd for $C_{32}H_{34}O_2$: C, 85.29; H, 7.61. Found: C, 85.28, 85.16; H, 7.57, 7.63.

2,2′-Diphenyl-*p,p*′-biphenol.—The previous product could be dealkylated directly or preferably several steps in the procedure could be combined as follows. To a 500-ml three-necked flask equipped with a gas inlet tube, Dry Ice condenser, thermometer, and magnetic stirrer was added 90 g (0.40 mol) of 2-*t*-butyl-6-phenylphenol and 88 g (0.196 mol) of 3,3′-di-*t*-butyl-5,5′-diphenyl-4,4′-diphenoquinone. The reaction mixture was heated to 182° for 1 hr while trimethylamine was slowly bubbled through. The reaction mixture was then cooled and the trimethylamine was replaced with nitrogen. There was added 0.3 g of aluminum and 50 g of *p*-*t*-butylphenol. The reaction mixture was heated to 220° and after 1.5 hr a total of 45 ml of isobutylene was collected. The products were distilled directly from the pot. There was obtained 95.9 g (0.28 mol, 72.0% yield) of 2,2′-diphenyl-*p,p*′-biphenol, bp 270–285° (0.5 mm), mp 140°.

Anal. Calcd for $C_{24}H_{18}O_2$: C, 85.18; H, 5.36. Found: C, 84.79, 85.11; H, 5.42, 5.39.

2-Phenyl-*p,p*′-biphenol.—Oxygen was passed through a vigorously stirred solution consisting of 0.2 g of copper(I) chloride and 0.4 ml of N,N,N′,N′-tetramethylenediamine in 200 ml of isopropyl alcohol. Over 30 min there was added dropwise a solution of 25.8 g (0.125 mol) 2,6-di-*t*-butylphenol and 28.2 g (0.125 mol) of 2-*t*-butyl-6-phenylphenol dissolved in 100 ml of isopropyl alcohol. The reaction was continued for 40 min and then the red precipitate was isolated by filtration and washed with a small amount of isopropyl alcohol and dried. The products from four identical reactions were combined to give a total yield of 161.7 g. This product was suspended in hot acetic acid and titrated with hydrazine until the red color disappeared. The mixture of biphenols was isolated by adding an equivalent volume of water and the product was removed by filtration and dried. To a 500-ml three-necked flask equipped with a magnetic stirrer, condenser, and thermometer was added 150 g of *p*-cresol and 0.3 g of aluminum foil. The aluminum was dissolved by heating and to this solution was added the mixture of biphenols. The reaction mixture was heated to 194° and over a 155-min period 101 ml of isobutylene was evolved. The reaction mixture was cooled and diluted with an equal volume of toluene. There was deposited 24.1 g (0.129 mol, 25.8% yield) of *p,p*′-biphenol. The filtrate was washed with dilute hydrochloric acid, then dried, and distilled. After removal of toluene and *p*-cresol, two fractions were obtained.

The first fraction consisted of 39.5 g (0.150 mol, 30% yield) of 2-phenyl-*p,p*′-biphenol, bp 225–30° (0.5 mm). Recrystallization from ethanol gave mp 185–186°.

Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.4; H, 5.4. Found: C, 82.3; H, 5.4.

The second consisted of 24.1 g (0.07 mol, 14% yield) of 2,2′-diphenyl-*p,p*′-biphenol.

2,6-Diisopropyl-*p,p*′-biphenol.—Following a procedure similar to the preceding, there was obtained from 30.9 g (0.15 mol) of 2,6-di-*t*-butylphenol and 26.7 g (0.15 mol) of 2,6-diisopropylphenol 11.2 g (0.04 mol, 27.6% yield) of 2,6-diisopropyl-*p,p*′-biphenol, mp 185–186.5°.

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.8; H, 7.9.

The other products, *p,p*′-biphenol and 2,2′,6,6′-tetraisopropyl-*p,p*′-biphenol, were not isolated.

Registry No.—*p,p*′-biphenol, 92-88-6; 2-*t*-butyl-6-phenylphenol, 2416-98-0; 3,3′-di-*t*-butyl-5,5′-diphenyldiphenoquinone, 2416-99-1; 2,2′-di-*t*-butyl-6,6′-diphenyl-*p,p*′-biphenol, 2401-41-4; 2,2′-diphenyl-*p,p*′-biphenol, 2401-43-6; 2-phenyl-*p,p*′-biphenol, 18801-72-4; 2,6-diisopropyl-*p,p*′-biphenol, 18801-73-5.

The Radiolytic Oxidation of Cysteine[1]

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A recent communication by Packer[2] on the radiolysis of cysteine in neutral solution has prompted us to report our observations of its behavior in more acidic buffer solutions. It is well known that cysteine in aqueous solution is oxidized to cystine upon exposure to ionizing radiations. In aerated solution more thiol is destroyed than would be expected, and chain reactions involving dissolved oxygen have been postulated by several workers.[3]

The sequence given in eq 1–7 seemed plausible to us.

initiation

$$H_2O \rightsquigarrow e^- + \cdot OH + H^+ \quad (1)$$

$$e^- + O_2 + H^+ \rightarrow \cdot O_2H \quad (2)$$

$$RS\text{–}H + \cdot O_2H \text{ or } \cdot OH \rightarrow RS\cdot + H_2O_2 \text{ or } H_2O \quad (3)$$

propagation and product formation

$$RS\cdot + O_2 \rightarrow RS\text{–}O\text{–}O\cdot \quad (4)$$

and

$$RS\text{–}O\text{–}O\cdot + RSH \rightarrow RS\text{–}O\text{–}O\text{–}H + RS\cdot \quad (5a)$$

$$RS\text{–}O\text{–}O\text{–}H + RSH \rightarrow RSSR + H_2O_2 \quad (5b)$$

or

$$RS\text{–}O\text{–}O\cdot + RSH \rightarrow RSSR + \cdot O_2H \quad (6a)$$

$$\cdot O_2H + RSH \rightarrow H_2O_2 + RS\cdot \quad (6b)$$

termination

$$2RS\cdot \rightarrow RSSR \quad (7)$$

with minor contributions from other reactions such as

$$RS\cdot + \cdot O_2H \rightarrow RS\text{–}O\text{–}O\text{–}H$$

$$RS\cdot + e^- + H^+ \rightarrow RSH$$

The scheme is compatible with previously published data. The propagation steps (5 and 6) are reasonable reactions of sulfenyl compounds[4] and would be expected to occur cleanly in the presence of a large excess of thiol. They require the production of cystine and hydrogen peroxide in amounts which should be approximately equal and should increase with increasing thiol concentration. The results in Table I are consistent with these requirements.

The chain obviously is very short. At the highest cysteine concentration studied (30 m*M*), the yield of destruction of thiol was only three times the yield of primary radicals from water, and the yields of both cystine and hydrogen peroxide in 1 m*M* cysteine (pH ~3) were such that they could have resulted from the initiating and terminating steps alone.

Much higher yields of oxidation have been reported to result upon radiolysis of aerated neutral or alkaline, as opposed to acidic, thiol solutions. The most recent report, for example, records values for cysteine oxidation at pH 7 some five times as great as those at pH ~3 and similar concentrations observed by us. Such

(1) Financial support from the Division of Radiological Health, B. S. S. (EH), Public Health Service, Research Grant RH 379, is gratefully acknowledged.

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(3) A. J. Swallow, *J. Chem Soc.*, 1334 (1952); J. E. Packer, *Nature*, **194**, 81 (1962); *J. Chem. Soc.*, 2320 (1963).

(4) See, *e.g.*, N. Kharasch, "Sulfenium Ions and Sulfenyl Compounds," in "Organic Sulfur Compounds," N. Kharasch, Ed., Pergamon Press, Inc., New York, N. Y., 1961.