Reaction of Sulfur with 2,6-Disubstituted Phenols

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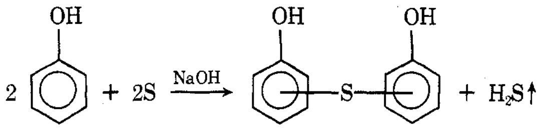
In the presence of catalytic amounts of base, no reaction occurs between 2,6-disubstituted phenols and sulfur. When epoxides or activated olefins such as acrylonitrile are continuously added to the reaction mixture, excellent yields of thiobisphenols are obtained.[1]

The early patent literature is replete with examples of the reactions of phenols with sulfur.[2] A typical example involves heating sulfur with phenol in the presence of a base for extended periods of time at elevated temperatures to yield resinous materials. As a side product hydrogen sulfide is evolved equivalent to approximately one-half of the sulfur introduced.

Recently Neale et al.[3] demonstrated that phenol in large excess reacts with sulfur at elevated temperatures (140–180 °C) and long times (6–24 h) according to the equation



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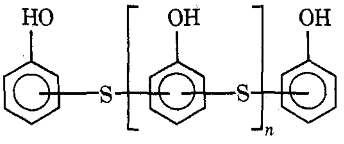
During the course of the reaction H_2S is slowly evolved. The three isomeric monothiobisphenols (2,2′-, 2,4′-, 4,4′-) were obtained in quantitative yield in the approximate ratio 45:45:10. When lower ratios of phenol to sulfur are used, oligomeric materials (2) resulting from reaction at more than one site on the phenol are obtained.



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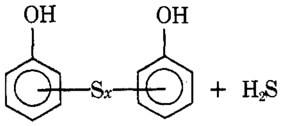
Geering[4] has prepared polythiobisphenols (3) by allowing equivalent amounts of phenol and sulfur to react at elevated temperatures in the presence of catalytic amounts of sodium hydroxide. The reaction is carried to about 40% conversion, as measured by the H_2S evolved, and the product obtained is principally the ortho,ortho′ isomer. Subsequent hydrogenation with a cobalt sulfide catalyst yields the *o*-mercapto phenols in overall 65% yield.



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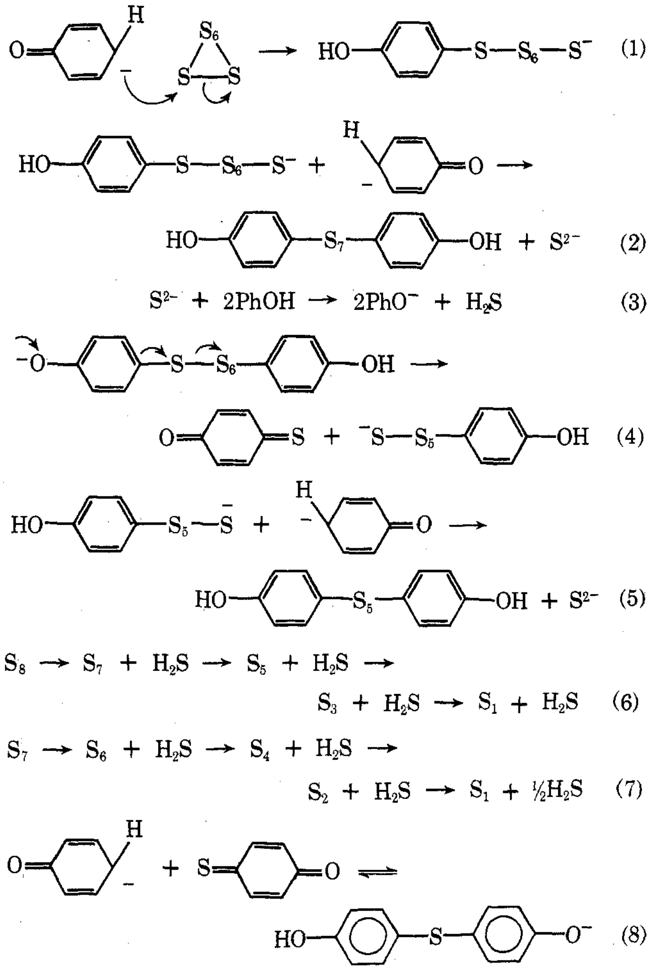
Results and Discussion

When we attempted the reaction of 2,6-dimethylphenol or 2,6-diphenylphenol with sulfur and catalytic amounts of sodium hydroxide according to Neale et al., no reaction occurred. Neale et al. have proposed the mechanism outlined in Scheme I for the reaction between phenol and sulfur. The phenoxide nucleophile is regenerated by reaction 3, and this step would appear to be rate determining. When the hindered phenols, which are weaker acids, are used the equilibrium

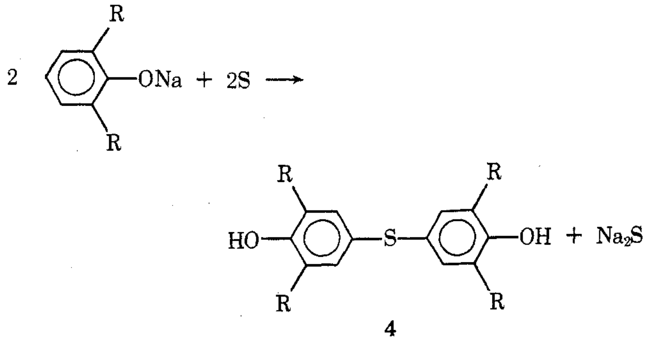
$$ArOH + HS^- \rightleftharpoons ArO^- + H_2S$$

would be expected to be displaced to the left, the concentration of the phenoxide ion decreased, and H_2S evolved much more slowly.

Scheme I



We next found that reaction of 2,6-dimethyl- or 2,6-diphenylphenol would occur to a limited extent (up to 30% conversion to the thiobisphenol 4) if stoichiometric amounts of base were used. The reaction apparently does not go to



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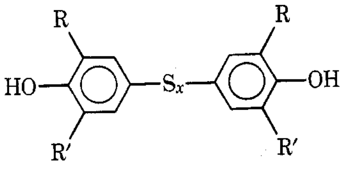
completion because of depletion of the base and sulfur as polysulfides.

Fujisawa[5] was able to treat hindered phenols with sulfur under mild conditions, refluxing ethanol in the presence of equivalent amounts of potassium hydroxide, to yield mixtures of the polythiobisphenols **5**. The higher temperatures used in the present work are necessary to drive the reaction to the monosulfide product.



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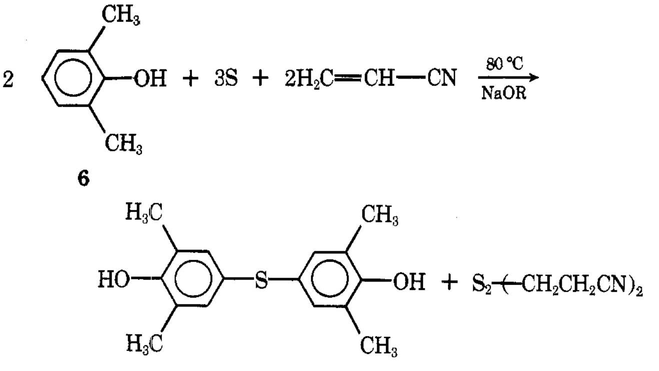
The key to improving the reaction appeared to us to be the removal of sulfide ion which can tie up sulfur as polysulfides. It appeared that what was necessary to facilitate the reaction was the addition of a species that would react with the S^{2-} or HS$^-$ or any nucleophilic sulfur species, but not with phenoxide ion. When acrylonitrile was slowly added to a mixture of 2,6-dimethylphenol (**6**) and sulfur in the absence of a solvent and in the presence of catalytic amounts of the sodium phenoxide, 85–90% yields of thiobis(2,6-dimethylphenol) (**7**) were obtained according to the equation



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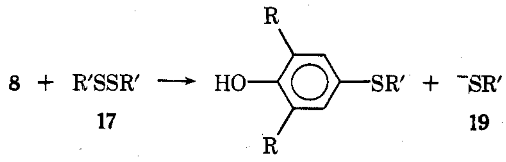
The acrylonitrile must be added slowly to the reaction mixture and the optimum temperature for the reaction is about 80 °C. At 50 °C the principal product is β-2,6-dimethylphenoxypropionitrile and at higher temperatures side reactions occur.

Continuous addition of a reagent which would react preferentially with any nucleophilic sulfur species present and at the same time regenerate phenoxide ion would be expected to alter the course of the reaction as outlined in Scheme II (R = CH$_3$).

Polysulfide species such as **16** would react with phenoxide ion similar to the reaction with elemental sulfur. Fujisawa[6] has demonstrated the reaction of disulfides with hindered phenoxide ions. The reaction proceeds readily when the substituents are large and bulky (*tert*-butyl, isopropyl) but they found that no reaction occurs with 2,6-dimethylphenol.



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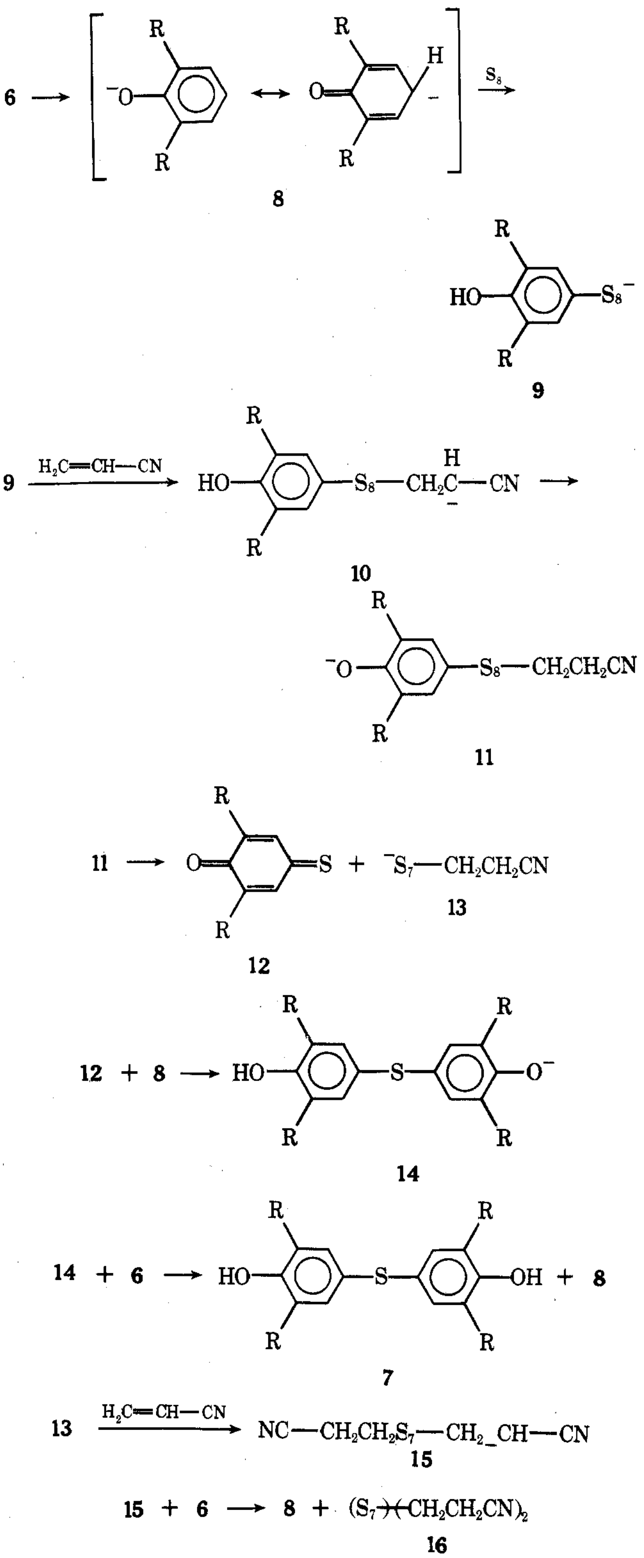
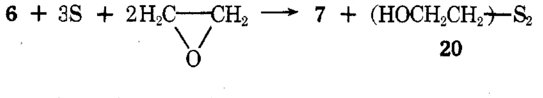
In the above postulated sequence of reactions, this would explain the preponderance of biscyanoethyl disulfide formed as a coproduct. The polysulfide species such as **16** would continue to react with phenoxide ion giving intermediates such as **11** and **13** with fewer sulfurs until the eventual products, thiobisphenol and cyanoethylated disulfide, are formed. Other activated olefins such as methacrylonitrile and ethyl acrylate have been shown to function in the same manner.

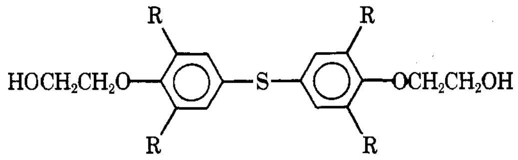
Scheme II



The reaction with epoxides is also analogous to the reaction with the activated olefins.



If 4 equiv of the epoxide is used, the bishydroxyethoxylated product (**21**) is obtained directly in 76% yield (isolated).



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The reaction of phenol and monosubstituted phenols with sulfur under these conditions takes a different course and will be the subject of a future publication.

Experimental Section

4,4′-Thiobis(2,6-diphenylphenol). To a 3-l., round-bottom, three-necked flask equipped with stirrer, thermometer, Dean-Stark trap, and condenser and maintained under a nitrogen atmosphere were placed 246 g (1.0 mol) of 2,6-diphenylphenol and 1230 ml of xylene. A solution of 40 g (1.0 mol) of sodium hydroxide in 80 ml of water was then added. The mixture was heated to reflux with stirring and the water removed. When removal of the water was complete, the reaction mixture was cooled to about 70–80 °C and 32 g (1.0 mol) of sulfur was added. The reaction mixture was again heated to reflux and the xylene was removed via the Dean-Stark trap until the temperature reached 169 °C. The reaction mixture was not homogeneous and vigorous stirring was needed. After 2 h, the reaction mixture was cooled and water was added. The solidified product was separated by filtration, washed well with more water and finally with pentane, and then dried in the vacuum oven overnight. The crude product was then triturated with 2 l. of hot heptane and the heptane-insoluble material was recrystallized from acetic acid. There was obtained 83.7 g (0.16 mol, 32.0% yield) of material melting at 151 °C. Recrystallization raised the melting point to 162–163 °C. Anal. Calcd for $C_{36}H_{26}O_2S$: C, 82.73; H, 5.01; S, 6.13. Found: C, 82.4; H, 4.98; S, 5.9.

General Procedure for the Reaction of 2,6-Dimethylphenol and Sulfur in the Presence of Acrylonitrile or Alkylene Oxides. A. Acrylonitrile. To a 500-ml round-bottom flask equipped with a Vibromixer stirrer , condenser, and thermometer with temperature controller attached, there was added 122.2 g (1.0 mol) of 2,6-xylenol and 2.3 g (0.1 g-atom) of sodium metal. The reaction mixture was heated under N_2 until the sodium dissolved, then cooled. There was added 48.0 g (1.5 g-atoms) of sulfur and the reaction mixture was heated and maintained at 80 °C. Over a period of 4.25 h there was added 53.0 g. (1.0 mol) of acrylonitrile. During this period the sulfur slowly went into solution. The reaction mixture was cooled and after diluting with ether it was washed with 10% hydrochloric acid and then with water until neutral. The ether was then removed by distillation to yield 201.6 g of crude product. The unreacted 2,6-xylenol (24.0 g) was removed by distillation at 0.2 mm, leaving a residue of 177.6 g. The residue was dissolved in ether and washed with 10% sodium hydroxide solution, leaving 12.1 g of base-insoluble material, principally β,β'-dithiodipropionitrile. After acidification with dilute hydrochloric acid the base-soluble fraction weighed 139.7 g. Recrystallization from heptane yielded 90.7 g (66.2% yield) of thiobis(2,6-dimethylphenol), mp 124 °C.

B. Propylene Oxide. 1. 2 Equiv. The reaction was performed in the same manner as the preceding example using 122.2 g (1.0 mol) of 2,6-xylenol, 1.2 g (0.05 g-atom) of sodium, 4.8 g (1.5 g-atoms) of sulfur, and 58.1 g (1.0 mol) of propylene oxide. The reaction was performed at 100 °C and the propylene oxide was added over a 4-h period. There was obtained 17.7 g (0.15 mol) of unreacted 2,6-xylenol (conversion 85%), 20.9 g (0.12 mol) of 2,6-dimethylphenoxy-2-propanol, 100.0 g (0.73 mol, 85.8% yield) of thiobisxylenol, and 3.4 g of the mono-O-alkylated thiobisxylenol.

When this reaction was performed at 50 °C, the only significant product was 2,6-dimethylphenoxy-2-propanol.

2. 4 Equiv. The reaction was performed as above except that an additional 2 mol of propylene oxide was added in the same time period. After the addition was complete, there was added 50 ml of 20% sodium hydroxide solution and the reaction was maintained at temperature for 30 min. The reaction mixture was then cooled, washed with water, and distilled. There was obtained a 76% yield of 4,4′-thiobis[1-(2,6-dimethylphenoxy)-2-propanol], mp 90–92 °C. Anal. Calcd for $C_{22}H_{30}O_4S$: C, 67.67; H, 7.74; S, 8.20. Found: C, 67.40; H, 7.98; S, 8.3.

C. Ethylene Oxide. Reactions with ethylene oxide were performed as above except that introduction of the ethylene oxide from a cylinder was continued until completion of the reaction was indicated by gas chromatography.

4,4′-Thiobis[2-(2,6-dimethylphenoxy)ethanol]. Yield 67%; mp 99 °C. Anal. Calcd for $C_{20}H_{26}O_4S$: C, 66.28; H, 7.23; S, 8.83. Found: C, 66.4; H, 7.2; S, 8.9.

Registry No.—4 (R = Ph), 58426-07-6; **6**, 576-26-1; **7**, 18525-99-0; 21 (R = CH_3), 58426-08-7; sulfur, 7704-34-9; acrylonitrile, 107-13-1; propylene oxide, 75-56-9; 4,4′-thiobis[1-(2,6-dimethylphenoxy)]-2-propanol, 58426-09-8; 2,6-diphenylphenol, 2432-11-3; ethylene oxide, 75-21-8.

References and Notes

(1) Presented in part at the VIth Symposium on Organic Sulphur Chemistry, Bangor, U.K., July 1974.
(2) For leading references, see C. Ellis, "The Chemistry of Synthetic Resins", Reinhold, New York, N.Y., 1935.
(3) A. J. Neale, P. J. S. Bain, and T. J. Rawlings, *Tetrahedron*, **25**, 4583, 4593 (1969).
(4) E. J. Geering, U.S. Patent 3 717 682 (Feb 20, 1973).
(5) T. Fujisawa, K. Hata, and T. Kojima, *Synthesis*, **5**, 38 (1973).
(6) T. Fujisawa and T. Kojima, *J. Org. Chem.*, **38**, 687 (1973).

Stereochemistry of Nucleophilic Addition Reactions. Addition of Thiophenol to Ethyl 4-*tert*-Butylcyclohexene-1-carboxylate

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The addition of thiophenoxide ion to ethyl 4-*tert*-butylcyclohexene-1-carboxylate gives the two products 4 and 5 containing an axial thiophenoxy group. The stereochemistries of the products were established by a combination of NMR spectroscopy and chemical transformations into compounds of known stereochemistry. Under conditions of kinetic control the ratio of 4 to 5 was 5.5:94.5. Under conditions of thermodynamic control it was 14:86. The results are discussed. A number of sulfones in this series were also prepared and their NMR spectra discussed.

In previous papers in this series we have described the nucleophilic addition of malonate anion to two activated olefins of biased conformation, namely 4-*tert*-butyl-1-cyanocyclohexene[1] and ethyl 4-*tert*-butylcyclohexene-1-carboxylate (1),[2] and the addition of thiophenoxide ion and of hydrogen chloride to the above unsaturated nitrile.[3] In the additions of the malonate anion, the main product formed in protic solvents under conditions of kinetic control is the equatorial malonate, with an axial nitrile or ethoxycarbonyl compound. Under conditions of thermodynamic control the diequatorial product predominates. In the addition of thiophenoxide to the unsaturated nitrile, kinetic and thermodynamic control of the addition gave the axial thiophenoxy, equatorial nitrile isomer as the main product, but the pro-