Sulfenylation of Hindered Phenols with Aryl Disulfides

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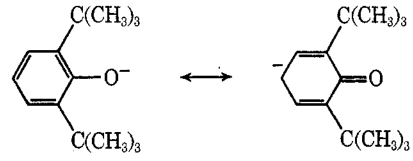
A series of 4-arylthio-2,6-di-*tert*-butylphenols have been prepared in good yields by the reaction of 2,6-di-*tert*-butylphenol with aryl disulfides in basic media. As a base sodium ethoxide was effective. Some other 4-arylthio-2,6-dialkylphenols were also prepared, and their yields were greatly influenced by the bulkiness of the ortho substituents of the starting phenols. The effects of steric hindrance on the reaction and the reaction path are discussed.

Hindered phenols, which have bulky groups such as *tert*-butyl at both ortho positions, show considerably different reactivities from other phenolic compounds.[1] Some of them are known to give stable radicals on oxidation,[2] while 2,6-di-*tert*-butylphenol is readily oxidized to give a diphenoquinone derivative.[3] The electrophilic reaction of the hindered phenol with compounds bearing a sulfur–chlorine bond such as sulfur chlorides and sulfenyl chlorides, which are commonly used for the direct sulfuration to aromatic nuclei,[4] is usually accompanied by a homolytic reaction, although it has been found to proceed smoothly in such a polar solvent as acetonitrile, giving the corresponding arylthiolated phenols in good yields.[5] Furthermore, 2,6-di-*tert*-butylphenol (**1**) is known to exist as an ambident anion between phenolate anion I and carbanion II in basic media.[6] The carbanion II reacts with various electrophiles: substitution with alkyl halides[6] and acyl halides,[7] condensation with carbonyl compounds,[7] and Michael-type addition to acrylonitrile.[6] In addition, it has been used in alkylation reaction with trialkylboranes as an effective base.[8]

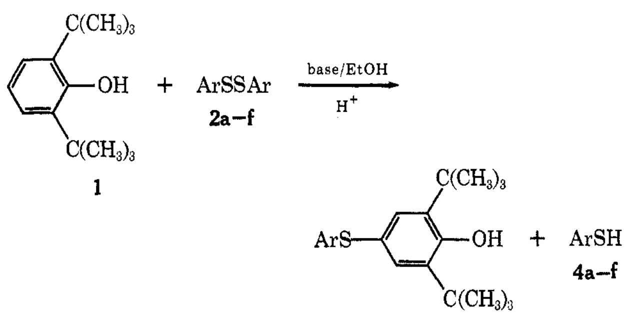


I II

Meanwhile, cleavage reactions of sulfur–sulfur bonds have attracted much attention for much synthetic and biochemical interest. The ionic scission of the sulfur–sulfur bonds by such nucleophilic reagents as phosphine and thiolate, cyano, hydroxy, and thiocyano anions is well documented and involves an S_N2 mechanism.[9] The reactivity of the nucleophiles toward divalent sulfur is designated by the term thiophilicity, and a carbanion has more thiophilic character than an alkoxide or phenolate anion.[9] Thus, the disulfide may be one of the useful sulfenylating agents and the cleavage reaction may provide a convenient method for the formation of sulfides. The examples recently disclosed are reactions with Grignard reagents[10] and amines[11] to give alkyl sulfide and sulfenamide, respectively, in good yields. A facile reaction of the carbanion, readily prepared from hindered phenols in basic media, with elemental sulfur has also been reported.[12]

In the present paper, we describe a sulfenylation reaction of hindered phenols with aryl disulfides which provides a convenient means of preparing arylthiolated phenols. The only compound of this class reported so far is 4-phenylthio-2,6-di-*tert*-butylphenol (**3c**), which was obtained by a tedious route.[13]

When an ethanol solution of 2,6-di-*tert*-butylphenol (**1**), aryl disulfide (**2**), and a base was refluxed for 20 hr, 4-arylthio-2,6-di-*tert*-butylphenol (**3**) was obtained after neutralization with hydrochloric acid, along with the corresponding thiophenol (**4**). Results of the reaction with various aryl disulfides are summarized in Table I. The optimal molar ratio for **1**, **2**, and base was found to be 2:1:4. As a base, potassium hydroxide or sodium ethoxide led to a successful result, while no reaction took place with triethylamine. When potassium hydroxide was used as a base, yields of asymmetric sulfides (**3a**–**e**) were moderate, although the corresponding thiophenols (**4a**–**e**) were obtained in good yields at the same time. In these cases, nucleophilic scission of disulfides by hydroxide anion[14] occurred simultaneously. A control experiment with-



3a–f

a, Ar = $4\text{-}CH_3OC_6H_4$
b, Ar = $4\text{-}CH_3C_6H_4$
c, Ar = C_6H_5
d, Ar = $4\text{-}ClC_6H_4$
e, Ar = $4\text{-}BrC_6H_4$
f, Ar = $4\text{-}OH\text{-}3,5\text{-}(t\text{-}C_4H_9)_2C_6H_2$

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(1) G. H. Stillson, D. W. Sawyer, and C. K. Hunt, *J. Amer. Chem. Soc.*, **67**, 303 (1945).

(2) E. R. Altwicker, *Chem. Rev.*, **67**, 475 (1967).

(3) M. S. Kharasch and B. S. Joshi, *J. Org. Chem.*, **22**, 1439 (1957).

(4) E. Müller, Ed., "Methoden der Organischen Chemie," Vol. IX, Georg Thieme Verlag, Stuttgart, 1955, p 136.

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(6) N. Kornblum and R. Seltzer, *J. Amer. Chem. Soc.*, **83**, 3668 (1961).

(7) T. H. Coffield, A. H. Filbey, G. G. Ecke, and A. J. Kolka, *ibid.*, **79**, 5019 (1957).

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(9) (a) A. J. Parker, *Acta Chem. Scand.*, **16**, 855 (1962); (b) A. J. Parker and N. Kharasch, *Chem. Rev.*, **59**, 583 (1959).

(10) A. W. P. Jarvie and D. Skelton, *J. Organometal. Chem.*, **30**, 145 (1971).

(11) M. D. Bentley, I. B. Douglass, J. A. Lacadie, and D. C. Weaver, *Chem. Commun.*, 1625 (1971).

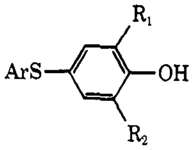
(12) T. Fujisawa, K. Hata, and T. Kojima, *Synthesis*, in press.

(13) E. Müller, H. B. Stegmann, and K. Scheffler, *Justus Liebigs Ann. Chem.*, **645**, 79 (1961).

(14) J. P. Danehy and K. N. Parameswaran, *J. Org. Chem.*, **33**, 568 (1968).

TABLE I[a]

SULFENYLATION OF 2,6-DIALKYLPHENOL WITH ARYL DISULFIDE



Compd	R₁	R₂	Ar	Mp, °C	Yield, %[b] With potassium hydroxide	Yield, %[b] With sodium ethoxide
3a	t-C_4H_9	t-C_4H_9	4-$CH_3OC_6H_4$	141–142°	61	88
3b	t-C_4H_9	t-C_4H_9	4-$CH_3C_6H_4$	96–98	44	108
3c	t-C_4H_9	t-C_4H_9	C_6H_5	101–102[c]	36	113
3d	t-C_4H_9	t-C_4H_9	4-ClC_6H_4	89–90	59	88
3e	t-C_4H_9	t-C_4H_9	4-BrC_6H_4	100–101	36	98
3f	t-C_4H_9	t-C_4H_9	4-OH-3,5-(t-C_4H_9)$_2C_6H_2$	137–138[d]	84[e]	80[e]
9a	CH_3	t-C_4H_9	4-$CH_3OC_6H_4$	104–105		28
9c	CH_3	t-C_4H_9	C_6H_5	Oil		24
9e	CH_3	t-C_4H_9	4-BrC_6H_4	Oil		46
10a	$CH(CH_3)_2$	$CH(CH_3)_2$	4-$CH_3OC_6H_4$	Oil		26
10c	$CH(CH_3)_2$	$CH(CH_3)_2$	C_6H_5	Oil		18
10e	$CH(CH_3)_2$	$CH(CH_3)_2$	4-BrC_6H_4	Oil		31

[a] Satisfactory analytical data (±0.3% for C, H, and S) were reported for all new compounds listed in the table.[24] [b] Based on the phenols. Determined by glpc. [c] Lit.[14] mp 99–101°. [d] Lit.[14] mp 135–136°. [e] Determined by nmr.

out **1** showed the formation of **4** and the corresponding sulfinic acid **5**. In the case of **2f** the high yield of **3f**

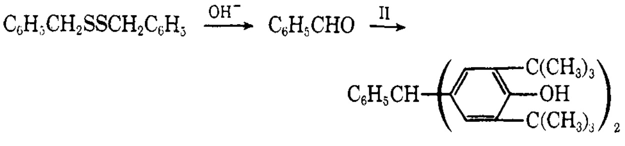
$$\underset{\mathbf{2}}{\text{ArSSAr}} \xrightarrow[\text{H}^+]{\text{OH}^-/\text{EtOH}} \underset{\mathbf{4}}{\text{ArSH}} + \underset{\mathbf{5}}{\text{ArSO}_2\text{H}}$$

is due to the simultaneous desulfuration reaction of the disulfide with alcoholic potassium hydroxide.[13] On the other hand, sodium ethoxide, which has less thiophilic character, was found to be a better base for the reaction and the yields of **3** were greatly increased. The yields exceeding the stoichiometric amount are due to the partial oxidation of the anion of the resulting **4** to the starting disulfide during the reaction course. This is verified by a control experiment on the reaction of **1** with *p*-thiocresol in place of **2b**, where **3b** was obtained in a yield of 5%.

$$\text{ArS}^- \xrightarrow{[\text{O}]} \underset{\mathbf{2}}{\text{ArSSAr}}$$

The reaction proceeds substantially even at lower temperature (50°) in a more diluted solution (see kinetic runs). In the case of aryl disulfides having electron-withdrawing groups (**2d**–**e**), the reaction was accomplished quantitatively within 1 hr. Even in the case of tolyl disulfide (**2b**), *ca.* 80% **3b** was formed within 3 hr. *p*-Nitrophenyl disulfide, however, gave not the expected sulfide, but thiobis(2,6-di-*tert*-butylphenol) (**3f**), which may be formed by further reaction of the primary product with **1**.

On the other hand, *n*-butyl disulfide did not react with **1** under the same conditions and the starting materials were recovered intact. When benzyl disulfide was used as a substrate, the reaction proceeded in quite a different way. Bis(3,5-di-*tert*-butyl-4-hydroxyphenyl)phenylmethane (**6**), which has been reported to be prepared from benzaldehyde and **1**,[7] was obtained in 65% yield. The product may result from benzaldehyde intermediately formed by alkaline decomposition of benzyl disulfide.[14]



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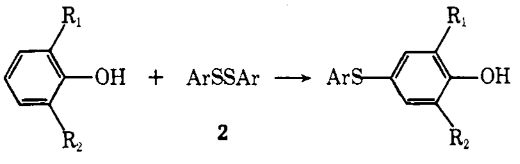
The effect of substituents of phenols plays an important role in the reaction. The sulfenylation using various 2,6-dialkylphenols as nucleophiles was studied and the yields of the products, 4-arylthio-2,6-dialkylphenols, are also shown in Table I. Compared with the data on 2,6-di-*tert*-butylphenol, 2-methyl-6-*tert*-butylphenol (**7**), and 2,6-diisopropylphenol (**8**) gave the corresponding sulfides (**9** and **10**) in low yields, while 2,6-dimethylphenol and unsubstituted phenol did not react with disulfides. The order of yields of the products was inversely related to the specific conductivities of the phenols,[15] which are reported to be in close correlation with steric hindrance. Accordingly, this order indicates that the reaction was affected by the bulkiness of the substituents of the phenols.



7, $R_1 = t$-C_4H_9; $R_2 = CH_3$
8, $R_1 = R_2 = CH(CH_3)_2$
9, $R_1 = t$-C_4H_9; $R_2 = CH_3$
10, $R_1 = R_2 = CH(CH_3)_2$

These results indicate a low reactivity of phenolate anions toward disulfides. The electron density of the aromatic ring, especially at the para position, of 2,6-disubstituted phenols increases according to the bulkiness of the substituent in the order dimethyl ≪ diisopropyl ≤ *tert*-butylmethyl < di-*tert*-butyl. Accordingly, their reactivities vary in the above order. This effect is best explained by "steric hindrance to solva-

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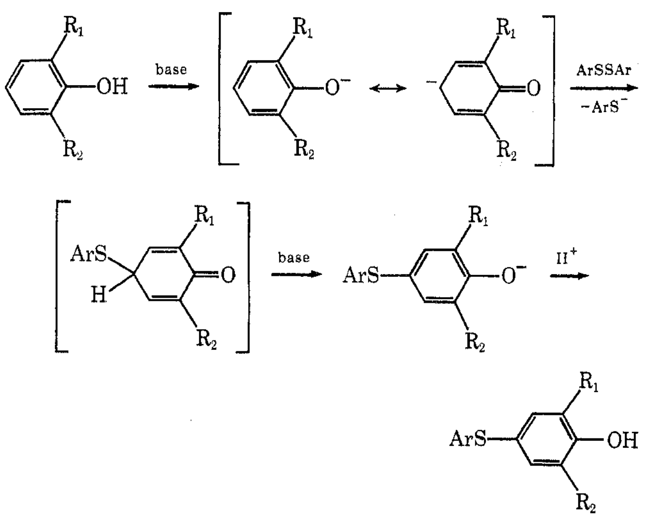
[15] R. Perrin and N. Brondel, *C. R. Acad. Sci.*, **260**, 2809 (1965).

tion";[16] solvation of I is prevented by the bulky *tert*-butyl groups. This concept has also been seen in properties[17] and oxidation reactions[18] of hindered phenols. 2,6-Dimethylphenol showed no reactivity in this system, while it gave thiobis(2,6-dimethylphenol) by the sulfenylation with elemental sulfur as reported previously.[12] The difference of its reactivities toward aryl disulfide and toward sulfur may be due to the susceptibility of the S–S bond to nucleophilic attack, which is related to the bond energies: 64 kcal/mol for phenyl disulfide[19] and 33 kcal/mol for the eight-membered sulfur molecule.[20]

To corroborate the reaction pathway, the reaction rates were measured in ethanol at 50.0° using **1** and various para-substituted diphenyl disulfides. The rate of the scission of the sulfur–sulfur bond of the disulfides by hydroxide anion was also measured under the same conditions. As shown in Figure 1, linear relationships for both reactions were observed between the logarithms of the second-order rate constant and the Hammett para-substituent constant σ_p, and the gradient of the plots gave a value for the reaction constant ρ of +3.1 for both reactions. The rate of the bond scission of a disulfide by hydroxide anion was observed to be almost the same as that by the carbanion II. This is in substantial accord with the experimental data in Table I, which show a reduction of the yields of **3** in the use of potassium hydroxide as a base. In this case a half of the disulfide was consumed simultaneously by the attack of hydroxide anions. On the other hand, the use of sodium ethoxide as a base gave exclusively the product **3**, since the rate of disulfide scission by the ethoxide anion is negligibly slow.

Reactions of both the carbanion and the hydroxide anion proceed faster in the cases of aryl disulfides with electron-withdrawing groups rather than those with electron-releasing ones. This shows that the smaller the pK_a value of thiol, *i.e.*, the more stable the leaving thiolate anion, the faster is the reaction.[14] Therefore, the reaction of disulfides with the carbanion of hindered phenols involves a bimolecular nucleophilic mechanism as follows.



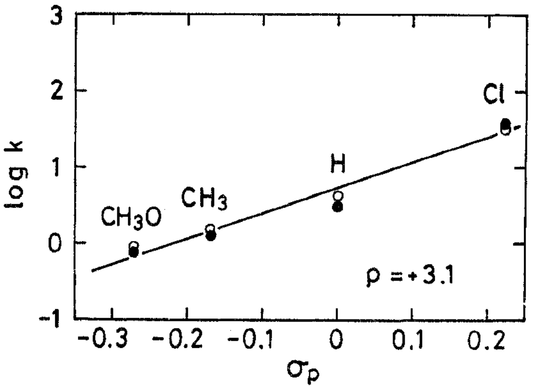


Figure 1.—Correlation of the rate constant with Hammett substituent constant σ_p: Reaction was conducted in ethanol at 50.0°: ●, reaction of **1** with **2**; ○, reaction of **2** with KOH.

In conclusion, aryl disulfides react only at carbon in the ambident anion of hindered phenols, giving 4-arylthiophenols.

Experimental Section

All melting points are uncorrected. Proton nmr spectra were measured with a Varian HA-100 spectrometer. Glpc analyses were conducted using a Hitachi K-53 chromatograph with a 1-m SE-30 column (3% on Chromosorb W). Aryl disulfides and benzyl disulfide were prepared by the oxidation of the corresponding thiophenols in dimethyl sulfoxide.[21] Bis(p-bromophenyl) disulfide[22] and bis(p-nitrophenyl) disulfide[23] were prepared by known procedures as referenced. Phenol and 2,6-dialkylated phenols were obtained commercially.

General Procedure for Preparation of 4-Arylthio-2,6-di-*tert*-butylphenol (3).—2,6-Di-*tert*-butylphenol (**1**) (10 mmol) and aryl disulfide **2** (5 mmol) were dissolved in ethanol (25 ml) containing a base (20 mmol). The solution was heated under reflux for 20 hr, and then was poured into 2 *N* hydrochloric acid. The products were extracted with benzene (20 ml). The benzene extract was washed with 1 *N* NaOH solution, dried ($MgSO_4$), concentrated, and subjected to distillation to remove **1**. The resulting sulfide **3** was recrystallized from ethanol-water. The yields and the melting points are shown in Table I. Nmr spectra consistent with the structure were obtained for all compounds.[24]

Reaction of Aryl Disulfides with Potassium Hydroxide.—An ethanol solution of **2b–d** (5 mmol) and potassium hydroxide (20 mmol) was heated under reflux for 20 hr. After neutralization with hydrochloric acid, the products were extracted with benzene, and the extract was submitted to glpc analysis. The yields of **4** based on **2** were as follows: **4b**, 68%; **4c**, 84%; **4d**, 48%. After evaporation of benzene from the extract, crystalline sulfinic acid was filtered. The yields were as follows: **5b**, 28%; **5c**, 15%; **5d**, 18%.

Reaction of 1 with *p*-Thiocresol.—In place of **2b**, *p*-thiocresol (**4b**) (10 mmol) was used in the presence of sodium ethoxide, other conditions being the same as the general procedure. 4-*p*-Tolylthio-2,6-di-*tert*-butylphenol (**3b**) was obtained in a yield of 5%.

Reaction of 1 with Bis(*p*-nitrophenyl) Disulfide.—The reaction was carried out in the same manner as the general procedure described above, using bis(p-nitrophenyl) disulfide (1.55 g, 5 mmol) in the presence of potassium hydroxide. The product obtained from the reaction mixture was thiobis(2,6-di-*tert*-butylphenol) (**3f**), 0.50 g (23%), mp 135–138°.

Reaction of 1 with Benzyl Disulfide.—As a disulfide, benzyl disulfide (1.25 g, 5 mmol) was used in the presence of sodium

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[16] P. D. Bartlett, M. Roha, and R. M. Stiles, *J. Amer. Chem. Soc.*, **76**, 2349 (1954).

[17] L. A. Cohen, *J. Org. Chem.*, **22**, 1333 (1957).

[18] H. R. Gersmann and A. F. Bickel, *J. Chem. Soc.*, 2356 (1962).

[19] H. Mackle and R. G. Mayrick, *Trans. Faraday Soc.*, **58**, 238 (1962).

[20] A. V. Tobolsky and A. Eisenberg, *J. Amer. Chem. Soc.*, **81**, 780 (1959).

[21] C. N. Yiannios and J. V. Karabinos, *J. Org. Chem.*, **28**, 3246 (1963).

[22] E. Bourgeois and A. Abraham, *Recl. Trav. Chim. Pays-Bas*, **30**, 407 (1911).

[23] T. Zincke and S. Lenhardt, *Justus Liebigs Ann. Chem.*, **400**, 2 (1913).

[24] Additional tables of analytical and nmr spectral data will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth Street, N.W., Washington, D. C. 20036, by referring to code number JOC-73-687. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

ethoxide, other conditions being the same as the general procedure. After evaporation of the solvent from the benzene extract, bis(3,5-di-*tert*-butyl-4-hydroxyphenyl)phenylmethane (**6**) was obtained as white crystals, yield 1.63 g (65%), mp 161–162° (lit.[3] mp 161–163°).

When potassium hydroxide was used as a base, 1.49 g (60%) of **6** was obtained.

Reaction of 2,6-Dialkylphenols 7 and 8 with Aryl Disulfide.—The reaction was conducted in the same manner as the general procedure using 2,6-di-*tert*-butylphenol. The base used in the reaction was sodium ethoxide. The separation and purification was achieved by column chromatography on silica gel and preparative glpc. The yields of the products, 4-arylthio-2,6-dialkylphenols (**9** and **10**), are summarized in Table I.[24]

Procedure of Kinetic Runs. A. Reaction of 1 with 2.—In a typical experiment, an ethanol solution (25 ml) of **1** (1.25 mmol) and **2** (0.50 mmol) in a stoppered ampoule was flushed with argon and placed in a constant-temperature bath at 50.0°. An ethanolic sodium ethoxide solution (0.50 *N*, 25 ml) at the same temperature was added to the above solution. A 1-ml aliquot of the resulting solution was pipetted out at definite intervals and poured into a mixture of benzene (2 ml) and 1 *N* hydrochloric acid (5 ml). The amount of **3** in the benzene layer was determined by glpc. The initial rate was determined graphically from the yield of **3** *vs.* time. This rate was confirmed to be the same as that of the consumption of **2** within experimental error (5%).

B. Reaction of 2 with Potassium Hydroxide.—An ethanol solution (25 ml) of **2** (0.50 mmol) and an ethanolic potassium hydroxide solution (0.50 *N*, 25 ml) were treated in the same manner as described above. In this reaction, the rate was determined from the consumption of **2**: $-d[2]/dt = k[2]\,[KOH]$.

Registry No.—**1**, 128-39-2; **2a**, 5335-87-5; **2b**, 103-19-5; **2c**, 882-33-7; **2d**, 1142-19-4; **2e**, 5335-84-2; **2f**, 6386-58-9; **3a**, 32551-11-4; **3b**, 32551-15-8; **3c**, 32551-12-5; **3d**, 32551-13-6; **3e**, 32551-14-7; **3f**, 4673-51-2; **7**, 2219-82-1; **8**, 2078-54-8; **9a**, 37610-74-5; **9c**, 37610-75-6; **9e**, 37610-76-7; **10a**, 37610-77-8; **10c**, 37610-78-9; **10e**, 37610-79-0; bis(*p*-nitrophenyl) disulfide, 100-32-3.

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Chemistry of the Sulfur–Nitrogen Bond. IV.[1,2] The Effects of Nuclear Substitution, Solvent, Temperature, and Time on the Rearrangement of Arenesulfenanilides to *o*- and *p*-Aminodiphenyl Sulfides

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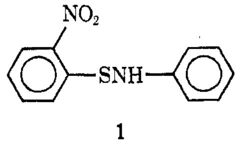
The scope and limitations of the thermal rearrangement of arenesulfenanilides to 2- and 4-aminodiphenyl sulfides has been investigated. Arenesulfenanilides undergo two thermal reactions: disproportionation to give aryl disulfides and azobenzenes and rearrangement to 2- and 4-aminodiphenyl sulfides. Electron-withdrawing groups favor rearrangement as does the addition of aniline hydrochloride. Electron-donating groups accelerate the rate of rearrangement. The effects of nuclear substitution, solvent, temperature, and time on the composition of the reaction products are discussed.

Compounds containing the sulfur–nitrogen bond are of considerable importance both from a practical as well as a theoretical standpoint. An understanding of the chemistry of sulfenamides is important in elucidating the various types of interaction possible between adjacent sulfur and nitrogen. At least three types of interactions may be considered: lone-pair interactions resulting from the presence of lone pairs of electrons on sulfur and nitrogen; bond polarization resulting from the difference in electronegativity between sulfur and nitrogen; and the donation of electrons from nitrogen to sulfur (p–d π bonding).

There is considerable evidence in support of some sort of electron donation from nitrogen to sulfur in the ground state of arenesulfenanilides which affects both torsional barriers[4] and displacement reactions at the S–N bond.[5] However, the extent to which this effect, as well as the other effects, determine reactions of sulfenamides is less well understood.

Recently, we reported an unusual thermal reaction for 2-nitrobenzene sulfenanilide (**1**).[6] When heated in aniline at 200°, **1** gave 2- and 4-aminodiphenyl sulfides (**2a–b**), phenothiazine (**3**), and 2-aminobenzenesulfonanilide (**4**). It was inferred at that time that arenesulfenanilides undergo two types of reactions: rearrangement to 2- and 4-aminodiphenyl sulfides and disproportionation to give amino and sulfenyl radicals.[6]



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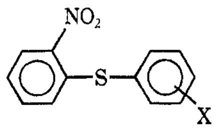
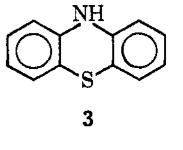


2a, X = 2–NH$_2$
b, X = 4–NH$_2$



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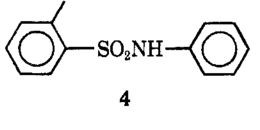

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Subsequently it was shown that the 2-nitrobenzenesulfenyl radical resulting from the disproportionation reaction underwent an intramolecular oxidation– reduc-

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[1] Part III: F. A. Davis and R. P. Johnston II, *J. Org. Chem.*, **37**, 859 (1972).

[2] Presented in part at the 7th MARM, Philadelphia, Pa., Feb 1972.

[3] National Science Foundation Undergraduate Research Participant, 1971.

[4] M. Raban and F. B. Jones, Jr., *J. Amer. Chem. Soc.*, **93**, 2692 (1971).

[5] F. A. Davis, S. Divald, and A. H. Confer, *Chem. Commun.*, 678 (1971).

[6] F. A. David, R. B. Wetzel, T. J. Devon, and J. F. Stackhouse, *J. Org. Chem.*, **36**, 799 (1971).