Sulfoxide–Carbodiimide Reactions. IV.[1] Acid-Catalyzed Reactions of Phenols with Sulfoxides and Carbodiimides

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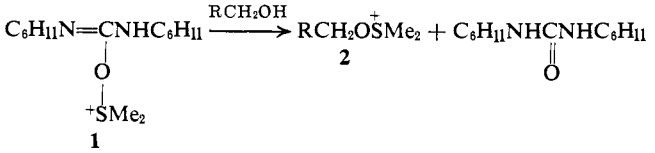
Abstract: Acid-catalyzed reactions of various phenols with dicyclohexylcarbodiimide (DCC) in dimethyl sulfoxide (DMSO) have been studied. The principal products were phenols alkylated in the available *ortho* positions with thiomethoxymethyl groups. In addition, products containing the previously undescribed 1,3-benzoxathian ring system were frequently formed in low yields. More strongly acidic phenols also lead to aryl thiomethoxymethyl ethers. The major products from 1- and 2-naphthol were the doubly alkylated dihydronaphthalenones **26** and **29.** The various products have been characterized by spectral methods and by desulfurization to known compounds. Reaction mechanisms are proposed for the various types of products. Thiophenols have been shown to be oxidized to disulfides by DMSO, this reaction being dramatically catalyzed by acids.

Recent reports from this laboratory[3] have described a facile and efficient oxidation of alcohols to the corresponding carbonyl compounds through their reaction with dimethyl sulfoxide (DMSO) and dicyclohexylcarbodiimide (DCC) in the presence of an appropriate proton source. The oxidation reaction proceeds under extremely mild conditions and is admirably suited for use with sensitive compounds.[4] A particular merit lies in the selectivityof the method when applied to primary alcohols, which are oxidized exclusively to aldehydes with no observable formation of acidic products. The mechanism of the reaction has recently been elucidated by isotope experiments[1] which showed the initial step to be the formation of the sulfonium isourea derivative **1** through acid-catalyzed addition of DMSO to DCC. Nucleophilic attack by the alcohol upon the sulfur atom of **1** then leads to the alkoxysulfonium derivative **2** which undergoes intramolecular proton abstraction and concerted collapse to the carbonyl compound and dimethyl sulfide.



In view of this mechanism it was of interest to determine whether other nucleophiles might also attack the key intermediate **1**. In this paper, and in a forthcoming publication,[5] we report the results of studies on the reactions of phenols with sulfonium isoureas of type **1**. A preliminary report of this work has already appeared[6] and related studies have been described in preliminary form by Pfitzner, *et al.*[7]

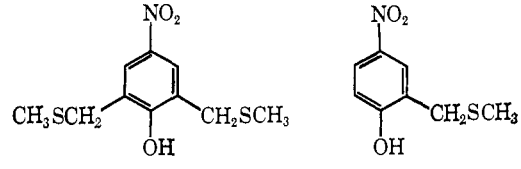
In general, our reactions were carried out by adding 0.5 molar equiv of anhydrous orthophosphoric acid to a solution of the appropriate phenol (1 equiv) and DCC (3 equiv) in anhydrous DMSO or mixtures of DMSO and inert solvents such as benzene. Under these conditions an exothermic reaction takes place after a few minutes and is accompanied by the deposition of highly insoluble dicyclohexylurea. After a few hours the urea is removed by filtration and the DMSO by aqueous extraction. The phenolic and nonphenolic products are then separated by alkaline extraction and fractionated by chromatography on silicic acid. The conditions selected are essentially identical with those found to be optimal for the oxidation of alcohols.[3a] The use of pyridinium trifluoroacetate in place of orthophosphoric acid leads to an almost identical array of products as judged by thin layer chromatography but is somewhat complicated by the formation of N-trifluoroacetyl-N,N′-dicyclohexylurea (mp 137–139°)[3b] and lesser amounts of N-cyclohexyltrifluoroacetamide (mp 93–94°). Vigorous reactions also take place using dichloroacetic acid but the yields appear to be somewhat lower and substantial amounts of N-dichloroacetyl-N,N′-dicyclohexylurea (mp 146–148°) are formed. To avoid these by-products we have routinely used anhydrous orthophosphoric acid in the experiments to be described.

Our initial experiments were done with *p*-nitrophenol and led to an extraordinary array of crystalline and readily characterized products. Since the most general types of products that we have encountered in this work were formed from *p*-nitrophenol, we will consider this reaction in some detail. The phenolic products from the reaction of *p*-nitrophenol were separated into three crystalline compounds in addition to some unreacted starting material by chromatography on silicic acid. These products have been identified as 4-nitro-2,6-di(thiomethoxymethyl)phenol (**3**), 4-nitro-2-(thiomethoxymethyl)phenol (**4**), and 1,3-dicylohexyl-1-(2-hydroxy-5-nitro-3-thiomethoxymethyl)benzylurea (**5**) by their elemental analysis and the following spectral data. Each compound was shown to be phenolic both by its infrared spectrum and by the typical bathochromic shift of roughly 100 mμ in alkaline solution (see Table II). The presence of the thiomethoxymethyl group in each compound is indicated by their nmr spectra which

(1) For part III see A. H. Fenselau and J. G. Moffatt, *J. Am. Chem. Soc.*, **88**, 1762 (1966).
(2) Syntex Postdoctoral Fellow, 1964–1965, and recipient of a Wellcome Trust Travel Grant, for which we express our thanks.
(3) (a) K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, **87**, 5661 (1965); (b) K. E. Pfitzner and J. G. Moffatt, *ibid.*, **87**, 5670 (1965).
(4) See, *e.g.* (a) J. D. Albright and L. Goldman, *J. Org. Chem.*, **30**, 1107 (1965); (b) B. R. Baker and D. H. Buss, *ibid.*, **30**, 2304, 2308 (1965); and (c) A. G. Brook and J. B. Pierce, *ibid.*, 30, 2566 (1965).
(5) M. G. Burdon and J. G. Moffatt, In preparation.
(6) M. G. Burdon and J. G. Moffatt, *J. Am. Chem. Soc.*, **87**, 4656 (1965).
(7) K. E. Pfitzner, J. P. Marino, and R. A. Olofson, *ibid.*, **87**, 4658 (1965).

contain sharp 3-proton singlets at 122–125 cps and 2-proton singlets at 224–231 cps. These chemical shifts are in agreement with those reported in the literature for CH_3S[8] and $ArCH_2S$[9] groups, respectively. Localization of the thiomethoxymethyl group in exclusively the *ortho* positions was also possible from the nmr spectra. Thus in deuteriochloroform the aromatic protons of *p*-nitrophenol are divided into two 2-proton groups, those adjacent to the nitro group appearing as an *ortho*-coupled doublet centered at 491 cps (J = 9 cps), and those adjacent to the phenolic group as a doublet at 416 cps (J = 9 cps).[10] Compound **3** showed only a 2-proton singlet at 484 cps in the aromatic region, thus confirming the symmetrical nature of the molecule and the absence of protons adjacent to the phenolic group. Similarly **4** showed the presence of a single proton adjacent to the phenolic group as a doublet at 421 cps (J = 9 cps) and two protons adjacent to the nitro group. Oxidation of the thiomethoxymethyl phenols with hydrogen peroxide readily gave the corresponding sulfoxides.

The third phenolic compound is unique in that it contains a bound molecule of dicyclohexylurea indicated by the presence of 20 aliphatic protons as a broad resonance at 100–120 cps in the nmr spectrum. In addition, the presence of single thiomethoxymethyl and phenolic groups and of a singlet methylene group ($ArCH_2N$ at 269 cps) were indicated. Only two aromatic protons were present as a pair of doublets (J = 2.5 cps, *meta* coupling) at 483 and 490 cps which is consistent only with an unsymmetrically 2,6-disubstituted 4-nitrophenol structure. These data, together with the observed elemental analyses, point to structure **5**.[11] Only one other compound related to **5** has been observed in the present work, namely **19** arising in low yield from *o*-cresol. A common feature of these two reactions is that both were done on a somewhat larger scale than usual and became extremely hot. More carefully controlled reactions with *o*-cresol did not appear to produce **19**, The formation of urea-containing products would thus appear to be a side reaction induced by excessive heating. There is seemingly no connection between these results and the formation of 1-aryl-1,3-dicyclohexylureas upon prolonged heating of nitrophenols with DCC as described by Vowinkel[12] since the products obtained in that work were nonphenolic. We have not observed this type of product in our work.



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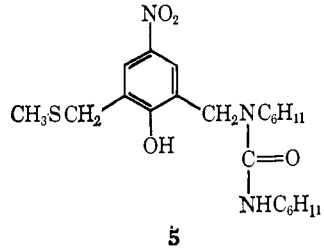

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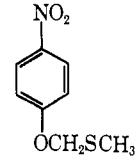
The nonphenolic products, which were present in much smaller amounts, were also separated into three new crystalline products and an additional amount of **5** which has only limited solubility in alkali. The ultraviolet and infrared spectra of these compounds showed them to be nonphenolic, and the cyclic and acyclic hemithioacetal structures **6–8** have been assigned from analytical and spectral data.



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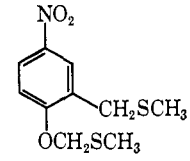

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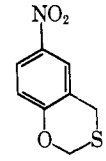

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The $ArOCH_2SCH_3$ group in **6** and **7** appears in the nmr spectra of these compounds as singlets at 135–138 cps (SCH_3) and at 314–319 cps (OCH_2S), and the spectrum of **8** shows the presence of both O- and C-thiomethoxymethyl groups. The 1,3-benzoxathian ring system present in **8** has not been described prior to the present work. Recently, however, Onodera, *et al.*,[13] have identified **8** as a product arising from the reaction of *p*-nitrophenol and phosphorus pentoxide in DMSO. As expected, the nmr spectrum of **8** contains 2-proton singlets at 237 ($ArCH_2S$) and 320 cps (OCH_2S). Compounds **6** and **7**, being hemithioacetals, are readily hydrolyzed by acid to the parent phenol, methyl mercaptan, and formaldehyde. The cyclic compound **8**, however, is more resistant to hydrolysis and remains unchanged under conditions that lead to complete cleavage of **6** or **7**. An independent synthesis of **6** was also achieved in 43% yield through reaction of sodium *p*-nitrophenolate with chloromethyl methyl sulfide in benzene. Desulfurization of the products from nitrophenols proved to be impracticable due to concomitant reduction of the nitro group, but this approach has been highly successful in confirming the structures of products from other phenols (see below).

A number of other simple phenols containing unsubstituted *ortho* positions have been treated with DMSO and DCC under conditions similar to those used with *p*-nitrophenol. In general, the major isolated products in each case were, once again, those containing *o*-thiomethoxymethyl groups. Thus, for example, phenol itself gave both 27% of 2-(thiomethoxymethyl)phenol (**12**) and 12% of 2,6-di(thiomethoxymethyl)phenol (**13**). A summary of these reactions together with analytical data is to be found in Table I, and pertinent nmr and ultraviolet spectral data on the products are given in Table II.

As can be seen from Table I, low yields of thiomethoxymethyl ethers (*e.g.*, **6**, **7**, **10**) and benzoxathian derivatives (*e.g.*, **8**, **14**, **15**, **16**, **25**, **28**) were frequently found in these reactions. The formation of thiomethoxymethyl ethers appears to be unique to rather

(8) G. R. Pettit, I. B. Douglass, and R. A. Hill, *Can. J. Chem.*, **42**, 2357 (1964).

(9) N.M.R. Spectra Catalog, Vol. I and II, Varian Associates, Palo Alto, Calif., 1963.

(10) These assignments are confirmed by the spectrum of 2-methyl-4-nitrophenol which contains a 2-proton pattern at 475–485 cps and a 1-proton doublet (J = 9 cps) at 412 cps.

(11) The methylene group was inadvertently omitted from the structure of this compound in our preliminary report.[6]

(12) E. Vowinkel, *Chem. Ber.*, **96**, 1702 (1963).

(13) K. Onodera, S. Hirano, N. Kashimura, and T. Yajima, *Tetrahedron Letters*, 4327 (1965).

Table I. Products from Reactions of Phenols with DMSO and DCC

Starting material and products		% yield	Mp or bp, °C (mm)[a]	Molecular formula	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % S	Found, % C	Found, % H	Found, % N	Found, % S
4-Nitrophenol												
4-Nitro-2,6-di(TMM)phenol[b]	(3)	11	76.5–77.5	$C_{10}H_{13}NO_3S_2$	46.30	5.05	5.40	24.70	46.57	5.11	5.26	24.78
4-Nitro-2-(TMM)phenol	(4)	26	127.5–128.5	$C_8H_9NO_3S$	48.21	4.55	7.04	16.09	48.41	4.46	6.96	16.12
1,3-Dicyclohexyl-1-(2-hydroxy-5-nitro-3-TMM)benzylurea	(5)	14	149–150	$C_{22}H_{35}N_3O_4S$	60.70	7.64	9.65	7.36	61.00	7.55	9.37	7.52
4-Nitro-O-(TMM)phenol	(6)	3	50–51	$C_8H_9NO_3S$	48.24	4.56	7.03	16.10	48.22	4.62	6.96	16.19
4-Nitro-O,2-di(TMM)phenol	(7)	14	61–62	$C_{10}H_{13}NO_3S_2$	46.30	5.05	5.40	24.70	46.42	5.10	5.21	24.61
6-Nitro-1,3-benzoxathian	(8)	3	135–136	$C_8H_7NO_3S$	48.74	3.58	7.11		49.27	3.57	7.52	
2-Nitrophenol												
2-Nitro-6-(TMM)phenol	(9)	38	78–79	$C_8H_9NO_3S$	48.24	4.56	7.03	16.09	48.35	4.60	7.09	16.30
2-Nitro-O-(TMM)phenol	(10)	10	80 (10^{-3})	$C_8H_9NO_3S$	48.24	4.56	7.03	16.09	48.43	4.65	7.22	16.48
2-Nitro-O,6-di(TMM)phenol	(11)	7	100 (10^{-4})	$C_{10}H_{13}NO_3S_2$	46.30	5.05	5.40	24.70	46.57	5.08	5.37	24.36
Phenol												
2-(TMM)phenol	(12)	27	70 (10^{-2})	$C_8H_{10}OS$	62.32	6.54	...	20.78	62.29	6.54	...	21.02
2,6-di(TMM)phenol	(13)	16	80 (10^{-3})	$C_{10}H_{14}OS_2$	56.07	6.59	...	29.90	55.97	6.39	...	29.77
1,3-Benzoxathian	(14)	4	80 (10^{-2})	C_8H_8OS	63.15	5.30	...	21.08	63.27	5.40	...	21.26
8-(TMM)-1,3-benzoxathian	(15)	4	80 (10^{-3})	$C_{10}H_{12}OS_2$	56.60	5.70	...	30.20	56.53	5.69	...	30.15
o-Cresol												
2-Methyl-6-(TMM)phenol	(17)	28	70 (10^{-3})	$C_9H_{12}OS$	64.27	7.19	...	19.02	64.37	7.30	...	19.21
8-Methyl-1,3-benzoxathian	(16)	7	60 (10^{-3})	$C_9H_{12}OS$	65.05	6.07	...	19.28	64.95	6.16	...	19.44
2-Methyl-4,6-di(TMM)phenol	(18)	4[c]	75 (10^{-4})	$C_{11}H_{16}OS_2$	57.80	7.06	...	28.05	57.04	7.04	...	28.12
1,3-Dicyclohexyl-1-(2-hydroxy-3-methyl)benzylurea	(19)	8[c]	146–147	$C_{21}H_{32}N_2O_2$	73.21	9.36	8.13	*d*	73.15	9.24	8.27	*d*
2,5-Dimethylphenol												
3,6-Dimethyl-2-(TMM)phenol	(20)	35	80 (10^{-3})	$C_{10}H_{14}OS$	65.91	7.74	...	17.56	65.85	7.58	...	17.40
2,4,5-Trimethylphenol												
2,4,5-Trimethyl-6-(TMM)-phenol	(21)	23	51–53	$C_{11}H_{16}OS$	67.32	8.22	...	16.30	67.11	8.25	...	16.41
Estrone												
2-(TMM)estrone	(22)	(*e*)	205–207	$C_{20}H_{26}O_2S$	72.70	7.93	...	9.70	72.67	8.03	...	9.93
4-(TMM)estrone	(23)	(*e*)	154–156	$C_{20}H_{26}O_2S$	72.70	7.93	...	9.70	72.66	7.84	...	9.54
1-Naphthol												
2-(TMM)-1-naphthol	(24)	12	100 (10^{-3})	$C_{12}H_{12}OS$	70.57	5.92	...	15.69	70.76	5.98	...	15.71
4H-Naphtho[2,1-*e*]-1,3-oxathiin	(25)	3	60–62	$C_{12}H_{10}OS$	71.28	4.99	...	15.85	71.51	5.10	...	15.66
2,2-di(TMM)-1(2H)-naphthalenone	(26)	36	50–51	$C_{14}H_{16}OS_2$	63.62	6.10	...	24.23	63.57	5.96	...	24.20
2-Naphthol												
1-(TMM)-2-naphthol	(27)	15	100 (10^{-3})	$C_{12}H_{12}OS$	70.57	5.92	...	15.69	70.45	5.76	...	15.55
1H-Naphtho[1,2-*e*][1,3]oxathiin	(28)	3	62–63	$C_{12}H_{10}OS$	71.28	4.99	...	15.85	71.26	5.11	...	15.76
1,1-Di(TMM)-2-(1H)-naphthalenone	(29)	36	Oil	$C_{14}H_{16}OS_2$	63.62	6.10	...	24.23	63.88	6.36	...	24.12

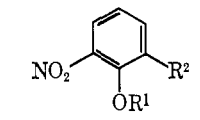
[a] Boiling points refer to the bath temperature in a "Kugelrohr" short-path apparatus: R. Graeve and G. H. Wahl, *J. Chem. Educ.*, **41**, 279 (1964). [b] TMM is used in this table as an abbreviation for thiomethoxymethyl. [c] These products were isolated from a reaction that became unusually hot and did not appear to be formed under milder conditions. [d] *Anal.* Calcd: O, 9.38. Found: O, 9.29. [e] Five products moving very close together on thin layer chromatograms were formed in this reaction and could not be adequately separated. The products reported were only isolated after repeated chromatography and crystallization accompanied by extensive losses.

acidic phenols (*o*- and *p*-nitrophenols have pK = 7.23 and 7.15, respectively[14]) and becomes the sole observed reaction in the case of pentachlorophenol (pK = 5.2[15]) which gave O-(thiomethoxymethyl)pentachlorophenol in 60% yield.[5] This same compound was prepared in 62% yield from sodium pentachlorophenolate and chloromethyl methyl sulfide. Benzoxathian derivatives, on the other hand, appear to be formed in low yield from many phenols.

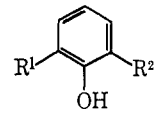
Further confirmation of the structures of the products from nonnitrated phenols was achieved through desulfurization. In general, the various thiomethoxymethyl derivatives and their homologs were found to be very readily desulfurized, complete reaction usually occurring in methanol within 30 min at room temperature in the presence of a large excess of a sponge nickel catalyst.[16] In this way all the *o*-thiomethoxymethylphenols were converted into known derivatives of *o*-cresol as shown in Table III. The benzoxathian derivatives were also readily desulfurized but gave rise to several different cleavage patterns as has been previously shown with other hemithioketals.[17] Thus desulfurization of **14** led exclusively to *o*-cresol while similar treatment of **25** gave only 1-methoxy-2-methylnaphthalene which was independently prepared by methylation of 2-methyl-1-naphthol[18] with dimethyl sulfate and alkali. Similar desulfurization of **15** led to roughly equal amounts of both types of cleavage and formation of a mixture of 2,6-dimethylphenol and 2,6-dimethylanisole. A summary of the various desulfurization reactions is given in Table III.

Under the usual reaction conditions 1-naphthol behaved quite abnormally and gave only a 12% yield of the expected *ortho*-alkylation product **24**. In

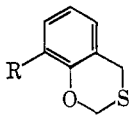
(14) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," John Wiley and Sons, Inc., New York, N. Y., 1962, p 130.
(15) G. J. Tiessens, *Rec. Trav. Chim.*, **50**, 112 (1931).
(16) Davidson Chemical Division of W. R. Grace and Co., Cincinnati, Ohio.
(17) (a) C. Djerassi, M. Shamma, and T. Y. Kan, *J. Am. Chem. Soc.*, **80**, 4723 (1958); (b) E. L. Eliel and S. Krishnamurthy, *J. Org. Chem.*, **30**, 848 (1965).
(18) T. L. Yarboro and C. Karr, *ibid.*, **24**, 1141 (1959).



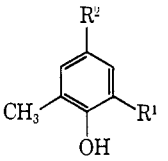
9, $R^1=H$; $R^2=CH_2SCH_3$
10, $R^1=CH_2SCH_3$; $R^2=H$
11, $R^1=R^2=CH_2SCH_3$



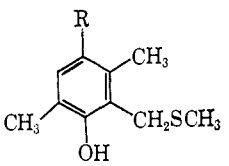
12, $R^1=H$; $R^2=CH_2SCH_3$
13, $R^1=R^2=CH_2SCH_3$



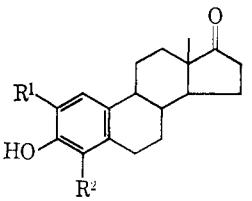
14, R=H
15, $R=CH_2SCH_3$
16, $R=CH_3$



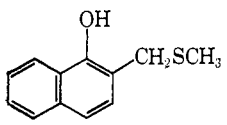
17, $R^1=CH_2SCH_3$; $R^2=H$
18, $R^1=R^2=CH_2SCH_3$
19, $R^1=CH_2-NC_6H_{11}$; $R^2=H$
$O=CNHC_6H_{11}$



20, R=H
21, $R=CH_3$



22, $R^1=CH_2SCH_3$; $R^2=H$
23, $R^1=H$; $R^2=CH_2SCH_3$



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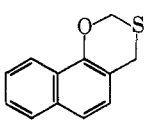

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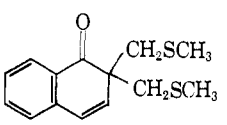

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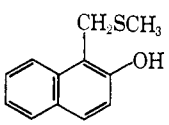

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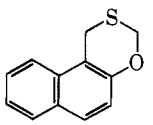

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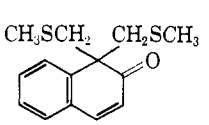
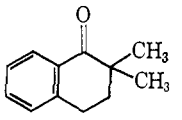


29

addition to a small yield of crystalline 4H-naphtho-[2,1-*e*]-1,3-oxathiin (**25**) the major isolated product (36%) was identified as 2,2-di(thiomethoxymethyl)-1-(2H)-naphthalenone (**26**). This compound was ketonic (ν_{max} 1680 in KBr) and contained two almost equivalent thiomethoxymethyl groups (6-proton singlet at 120 cps and two 2-proton singlets at 177 and 178 cps in the nmr). The styrenoid vinyl protons appeared as a pair of 1-proton doublets (J = 10 cps) at 370 and 407 cps. Desulfurization was accompanied by reduction of this double bond and gave a high yield of 2,2-dimethyltetralone[19] (**30**) that was indistinguishable from a sample prepared by exhaustive alkylation of 1-tetralone with methyl iodide and sodium hydride. Treatment of **26** with 10% concentrated hydrochloric acid in methanol led to its rapid conversion into 2-(thiomethoxymethyl)-1-naphthol (**24**) and a small amount of a phenolic compound still containing two thiomethoxymethyl groups (two 3-proton singlets at 116 and 120 cps, two 2-proton singlets at 233 and 242 cps, and five aromatic protons between 424 and 500 cps). This compound gave an intense red color on reaction with diazotized aniline and is considered to be 2,3-di(thiomethoxymethyl)-1-naphthol (**31a**). A similar acid-catalyzed rearrangement of 2,2-dimethyl-(2H)1-naphthalenone (**32**) to 2,3-dimethyl-1-naphthol (**31b**) has been reported by Marvell and Geiszler.[20]



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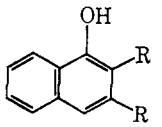
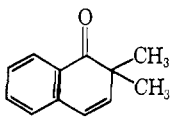


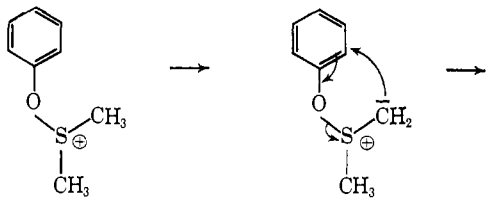
31a, $R=CH_2SCH_3$
b, $R=CH_3$



32

An almost identical array of product types (**27**–**29**) resulted from a similar reaction with 2-naphthol, the ketone 1,1-di(thiomethoxymethyl)-2-(1H)-naphthalenone (**29**) being the major product. The nmr spectra of all three products clearly confirmed the proposed structures.

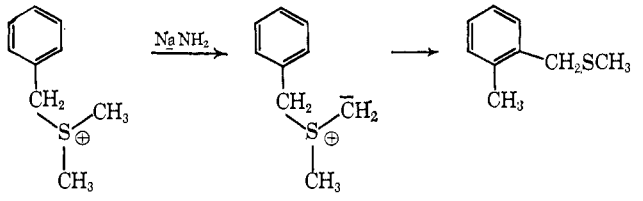
Reasonable mechanisms can be proposed for most of the reactions of phenols with sulfoxides and carbodiimides described above. Thus the *ortho*-alkylation reaction can be explained by nucleophilic attack of the phenolic oxygen upon the sulfonium isourea **1** leading to the phenoxysulfonium derivative **33**. Typical of sulfonium compounds[21] **33** will very readily lose a proton giving a d orbital stabilized ylid **34**, the carbanion of which can intramolecularly alkylate the available *ortho* positions giving the *o*-(thiomethoxymethyl)-phenol (**36**) by way of a transient cyclohexadienone (**35**).



33 **34**

35 **36**

If both *ortho* positions are free in the parent phenol, this sequence can be repeated leading to 2,6-di(thiomethoxymethyl)phenols such as **3** and **13**. This mechanism is closely related to that of the Sommelet reaction as applied to benzylsulfonium salts by Hauser, *et al.*[22] In the latter reaction treatment of benzyldimethylsulfonium salts (**37**) with sodamide in liquid ammonia gave 2-(thiomethoxymethyl)toluene (**39**) *via*



37 **38** **39**

(19) M. Mousseron, R. Jacquier, and H. Crlstol, *Bull. Soc. Chim. France*, 346 (1957).

(20) E. N. Marvell and A. O. Gelszler, *J. Am. Chem. Soc.*, 74, 1259 (1952).

(21) G. Cilento, *Chem. Rev.*, 60, 147 (1960).

(22) C. R. Hauser, S. W. Kantor, and W. R. Brasen, *J. Am. Chem. Soc.*, 75, 2260 (1953).

Table II. Spectral Properties of the Products Obtained

Compd	Ultraviolet spectra, λ_{max} mμ (ϵ_{max}) MeOH	MeOH + KOH	Nmr spectra, cps (integrated intensity and multiplicity[a]) $ArCH_2S$	SCH_3	OCH_2S	Other
3	317 (7,320)	422 (20,800)	231 (4, s)	123 (6, s)	...	484 (2, s)
4	318 (6,920)	410 (18,900)	224 (2, s)	122 (3, s)	...	421 (1, d), 477–488 (2, m)
5	324 (9,020)	414 (20,000)	226 (2, s)	125 (3, s)	...	60–120 (20, m), 269 (2, s), 480–490 (2, m), 770 (1, s)
6	309 (11,600)	Unchanged	...	136 (3, s)	314 (2, s)	421 (2, d), 492 (2, d)
7	309 (10,290)	Unchanged	224 (2, s)	124 (3, s), 138 (3, s)	318 (2, s)	421 (1, d), 489 (2, m)
8	309 (9,520)	Unchanged	237 (2, s)	...	320 (2, s)	418 (1, d), 480 (2, m)
9	280 (5,880), 353 (3,690)	263 (12,400), 425 (5,380)	228 (2, s)	125 (3, s)	...	405–493 (3, m), 658 (1, s)
10	257 (2,900), 320 (1,900)	Unchanged	...	135 (3, s)	316 (2, s)	412–470 (4, m)
11	250 (4,700)	Unchanged	231 (2, s)	124 (3, s), 134 (3, s)	312 (2, s)	414–470 (3, m)
12	278 (2,900)	297 (4,100)	222 (2, s)	114 (3, s)	...	405–430 (4, m)
13	283 (2,870)	307 (5,530)	224 (4, s)	117 (6, s)	...	404–430 (4, m)
14	273 (1,700), 281 (1,800)	Unchanged	227 (2, s)	...	308 (2, s)	406–440 (4, m)
15	227 (2,300)	Unchanged	216 (2, s), 227 (2, s)	118 (3, s)	312 (2, s)	406–435 (3, m)
16	273 (1,470), 282 (1,500)	Unchanged	233 (2, s)	...	317 (2, s)	130 (3, s), 405–430 (3, m)
17	276 (2,000)	240 (3,400), 283 (2,000), 297 (1,700)	222 (2, s)	114 (3, s)	...	136 (3, s), 395 (1, s), 405–440 (3, m)
18	285 (2,190)	256 (9,720), 305 (3,800)	214 (2, s), 225 (2, s)	118 (6, s)	...	134 (3, s), 390 (1, s), 413 (1, d; J = 1.5 cps), 422 (1, d; J = 1.5 cps)
19	278 (2,100)	242 (5,640), 294 (3,110)	...	...	...	133 (3, s), 265 (2, s), 626 (1, s)
20	282 (2,200)	285 (2,200), 303 (1,200)	225 (2, s)	117 (3, s)	...	130 (3, s), 135 (3, s), 369 (1, s), 397 (1, d; J = 8 cps), 415 (1, d; J = 8 cps)
21	287 (2,400)	287 (2,270, 312 (180)	230 (2, s)	121 (3, s)	...	130 (9, s), 346 (1, s), 410 (1, s)
22	288 (3,000)	293 (2,700)	225 (2, s)	121 (3, s)	...	399 (1, s), 422 (1, s), 54 (3, s)
23	287 (2,400)	292 (2,300)	230 (2, s)	126 (3, s)	...	403 (1, d; J = 8 cps), 429 (1, d; J = 8 cps), 54 (3, s)
24	214 (42,700), 237 (43,600), 295 (4,100)	219 (27,600), 255 (31,200), 343 (9,100)	227 (2, s)	110 (3, s)	...	418–501 (7, m)
25	216 (53,800), 235 (38,300), 291 (4,720), 309 (3,150), 323 (2,550)	Unchanged	233 (2, s)	...	319 (2, s)	415–497 (6, m)
26	234 (32,800)	Unchanged	177 (2, s), 178 (2, s)	120 (6, s)	...	370 (1, d; J = 10 cps), 407 (1, d; J = 10 cps), 426–490 (4, m)
27	231 (62,400), 281 (5,200), 293 (4,700), 338 (3,200)	243 (56,400), 286 (6,000), 357 (4,100)	250 (2, s)	119 (3, s)	...	370–485 (7, m)
28	232 (75,000), 266 (4,300), 276 (5,050), 288 (3,850), 316 (1,750), 332 (2,250)	Unchanged	244 (2, s)	...	311 (2, s)	422 (1, d; J = 9 cps), 446 (1, d; J = 9 cps), 435–470 (4, m)
29	235 (9,300), 310 (6,500)	Unchanged	188 (2, s), 190 (2, s)	109 (6, s)	...	379 (1, d; J = 10 cps), 446 (1, d; J = 10 cps), 445–465 (4, m)

[a] s, d, and m refer to singlet, doublet, and multiplet, respectively.

Table III. Products from Desulfurization of Various Compounds

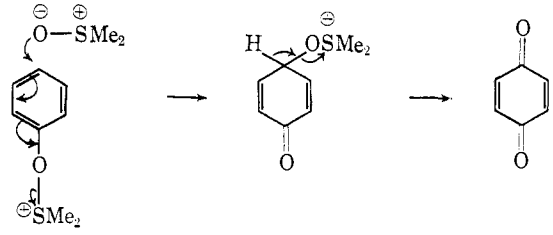
Starting material	Product	Characterization[a]
2-(TMM)phenol (**12**)	*o*-Cresol	Tlc, infrared
2,6-Di(TMM) phenol (**13**)	2,6-Dimethylphenol	Mp 44–46°, tlc, infrared
2-Methyl-6-(TMM)phenol (**17**)	2,6-Dimethylphenol	Mp 45–46°, tlc, infrared
3,6-Dimethyl-2-(TMM)phenol (**20**)	2,3,6-Trimethylphenol	Mp 60–62°,[b] nmr
3,4,6-Trimethyl-2-(TMM)phenol (**21**)	2,3,4,6-Tetramethylphenol	Mp 79–80°,[c] nmr
2-(TMM)-1-naphthol (**24**)	2-Methyl-1-naphthol	Mp 61–63°, tlc, infrared
1,3-Benzoxathian (**14**)	*o*-Cresol	Tlc, infrared
8-(TMM)-1,3-benzoxathian (**15**)	2,6-Dimethylphenol	Mp 44–46°, tlc, infrared
	2,6-Dimethylanisole	Tlc, nmr, infrared[d]
4H-Naphtho[2,1-*d*]-1,3-oxathiin (**28**)	1-Methoxy-2-methylnaphthalene	Tlc, nmr, infrared[d]

[a] Identifications were made by comparisons with known compounds using thin layer chromatography (tlc), infrared, and nuclear magnetic resonance (nmr) spectroscopy. [b] W. C. Sears and L. J. Kitchen, *J. Am. Chem. Soc.*, **71**, 4110 (1949), report mp 61.8–62.8°. [c] A. W. Kofmann, *Ber.*, **17**, 1916 (1884), reports mp 80°. [d] Identical with an authentic sample prepared by methylation of the corresponding phenol with dimethyl sulfate.

the sulfur ylid **38**. The mildness of the present reaction conditions is doubtless a consequence of an increased lability of the methyl protons brought about by replacement of the benzyl group in **38** by a phenoxy group.

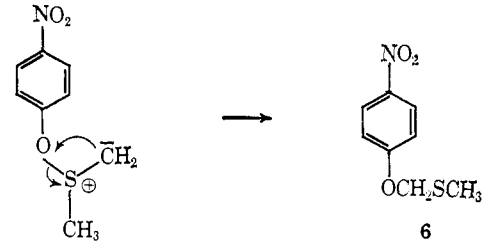
The intervention of the phenolic group in this reaction is indicated by the lack of any observable products, other than those from DCC and the acid alone, when phenol is replaced by anisole. The intramolecular

nature of the reaction is also strongly suggested by the lack of *para*-alkylated products from phenols containing both available *ortho* and *para* positions. Indeed, only in one case have we isolated a product alkylated in both *ortho* and *para* positions, a 4% yield of 2-methyl-4,6-di(thiomethoxymethyl)phenol (**18**) being isolated from the same unusually vigorous reaction previously mentioned as leading to the urea-containing product **19**. In no case has selective *para* alkylation been observed in the presence of a free *ortho* position. It is, however, to be noted from Table I that in most reactions the total isolated yields of the various products amounted to only 50–70%. The actual yields were doubtless considerably higher in most cases than those reported in Table I, since we have reported only isolated yields of chromatographically homogeneous products and have not attempted to optimize reaction and isolation conditions. A primary cause of the low yields, however, lies in the formation of a variety of difficultly separable and unstable polar by-products. The yellow color and the ready air oxidation of some of these products (*e.g.*, the slow formation of purple colors during chromatography of the products from α-naphthol) suggests the possible presence of quinones among these by-products. The formation of quinones could be explained by *ortho* or *para* attack of DMSO upon the phenoxysulfonium intermediate **33** followed by proton abstraction and collapse as in the oxidation of alcohols.[1]



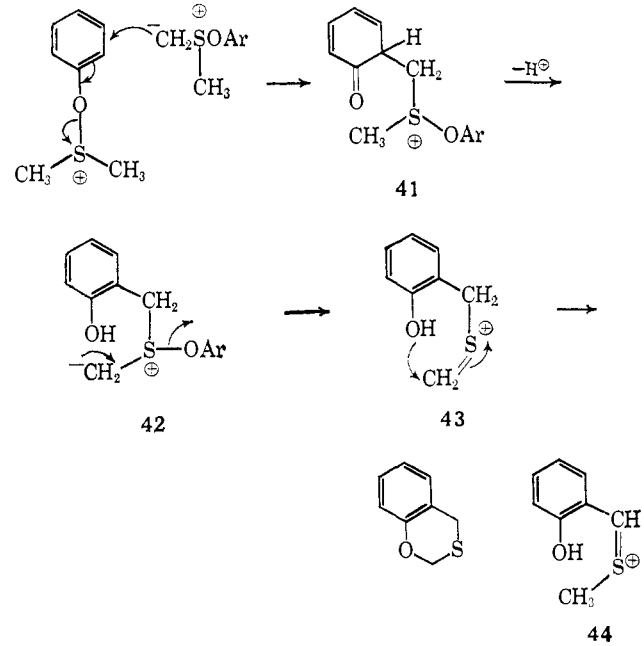
While we have no direct evidence of quinone formation from simple phenols,[23] the pronounced odor of dimethyl sulfide suggests the presence of an oxidation–reduction system. The reaction of hydroquinone with DMSO, DCC, and anhydrous phosphoric acid led to quantitative conversion to benzoquinone as judged by tlc and isolation of a crystalline product. The other by-products, which are observed as a slow-moving streak on tlc, as yet remain unidentified. By repeated chromatography several products are apparent, but as yet it has been impossible to obtain pure materials. The presence of unsaturated ketones containing thiomethoxymethyl groups is suggested by ultraviolet, infrared, and nmr spectroscopy, and further rearrangement into dienones (λ_{max} 308 mμ, ν_{max} 1640 cm^{-1}) occurs upon attempted short-path distillation. Characterization of these materials must await further study.

The formation of aryl thiomethoxymethyl ethers (*e.g.*, **6**, **7**, **10**, **11**) can be explained by a mechanism similar to that of the Stevens rearrangement[24] which has also been applied to sulfonium compounds.[25] Thus attack by the carbanion of the sulfur ylid **40** upon the phenolic oxygen rather than upon the aromatic ring leads directly to the thiomethoxymethyl ether **6**. Such a mechanism predicts the observed formation of ethers only from more acidic phenols in which the oxygen atom has greater positive character.



40 **6**

A satisfactory mechanism for the formation of benzoxathian derivatives (*e.g.*, **8**, **14**, **15**, **16**, **25**, **28**) is less apparent. A pathway involving cyclization of a preformed *o*-thiomethoxymethylphenol or its O-dimethylsulfonium derivative seems unlikely since such a route would presumably require proton abstraction from the unactivated terminal methyl group of the thiomethoxymethyl moiety. In support of this objection, treatment of both 2-nitro-6-(thiomethoxymethyl)-phenol (**9**) and 2,6-di(thiomethoxymethyl)phenol (**13**) with DMSO, DCC, and anhydrous phosphoric acid under the usual conditions failed to lead to any detectable cyclic products (*e.g.*, **15**). Appreciable amounts of the starting materials did disappear, however, with formation of unidentified, polar products similar to the by-products discussed earlier. In view of the low yields of benzoxathian derivatives formed from many phenols it is attractive to suggest that a bimolecular reaction involving two molecules of phenoxysulfonium ylid might be involved as follows.[26]



41 **42** **43** **44**

The advantage of such a scheme lies in retention of a positively charged sulfur atom in the substituted side chain of **41**, thus permitting ylid formation (**42**) and formation of the reactive unsaturated sulfonium deriv-

(23) In a forthcoming paper[5] we provide direct evidence for the oxidation of durophenol to duroquinone in a related reaction.

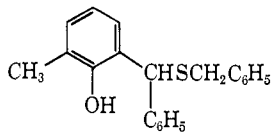
(24) H. E. Zimmerman in "Molecular Rearrangements," P. deMayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 378.

(25) T. Thompson and T. S. Stevens, *J. Chem. Soc.*, 69 (1932).

(26) The concept of a bimolecular mechanism to explain benzoxathian formation was originally suggested to us by Dr. R. A. Olofson of Pennsylvania State University and has been briefly referred to in ref 7.

ative **43** by displacement of phenolate anion. A potential disadvantage is the presumed greater ease of removal of one of the benzylic protons from **41**[27] leading to the isomeric ion (**44**) which could be a precursor of polymeric products rather than benzoxathians. As will be seen in a forthcoming paper,[5] the formation of benzoxathians becomes a major reaction with phenols containing suitable leaving groups such as chlorine atoms in the *ortho* positions.

Sulfoxides other than DMSO can also be used in these reactions. Thus *o*-cresol has been treated with dibenzyl sulfoxide and tetramethylene sulfoxide in the presence of DCC and anhydrous phosphoric acid leading to the *ortho*-alkylated products 2-(α-thiobenzyloxybenzyl)-6-methylphenol (**45**) and 2-methyl-6-(2-tetrahydrothienyl)phenol (**46**) in yields of 26 and 45%, respectively. In addition a 9% yield of the tricyclic derivative 2,5-epithio-2,3,4,5-tetrahydro-9-methyl-1-benzoxepin (**47**) was obtained from the latter reaction. Desulfurization of **45** and **46** led smoothly to the known 2-benzyl-6-methylphenol of mp 49–50°[28] and 2-*n*-butyl-6-methylphenol.[29] Phenylmethyl sulfoxide was much less reactive than its purely aliphatic analogs and gave only a low yield of 2-methyl-6-(thiophenoxymethyl)phenol (**48**) which upon desulfurization led to crystalline 2,6-dimethylphenol.



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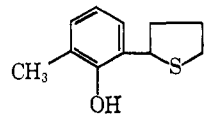

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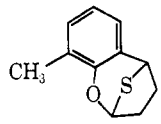

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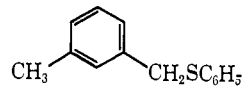

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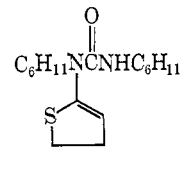
Several somewhat curious features of reactions involving tetramethylene sulfoxide were also noted. Firstly, from the reaction with *o*-cresol reported above, and from several other reactions with this sulfoxide to be reported later, a common, ultraviolet-absorbing, crystalline compound was isolated in modest yield. Elemental analysis, mass spectrometry, and nmr spectroscopy all indicate that this compound is an unsaturated adduct of tetramethylene sulfoxide and DCC probably having the structure **49** although the exact position of the sulfur atom in the dihydrothiophene ring is uncertain.



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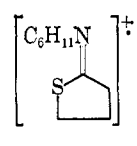

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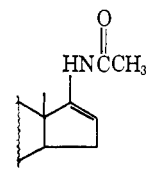

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In support of this structure mass spectrometry showed an intense (relative abundance 100%) molecular ion at *m/e* 308 and intense peaks, both supported by the presence of metastable peaks, at *m/e* 275 (M − SH) and at 262 (M − CH_2S). In addition an intense peak (relative abundance 98%) at *m/e* 183 corresponding to the fragment **50** was present which supports the indicated position of the double bond since hydrogen transfer from the urea NH would be readily accommodated *via* a six-membered cyclic transition state. The location of the double bond was also suggested by the ultraviolet spectrum with λ_{max} 242 mμ (ε 8900) which may be compared with the partial system (**51**)[30] which shows λ_{max} 240 mμ (ε 6600). While a facile mechanism for the formation of the saturated analog of **49** can be conceived *via* intramolecular rearrangement of a sulfur ylid arising from the initial tetramethylene sulfoxide–DDC adduct, the genesis of the unsaturated compound remains obscure. Also, quite unlike the results in DMSO, reaction of *p*-nitrophenol with tetramethylene sulfoxide, DCC, and anhydrous phosphoric acid resulted in almost complete conversion to the ether (**52**) which was unequivocally characterized by its nmr spectrum and analysis (see Experimental Section).

The reaction of thiophenol[31] with DMSO, DCC, and either anhydrous phosphoric or dichloroacetic acids under the usual conditions led to the essentially quantitative formation of diphenyl disulfide which was isolated in crystalline form in 64% yield. A similar, rapid reaction occurred with *p*-nitrothiophenol giving a high yield of di(4-nitrophenyl) disulfide which was isolated, crystalline, in 68% yield. Several minor byproducts were also detected including a low yield of a compound identified as *p*-nitrophenyl methyl disulfide by elemental analysis, nmr spectroscopy, and reduction to *p*-nitrothiophenol by sodium borohydride. At least in part these oxidations are brought about by DMSO alone,[32] and we have observed a dramatic acid catalysis of such reactions. Thus while both thiophenol and *p*-nitrothiophenol are only slowly oxidized to the disulfides in DMSO alone, complete reaction requiring at least 6 hr at room temperature, addition of 0.5 equiv of anhydrous phosphoric acid leads to almost instantaneous formation of the disulfide which crystallizes directly from the reaction mixture. Such an effect of added acid is consistent with the ionic mechanism proposed by Wallace.[32]

In contrast with these results, the reaction of *p*-nitrothiophenol with DCC in benzene alone leads to the very rapid and quantitative formation of S-*p*-nitrophenyl-N,N′-dicyclohexylisothiourea (**53**).[33]

Several other groups have recently described the reactions of phenols and other aromatic compounds

(27) I. R. Rothberg and E. R. Thornton, *J. Am. Chem. Soc.*, **86**, 3296 (1964), have demonstrated a greater rate of exchange of benzylic protons relative to methyl protons in *p*-nitrobenzyldimethylsulfonium salts.

(28) P. Shorigin, *Ber.*, **58B**, 2028 (1925), reports mp 51–52°.

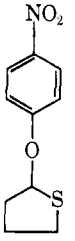
(29) P. Demerseman, J. P. Lechartier, R. Reynaud, A. Cheutin, R. Royer, and P. Rumpf, *Bull. Soc. Chim. France*, 2259 (1963).

(30) G. Rosenkranz, O. Mancera, F. Sondheimer, and C. Djerassi *J. Org. Chem.*, **21**, 520 (1956).

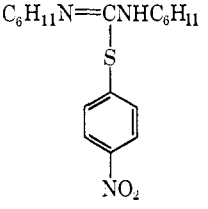
(31) We previously reported[3b] that, to our surprise, aliphatic thiols did not react with the DMSO–DCC reagent. Dr. J. B. Jones of the University of Toronto has recently informed us that simple mercaptans are, indeed, oxidized to the corresponding disulfides. Our error was due to the unexpected identical thin-layer chromatographic mobilities of the thiols and disulfides studied, sufficient unreacted thiol remaining to give a positive nitroprusside test. More recent analysis of such reactions by gas–liquid partition chromatography has confirmed the formation of disulfides. No such oxidation occurs in the absence of DCC. We are also grateful to Dr. Jones for communicating his results to us prior to publication.

(32) T. J. Wallace, *J. Am. Chem. Soc.*, **86**, 2018 (1964).

(33) The formation of isothiourea ethers upon heating thiophenols with aromatic carbodiimides has been known for many years: *e.g.*, M. Busch, G. Blume, and E. Prings, *J. Prakt. Chem.*, 79, 513 (1909).



52



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with sulfoxides in the presence of strong acids.[34] These reactions, however, lead primarily to sulfonium derivatives which can be thermally dealkylated to give, *e.g.*, aryl methyl sulfides. These reactions appear to bear no similarity to those described in this paper.

In a forthcoming paper[5] we describe studies on the reactions of DMSO and DCC on phenols substituted at both *ortho* positions. As will be seen, these reactions lead to a number of interesting and mechanistically different rearrangements.

Experimental Section

The phenols used in this work were all commerical products which were repurified, if necessary, in order to obtain homogeneous compounds. Tlc was carried out on 0.25-mm layers of Merck silica gel GF and the products were visualized by ultraviolet absorption or by spraying with a 5% solution of ammonium molybdate in 10% sulfuric acid followed by brief heating at 150°. Preparative tlc was done on 1.3-mm layers of Merck silica gel HF and column chromatography on Merck silica with 0.05–0.2 mm particles. Micro-short-path distillations were done under high vacuum using a "Kugelrohr" apparatus consisting of a series of bulbs blown in a Pyrex tube. The distillation temperatures recorded using this technique are those of the air bath. Nmr spectra were obtained using solutions in deuteriochloroform and a Varian A-60 spectrometer, and mass spectra were determined using an Atlas CH-4 spectrometer with a direct inlet system. Ultraviolet spectra were determined in methanol or in 0.01 *N* methanolic potassium hydroxide on a Cary Model 14 spectrophotometer, and infrared spectra were obtained from potassium bromide pellets or liquid films on a Perkin-Elmer Model 237 instrument. Melting points were determined on a calibrated hot-stage microscope. Dimethyl sulfoxide was dried by distillation *in vacuo* and storage over Linde molecular sieve Type 4A. Instrumental analyses were performed by the staff of the analytical laboratory of Syntex Research. We are particularly grateful to Mr. J. Murphy and Dr. T. Toube for their assistance with nmr and mass spectrometry. Elemental analyses were obtained from Dr. A. Bernhardt, Mulheim, Germany.

General Procedure with *p*-Nitrophenol. *p*-Nitrophenol (3.5 g, 25 mmoles) and DCC (15.5 g, 75 mmoles) were dissolved in anhydrous DMSO (10 ml) and benzene (10 ml). Anhydrous crystalline orthophosphoric acid[35] (1.2 g, 12 mmoles) was added; after a few minutes a vigorous exothermic reaction ensued requiring the mixture to be temporarily cooled in ice. After 1 hr at room temperature, ethyl acetate (100 ml) was added and dicyclohexylurea (13.2 g) removed by filtration. The ethyl acetate solution was extracted three times with 100-ml portions of water, dried over sodium sulfate, and evaporated leaving 8.8 g of a yellowish oil. This was dissolved in benzene (100 ml) and extracted repeatedly with 0.25 *N* sodium hydroxide until the extracts were essentially colorless. The aqueous extracts were washed with benzene, adjusted to pH 3.5 with phosphoric acid, and extracted three times with ethyl acetate. The extracts were washed with water, dried over sodium sulfate, and evaporated leaving 3.65 g of a semicrystalline mixture of phenolic products. The original, nonalkali-extractable fractions were washed with water, dried, and evaporated leaving 4.1 g of mixed nonphenolic products and dicyclohexylurea as an oil. The phenolic fraction was dissolved in acetone (10 ml) and cooled giving 0.72 g (7%) of 1,3-dicyclohexyl-1-(2-hydroxy-5-nitro-3-thiomethoxymethyl)benzylurea (**5**) as white crystals of mp 148–149°. Recrystallization from ether raised the melting point to 149–150°. (See Tables I and II for analytical and spectral data.)

The remainder of the phenolic materials was applied in benzene to a column containing 150 g of silicic acid. Elution with benzene gave traces of **5** followed by 705 mg (11%) of chromatographically homogeneous 4-nitro-2,6-di(thiomethoxymethyl)phenol (**3**) which immediately crystallized. Recrystallization from benzene–petroleum ether gave the analytical material of mp 76.5–77.5°. Further elution with benzene gave 1.30 g (26%) of crystalline 4-nitro-2-thiomethoxymethylphenol (**4**) which was recrystallized from benzene as plates of mp 127.5–128°. Elution with methylene chloride then gave 483 mg (14%) of unreacted *p*-nitrophenol.

The nonphenolic materials were dissolved in benzene–hexane (1:1) and applied to 150 g of silicic acid. Elution with benzene–hexane (2:1) gave 405 mg of a roughly equal mixture of two compounds that were separated with difficulty by crystallization from methanol into 4-nitro-O-(thiomethoxymethyl)phenol (**6**) of mp 50–51° (see below for an independent synthesis) and 6-nitro-1,3-benzoxathian (**8**) of mp 135–136°. Continued elution with the same solvent gave 906 mg (14%) of crystalline O-(thiomethoxymethyl)-4-nitro-2-thiomethoxymethylphenol (**7**) which could be recrystallized from methanol in the cold giving mp 61–62°.

Elution with methylene chloride gave a further 718 mg (7%, total yield 14%) of **5** of mp 148–149°.

4-Nitro-O-(thiomethoxymethyl)phenol (6). Anhydrous sodium *p*-nitrophenolate (3 g) was suspended in benzene (50 ml) and refluxed for 1 hr with chloromethyl methyl sulfide (7 ml). The benzene solution was extracted several times with 0.25 *M* sodium hydroxide, dried, and chromatographed on 100 g of silicic acid with benzene giving 1.60 g (43%) of pure **6** which was recrystallized from methanol (mp 50–51°) and was identical with the product described above.

Reaction with *o*-Nitrophenol. *o*-Nitrophenol (1.39 g, 10 mmoles and DCC (6 g, 30 mmoles) were treated in DMSO (5 ml) and benzene (5 ml) in the presence of anhydrous phosphoric acid (5 mmoles). After 2 hr, the phenolic and nonphenolic products were separated by alkali extraction as above and chromatographed on silicic acid. Elution of the phenolic products with benzene–hexane (1:1) gave 0.73 g (38%) of 2-nitro-6-thiomethoxymethylphenol (**9**) and some unreacted *o*-nitrophenol (0.27 g, 19%). Chromatography of the nonphenolic fraction with benzene–hexane (1:1) gave 200 mg (10%) of 2-nitro-O-(thiomethoxymethyl)phenol (**10**) which was distilled in a short-path apparatus with a bath temperature of 80° (10^{-3} mm) and melted below room temperature. Continued elution gave 174 mg (7%) of 2-nitro-O,6-di(thiomethoxymethyl)phenol (**11**) which gave an analytical sample upon distillation at 100° (10^{-4} mm).

2-Nitro-O-(thiomethoxymethyl)phenol (10). *o*-Nitrophenol (1.0 g, 7.2 mmoles) was dissolved in methanol containing potassium hydroxide (0.41 g, 7.2 mmoles). The mixture was taken to dryness and then refluxed in benzene (50 ml) with chloromethyl methyl sulfide (5 ml) for 1.5 hr. The mixture was then extracted with alkali, dried, and chromatographed on silicic acid with benzene–hexane (1:1) giving 425 mg (30%) of **10** with an infrared spectrum identical with that of **10** from the DMSO–DCC reaction above.

2-Nitro-O,6-di(thiomethoxymethyl)phenol (11). The potassium salt of 2-nitro-6-(thiomethoxymethyl)phenol was reacted with chloromethyl methyl sulfide in benzene as above. After alkaline extraction and chromatography on silica with benzene a 27% yield of **11** was isolated and shown to be identical with the product from the DMSO–DCC reaction.

Reaction with Phenol. Phenol (4.7 g, 50 mmoles) reacted exothermically in DMSO (25 ml) and benzene (50 ml) with DCC (30 g, 150 mmoles) and anhydrous phosphoric acid (50 mmoles). The phenolic and nonphenolic products were separated by alkali extraction and chromatographed on silicic acid columns with benzene. The phenolic fractions gave 1.65 g (16%)[36] of 2,6-di(thiomethoxymethyl)phenol (**13**) as a colorless oil which distilled in a short-path apparatus at 80° (10^{-3} mm), and 2.03 g (27%) of 2-(thiomethoxymethyl)phenol (**12**) which distilled at 70° (10^{-2} mm). Both **12** and **13** were quantitatively desulfurized (as shown by tlc) upon stirring in methanol at room temperature for 30 min in the presence of a tenfold weight of Davidson sponge nickel catalyst. After filtration through Celite the solvent was evaporated giving *o*-cresol

(34) (a) E. Goethals and P. De Radzitzky, *Bull. Soc. Chim. Belges*, 73, 546 (1964); (b) K. Hirose and S. Ukai, *Yakugaku Zasshi*, 86, 187 (1966); (c) R. Oda and Y. Hayashi, *Nippon Kagaku Zasshi*, 87, 291 (1966).

(35) Fluka A. G. obtained through the International Chemical and Nuclear Corp., City of Industry, Calif.

(36) Part of this product remained in the nonphenolic fractions and was separately isolated. The yield reported is the sum of these two portions.

(identified by infrared spectra and tlc) and 2,6-dimethylphenol of mp 44–46° (an authentic sample had the same melting point and infrared spectra), respectively.

The nonphenolic fractions were eluted from the silica column with benzene and gave 370 mg (4%) of 8-thiomethoxymethyl-1,3-benzoxathian (**15**) which distilled as a colorless oil at 80° (10^{-3} mm). Desulfurization of this material as above gave a roughly equal mixture of 2,6-dimethylphenol (mp 44–46°) and 2,6-dimethylanisole (identical infrared and nmr spectra with an authentic sample prepared by methylation of 2,6-dimethylphenol with dimethyl sulfate). Further elution gave 291 mg (4%) of 1,3-benzoxathian (**14**) which distilled at 80° (10^{-2} mm). Desulfurization as above gave *o*-cresol and a trace of 2-methylanisole both of which showed identical infrared spectra and tlc behavior with authentic samples.

Reactions with *o*-Cresol, 2,5-Dimethylphenol, and 2,4,5-Trimethylphenol. In each case the phenol (25 mmoles) was treated overnight at room temperature in DMSO (10 ml) and benzene (20 ml) with DCC (15.4 g, 75 mmoles) and anhydrous phosphoric acid (12.5 mmoles). Ether (100 ml) was added followed by a solution of oxalic acid (9.5 g) in methanol. After 30 min the dicylohexylurea was removed by filtration, and the solution was extracted with 5% sodium bicarbonate and then water. The phenolic compounds were then extracted with 0.25 *N* sodium hydroxide, acidified, extracted into ether, and chromatographed on silicic acid using benzene–hexane mixtures. From *o*-cresol a single phenolic product (see Table I, footnote *c*), 2-methyl-6-(thiomethoxymethyl)-phenol (**17**), was obtained as a chromatographically homogeneous oil that could be distilled at 70° (10^{-3} mm) in 28% yield. Desulfurization gave crystalline 2,6-dimethylphenol of mp 45–46°. From the nonphenolic products a 7% yield of 8-methyl-1,3-benzoxathian (**16**) was readily isolated in addition to several rather polar, ketonic products that remain unidentified.

From 2,5-dimethylphenol a 35% yield of pure 3,6-dimethyl-2-(thiomethoxymethyl)phenol (**20**) was obtained and distilled at 80° (10^{-3} mm). Desulfurization gave 2,3,6-trimethylphenol of mp 60–62° (lit. mp 61.8–62.8°, see Table III).

From 2,4,5-trimethylphenol[37] a 23% yield of crystalline 2,4,5-trimethyl-6-(thiomethoxymethyl)phenol (**21**) was obtained from hexane with mp 51–53°. Desulfurization gave crystalline 2,3,4,6-tetramethylphenol of mp 79–80° (lit. mp 80°, see Table III).

Reaction with 1-Naphthol. 1-Naphthol (3.6 g, 25 mmoles) was treated at room temperature overnight with DMSO (10 ml), benzene (10 ml), DCC (15.5 g, 75 mmoles), and anhydrous phosphoric acid (1.2 g, 12 mmoles). The phenolic and nonphenolic fractions were separated by alkali extraction and separately chromatographed on columns of silicic acid with benzene. The phenolic fraction contained a little unreacted 1-naphthol and a less polar compound (612 mg, 12%) that distilled at 100° (10^{-3} mm) and was identified as 2-thiomethoxymethyl-1-naphthol (**24**). Desulfurization in methanol gave crystalline 2-methyl-1-naphthol[18] of mp 61–63° from hexane. The nonphenolic fractions gave two crystalline compounds. The first, which was identified as 2,2-di-(thiomethoxymethyl)-1(2H)-naphthalenone (**26**) (2.38 g, 36%), had mp 50–51° from methanol and ν_{max}^{KBr} 1680 cm^{-1}. Treatment with 10% concentrated hydrochloric acid in methanol for 1 hr at 37° gave two phenolic products in a ratio of 9:1 which were separated by preparative tlc using benzene. The main product was indistinguishable from **24** while the second was characterized by its nmr spectrum (see text) as **31a** but was not obtained in crystalline form. Its ultraviolet spectrum showed λ_{max} 216 mμ (ε 49,500), 238 (41,700), and 304 (5800), very similar to that of **24** (see Table II). Desulfurization of **26** in methanol gave 2,2-dimethyltetralone (**30**) which was identical in its infrared and nmr spectra with an authentic sample prepared below.

The minor nonphenolic compound (161 mg, 3%) crystallized from methanol with mp 60–62° and was shown to be 4H-naphtho-[2,1-*e*]-1,3-oxathiin (**25**) by its nmr spectrum (Table II) and elemental analysis (Table I). Desulfurization in methanol gave primarily one compound that was purified by preparative tlc and found to be identical (infrared, nmr) with a sample of 1-methoxy-2-methylnaphthalene prepared below.

2,2-Dimethyltetralone (30).[19] Tetralone (5 g, 35 mmoles) and sodium hydride (10 g) were refluxed together in methyl iodide (25 ml) for 7 days until tlc using benzene showed a single spot moving faster than tetralone. After shorter reaction periods an intermediate spot, presumably monomethyltetralone, was apparent. The mixture was then cooled, filtered, and partitioned between water and ether. The ether layer was distilled at 145° (20 mm) giving 5.2 g (85%) of analytically pure **30** as a colorless oil with $\nu_{max}^{CHCl_3}$ 1680 cm^{-1}; λ_{max}^{MeOH} 246 mμ (ε 11,100) and 290 mμ (ε 1600). The nmr spectrum (cps) showed two methyl groups as a singlet at 70, two methylene groups as triplets centered at 114 and 176, and four aromatic protons between 425 and 490.

Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.92; H, 7.96.

1-Methoxy-2-methylnaphthalene. 2-Methyl-1-naphthol (200 mg obtained by desulfurization of **24**) was shaken at room temperature with 1 *N* sodium hydroxide (4 ml) and dimethyl sulfate (4 ml) for 10 min and then refluxed for 1 hr. The mixture was then partitioned between ether and dilute sodium hydroxide, and the ether layer was purified by preparative tlc using benzene. Elution of the major band followed by distillation at 70° (10^{-2} mm) gave 1-methoxy-2-methylnaphthalene as a colorless oil with three proton nmr singlets at 148 ($ArCH_3$) and 233 cps (OMe).

Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.59; H, 7.12.

Reaction with 2-Naphthol. 2-Naphthol (3.6 g, 25 mmoles) was treated overnight with DCC (75 mmoles) and anhydrous phosphoric acid (12 mmoles) in a mixture of DMSO (20 ml) and benzene (10 ml). Following addition of ether and extraction of the DMSO, the phenolic and nonphenolic fractions were separated by alkali extraction. Chromatography of the phenolic components (1.13 g) on 100 g of silicic acid using benzene gave 0.74 g (15%) of chromatographically homogeneous 1-(thiomethoxymethyl)-2-naphthol (**27**) which was distilled at 100° (10^{-3} mm) for analysis (see Tables I and II). Chromatography of the nonphenolic materials (6.1 g) on 400 g of silicic acid with benzene gave 145 mg (3%) of crystalline 1H-naphtho[1,2-*e*][1,3]oxathiin (**28**) which was recrystallized from methanol and had mp 62–63°. Continued elution gave 2.40 g (36%) of homogeneous 1,1-di(thiomethoxymethyl)-2(1H)-naphthalenone (**29**) which did not crystallize but was analytically pure.

Reaction of *o*-Cresol with Dibenzyl Sulfoxide. *o*-Cresol (1.08 g, 10 mmoles) was treated overnight at room temperature with dibenzyl sulfoxide[38] (2.3 g, 10 mmoles), DCC (6.2 g, 30 mmoles), and anhydrous phosphoric acid (5 mmoles) in ether (10 ml). After filtration of dicyclohexylurea and extraction with water the products were chromatographed on a column of silicic acid with benzene–hexane (1:1) giving 0.83 g (26%) of 2-(α-thiobenzyloxybenzyl)-6-methylphenol (**45**) as a viscous syrup which could be distilled at 130° (10^{-3} mm). It had λ_{max}^{MeOH} 278 mμ (ε 2800) and $\lambda_{max}^{OH^-}$ 283 mμ (ε 2300) and 306 mμ (ε 2300). Its nmr spectrum (cps) showed a methyl singlet at 134, a 2-proton singlet (SCH_2Ar) at 214, a 1-proton singlet (Ar_2CHS) at 307, a phenolic proton at 409, and 13 aromatic protons between 400 and 450.

Anal. Calcd for $C_{21}H_{20}OS$: C, 78.72; H, 6.29; S, 9.98. Found: C, 78.97; H, 6.43; S, 10.08.

2-Benzyl-6-methylphenol. 2-(α-Thiobenzyloxybenzyl)-6-methylphenol (380 mg, 1.2 mmoles) was stirred with Davidson sponge nickel[16] (3 g) in methanol (10 ml) for 30 min at room temperature and then filtered through Celite. Evaporation of the solvent left a chromatographically homogeneous oil that was distilled at 100° (10^{-3} mm) giving crystalline 2-benzyl-6-methylphenol of mp 49–50°; λ_{max}^{MeOH} 274 mμ (ε 1900); $\lambda_{max}^{OH^-}$ 279 mμ (ε 2000) and 293 mμ (ε 1100). It showed nmr singlets (cps) at 128 ($ArCH_3$), 235 ($ArCH_2Ar$), 273 (phenol), five aromatic benzyl protons at 430, and three aromatic protons at 410–420.

Anal. Calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 85.04; H, 7.21.

Reaction of *o*-Cresol with Tetramethylene Sulfoxide. *o*-Cresol (2.7 g, 25 mmoles) was dissolved in tetramethylene sulfoxide (15 ml) and benzene (20 ml) containing DCC (15.5 g, 75 mmoles) and anhydrous phosphoric acid (12 mmoles). After storage overnight the mixture was diluted with benzene and treated with oxalic acid (9 g) to destroy excess DCC. After filtration of the dicyclohexylurea and several extractions with water the benzene solution was chromatographed on silicic acid with benzene giving 2-methyl-6-(2-tetrahydrothienyl)phenol (**46**, 2.27 g, 45%) as a colorless oil distilling at 80° (10^{-3} mm); λ_{max}^{MeOH} 278 mμ (ε 2100); $\lambda_{max}^{OH^-}$ 283 mμ (ε 2400) and 297 mμ (ε 2000). The nmr spectrum (cps) showed a singlet at 135 ($ArCH_3$), a 4-proton multiplet at 120–150, a 2-proton multiplet centered at 188 (CH_2S), a 1-proton triplet at 278 (ArCHS),

(37) In the case of 2,4,5-trimethylphenol, dichloroacetic acid was used in place of phosphoric acid.

(38) Aldrich Chemical Co., Milwaukee, Wis. In view of the difficulty of separating excess sulfoxide only 1 equiv was used.

a phenolic proton at 443, and three aromatic protons between 400 and 440.

Anal. Calcd for $C_{11}H_{14}OS$: C, 68.02; H, 7.27; S, 16.48. Found: C, 67.97; H, 7.30; S, 16.23.

Prior to this peak 460 mg (9%) of 2,5-epithio-2,3,4,5-tetrahydro-9-methyl-1-benzoxepin (**47**) was eluted in pure form and distilled at 80° (10^{-3} mm); λ_{max}^{MeOH} 275 mμ (ε 1800) and 285 mμ (ε 2000) and unchanged in alkali. The nmr spectrum (cps) showed a 3-proton singlet ($ArCH_3$) at 128, two methylene groups as a multiplet centered at 143, a broad 1-proton singlet (ArCHS) at 261, a broad 1-proton signal (OCHS) at 376, and three aromatic protons between 405 and 430.

Anal. Calcd for $C_{11}H_{12}OS$: C, 68.73; H, 6.29; S, 6.64. Found: C, 68.63; H, 6.25; S, 16.84.

Continued elution with chloroform gave 0.70 g of an impure, quite strongly ultraviolet-absorbing product that was further purified by preparative tlc using chloroform–ethyl acetate (19:1). This gave 400 mg (4%) of the crystalline urea adduct (**49**) which could be recrystallized from methanol at −15° and had mp 127–128°; λ_{max}^{MeOH} 242 mμ, (ε 8900); ν_{max}^{KBr} 3315, 1635, and 1520 cm^{-1}.

Anal. Calcd for $C_{17}H_{28}N_2OS$: C, 66.20; H, 9.19; N, 9.08; O, 5.19; S, 10.39; mol wt, 308. Found: C, 66.18; H, 9.05; N, 9.07; O, 5.34; S, 10.52; mol wt, 308 by mass spectrometry.

This compound did not appear to be formed if *o*-cresol was omitted from the reaction mixture.

***p*-Nitrophenyl 2-Tetrahydrothienyl Ether (52).** *p*-Nitrophenol (1.39 g, 10 mmoles) was dissolved in tetramethylene sulfoxide (5 ml) and benzene (5 ml) containing DCC (6.18 g, 30 mmoles) and anhydrous phosphoric acid (5 mmoles). After 3 hr, ether (25 ml) was added, and after filtration of dicyclohexylurea the filtrate was extracted three times with water. After evaporation of the solvent, the residue was dissolved in methanol from which 1.3 g (59%) of pale yellow crystals, mp 100–101°, immediately separated. Recrystallization from methanol did not change the melting point. The product showed λ_{max}^{MeOH} 308 mμ (ε 12,250) and 221 mμ (ε 8050). The nmr spectrum (cps) showed four aromatic protons as doublets (J = 9 cps) at 491 and 415, a single hemithioketal proton as a rough triplet at 357, and six methylene protons in groups of two and four between 120 and 190.

Anal. Calcd for $C_{10}H_{11}NO_3S$: C, 53.33; H, 4.92; N, 6.22; S, 14.23. Found: C, 53.19; H, 4.88; N, 6.27; S, 14.21.

2-Methyl-6-(phenylthiomethyl)phenol (48). *o*-Cresol (1.08 g, 10 mmoles), phenyl methyl sulfoxide[39] (2.89 g, 20 mmoles), DCC (6 g), and anhydrous phosphoric acid (0.5 g) were treated overnight in ether (20 ml). Following filtration of dicyclohexylurea and extraction with water, the mixture was chromatographed on 100 g of silicic acid giving 149 mg (10%) of **48** as a colorless oil which distilled at 100° (10^{-4} mm). This material had λ_{max}^{MeOH} 257 mμ (ε 7600) and $\lambda_{max}^{OH^-}$ 254 mμ (ε 10,300). The nmr spectrum (cps) showed a 3-proton singlet ($ArCH_3$) at 132, a 2-proton singlet ($ArCH_2S$) at 246, a phenolic proton at 354, and eight aromatic protons between 400 and 440.

Anal. Calcd for $C_{14}H_{14}OS$: C, 73.02; H, 6.13; S, 13.90. Found: C, 72.96; H, 6.32; S, 14.09.

Desulfurization gave a quantitative yield of crystalline 2,6-dimethylphenol of mp 44–45° after sublimation.

Reaction with Hydroquinone. Hydroquinone (1.1 g, 10 mmoles), DCC (5 g), and anhydrous phosphoric acid (5 mmoles) were treated overnight in DMSO (5 ml) and benzene (10 ml). Tlc of the resulting deep yellow solution showed quantitative conversion to benzoquinone. After destruction of excess DCC with oxalic acid, however, the product tended to distribute itself into both the ether and water layers. Evaporation of the ether layer and sublimation gave *p*-benzoquinone, as yellow prisms of mp 115°, which was indistinguishable from an authentic sample.

Reaction with Thiophenol. Thiophenol (2.8 g, 25 mmoles) was treated overnight at room temperature with DCC (15.5 g, 75 mmoles) and dichloroacetic acid (1.0 ml, 12 mmoles) in DMSO (10 ml) and benzene (20 ml). After filtration of dicyclohexylurea and extraction with water, a small amount of unreacted thiophenol was extracted with dilute alkali. The nonphenolic materials were chromatographed on 150 g of silicic acid with benzene–hexane (1:1) giving 1.72 g (64%) of crystalline diphenyl disulfide with mp 59–60° (reported mp 60–61°); λ_{max}^{MeOH} 241 mμ (ε 16,400) unchanged in alkali and only aromatic protons between 420 and 450 cps in the nmr.

Anal. Calcd for $C_{12}H_{10}S_2$: C, 66.05; H, 4.62; S, 29.33. Found: C, 66.19; H, 4.59; S, 29.24.

Continued elution of the column gave a second product (1.05 g) as an oil that we have been unable to identify. On attempted distillation this material partially decomposed to diphenyl disulfide. A further by-product was identified as N-dichloroacetyldicyclohexylurea which could be crystallized from ether with mp 146–148°.

Anal. Calcd for $C_{15}H_{24}N_2O_2Cl_2$: C, 53.73; H, 7.21; N, 8.36. Found: C, 53.66; H, 7.25; N, 8.26.

Reaction with *p*-Nitrothiophenol. Freshly purified *p*-nitrothiophenol (310 mg, 2 mmoles) was dissolved in DMSO (5 ml), and in rapid succession anhydrous phosphoric acid (1 mmole in DMSO) and DCC (1.24 g, 6 mmoles) were added. After about 3 min, the dark red solution faded to a pale yellow color and after 1 hr chloroform (50 ml) was added, dicyclohexylurea (650 mg) was removed, and the solution was extracted three times with water. The chloroform solution was dried and evaporated leaving 1.1 g of oily crystals. This was washed twice with cold methanol leaving 340 mg of di-*p*-nitrophenyl disulfide contaminated with a little dicyclohexylurea. Extraction with boiling methanol left the pure disulfide (160 mg), and preparative tlc (chloroform–carbon tetrachloride, 9:1) gave a further 50 mg; total yield of crystalline product was 210 mg (68%). An analytical sample from chloroform–methanol had mp 181–183°.[40] Silica chromatography of the material soluble in cold methanol gave a tiny amount (25 mg) of crystalline *p*-nitrophenyl methyl disulfide (mp 36–38° from methanol). The nmr spectrum (cps) showed only four aromatic protons as two doublets (J = 9 cps) at 457 and 490 and a 3-proton singlet at 148.

Anal. Calcd for $C_7H_7NO_2S_2$: N, 6.96; S, 31.82. Found: N, 7.19; S, 31.98.

Treatment with sodium borohydride in methanol immediately liberated *p*-nitrothiophenol.

S-*p*-Nitrophenyl-N,N′-dicyclohexylisothiourea (53). *p*-Nitrothiophenol (155 mg, 1 mmole) was dissolved in benzene (3 ml) containing DCC (216 mg, 1.05 mmoles). After 1 hr the mixture was evaporated to dryness, dissolved in hexane (2 ml), and chilled giving 300 mg (84%) of **53** as pale yellow needles of mp 92–93°; $\lambda_{max}^{dioxane}$ 232 mμ (ε 11,600).

Anal. Calcd for $C_{19}H_{27}N_3O_2S$: C, 63.15; H, 7.53; N, 11.62; S, 8.87. Found: C, 63.68; H, 7.93; N, 11.94; S, 9.44.

Reactions of Thiophenols in DMSO without DCC. a. *p*-Nitrothiophenol (155 mg, 1 mmole) was dissolved in DMSO (1 ml) containing anhydrous phosphoric acid (0.5 mmole). The red color almost immediately disappeared and crystals separated. After 10 min methanol (5 ml) was added and the crystalline di-*p*-nitrophenyl disulfide (135 mg, 88%) was removed by filtration and shown to be identical with an authentic sample. A similar reaction without added phosphoric acid only became colorless and deposited the crystalline disulfide after more than 8 hr at room temperature.

b. Two parallel reactions were set up containing 0.10 ml of thiophenol and 0.90 ml of DMSO in the presence and absence of 0.5 mmole of anhydrous phosphoric acid. The formation of diphenyl disulfide was followed by glpc (Wilkins 204 instrument using a 5 ft column of 5% SE-30 on Gaschrom-Q with a column temperature of 135°) using an internal standard of benzophenone. The reaction with phosphoric acid gave a quantitative yield of diphenyl disulfide within 5 min at room temperature while the reaction without acid was not yet complete in 6 hr (43% in 3 hr). A similar reaction with acid but using only 0.3 ml of DMSO led to to immediate crystallization of pure diphenyl disulfide.

2-Hydroxy-3-nitrobenzyl Methyl Sulfoxide. 2-Nitro-6-(thiomethoxymethyl)phenol (**9**, 283 mg, 1.4 mmoles) was dissolved in glacial acetic acid (4 ml) and stirred in ice while 30% hydrogen peroxide (0.14 ml) was added dropwise. After 15 min tlc showed disappearance of the starting material and formation of a single, slow-moving product. The solvent was evaporated under high vacuum, and upon addition of a little pentane the residue (300 mg) crystallized with mp 100–102°; λ_{max}^{MeOH} 275 mμ (ε 5500) and 353 mμ (ε 3200); $\lambda_{max}^{OH^-}$ 235 mμ (ε 12,200) and 260 mμ (ε 4700). The nmr spectrum (cps) showed a 3-proton singlet at 152 (CH_3SO), a barely resolved 2-proton doublet (J = 0.5 cps) at 247 ($ArCH_2SO-$), and three aromatic protons and a phenolic proton between 413 and 493.

Anal. Calcd for $C_8H_9NO_4S$: C, 44.66; H, 4.22; N, 6.51; S, 14.87. Found: C, 44.57; H, 4.21; N, 7.32; S, 14.68.

(39) Prepared from thioanisole and hydrogen peroxide in acetic acid according to the general method of O. Hinsberg, *Ber.*, **41**, 2836 (1908), bp 90° (0.1 mm).

(40) E. Bamberger and E. Kraus, *ibid.*, **29**, 278 (1896), report mp 181°.