tion, and x = the amount of CrO_3 reacted at time t. All rates are expressed in Table II relative to 3β-hydroxy-5α-androstan-3-one (**1**) which had a second-order rate constant of 2.80×10^{-3} l. mole^{-1} sec^{-1}.

The reactions were initiated by mixing nine parts of a freshly prepared solution of the steroid in glacial acetic acid with one part of an aqueous solution of chromium trioxide which was 0.20 *M* in sodium acetate. In the case of the slower reactions, the steroid was 30.9×10^{-3} *M* and chromic acid 3.09×10^{-3} *M*. In the faster reactions, the concentrations were 30.9×10^{-4} and 3.09×10^{-4} *M*, respectively. All reactions were allowed to proceed for at least one half-life. With one exception the steroidal substrates were stable in acetic acid over the period of measurement and no side reaction would be detected by product analysis. In the case of 3α-hydroxyandrost-4-ene (**6**) and the corresponding deuterio compound, a small amount of dehydration was noted. However, this side reaction was insufficient to cause noticeable deviation in the pseudo-first-order plot. All substrates were run in duplicate or triplicate.

Sulfoxide–Carbodiimide Reactions. V.[1] Reactions of 2,6-Disubstituted Phenols

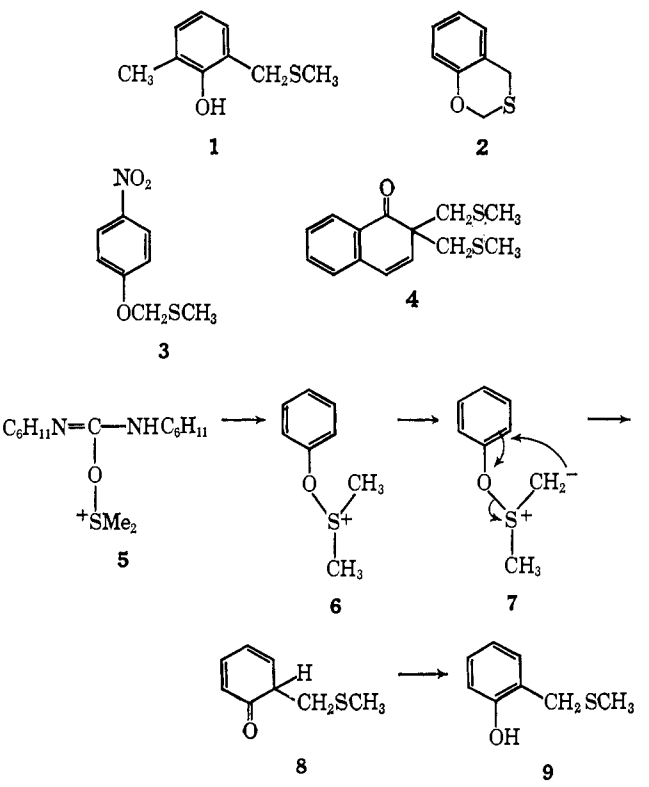
M. G. Burdon[2] and J. G. Moffatt

Contribution No. 38 from the Institute of Molecular Biology, Syntex Research, Palo Alto, California. *Received March 29, 1967*

Abstract: Phenols substituted in the 2 and 6 positions with alkyl groups react with dimethyl sulfoxide and dicyclohexylcarbodiimide in the presence of anhydrous phosphoric acid to give 2,6-disubstituted 6-(thiomethoxymethyl)cyclohexa-2,4-dien-1-ones. These dienones tend to rearrange to thiomethoxymethylphenols during silica chromatography or upon addition of acids, and studies designed to elucidate the mechanism of these rearrangements are described. Under suitable conditions the thiomethoxymethyl group can be efficiently transferred from a suitably substituted dienone to another acceptor molecule. *o*-Chlorophenols behave unusually and lead primarily to 1,3-benzoxathians.

Following the development of the mild, but efficient, dimethyl sulfoxide–dicyclohexylcarbodiimide (DMSO–DCC) method for the oxidation of hydroxyl groups[3] we have undertaken a general program studying the reactions of these reagents with other functional groups. In part IV of this series[1] we have described the mild, acid-catalyzed reactions of DMSO and DCC with a variety of phenols containing unsubstituted *ortho* positions. Such reactions led to a number of different types of products depending upon the nature of the starting material. The principal products were usually phenols substituted in one or both of the available *ortho* positions by thiomethoxymethyl groups (*e.g.*, **1**), and frequently low yields of products containing the previously undescribed 1,3-benzoxathian ring system (*e.g.*, **2**) were also isolated. More strongly acidic phenols, such as nitrophenols, gave rise to aryl thiomethoxymethyl ethers (*e.g.*, **3**), while thiophenols and naphthols were anomalous and gave diaryl disulfides and bis(thiomethoxymethyl)dihydronaphthalenones (*e.g.*, **4**), respectively. Comparable products were also found using sulfoxides other than DMSO.

Mechanisms were proposed for these various reactions[1] involving initial attack of the phenolic oxygen upon the DMSO–DCC adduct **5** which has been shown by isotopic experiments[3d] to be the first intermediate during oxidation of alcohols. The *ortho*-alkylation reaction then proceeds *via* the aryloxysulfonium salt **6** and the sulfonium ylide **7**, the carbanion of which intramolecularly alkylates the available *ortho* position, giving the phenol **9** *via* the dienone **8**.

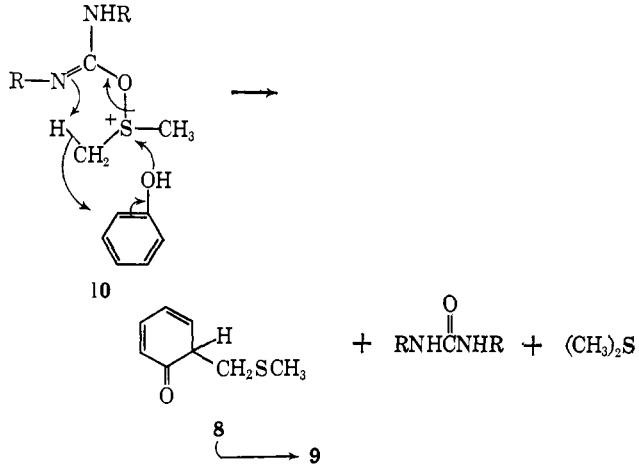


(1) For part IV see M. G. Burdon and J. G. Moffatt, *J. Am. Chem. Soc.*, **88**, 5855 (1966).

(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.*, **85**, 3027 (1963); (b) K. E. Pfitzner and J. G. Moffatt, *ibid.*, **87**, 5661 (1965); (c) K. E. Pfitzner and J. G. Moffatt, *ibid.*, **87**, 5670 (1965); (d) A. H. Fenselau and J. G. Moffatt, *ibid.*, **88**, 1762 (1966).

Very recently a brief paper by Torssell[4a] has questioned the free existance of the alkoxysulfonium compound[3b,d] analogous to **6** during oxidation of alcohols with the DMSO–DCC reagent. Further experimental details and study are necessary in order to assess this suggestion, but the possibility should not be excluded that the *ortho*-alkylation reaction may also proceed *via* a termolecular intermediate such as **10**. For convenience in the subsequent discussion we will continue to assume that the aryloxysulfonium compound **6** does indeed exist free since the Torssell mechanism differs from ours only in the intimate details of the proton-abstraction step.



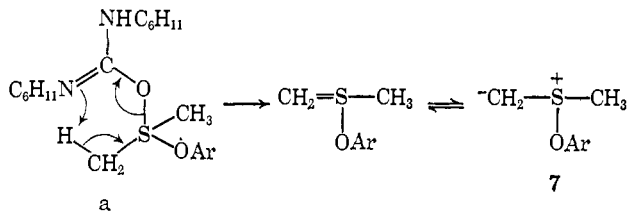
2,6-Disubstituted phenols would also be expected to react with the sulfonium pseudourea **5**, and the results of a number of such examples are reported in this paper. A preliminary report of part of this work has appeared,[5a] and some related observations have been briefly described by Pfitzner, *et al.*[5b]

Upon addition of anhydrous orthophosphoric acid (0.5 equiv) to a solution of 2,6-dimethylphenol (1 equiv) and DCC (3 equiv) in a mixture of DMSO and benzene an exothermic reaction took place and dicyclohexylurea was deposited. Thin layer chromatography indicated that within 30 min no starting material remained and a single ultraviolet-absorbing spot resulted. Following extraction of the DMSO with water the organic solvent soluble products were chromatographed on a column of silicic acid, giving a crystalline product identified as 2,6-dimethyl-4-(thiomethoxymethyl)phenol (**11**) in 66% yield. The structure of **11** was confirmed by its elemental analysis and also by its nuclear magnetic resonance (nmr) spectrum which showed the presence of a thiomethoxymethyl group as two singlets at 118 (SCH_3) and 214 cps ($ArCH_2S$). The product was phenolic (ultraviolet and infrared spectra) and its symmetrical nature was demonstrated by the appearance of two aromatic protons as a sharp singlet at 415 cps in the nmr spectrum. Desulfurization with a sponge nickel catalyst[6] led to the rapid and quantitative formation of crystalline 2,4,6-trimethylphenol, mp 72–73°, which was indistinguishable from an authentic sample. The formation in high yield of the *p*-(thiomethoxymethyl)phenol is in direct contrast with the exclusive formation of *o*-(thiomethoxymethyl) products arising from phenols containing unsubstituted *ortho* positions.[1]

A similar reaction with 2,4,6-trimethylphenol once again led to the very rapid consumption of all the starting material and formation of a single ultraviolet-absorbing spot on thin layer chromatograms. Silica column chromatography gave a high yield of a crude material which ran as an elongated spot on thin layer chromatography and from which crystalline 2,4,6-trimethyl-3-(thiomethoxymethyl)phenol (**12**) was obtained in moderate yield. The crystalline material gave the expected analysis (Table I) and spectral data (Table II) and the mother liquors were clearly a mixture of **12** and another product with λ_{max} 320 mμ (30% **12** by vapor phase chromatography) that will be discussed shortly. Desulfurization of **12** gave crystalline 2,3,4,6-tetramethylphenol, mp 77–78°.

Reexamination by vapor phase chromatography of the crude, extracted reaction mixtures from 2,6-dimethylphenol and 2,4,6-trimethylphenol showed that in each case *none* of the previously isolated thiomethoxymethylphenols (**11** and **12**) was present. The only detected products were excess DCC and a single major peak in each reaction, together with trace amounts of unreacted starting material. Following chromatography of this crude mixture from 2,6-dimethylphenol on a column of silicic acid, however, the previously isolated, crystalline 2,6-dimethyl-4-(thiomethoxymethyl)phenol (**11**) was once again isolated in excellent yield. Accordingly, **11** must not be a primary product of the reaction but rather the consequence of a facile chemical change occurring during chromatography. This situation became clear when it was observed that very rapid chromatography of the crude reaction mixture from 2,6-dimethylphenol on preparative 1-m-long glass plates with a 1.3-mm-thick silica layer[7] (total time for application, development, and elution was less than 2 hr) permitted isolation of the original reaction product contaminated by only about 20% of **11** which could be selectively removed by extraction with dilute alkali. The nonalkali-extracted product was then distilled under high vacuum, giving a 66% yield of a yellow oil which was shown to be 2,6-dimethyl-6-(thiomethoxymethyl)cyclohexa-2,4-dien-1-one (**13**). This compound, which was isomeric with **11**, was shown to be an unsaturated ketone by its infrared (ν_{max} 1650 cm^{-1}) and ultraviolet (λ_{max}^{MeOH} 308 mμ) spectra, and it rapidly rearranged to **11** upon addition of a trace of trifluoroacetic acid to its solution in methylene chloride. The nmr spectrum of **13** showed the pres-

(4) (a) K. Torssell, *Tetrahedron Letters*, 4445 (1966). (b) An alternative to the Torssell mechanism, suggested to us by a referee, involves addition of the phenol (or alcohol in the case of oxidation) to the adduct **5** with formation of the tetrasubstituted sulfur intermediate a which then collapses *via* a cyclic process directly to the sulfonium ylide **7** without intervention of the free sulfonium salt **6**.



(5) (a) M. G. Burdon and J. G. Moffatt, *J. Am. Chem. Soc.*, **87**, 4656 (1965); (b) K. E. Pfitzner, J. P. Marino, and R. A. Olofson, *ibid.*, **87**, 4658 (1965).

(6) Davidson Chemical Division of W. R. Grace and Co., Cincinnati, Ohio.

(7) H. Halpaap, *Chem. Ing. Tech.*, 35, 488 (1963).

Table I. Physical Properties of Thiomethoxymethyl Compounds

Compd	Yield, %	Mp or bp[a] (mm), °C	Molecular formula	Calcd, % C	Calcd, % H	Calcd, % S	Found, % C	Found, % H	Found, % S
2,6-Dimethyl-4-TMM-phenol[b] (**14**)	66	40–42	$C_{10}H_{14}OS$	65.91	7.74	17.60	66.20	7.62	17.80
2,4,6-Trimethyl-3-TMM-phenol (**12**)	18	85–86	$C_{11}H_{16}OS$	67.32	8.22	16.35	67.41	8.16	16.50
2,6-Dimethyl-6-TMM-cyclohexa-2,4-dien-1-one (**13**)	66	60 (10^{-4})	$C_{10}H_{14}OS$	65.91	7.74	17.58	65.89	7.70	17.51
Dimer (**14**)	40	130–131	$C_{20}H_{28}O_2S_2$	65.91	7.74	17.58	66.17	7.55	17.44
2,4,6-Trimethyl-6-TMM-cyclohexa-2,4-dien-1-one (**15**)	93	65 (10^{-4})	$C_{11}H_{16}OS$	67.32	8.22	16.32	67.60	8.55	16.03
2,3,5,6-Tetramethyl-6-TMM-cyclohexa-2,4-dien-1-one (**18**)	86	90 (10^{-3})	$C_{12}H_{18}OS$	68.54	8.63	15.22	68.37	8.47	15.32
2,3,4,5,6-Pentamethyl-6-TMM-cyclohexa-2,4-dien-1-one (**19**)	85	80 (10^{-4})	$C_{13}H_{20}OS$	69.61	8.99	14.28	69.40	8.84	14.46
2,3,5,6-Tetramethyl-4-TMM-phenol (**20**)	93	144–145	$C_{12}H_{18}OS$	68.54	8.63	15.22	68.63	8.53	15.18
2,3,4,6-Tetramethyl-6-TMM-cyclohexa-2,4-dien-1-one (**25**)	95	80 (10^{-3})	$C_{12}H_{18}OS$	68.54	8.63	15.22	68.90	8.86	14.62
2,4,5,6-Tetramethyl-6-TMM-cyclohexa-2,4-dien-1-one (**26**)									
2,4,5,6-Tetramethyl-3-TMM-phenol (**27**)	60	97–98	$C_{12}H_{18}OS$	68.54	8.63	15.22	68.84	8.57	15.17

[a] Boiling points refer to the bath temperature using a "Kugelrohr" short-path apparatus. [b] TMM refers to thiomethoxymethyl.

Table II. Spectral Properties of Thiomethoxymethyl Compounds

Compd	Ultraviolet spectra, λ_{max}, mμ (ϵ_{max}) MeOH	MeOH + KOH	Nmr spectra, cps SCH_3	$ArCH_2S$	Other
11	278 (1400)	255 (4500), 290 (1500)	118 (3, s)[a]	214 (2, s)	131 (6, s), 288 (1, s), 415 (2, s)
12	286 (2200)	290 (2000), 305 (sh) (700)	123 (3, s)	222 (2, s)	129 (3, s), 135 (3, s), 136 (3, s), 276 (1, s), 406 (1, s)
13	308 (3600)	Unchanged	122 (3, s)	162 (1, d, J = 12.5 cps) 182 (1, d, J = 12.5 cps)	72.5 (3, s), 113.5 (3, d, J = 1.5 cps) 370–420 (3, m)
14	241 (6800)	Unchanged	122 (3, s) 124 (3, s)	157 (2, s) 163 (2, s)	68 (3, s), 77 (3, s), 79 (3, s), 109 (3, s) 179 (1, d, J = 6 cps), 332 (1, q, J = 8 and 1.5 cps), 370–390 (2, m)
15	320 (3400)	Unchanged	121 (3, s)	159 (1, d, J = 13 cps) 179 (1, d, J = 13 cps)	71 (3, s), 113–117 (6, m) 356 (1, q), 405 (1, q)
18	325 (4650)	Unchanged	119 (3, s)	167 (1, d, J = 12 cps) 191 (1, d, J = 12 cps)	72 (3, s), 110–125 (9, m) 360 (1, s)
19	336 (4000)	Unchanged	117 (3, s)	169 (1, d, J = 12 cps) 190 (1, d, J = 12 cps)	70 (3, s), 110–130 (12, m)
20	278 (810), 284 (760)	283 (sh, 1150), 296 (sh, 500)	127 (3, s)	228 (2, s)	130 (3, s), 139 (3, s), 276 (1, s)
25	328 (3600)	Unchanged	121 (3, s)	178 (1, d, J = 12 cps) 158 (1, d, J = 12 cps) 188 (1, d, J = 12 cps) 169 (1, d, J = 12 cps)	358 (1, s) 117 (3, s), 113 (3, s) 405 (1, s) 112 (3, s), 69 (3, s)
26					
27	288 (1800)	289 (1650), 307 (sh, 400)	125 (3, s)	225 (2, s)	129 (6, s), 135 (6, s), 276 (1, s)

[a] Integrated intensity and multiplicity; s, d, q, and m refer to singlet, double, quartet, and multiplet. Thus 129 (3, s) refers to a three-proton singlet at 129 cps. All nmr data in this table were obtained on a Varian A-60 spectrometer using solutions in deuteriochloroform, and are recorded in cycles per second downfield from an internal standard of tetramethylsilane.

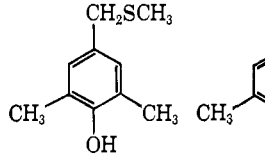
ence of a S–CH_3 group as a singlet at 122 cps, a quaternary methyl group at 72.5 cps, a vinyl methyl group as a doublet at 113.7 cps (J = 1.5 cps), three vinyl protons between 370 and 420 cps, and the isolated CH_2S group as a pair of geminally coupled doublets (J = 12.5 cps) centered at 162 and 182 cps. Such a four-line pattern is typical of an isolated methylene group adjacent to an asymmetric center,[8] and the nature of the magnetic nonequivalence of the methylene protons has received considerable attention.[9] Storage of the pure dienone **13** at room temperature for even 1 day led to separation of a white crystalline substance from which a pure isomer of the Diels–Alder dimerization product **14**a or **14b** could be obtained. The analogous spontaneous dimerization of 6,6-dimethylcyclohexa-2,4-dien-1-one and related compounds has previously been described.[10] No clear preference for structure **14**a or **14b** can be inferred from spectral data, and the broad melting point range of the crude product suggests that perhaps both isomers were originally formed. Dipole moment measurements, which have been used previously[10b] to study the dimer from 2,6,6-trimethylcyclohexa-2,4-dien-1-one, have not been made. The infrared spectrum of **14** showed the presence of both conjugated

(8) (a) J. D. Roberts, "Nuclear Magnetic Resonance. Applications to Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 58; (b) E. I. Snyder, *J. Am. Chem. Soc.*, **85**, 2624 (1963), and references therein.

(9) L. Martin and G. J. Martin, *Bull. Soc. Chim. France*, 2117 (1966).

(10) (a) K. Alder, F. H. Flock, and H. Lessinich, *Chem. Ber.*, **90**, 1709 (1957); (b) T. L. Brown, D. Y. Curtin, and R. R. Fraser, *J. Am. Chem. Soc.*, **80**, 4339 (1958).

(ν_{max}^{KBr} 1675 cm^{-1}) and nonconjugated (ν_{max}^{KBr} 1715 cm^{-1}) carbonyl groups, and the ultraviolet spectrum was that of an α,β-unsaturated ketone (λ_{max} 241 mμ (ϵ 6800)). The dimeric nature of **14** was confirmed by mass spectrometry which showed an intense molecular ion (relative abundance 56%) at *m/e* 364. Other interesting features of this spectrum include: (1) the ready cleavage of the thiomethoxymethyl side chains as demonstrated by both the presence of an intense peak (relative intensity 100%) at *m/e* 61 corresponding to the methylmethylenesulfonium ion $CH_3S{=}CH_2^+$ and the presence of intense peaks at M − 60 (M − $CH_2{=}S{=}CH_2$) and M − 75 (M − $CH_2{=}S{=}CH_2CH_3$); (2) reversion of the dimer to the monomer (*m/e* 182, relative intensity 14%). Thermal cracking of **14** to the monomer **13** could also be demonstrated during distillation at 100° (10^{-4} mm) and by vapor phase chromatography whereby **13** and **14** gave apparently identical retention times. Alder[10a] has also noted thermal cracking of the 6,6-dimethylcyclohexa-2,4-dien-1-one dimer. The nmr spectrum of the dimer was completely in accordance with the proposed structures **14a** or **14b** and is summarized in Table II. The only unusual feature of this spectrum is that the methylene groups attached to sulfur unexpectedly appeared as singlets, rather than as pairs of doublets as in **13**.



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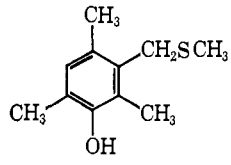

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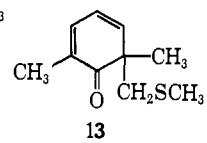

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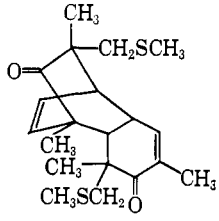
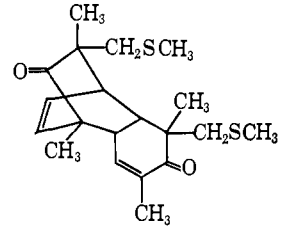


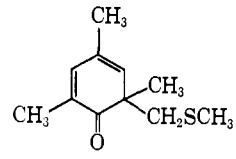
14a



14b

Chromatography of the pure ketone **13** on silicic acid columns, or storage of its solutions in the presence of silicic acid, led to complete rearrangement to the *para*-alkylated phenol **11**. In a similar way addition of a trace of trifluoroacetic acid to a solution of **13** in methylene chloride led to almost instantaneous rearrangement to **11**. The mechanism of this rearrangement is discussed later in this paper.

Rapid chromatography of the crude reaction products from 2,4,6-trimethylphenol on preparative silica plates led, in the same way, to the isolation of 2,4,6-trimethyl-6-(thiomethoxymethyl)cyclohexa-2,4-dien-1-one (**15**) in 93% yield. Unlike **13**, this ketone showed little tendency to dimerize and was only partially isomerized (~40%) to the *meta*-alkylated phenol **12** upon overnight chromatography on a silicic acid column. Brief treatment with trifluoroacetic acid in methylene chloride (0.1 *M*), however, led to rapid rearrangement to **12**. It is significant that it is exclusively the thiomethoxymethyl group which migrates, this being shown by comparison of the rearrangement product **12** (mp 85–86°) with the isomeric compound 2,4,5-trimethyl-6-(thiomethoxymethyl)phenol (**16**), mp 51–53°, obtained previously[1] from the reaction of 2,4,5-trimethylphenol with DMSO and DCC. A related rearrangement of 6,6-dimethylcyclohexa-2,4-dien-1-one (**17**) to 2,3-dimethylphenol upon treatment with sulfuric acid in acetic anhydride has been previously described,[11] although, as will be seen later, the mechanism is probably quite different.



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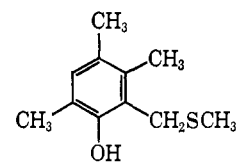

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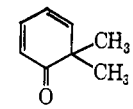
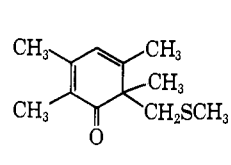


17

Similar reactions of DMSO and DCC upon 2,3,5,6-tetramethylphenol (durophenol) and 2,3,4,5,6-pentamethylphenol also led to the essentially quantitative formation of the cyclohexadienones **18** and **19** which were quite stable and could be chromatographed on columns of silicic acid without decomposition. Treatment of **18** with trifluoroacetic acid in methylene chloride or with one drop of concentrated hydrochloric acid in methanol led to an almost instantaneous rearrangement to 2,3,5,6-tetramethyl-4-(thiomethoxymethyl)phenol (**20**) which crystallized directly from the solvent. Desulfurization of **20** gave crystalline pentamethylphenol identical with an authentic sample. Treatment of **19** with hydrochloric acid in methanol led to a rapid conversion into pentamethylphenol. Further studies on these reactions are discussed later in this paper. Desulfurization of the dienones **18** and **19** was accompanied by reduction of the terminal double bond and gave, as the principal products isolated by preparative thin layer chromatography, 2,3,5,6,6-pentamethylcyclohex-2-en-1-one (**21**) and 2,3,4,5,6,6-hexamethylcyclohex-2-en-1-one (**22**), respectively, which were characterized by their ultraviolet (λ_{max} 245 mμ), infrared (λ_{max} 1660 cm^{-1}), and nmr spectra. A substantial amount of the intermediate product **23** which was reduced but not desulfurized was also isolated from the reaction of **18**. In addition, the presence of nonultraviolet-absorbing, fully reduced products was apparent from thin layer chromatography, but these have not been further studied. No sign of the previously described 2,3,4,5,6,6-hexamethylcyclohexa-2,4-dien-1-one[12] was observed.



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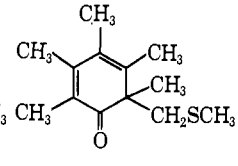

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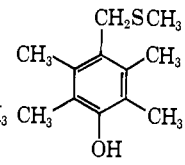

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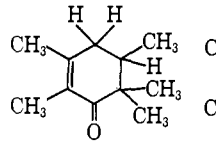

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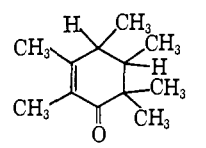

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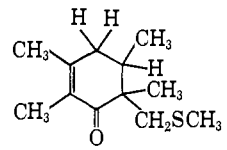
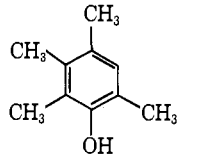


23

(11) (a) E. N. Marvel and E. Magoon, *J. Am. Chem. Soc.*, 77 2542 (1955); (b) H. Budzikiewicz, *Tetrahedron Letters*, 12 (1960).

(12) H. Hart and R. M. Lange, *J. Org. Chem.*, 31, 3776 (1966).

As might be expected, the reaction of 2,3,4,6-tetramethylphenol (**24**) led to a mixture of the two isomeric tetramethyl(thiomethoxymethyl)cyclohexadienones (**25** and **26**) which were indistinguishable by thin layer chromatography and barely resolved by vapor phase chromatography. The nmr spectrum of the mixture clearly showed it to consist of 60% of the less sterically hindered isomer **25** and 40% of **26**, the single vinylic proton of **26** appearing at lower field than that of **25**. The methylene groups of **25** and **26** also appeared as two overlapping, but clearly observable, quartets while the methyl groups were not resolvable. Treatment of the mixed ketones with acid led to a mixture of roughly equal amounts of the starting phenol **24** and 2,3,4,6-tetramethyl-5-(thiomethoxymethyl)phenol (**27**), the latter being identified by analysis and by desulfurization to pentamethylphenol. It therefore appears that the action of acid on ketone **25** leads to rearrangement of the thiomethoxymethyl group to the available *ortho* position while ketone **26** undergoes simple hydrolysis similar to that observed with **19**.



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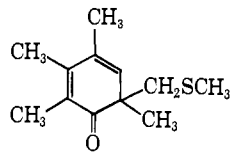

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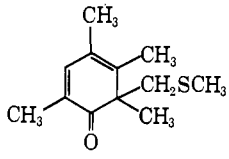

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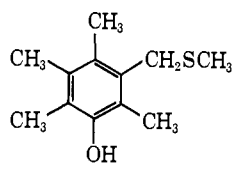
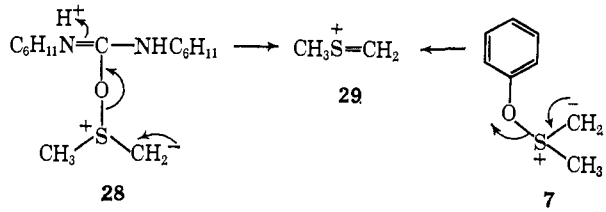


27

Since the (thiomethoxymethyl)cyclohexadienones (*e.g.*, **13**, **15**, and **18**) may, with care, be isolated in almost quantitative yields, it appears almost certain that they are the exclusive intermediates in the formation of the *meta*- and *para*-alkylated phenols which we originally isolated following chromatography on silicic acid columns. The possible alternative alkylation of the phenol by the methylmethylenesulfonium ion (**29**), which could conceivably be generated by collapse of the ylide **28** derived from the DMSO–DCC adduct **5**, seems to be ruled out by the complete inertness of anisole, 1,3-dimethoxybenzene, furan, and N,N-dimethylaniline under the usual reaction conditions. It has previously been shown that 1,3-dimethoxybenzene is alkylated by **29** derived from dimethylethoxysulfonium fluoroborate and triethylamine. The sulfonium compound **29** could also arise by expulsion of phenolate ion from the key phenoxysulfonium ylide intermediate **7**. Such a process is also ruled out by the quantitative formation of the dienone **13**, as shown by vapor phase chromatography, when 2,6-dimethylphenol is allowed to react with DCC,



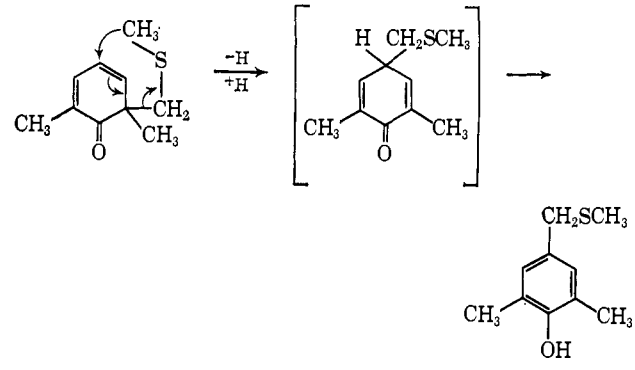
28 **29** **7**

DMSO, and phosphoric acid in the presence of a tenfold molar excess of 1,3-dimethoxybenzene, anisole, or furan. No alkylation of these relatively nucleophilic additives was observed. As will be seen later, however, such compounds can be alkylated by transfer of a thiomethoxymethyl group from a dienone such as **19** in the presence of acid.

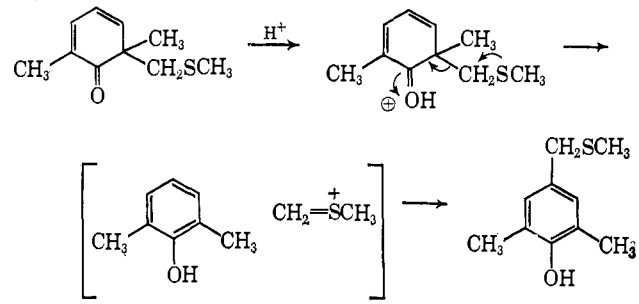
In order to cast light upon the mechanism by which the (thiomethoxymethyl)cyclohexadienones rearrange to *meta*- or *para*-alkylated phenols, we have studied the acid-catalyzed reactions of the ketone **18** derived from durophenol. We first checked whether the rearrangement of **18** to **20** was intra- or intermolecular by treating a mixture of **18** and 5 equiv of 2,6-dimethylphenol in methylene chloride with a trace of trifluoroacetic acid. The ketone **18** disappeared almost instantaneously and, in addition to 2,6-dimethylphenol and durophenol, the products were shown by quantitative vapor phase chromatography to be 67% 2,3,5,6-tetramethyl-4-(thiomethoxymethyl)phenol (**20**) and 33% 2,6-dimethyl-4-(thiomethoxymethyl)phenol (**11**).[13] Thus, even in the presence of a fivefold excess of another phenol, intramolecular rearrangement is favored by a factor of 2. A similar experiment using the dienone **13** from 2,6-dimethylphenol in the presence of 5 equiv of durophenol led to 75% intramolecular alkylation, giving **11**, and 25% intermolecular reaction, giving **20**.

The intramolecular rearrangements of (thiomethoxymethyl)cyclohexadienones could take place *via* a truly intramolecular cyclic process somewhat analogous to that operative in the *para* Claisen rearrangement[14] (path A) or by dissociation into the methylenemethylsulfonium ion and phenol followed by alkylation of the phenol at the nucleophilic *para* position (path B) if this is free.

Path A



Path B

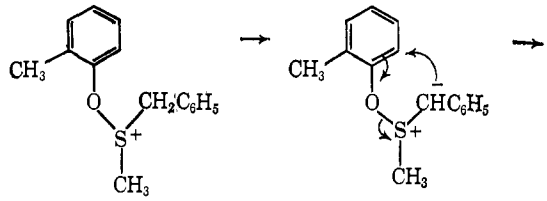


Path A seems generally unlikely since, unlike the case of the *para* Claisen rearrangement, the terminal S–CH_3

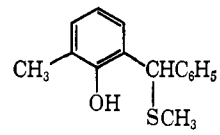
(13) These figures are corrected for a 2.15-fold greater hydrogen flame detector response toward **20** relative to **11**.

(14) S. J. Rhoads in "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 655.

group of the side chain is essentially unreactive and activation by, *e.g.*, proton abstraction would not be expected under the reaction conditions. We have, however, attempted to rule out the "cartwheel mechanism" of path A through studies with unsymmetrically substituted sulfoxides. To this end we have shown that *o*-cresol reacts quite normally with benzyl methyl sulfoxide[15] and DCC to give the *ortho*-alkylation product **32** in 34% yield. The linkage of the benzyl methyl sulfide grouping to the phenol was shown to be exclusively through the benzylic carbon by nmr spectroscopy, which showed a single benzyl proton and an intact S-methyl group, and by desulfurization to 2-benzyl-6-methylphenol.[1] The preferential formation of this isomer is to be expected since loss of a proton from the intermediate **30** will occur most readily from the benzylic carbon, giving the ylide **31** and thence the *ortho*-alkylated product **32** according to our general mechanism.[1]



30 **31**



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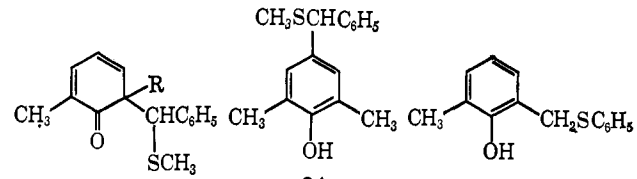
Unfortunately, however, we were unable to isolate any desired cyclohexadienone such as **33** from reaction of benzyl methyl sulfoxide with 2,6-dimethylphenol or durophenol. In both cases substantial amounts of benzaldehyde were formed and, in addition to unreacted phenol, a mixture of inseparable, more polar products was detected by thin layer chromatography. Some material with the characteristic yellow color of the desired dienones was present in this polar fraction but could not be isolated in pure form by preparative thin layer chromatography. From the 2,6-dimethylphenol reaction it was possible to isolate the *para*-alkylation product 2,6-dimethyl-4-(α-thiomethoxybenzyl)phenol (**34**) in 11% yield. The actual yield was undoubtedly much higher, but the separation of **34** from benzaldehyde and 2,6-dimethylphenol was difficult and wasteful. Thin layer chromatography of the crude, extracted reaction mixture showed the presence of **34** without excessive exposure to silicic acid and hence the presumed intermediate dienone must be less stable than those from DMSO (*e.g.*, **13**). As in **32**, the point of attachment of the benzyl methyl sulfide moiety to the phenol in **34** was once again shown to be through the benzylic carbon by nmr spectroscopy. Hence, if we assume that both the *ortho*- and *para*-alkylation products **32** and **34** arise *via* the appropriate dienones (**33a** and **33b**, respectively), a truly concerted intramolecular mechanism such as path A cannot obtain. Definitive proof of this rejection must, however, await the isolation of a pure ketone such as **33b**.

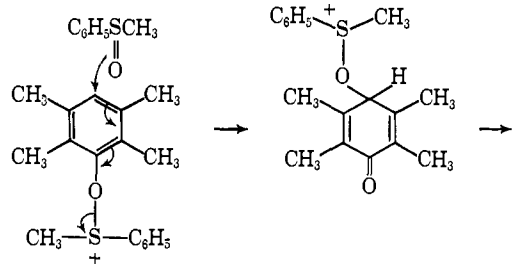
(15) F. G. Bordwell and B. M. Pitt, *J. Am. Chem. Soc.*, 77, 572 (1955).



33a, R = H
b, R = CH_3

34 **35**

We have also attempted similar studies with two other unsymmetrical sulfoxides which we anticipated could only react in a single way. Thus, while reaction of methyl phenyl sulfoxide and DCC with *o*-cresol was previously shown[1] to give the expected *ortho*-alkylation product **35** in low yield, this sulfoxide failed to give any observable products with 2,6-dimethylphenol.[16] Durophenol also reacted only sluggishly with methyl phenyl sulfoxide and was largely recovered unchanged. One other product was, however, present and was shown to be duroquinone (**37**) which was isolated crystalline in 10% yield. As yet this is the only instance of quinone formation from a monobasic phenol that we have observed,[17] and a likely mechanism involves *para* attack by a second molecule of sulfoxide upon the rather hindered phenoxysulfonium ion **36** followed by ylide formation and intramolecular proton abstraction as in the normal oxidation of alcohols.[3d]



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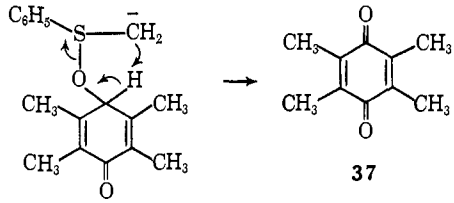

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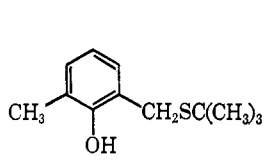
The reaction of *t*-butyl methyl sulfoxide[18] and DCC with *o*-cresol led to the isolation of 2-(*t*-butylthiomethyl)-6-methylphenol (**38**) which gave 2,6-dimethylphenol upon desulfurization. Once again this sulfoxide reacted only poorly with 2,6-dimethylphenol but did give a low yield of 4-(*t*-butylthiomethyl)-2,6-dimethylphenol (**39**) which, upon desulfurization, was converted into crystalline 2,4,6-trimethylphenol. The intermediate cyclohexadienone was not observed. The reaction of *t*-butyl methyl sulfoxide with durophenol did, however, give the very unstable dienone **40** which could not be freed from roughly 10% of an unidentified impurity by chromatography and which decomposed upon attempted distillation. The impure product was identi-

(16) Some slow formation of a dark, insoluble tar did result, but the starting materials were the only ultraviolet absorbing compounds detected in the soluble reaction mixture by thin layer chromatography.

(17) We previously described the conversion of hydroquinone to *p*-benzoquinone upon reaction with DMSO and DCC.[1]

(18) H. G. Henbest, J. A. W. Reid, and C. J. M. Stirling, *J. Chem. Soc.*, 1220 (1964).

fied by its ultraviolet and infrared spectra and particularly by its nmr spectrum which showed the SCH_2– group as a typical pair of geminally coupled doublets (J = 11 cps) centered at 189 and 162 cps. Attempted acid-catalyzed rearrangement of **40** to the *para*-alkylated phenol led only to the formation of durophenol. The lack of alkylation is perhaps due to facile fragmentation of the methylene-*t*-butylsulfonium ion (**41**) produced by path **B** into the *t*-butyl carbonium ion and thioformaldehyde.



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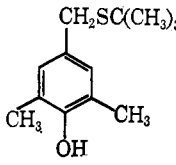

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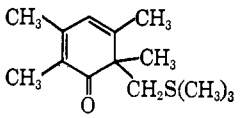

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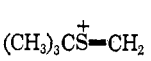

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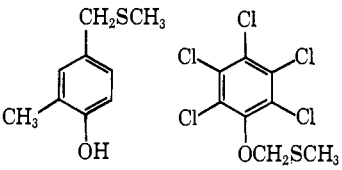
The above experiments generally speak against the formation of *meta*- and *para*-alkylated phenols *via* path A, and we have sought further evidence for the dissociation–recombination mechanism of path **B**. This was most readily provided by treating a mixture of the ketone **19** from pentamethylphenol and 3 equiv of *o*-cresol with a trace of trifluoroacetic acid. Vapor phase chromatography demonstrated the complete disappearance of **19** within a few minutes with formation of pentamethylphenol and two (thiomethoxymethyl)cresols in a ratio of 1:3. These products were isolated by preparative thin layer chromatography and shown to be 2-methyl-6-(thiomethoxymethyl)phenol (**1**) and 2-methyl-4-(thiomethoxymethyl)phenol (**42**). The minor product **1** was identical with the previously described compound from *o*-cresol, DMSO, and DCC,[1] while the major one was unequivocally identified by its nmr and ultraviolet spectra and by desulfurization to 2,4-dimethylphenol. The latter compound could be distinguished from other isomeric xylenols by vapor phase chromatography and by spectral methods. It is significant that the major point of alkylation is *para* to the phenolic group while the reaction of *o*-cresol with DMSO and DCC leads to exclusively *ortho*-substituted products, thus supporting the intramolecular mechanism previously proposed for the latter reaction.[1]

Thus, while it has been possible to demonstrate facile intermolecular transfer of the thiomethoxymethyl group from the pentamethyl ketone **19** to other nucleophiles, we have also noted a pronounced tendency toward intramolecular alkylation during acid treatment of ketones such as **13** or **18** having unsubstituted 4 positions. These observations are best reconciled by assuming that the methylmethylenesulfonium ion (**29**) and the phenol, which arise by acid-catalyzed dissociation of the dienone according to path **B**, exist as a rather firmly bound π complex. Such a complex would lead to preferential "intramolecular" recombination but could still give intermolecular alkylation if sufficient amounts of other nucleophiles were present. A similar type of π complex has been proposed by Miller as the transition state in dienone–phenol rearrangements.[19]

(19) B. Miller, *J. Am. Chem. Soc.*, 87, 5115 (1965).

Phenols containing halogen atoms in the 2 and 6 positions behave somewhat anomolously. Thus, the reaction of pentachlorophenol with DMSO, DCC, and anhydrous phosphoric acid led to the formation of pentachlorophenyl thiomethoxymethyl ether (**43**) which was isolated crystalline in 60% yield. This compound was also obtained in 63% yield through reaction of potassium pentachlorophenolate with chloromethyl methyl sulfide in benzene. The action of acid on **43** regenerated pentachlorophenol. The formation of aryl thiomethoxymethyl ethers was previously shown[1] to be characteristic of only strongly acidic phenols. The reaction with pentachlorophenol (pK = 5.2[20]) is, however, the only case we have studied in which ether formation was the principal reaction. We have previously suggested[1] that ether formation is the consequence either of rearrangement of the phenoxyphosphonium ylide **7** *via* attack by the carbanion on oxygen or of alkylation of the free phenol by the methylmethylenesulfonium species (**29**). On the basis of studies carried out in this laboratory on the reactions of sulfoxides and carbodiimides with a variety of other functional groups, we are now more inclined to accept the dissociation–recombination mechanism.

The reaction of DMSO and DCC with 2,6-dichlorophenol and 2,4,6-trichlorophenol, however, lead to quite different results, the major products being 8-chloro-1,3-benzoxathian (**44**) and 6,8-dichloro-1,3-benzoxathian (**45**), respectively. The formation of these products in yields of 25 and 42% contrast sharply with



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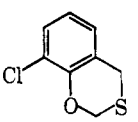

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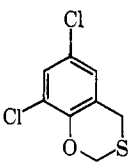

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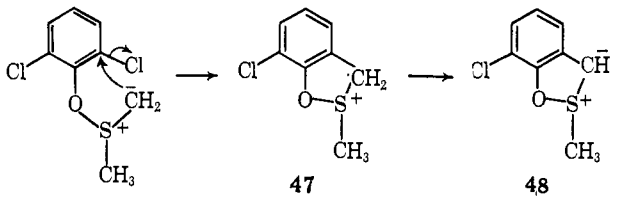
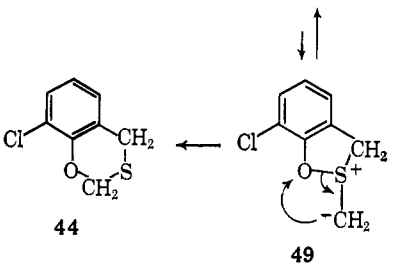
the very low yields (usually about 5%) of benzoxathians resulting from the reactions of most simple phenols.[1] Clearly displacement of chloride ion from one of the *ortho* positions constitutes a significant driving force favoring cyclic products. A possible mechanism would be as shown from **46** → **44**.



46 **47** **48**

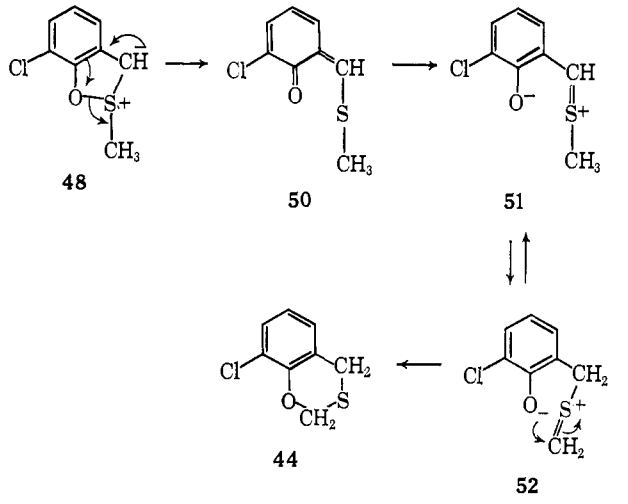


44 **49**

Loss of a proton from the cyclic sulfonium ion **47** would be expected to occur primarily at the benzylic

(20) G. J. Tiessens, *Rec. Trav. Chim.*, **50**, 112 (1931).

carbon, giving ylide **48** which would be relatively inert. The thermodynamically less stable ylide **49** could, however, rearrange with formation of the benzoxathian **44**. Alternatively the ylide **48** could rearrange *via* several noncyclic intermediates, as, *e.g.*, **48** → **44**.



The intervention of the thermodynamically less stable intermediates **49** and **52** in the mechanisms above is very similar to that considered by Wittig, Hauser, and others[21] to occur during the Sommelet rearrangement of benzyltrimethylammonium ions. A decision between these two related pathways cannot be made at this time. An anomalous result accompanied the reaction of *o*-chlorophenol with DMSO and DCC since, instead of the expected unsubstituted 1,3-benzoxathian, the major new product was 8-chloro-1,3-benzoxathian (**44**), identical with the product from 2,6-dichlorophenol. The yield of **44** was only 20%, however, and greater than 50% of the starting material was recovered unchanged. The reason for this relatively high yield of benzoxathian *without* loss of chlorine remains obscure.

Very recently Hayashi and Oda[22] have described the thiomethoxymethylation of several phenols by dimethyl sulfoxide and acetic anhydride and have shown that *para* alkylation of 2,6-dimethylphenol does occur. We, too, have performed some experiments using the DMSO–acetic anhydride mixture and have observed both ring alkylation and O-alkylation, the latter becoming the predominant reaction with more strongly acidic phenols.

In future papers in this series we will describe the reactions of sulfoxides and carbodiimides with a considerable number of other functional groups leading to some unusual products.

Experimental Section

Methods. The general experimental methods used in this work are similar to those described previously.[1] Instrumental analyses were performed by the staff of the Analytical Laboratories of Syntex Research under the direction of Dr. L. Throop. We are particularly grateful to Mr. John Murphy and Dr. Laszlo Tökés for their assistance with nmr and mass spectrometry.

Reactions of 2,6-Dimethylphenol with DMSO and DCC. 2,6-Dimethylphenol (2.44 g, 20 mmoles) was dissolved in a mixture of anhydrous DMSO[23] (20 ml) and benzene (20 ml) containing DCC (12.36 g, 60 mmoles). A solution of anhydrous orthophosphoric acid in DMSO (2 ml of 5 *M*) was added, and after several minutes an exothermic reaction ensued. After 45 min, thin layer chromatography using benzene showed the starting phenol to be completely absent, having been replaced by a slower moving product. Ether (100 ml) was added and the crystalline dicyclohexylurea (7.2 g) was removed by filtration. The ether solution was then extracted four times with equal volumes of water, dried over sodium sulfate, and evaporated to dryness, leaving 7.40 g of a pale yellow syrup. This was divided into two equal portions which were worked up separately.

a. One portion was chromatographed on a column containing 300 g of Merck silicic acid (0.05–0.12-mm particles) using benzene as eluent. A single, ultraviolet-absorbing product was detected in fractions 60–100 (25 ml each), and these were pooled and evaporated to dryness. The residue immediately crystallized, giving 1.20 g (66%) of 2,6-dimethyl-4-(thiomethoxymethyl)phenol (**11**), mp 40–42°, unchanged on recrystallization from hexane. Analytical and spectral data are given in Tables I and II. A small sample (100 mg) was stirred in methanol (5 ml) with Davidson sponge nickel[6] (1 g) for 1 hr. The nickel was then removed by filtration through Celite and, upon evaporation of the solvent, the residue crystallized. This material was chromatographically homogeneous and, following sublimation, had mp 72–73°. It was indistinguishable from an authentic sample of 2,4,6-trimethylphenol by its infrared and nmr spectra.

b. Examination of the second portion by vapor phase chromatography on a 5-ft column of 5% SE-30 on Gas Chrom Q using a temperature of 130° showed the presence of only a trace of the phenol **11** (retention time 9.8 min) together with major peaks of DCC (retention time 15.7 min) and a more volatile compound (retention time 3.3 min). This material was rapidly[24] chromatographed on four 1 m × 20 cm preparative silica plates coated with a 1.3-mm layer of Merck silica HF.[7] The yellowish band with an R_f of 0.2–0.3 was removed, eluted with methylene chloride, and evaporated to dryness, leaving 1.60 g of a pale yellow oil. Vapor phase chromatography of this material showed the presence of about 20% of the rearranged phenol **11** which was removed by repeated extraction of a solution of the mixture in ether with 0.25 *N* sodium hydroxide. The ether solution was then washed with water, dried over sodium sulfate, and evaporated, leaving 1.20 g (66%) of 2,6-dimethyl-6-(thiomethoxymethyl)cyclohexa-2,4-dien-1-one (**13**) which was homogeneous by thin layer and vapor phase chromatography. The product could be distilled as a clear yellow oil in a "Kugelrohr" short-path apparatus[25] with a bath temperature of 60° at 10^{-4} mm. Immediately following distillation **13** showed a single carbonyl band at 1650 cm^{-1} (see Tables I and II for other analytical and spectral data). Upon storage of 300 mg of pure **13** at room temperature for several days a considerable amount of crystalline material separated. The mixture was diluted with pentane and filtered, leaving 120 mg (40%) of white crystals, mp 116–125°, which behaved identically with **13** on vapor phase chromatography. Repeated crystallization from ethanol gave a pure isomer of the dimer **14**, mp 130–131°. This material showed carbonyl bands at 1675 and 1715 cm^{-1}. Mass spectrometry showed a molecular ion (relative intensity 56%) at *m/e* 364 and other significant features which are discussed in the text.

Addition of trifluoroacetic acid (10 μl) to a solution of **13** (100 mg) in methylene chloride led to the immediate disappearance of the yellow color and complete rearrangement to the phenol **11** which was identified by vapor phase chromatography and by crystallization of the evaporated reaction mixture.

Similar reactions between 2,6-dimethylphenol, DMSO, and DCC in the presence of 10 equiv of furan, anisole, or 1,3-dimethoxybenzene led to identical products, as judged by vapor phase chromatography. No evidence of alkylation of the additives could be detected.

Reaction of 2,4,6-Trimethylphenol with DMSO and DCC. A reaction between 2,4,6-trimethylphenol (2.72 g, 20 mmoles) and DCC (12.36 g, 60 mmoles) in DMSO (20 ml) and benzene (20 ml) containing 10 mmoles of anhydrous orthophosphoric acid was worked up after 2 hr exactly as described above with 2,6-dimethylphenol. The crude, extracted product (6.6 g) was divided into two equal portions and handled separately as follows.

(21) (a) G. Wittig, R. Mangold, and G. Felletschin, *Ann.*, **560**, 117 (1948); (b) K. P. Klein and C. R. Hauser, *J. Org. Chem.*, 31, 4276 (1966); (c) H. E. Zimmerman, ref 14, p 378.

(22) Y. Hayashi and R. Oda, *J. Org. Chem.*, 32, 457 (1967).

(23) Dried by distillation *in vacuo* and storage over Linde Molecular Sieve Type 4A.

(24) The entire procedure, including application to the plates, development, and elution of the product, was completed in less than 2 hr.

(25) R. Graeve and G. H. Wahl, *J. Chem. Educ.*, 41, 279 (1964).

a. One portion was rapidly chromatographed on four 1 m × 20 cm preparative silica plates using benzene, and the resulting major band was eluted with methylene chloride, leaving 1.83 g (93%) of 2,4,6-trimethyl-6-(thiomethoxymethyl)cyclohexa-2,4-dien-1-one (**15**) as a clear yellow oil that was homogeneous by vapor phase chromatography (retention time 4.9 min at 130° on a 5-ft SE-30 column). This material could be distilled in a short-path apparatus (65° (10^{-4} mm)) with negligible loss and showed ν_{max} 1645 cm^{-1}. Other analytical and spectral data are in Tables I and II. Addition of trifluoroacetic acid (5 μl) to a solution of **15** (10 mg) in methylene chloride (0.05 ml) led to the formation of 90–95% of the isomeric phenol **12** and 5–10% of 2,4,6-trimethylphenol as determined by vapor phase chromatography.

b. The second portion was chromatographed on a column containing 300 g of Merck silicic acid using benzene and collecting 20-ml fractions. Fractions 69–102 contained 0.35 g (18%) of 2,4,6-trimethyl-3-(thiomethoxymethyl)phenol (**12**) which crystallized spontaneously and could be recrystallized from hexane, mp 85–86° (see Tables I and II). Fractions 103–240 contained 1.20 g of a yellow oil that was shown by vapor phase chromatography to be a mixture of 30% **12** and 70% of the ketone **15**. In this case the phenol could not be extracted with alkali.

Desulfurization of **12** with sponge nickel in methanol at room temperature led to complete conversion to 2,3,4,6-tetramethylphenol, mp 77–78°, which was identical with an authentic sample.

Reaction of Durophenol with DMSO and DCC. a. Freshly crystallized (methanol) durophenol (1.50 g, 10 mmoles) was allowed to react at room temperature for 2 hr with DCC (6.18 g, 30 mmoles) and anhydrous phosphoric acid (5 mmoles) in a mixture of DMSO (10 ml) and benzene (10 ml). The reaction was worked up as above, giving 3.70 g of a yellow oil that was shown by vapor phase chromatography on a 5-ft column of 10% NPGS on Gas Chrom Q at 145° to contain essentially nothing but a mixture of DCC (5.7 min) and the desired ketone (4.5 min). This material was chromatographed on four 1 m × 20 cm preparative silica plates using benzene, elution of the ultraviolet-absorbing band giving 1.80 g (86%) of 2,3,5,6-tetramethyl-6-(thiomethoxymethyl)cyclohexa-2,4-dien-1-one (**18**) as a chromatographically homogeneous yellow oil that was distilled in a short-path apparatus (90° bath at 10^{-3} mm) with 1.60-g recovery; $\nu_{max}^{CHCl_3}$ 1635 cm^{-1} (see Tables I and II for other data).

Desulfurization of 18. The thiomethoxymethyl ketone **18** (420 mg, 2 mmoles) was dissolved in methanol (20 ml) and Davidson sponge nickel (4–5 g) was added. After stirring at room temperature for 2 hr thin layer chromatography with benzene showed the disappearance of the starting material accompanied by the appearance of two ultraviolet-absorbing and one nonultraviolet-absorbing products. The mixture was filtered through Celite and the filtrate was chromatographed on a 1-m-long preparative silica plate using benzene–chloroform (7:2), the two ultraviolet-absorbing bands then being eluted with acetone. The faster band (100 mg) was distilled in a micro short-path apparatus at 40° (10^{-4} mm), giving 90 mg of 2,3,5,6,6-pentamethylcyclohex-2-en-1-one (**21**) as a colorless oil, λ_{max}^{MeOH} 243 mμ (ε 9100) ν_{max} 1655 cm^{-1}. The nmr spectrum showed two vinyl methyl groups as singlets at 113 and 106 cps, two quaternary methyl groups as singlets at 54 and 66 cps, one secondary methyl group as a multiplet at 50–75 cps, and two allylic protons at 120–140 cps.

Anal. Calcd for $C_{11}H_{18}O$: C, 77.86; H, 11.76; O, 10.37. Found: C, 78.33; H, 11.26; O, 10.20.

The slower band (130 mg) was distilled *in vacuo* at 60° (10^{-4} mm), giving 2,3,5,6-tetramethyl-6-(thiomethoxymethyl)cyclohex-2-en-1-one (**23**), λ_{max}^{MeOH} 243 mμ (ε 10,800); ν_{max} 1650 cm^{-1}. The nmr spectrum in deuteriochloroform clearly confirmed structure **23** and showed a $-SCH_3$ group as a singlet at 115 cps, the $-CH_2S$ as a pair of geminally coupled doublets (J = 13 cps) at 151 and 193 cps, two aliphatic methyl groups as a broad singlet at 57 cps, two vinylic methyl groups as singlets at 107 and 127 cps, and two allylic protons as a broad singlet at 138 cps.

2,3,5,6-Tetramethyl-4-(thiomethoxymethyl)phenol (20). 2,3,5,6-Tetramethyl-6-(thiomethoxymethyl)cyclohexa-2,4-dien-1-one (**18**, 210 mg, 1 mmole) was dissolved in methylene chloride, and trifluoroacetic acid (25 μl) was added. Within 10 min the yellow color had disappeared and a mass of white crystals had separated. The solvent was evaporated *in vacuo* and the residue was crystallized from methanol, giving 195 mg (93%) of 2,3,5,6-tetramethyl-4-(thiomethoxymethyl)phenol (**20**), mp 144–145° (see Tables I and II for analytical and spectral data).

Desulfurization of **20** with Davidson sponge nickel in methanol led to quantitative conversion to pentamethylphenol, mp 129–130°, following sublimation *in vacuo* at 100°. This product had an identical infrared spectrum with that of an authentic sample.

2,3,4,5,6-Pentamethyl-6-(thiomethoxymethyl)cyclohexa-2,4-dien-1-one (19). Commercial pentamethylphenol[26] was purified by repeated treatment with activated charcoal in hot methanol and then crystallized twice from methanol to give pale yellow needles, mp 129–130°. This material (1.64 g, 10 mmoles) was dissolved in a mixture of DMSO (20 ml) and benzene (20 ml) and allowed to react with DCC (6.18 g, 30 mmoles) and anhydrous orthophosphoric acid (5 mmoles). After 1 hr the reaction was worked up as described for 2,6-dimethylphenol and chromatographed on six 1-m-long preparative silica plates using benzene–chloroform (6:1). The resulting yellow band was eluted with methylene chloride and the extracts were evaporated, leaving 0.95 g (85%) of **19** as a chromatographically homogeneous clear yellow oil which was distilled in a short-path apparatus at 80° (10^{-4} mm); $\nu_{max}^{CHCl_3}$ 1630 and 1650 cm^{-1}. Other analytical and spectral data are in Tables I and II.

Desulfurization of 440 mg (2 mmoles) of **19** in methanol (20 ml) containing 4–5 g of Davidson sponge nickel was carried out at room temperature for 4 hr. Following filtration through Celite the filtrate was chromatographed on 2-m-long preparative silica plates using two consecutive developments with benzene–chloroform (7:2). The main ultraviolet-absorbing band was eluted with methylene chloride and evaporated, leaving 150 mg (42%) of 2,3,4,5,6,6-hexamethylcyclohex-2-en-1-one (**22**) which was distilled in a micro short-path apparatus at 60° (10^{-4} mm); λ_{max}^{MeOH} 246 mμ (ε 10,700); ν_{max} 1660 cm^{-1}. The nmr spectrum in deuteriochloroform showed two vinylic methyl groups as rough singlets at 107 and 114 cps, a secondary methyl group as a doublet (J = 7 cps) at 52 cps, and three other methyl groups as superimposed signals at 65–73 cps.

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.75; H, 11.00.

Reaction of 2,3,4,6-Tetramethylphenol with DMSO and DCC. 2,3,4,6-Tetramethylphenol (1.50 g, 10 mmoles) was allowed to react overnight at room temperature with DCC (6.18 g) and anhydrous orthophosphoric acid (5 mmoles) in DMSO (15 ml) and benzene (5 ml). The reaction was worked up as above for 2,6-dimethylphenol, giving 4.0 g of a yellow oil which was chromatographed on four 1-m-long preparative silica plates using benzene–chloroform (4:1). The single yellow band was eluted with methylene chloride, giving 2.0 g (95%) of a yellow oil that was distilled in a short-path apparatus at 80° (10^{-3} mm). This product appeared homogeneous by vapor phase and thin layer chromatography but, from its nmr spectrum, was clearly a mixture of roughly 60% 2,3,4,-6-tetramethyl-6-(thiomethoxymethyl)cyclohexa-2,4-dien-1-one (**25**) and 40% of the 2,4,5,6-tetramethyl isomer **26**. The spectrum of the mixture showed a quaternary methyl group as a singlet at 69 cps, a $-SCH_3$ singlet at 121 cps, and three vinylic methyl singlets at 112, 113, and 117 cps. The single vinyl proton of **25** was a broadened singlet at 358 cps, while that of **26** appeared at 405 cps. The $S-CH_2$ groups appeared as overlapping quartets at 151–194 cps, all showing geminal coupling of 12 cps; $\nu_{max}^{CHCl_3}$ 1645 cm^{-1} (other analytical and spectral data are in Tables I and II).

2,3,4,6-Tetramethyl-5-(thiomethoxymethyl)phenol (27). The mixed ketones **25** and **26** (420 mg, 2 mmoles) were dissolved in methylene chloride (8 ml), and trifluoroacetic acid (0.1 ml) was added. After 1 hr the colorless solution was evaporated to dryness and chromatographed on a 1-m-long preparative silica plate using benzene. Two ultraviolet-absorbing bands resulted and were eluted with methylene chloride. The material from the faster band (130 mg) proved to be 2,3,4,6-tetramethylphenol while that from the slower band (150 mg, 60% from **25**) was recrystallized from cyclohexane, giving 2,3,4,6-tetramethyl-5-(thiomethoxymethyl)-phenol (**27**), mp 97–98° (see Tables I and II). Desulfurization of 25 mg of **27** gave crystalline pentamethylphenol, identical with an authentic sample.

Benzyl Methyl Sulfoxide. Benzyl methyl sulfide[27] (35 g) was dissolved in acetic acid (100 ml), and 30% hydrogen peroxide (25 ml) was added slowly over 30 min with ice cooling. The mixture was allowed to stand overnight and then added to a solution of sodium hydroxide (80 g) in water (500 ml). Extraction of the clear solution with ether according to Bordwell and Pitt[15] failed to extract the sulfoxide, but extraction with methylene chloride gave 36 g of a colorless oil. Upon addition of ether the entire mass crystal-

(26) Aldrich Chemical Co., Milwaukee, Wis.
(27) Columbia Organic Chemicals Co., Columbia, S. C.

lized, giving 29 g of colorless benzyl methyl sulfoxide, mp 55–56°.[28]

2-Methyl-6-(α-thiomethoxybenzyl)phenol (32). *o*-Cresol (1.1 g, 10 mmoles), benzyl methyl sulfoxide (3.1 g, 20 mmoles), DCC (6.18 g, 30 mmoles), and anhydrous phosphoric acid (5 mmoles) were dissolved in dry ether (20 ml) and allowed to stand overnight. A gummy precipitate separated rapidly.[29] A solution of oxalic acid (3.78 g, 30 mmoles) in methanol was added, and after 30 min the mixture was diluted with water (100 ml) and ether (100 ml) and filtered. The ether layer was extracted with aqueous sodium bicarbonate, then twice with water, and dried over sodium sulfate. Thin layer chromatography using benzene showed the presence of considerable unreacted *o*-cresol, an intense spot of benzaldehyde, two minor by-products near the solvent front, and a principal product with R_f 0.7. The mixture was chromatographed on a column containing 150 g of Merck silicic acid using benzene, giving 828 mg (34%) of 2-methyl-6-(α-thiomethoxybenzyl)phenol (**32**) as a chromatographically homogeneous oil that could be distilled in a short-path apparatus at 100° (10^{-4} mm); λ_{max}^{MeOH} 277 mμ (ε 2400); $\lambda_{max}^{OH^-}$ 283 mμ (ε 2100), 303 mμ (ε 2300). The nmr spectrum showed three-proton singlets at 122 (SCH_3) and 137 cps ($ArCH_3$), a one-proton singlet at 315 cps (Ar_2CHS), eight aromatic protons as a multiplet at 400–460 cps, and a phenolic proton at 422 cps.

Anal. Calcd for $C_{15}H_{16}OS$: C, 73.75; H, 6.60; S, 13.10. Found: C, 73.94; H, 6.71; S, 13.42.

Desulfurization with sponge nickel catalyst in refluxing methanol for 1 hr gave 2-benzyl-6-methylphenol identical with an authentic sample.[1]

2,6-Dimethyl-4-(α-thiomethoxybenzyl)phenol (34). 2,6-Dimethylphenol (610 mg, 5 mmoles), benzyl methyl sulfoxide (1.54 g, 10 mmoles), and DCC (3.09 g, 15 mmoles) were dissolved in anhydrous dimethylformamide (5 ml), and a solution of anhydrous orthophosphoric acid in ether (1.0 ml of 2.5 *M*) was added. An exothermic reaction ensued, and the mixture was allowed to stand overnight. Ether (100 ml) was added and, after filtration of dicyclohexylurea, the solution was extracted four times with water and then dried over sodium sulfate. Evaporation left 3.4 g of a yellow oil that was chromatographed on six 1-m-long preparative silica plates using benzene. The desired product ran immediately behind unreacted 2,6-dimethylphenol, from which it was largely resolved. A slightly faster band containing 100 mg of benzaldehyde (identified by vapor phase chromatography and formation of a 2,4-dinitrophenylhydrazone) and a slower moving yellowish band containing at least three different products were also present. The desired band was eluted with methylene chloride, giving 0.50 g of product still contaminated with some starting material and benzaldehyde. This was rechromatographed on two preparative silica plates using three consecutive developments with benzene–carbon tetrachloride (9:1) which gave 142 mg (11%) of chromatographically pure 2,6-dimethyl-4-(α-thiomethoxybenzyl)phenol (**34**) as an oil that was distilled in a short-path apparatus at 100° (10^{-4} mm); λ_{max}^{MeOH} 233 mμ (shoulder) (ε 8000), 278 mμ (ε 1600). The nmr spectrum showed a three-proton singlet at 117 cps (SCH_3), a six-proton singlet at 130 cps (2 $ArCH_3$), and a one-proton singlet at 298 cps (Ar_2CHS), as well as a phenolic proton and seven aromatic protons between 410 and 460 cps.

Anal. Calcd for $C_{16}H_{18}OS$: C, 74.39; H, 7.02; S, 12.38. Found: C, 74.64; H, 7.20; S, 12.46.

Reaction of Durophenol with Methyl Phenyl Sulfoxide. Durophenol (1.5 g, 10 mmoles) was dissolved in ether (20 ml) containing methyl phenyl sulfoxide[30] (2.8 g, 20 mmoles), DCC (6.18 g, 30 mmoles), and anhydrous phosphoric acid (5 mmoles). Ether (100 ml) was added and, after filtration of dicyclohexylurea, the solution was extracted with water and dried. Chromatography of the residue on a column containing 150 g of silicic acid with benzene gave a mixture (1.2 g) of unreacted durophenol and a more polar product, rechromatography of which gave 163 mg (10%) of 1,4-duroquinone as yellow needles, mp 112–115° after crystallization from hexane. This product had an identical melting point and infrared spectrum with that of an authentic sample of duroquinone.

2-(*t*-Butylthiomethyl)-6-methylphenol (38). *o*-Cresol (1.1 g, 10 mmoles) was allowed to react overnight in ether (20 ml) containing *t*-butyl methyl sulfoxide[13] (3.0 ml, 25 mmoles), DCC (6.18 g, 30 mmoles), and anhydrous phosphoric acid (5 mmoles). Following filtration and extraction with water the residue was chromatographed with benzene on a column containing 100 g of silicic acid. A fast-moving, ultraviolet-absorbing band was eluted giving 565 mg (27%) of chromatographically pure **38** which was distilled in a short-path apparatus at 80° (10^{-3} mm); λ_{max}^{MeOH} 277 mμ (ε 1800); $\lambda_{max}^{OH^-}$ 297 mμ (ε 1100) and 282 mμ (ε 2000). The nmr spectrum showed the *t*-butyl group as a nine-proton singlet at 81 cps, a three-proton singlet ($ArCH_3$) at 135 cps, a two-proton singlet ($ArCH_2S$) at 231 cps, and three aromatic protons and a phenolic proton between 400 and 440 cps.

Anal. Calcd for $C_{12}H_{18}OS$: C, 68.54; H, 8.63; S, 15.22. Found: C, 68.43; H, 8.51; S, 15.26.

4-(*t*-Butylthiomethyl)-2,6-dimethylphenol (39). 2,6-Dimethylphenol (3.05 g, 25 moles) was allowed to react overnight in benzene (20 ml) with *t*-butyl methyl sulfoxide (10 ml), DCC (15 g), and anhydrous phosphoric acid (1.2 g). Thin layer chromatography detected the presence of much unreacted 2,6-dimethylphenol together with a slightly slower moving product and a second trace compound. The reaction was worked up in the usual way and gave, after chromatography twice on columns of silicic acid with benzene and distillation at 100° (10^{-3} mm), 100 mg (2%) of pure **39** as an oil; λ_{max}^{MeOH} 277 mμ (ε 1700). The nmr spectrum showed the *t*-butyl group as a nine-proton singlet at 81 cps, a six-proton singlet (2 $ArCH_3$) at 133 cps, a two-proton singlet ($ArCH_2S$) at 220 cps, a one-proton singlet (phenol) at 274 cps, and two aromatic protons as a singlet at 418 cps.

Anal. Calcd for $C_{13}H_{20}OS$: C, 69.61; H, 8.99; S, 14.28. Found: C, 69.41; H, 8.82; S, 14.01.

Desulfurization of this product (25 mg) with Davidson sponge nickel in boiling methanol gave a single crystalline product, mp 70–71°, which was physically and spectrally identical with 2,4,6-trimethylphenol.

6-(*t*-Butylthiomethyl)-2,3,5,6-tetramethylcyclohexa-2,4-dien-1-one (40). Durophenol (2.8 g, 25 mmoles) was allowed to react overnight in benzene (25 ml) with DCC (15.5 g, 75 mmoles), *t*-butyl methyl sulfoxide (10 ml), and dichloroacetic acid (1.03 ml, 12.5 mmoles). The reaction was worked up in the usual way and chromatographed on a column containing 250 g of silicic acid using benzene.[31] A yellow band (2.0 g) was obtained and rechromatographed on a second column, but completely homogeneous material was not obtained. The yellow oil decomposed to a black tar containing durophenol upon attempted short-path distillation and appeared to be unstable on storage at room temperature. Its identification as **40** was based on its ultraviolet (λ_{max}^{MeOH} 323 mμ), infrared (ν_{max} 1650, 1680 cm^{-1}), and nmr spectra (*t*-butyl and quaternary methyl groups as a singlet at 75 cps, the $-CH_2S-$ group as a pair of geminally coupled doublets (J = 11 cps) at 162 and 189 cps, a single vinyl proton as a singlet at 365 cps, and the vinyl methyl groups plus an unidentified impurity corresponding to roughly three protons as a multiplet at 105–135 cps). Treatment with one drop of concentrated hydrochloric acid in methanol led to complete conversion to durophenol.

Pentachlorophenyl Thiomethoxymethyl Ether (43). **a.** Pentachlorophenol (6.6 g, 25 mmoles) was allowed to react exothermically in benzene (20 ml) with DCC (15.5 g, 75 mmoles), DMSO (15 ml), and anhydrous phosphoric acid (12.5 mmoles). After standing overnight the mixture was diluted with ether (100 ml), filtered, and extracted four times with water. It was then extracted several times with 0.5 *N* sodium hydroxide and the nonphenolic fraction was chromatographed on a column containing 150 g of silicic acid with benzene–hexane (1:1). A single ultraviolet-absorbing product (4.9 g, 60%) was obtained and crystallized from methanol, giving **43** as white needles, mp 87–88°; λ_{max}^{MeOH} 214 (ε 85,500), 292 (520), and 300 mμ (550). The nmr spectrum shows only a three-proton singlet (SCH_3) at 143 cps and a two-proton singlet (OCH_2S) at 315 cps.

b. Pentachlorophenol (2.64 g, 10 mmoles) and potassium hydroxide (0.56 g, 10 mmoles) were dissolved in methanol (20 ml) and the solution was evaporated to dryness, leaving the crystalline potassium salt which was dried *in vacuo*. It was then suspended in benzene (50 ml) together with chloromethyl methyl sulfide (10 ml) and refluxed for 1 hr. Ether (50 ml) was added and the solution was extracted three times with 0.5 *N* sodium hydroxide. The ether solution was dried, evaporated, and chromatographed on a column containing 80 g of silicic acid with benzene–hexane (1:1). The major product was evaporated and crystallized from methanol, giving 2.06 g (63%) of **43** identical with that above.

(28) A. Cerniani, G. Modena, and P. E. Todesco, *Gazz. Chim. Ital.*, **90**, 3 (1960), report mp 57–58° by a different route.

(29) We later showed that only dicyclohexylurea separated if dimethylformamide was used as the solvent. The yield of **32** was similar.

(30) C. C. Price and J. J. Hydock, *J. Am. Chem. Soc.*, 74, 1943 (1952).

(31) When the crude, extracted reaction mixture was dissolved in ether, 1.0 g of N-dichloroacetyl-N,N′-dicyclohexylurea, mp 145–147°, crystallized out.

6,8-Dichloro-1,3-benzoxathian (45). 2,4,6-Trichlorophenol (4.92 g, 25 mmoles) was allowed to react overnight with DCC (15.5 g, 75 mmoles) and anhydrous phosphoric acid (12.5 mmoles) in a mixture of benzene (25 ml) and DMSO (15 ml). Following removal of dicyclohexylurea and extraction with water, the phenolic and nonphenolic components were separated by extraction with 0.5 *N* sodium hydroxide. The nonphenolic fraction contained one major product that was isolated by chromatography on a column of silicic acid using benzene–hexane (1:1). On evaporation of the solvent the product crystallized spontaneously and, after recrystallization from hexane, gave 2.3 g (42%) of **45**, mp 126–127°; λ_{max}^{MeOH} 231 (ε 10,600), 285 (2900), and 295 mμ (2900). The nmr spectrum showed a two-proton singlet ($ArCH_2S$) at 231 cps, a two-proton singlet (OCH_2S) at 319 cps, and two aromatic protons as doublets (J = 2.5 cps) at 417 and 436 cps.

Anal. Calcd for $C_8H_6OSCl_2$: C, 43.48; H, 2.74; S, 14.51; Cl, 32.16. Found: C, 43.64; H, 2.89; S, 14.31; Cl, 32.03.

8-Chloro-1,3-benzoxathian (44). a. 2,6-Dichlorophenol (4.1 g, 25 mmoles) and DCC (15.5 g, 75 mmoles) were allowed to react overnight in benzene (20 ml) and DMSO (15 ml) containing anhydrous phosphoric acid (12.5 mmoles). After removal of dicyclohexylurea and extraction of the DMSO the resulting ether solution was extracted three times with 0.5 *N* sodium hydroxide, giving primarily unreacted starting phenol. The nonphenolic fraction was chromatographed on a column of silicic acid using benzene–hexane (1:1), giving one principal ultraviolet-absorbing product. This was then distilled in a short-path apparatus at 50° (10^{-3} mm), giving 1.17 g (25%) of 8-chloro-1,3-benzoxathian; λ_{max}^{MeOH} 277 mμ (ε 1950) and 285 mμ (ε 1850). The nmr spectrum showed two-proton singlets at 231 ($ArCH_2S$) and 318 cps (SCH_2O) and three aromatic protons between 405 and 440 cps.

Anal. Calcd for C_8H_7OSCl: C, 51.46; H, 3.78; S, 17.19; Cl, 19.02. Found: C, 51.17; H, 3.89; S, 17.04; Cl, 18.74.

b. *o*-Chlorophenol (2.06 ml, 20 mmoles) was allowed to react for 4 hr with DCC (12.4 g, 60 mmoles) and anhydrous phosphoric acid (10 mmoles) in a mixture of benzene (10 ml) and DMSO (20 ml). The mixture was worked up as above, giving 1.26 g (50%) of almost pure unreacted *o*-chlorophenol in the phenolic fraction and 0.75 g (20%) of **44** after chromatography of the nonphenolic portion. The material was indistinguishable from that obtained above.

Intramolecularity of Rearrangement of Dienones. Vapor phase chromatography of an equimolar mixture of 2,6-dimethyl-4-(thiomethoxymethyl)phenol (**11**) and 2,3,4,6-tetramethyl-4-(thiomethoxymethyl)phenol (**20**) on a 5-ft column of 10% neopentyl glycol succinate on Gas Chrom Q[32] at 160° consistently showed that the integrated detector response toward **20** was 2.15 times that toward **11**.[33]

a. A mixture of the dienone **18** (21 mg, 0.1 mmole) and 2,6-dimethylphenol (61 mg, 0.5 mmole) was dissolved in methylene chloride (0.25 ml), and trifluoroacetic acid (10 μl) was added. Almost immediately the yellow color disappeared, and after 20 min the mixture was directly examined by vapor phase chromatography as above. The integrated intensities of the peaks corresponding to **20** and **11** were in a ratio of 4.40:1, which, after correction for the differences of detector response, indicated the formation of 67% **20** and 33% **11**. The only other peaks present were those of excess 2,6-dimethylphenol and durophenol.

b. The 2,6-dimethyldienone **13** (18 mg, 0.1 mmole) and durophenol (75 mg, 0.5 mmole) were dissolved in methylene chloride (0.25 ml), and trifluoroacetic acid (10 μl) was added. Disappearance of the yellow color was almost instantaneous, and after 20 min vapor phase chromatography showed the products to be **11** and **20** in a ratio of 3.0:1.

Alkylation of *o*-Cresol by the Pentamethyl Ketone 19. 2,3,4,5,6-Pentamethyl-6-(thiomethoxymethyl)cyclohexa-2,4-dien-1-one (**19**, 224 mg, 1 mmole) and *o*-cresol (324 mg, 3 mmoles) were dissolved in methylene chloride (0.5 ml), and trifluoroacetic acid (25 μl) was added. After 10 min vapor phase chromatography (5-ft NPGS column at 150°) showed the complete absence of **19** and formation of two products with retention times of 15.7 and 3.1 min with integrated intensities in a ratio of 3.0:1. The latter peak was identical with that of authentic **1**. The only other significant products were excess *o*-cresol (1.2 min) and pentamethylphenol (7.7 min). The entire mixture was then evaporated to dryness and chromatographed on 2-m-long preparative silica plates using benzene as eluent. Four ultraviolet-absorbing bands were obtained and were eluted with methylene chloride. The fastest band gave 33 mg (20%) of a homogeneous oil that was identical in all respects with an authentic sample of **1**. The second and third bands contained respectively 140 mg of crystalline pentamethylphenol and 133 mg of *o*-cresol, while the slowest band gave 76 mg (45%) of a chromatographically homogeneous oil identified as 2-methyl-4-(thiomethoxymethyl)phenol (**42**) which was distilled in a short-path apparatus at 60° (10^{-3} mm); λ_{max}^{MeOH} 280 mμ (ε 1850) and 229 mμ (ε 7850); $\lambda_{max}^{OH^-}$ 289 mμ (ε 2350) and 252 mμ (ε 8200).[34] The 100-Mc nmr spectrum showed the thiomethoxymethyl group as two singlets at δ 2.01 (SCH_3) and 3.59 ($ArCH_2S$), and the aromatic methyl group as a singlet at δ 2.24. The aromatic protons appeared as a doublet (J = 8 cps) at δ 6.68 (C-6) and a quartet (J_{ortho} = 8 cps, J_{meta} = 3 cps) centered at δ 6.98 (C-5) The C-3 proton appeared as a broad singlet at δ 7.04 overlapping the low-field half of the C-5 quartet.[35]

Anal. Calcd for $C_9H_{12}OS$: C, 64.27; H, 7.19; S, 19.02. Found: C, 64.17; H, 7.26; S, 18.94.

Desulfurization of a sample of **42** with Davidson sponge nickel in methanol at room temperature for 30 min gave a single spot on thin layer chromatograms with an R_f identical with that of 2,4-dimethylphenol. This identity was confirmed by vapor phase chromatography on a 5-ft column of 10% NPGS on Gas Chrom Q[32] at 105° which clearly separated the desulfurization product from 2,6- and 2,3-dimethylphenols. It ran identically with 2,4- and 2,5-dimethylphenols, but the latter structure could be ruled out by the nmr spectrum of **42**.

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(33) 2,6-Dimethylphenol (retention time 1.4 min), durophenol (2.6 min), and the ketone **18** (2.3 min) were all clearly separated from substituting phenols **11** (11.2 min) and **20** (35.7 min) on this column.

(34) These spectra are reasonably consistent with those of 2,4-dimethylphenol but differ markedly from those of the isomeric xylenols. See "Organic Electronic Spectral Data," Vol. IV, J. P. Phillips and F. C. Nachod, Ed., Interscience Publishers, Inc., New York, N. Y., 1959, p 179.

(35) This aromatic pattern closely resembles that of 2,4-dimethylphenol and is not consistent with that from 2,3-, 2,5-, or 2,6-dimethylphenols.