# Exclusive Ortho Substitution of Phenols via [2,3]-Sigmatropic Rearrangements

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Abstract: General methods have been developed for the ortho alkylation and the ortho formylation of phenols. The processes are based on the rearrangement of ylides formed from the treatment of oxasulfonium salts with triethylamine. The oxasulfonium salts were prepared through the reaction of a phenol with either a chlorosulfonium chloride or an S-(N-succinimido)sulfonium chloride and used in situ. The intramolecular rearrangement of the ylides in a [2,3]-sigmatropic manner led to exclusive ortho substitution via an intermediate cyclohexadienone. Hydrogen transfer and accompanying rearomatization of the cyclohexadienone gave a phenol with sulfur in the side chain. Raney-nickel reduction gave an ortho-alkylated phenol. When dithiane was used as the sulfide, hydrolysis of the ortho-substituted product gave an ortho-formylated phenol. Alternatively, ortho formylation could be accomplished through an efficient process involving α-chlorination of an o-methylthiomethylphenol with N-chlorosuccinimide, followed by hydrolysis. A general discussion of the utility and mechanistic details of these reactions is given below.

Recently, we provided descriptions of a number of different transformations of the ylides derived from the base treatment of azasulfonium salts.[3-7] Through the utilization of these processes, both carbocyclic and heterocyclic aromatic amines could be ortho substituted. The ortho alkylation of anilines[3,6] and aminopyridines,[8] the synthesis of indoles,[4] the preparation of oxindoles,[5] and the ortho formylation of anilines[7] and aminopyridines[9] represent a sampling of the possible transformation of aromatic amines which can be accomplished in good yields with a minimum of effort. Mechanistically, the key step in the transformation involved the [2,3]-sigmatropic rearrangement of an ylide, **2**, derived from the base treatment of an N-phenylazasulfonium salt, **1**. The rearrangement produced
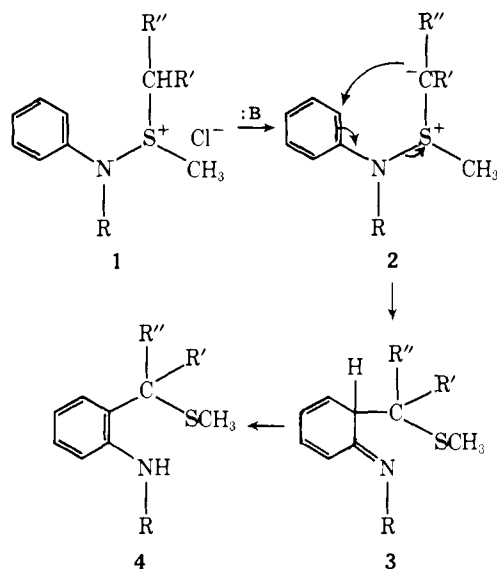
a cyclohexadienone imine, **3**, which on hydrogen transfer and accompanying rearomatization gave an ortho-substituted aniline, **4**. When **4** was prepared from a sulfide which contained a β-carbonyl group, an intramolecular condensation could occur subsequently to yield either an indole, indolenine, or oxindole derivative.

In principle, the same type of [2,3]-sigmatropic rearrangement should be possible with ylides derived from oxasulfonium salts. In fact, ample precedent exists for such a suggestion. During attempted Moffatt oxidation[10] of phenols with dimethyl sulfoxide (Me$_2$SO) and dicyclohexylcarbodiimide (DCC), it was noted that o-methylthiomethylphenols

were formed.[11] More detailed investigations of the reaction of phenols with dimethyl sulfoxide showed that the conversion to o-methylthiomethylphenols could be accomplished in the presence of the following: (a) DCC and pyridinium trifluoroacetate,[11,12] (b) pyridine–sulfur trioxide,[13] (c) acetic anhydride,[14] and (d) extensive heating.[15] In general, the various modifications of the Moffatt o-methylthiomethylation procedure were thought to involve initial formation of an oxasulfonium salt, **5**, followed by conversion of this salt into an ylide, **6**. Sommelet–Hauser type rearrangement[16] of such an
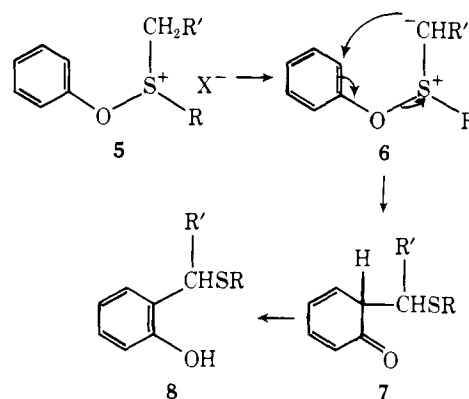
ylide would then produce a cyclohexadienone, **7**, which on hydrogen transfer and accompanying rearomatization would produce the observed o-methylthiomethylphenol, **8**. Unfortunately, the procedures which utilized DCC were complicated by the necessity of separating large amounts of dicyclohexylurea from the products, while the other methods generally gave unimpressive yields. In view of the excellent results observed in our laboratories for the ortho substitution of anilines, we felt that our methodology should provide an insight into the development of superior processes for the ortho substitution of phenols. We now wish to give a detailed account of our methods for the ortho alkylation and ortho formylation of phenols.[17]

Ortho Alkylation

Through analogy with the ortho substitution of anilines,[3-9] it might be anticipated that the requisite oxasulfonium salts of general formula **5** could be prepared either from the reaction of phenol with an active halogenating agent followed by addition of a sulfide, or from the reaction of phenol with a halosulfonium halide or an S-(N-succinimido)sulfonium halide.

Table I. Yields Obtained in the Methylthiomethylation of Phenols

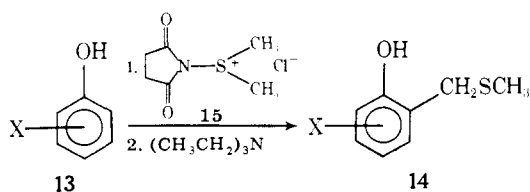| substituent on phenol	S-(N-succinimido) sulfonium salt	% yield (this study)[a]	previously reported yields
H	15	58	27,[11] 29,[12] 37,[13] 14[15]
p-CH₃	15	62	18,[12] 18[15]
p-OCH₃	15	49	38[13]
p-Cl	15	63	33[13]
o-CH₃	15	62	28,[11] 53,[12] 14[15]

[a] Yields are based on unrecovered phenol. All yields represent material of greater than 97% purity. In addition to the yields of o-methylthiomethylation products given, up to 4.5% of disubstitution product was observed in some cases.

Unfortunately, it has been well established that phenols react with active halogenating agents such as *tert*-butyl hypochlorite to yield ring-chlorinated phenols.[18] Reports on the reaction of phenols with either halosulfonium halides[19,20] or S-(N-succinimido)sulfonium halides[21] would seem equally discouraging. Claus and Rieder reported[19] that phenol (9) reacted with


9   10

11   12
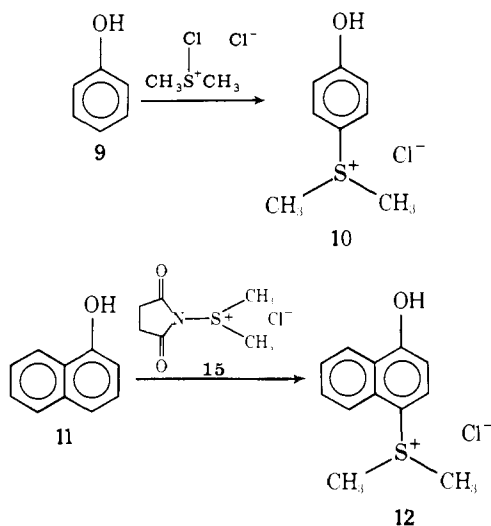
dimethylchlorosulfonium chloride to yield the sulfonium salt 10, while Vilsmaier and Sprügel noted[21] that α-naphthol (11) gave the sulfonium salt 12 on treatment with the azasulfonium salt derived from N-chlorosuccinimide and dimethyl sulfide. Interestingly, examination of the available experimental details which accompanied these reports[19,21] indicated that conditions were not ideal for formation of the requisite ylide.

In an attempt to develop a general method for the alkylation of phenols, we first explored the reaction of 13 with the azasulfonium salt (15) derived from N-chlorosuccinimide and dimethyl sulfide.[22] The salt was generated and used in situ in methylene chloride. The phenol was added at −25°C and the reaction mixture was stirred for 15 min. An equivalent of triethylamine was added at −25 °C and the reaction mixture was allowed to warm to room temperature. Removal of the solvent and salts followed by distillation of the residue gave 14. The yield and percent conversion of 13 into 14 were dependent on

13   14

the ratio of phenol to the S-(N-succinimido)sulfonium chloride. When a 20% excess of 15 was used (relative to starting

phenol), disubstitution became a major problem if both ortho positions of the phenol were available. Under these conditions, phenol gave 23% of 2,6-di(methylthiomethyl)phenol (16) in


16
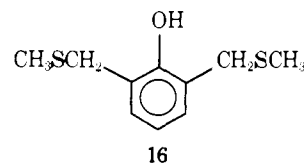
addition to 46% of 2-methylthiomethylphenol. Similarly, *p*-cresol gave 28% of 2,6-di(methylthiomethyl)-4-methylphenol and 46% of 4-methyl-2-methylthiomethylphenol, while *p*-methoxyphenol gave 9% of 2,6-di(methylthiomethyl)-4-methoxyphenol and 42% of 4-methoxy-2-methylthiomethylphenol. Obviously, if one of the ortho positions was already functionalized, 2,6-disubstitution would not represent a problem. This concept was established through the use of *o*-cresol, which gave 53% of 2-methyl-6-methylthiomethylphenol on reaction with 15 followed by base treatment. When 17 or 18 was used in place of 15 in the reaction with *o*-cresol,


17   18
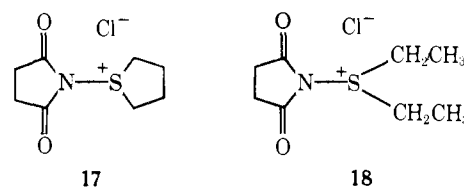
we obtained 58% of 2-methyl-6-(2-tetrahydrothienyl)phenol (19) and 30% of 2-methyl-6-(α-thioethoxy)ethylphenol, respectively. An unusual feature of the reactions of *o*-cresol with 15 and 18 was the formation of dithiomethoxymethane and dithioethoxyethane, respectively, as byproducts. The source of these dithioacetals was not established.

The elimination of the formation of major amounts of disubstitution products was readily accomplished through the use of excess phenol instead of excess S-(N-succinimido)sulfonium chloride. Yields were optimized (based on unrecovered phenol) when a 2:1 ratio of the phenol to the S-(N-succinimido)sulfonium salt was used. Table I lists the yields of o-methylthiomethylation and provides a comparison with the yields obtained by alternate methods, which were previously referenced. As shown in Table I, the yields obtained through the use of our process represent a considerable improvement over previously described methods. When 17 was used with a 1-equiv excess of *o*-cresol, we obtained 73% of 19 compared to a "best yield" of 45% by other methods.[11] The usefulness of this transformation is better appreciated when it is realized that Raney-nickel desulfurization of 19 gave 2-methyl-6-*n*-butylphenol (20) in 92% yield. Thus, the overall yield for the ortho *n*-butylation of *o*-cresol was 67%.

19

20
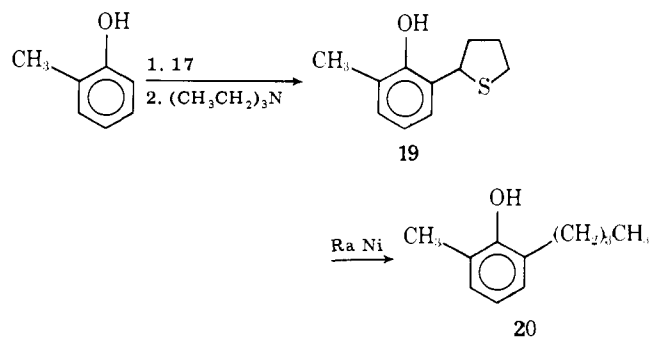
When *o*-nitrophenol (21) was subjected to our reaction conditions with 15, no *o*-methylthiomethylated product, 22, was formed. Instead, a 48% yield of 23 was obtained as the sole product. On initial inspection, it might appear that 23 was
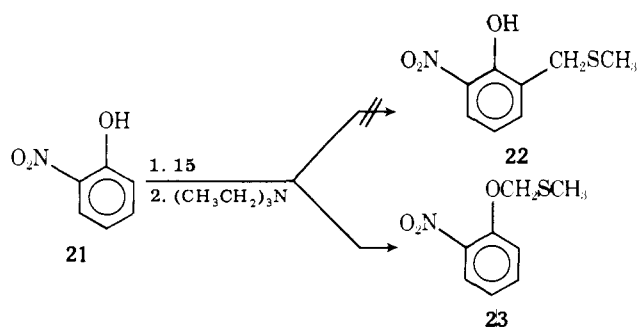
formed via a Stevens-type rearrangement[23,24] of an intermediate ylide, **24,** derived from base treatment of the appropriate
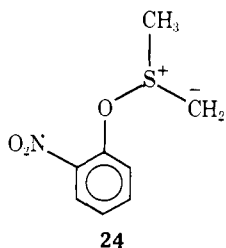

oxasulfonium salt. Experimental evidence discussed below demonstrates that this cannot be the correct explanation.

Our success with S-(N-succinimido)sulfonium chlorides in the o-methylthiomethylation of phenols prompted us to examine the use of halosulfonium halides[6,19] for this same purpose. Table II lists the yields of ortho substitution obtained when an appropriate chlorosulfonium chloride was allowed to react with a 1-equiv excess of a phenol and the resulting product was treated with triethylamine. A comparison of Table II with Table I shows that, in general, the yields of ortho substitution are better when the active reagent is a chlorosulfonium chloride than when it is an S-(N-succinimido)sulfonium chloride. Of special significance in Table II is the yield of **22** obtained when o-nitrophenol was used. As noted above, none of **22** was obtained in the reaction of **21** with **15** and base. These results can only be interpreted in terms of the formation of **24** when the active reagent was a chlorosulfonium chloride, and no formation of **24** when the active reagent was an S-(N-succinimido)sulfonium chloride. Had **24** been formed in both reactions, each should have provided **22.** The question of the mode of formation of **23** then becomes of interest. In the normal reaction of phenols with either a chlorosulfonium chloride or with **15,** we envisage a nucleophilic displacement of chloride and succinimide anion, respectively, from the sulfur by the oxygen of the phenol. This would be followed by loss of a proton to produce the oxasulfonium salt. In the case of o-nitrophenol, we have a fairly strong electron-withdrawing group on the ring. This should significantly decrease the nucleophilicity of this phenol. This decreased nucleophilicity should be reflected in both of the reaction classes discussed above unless succinimide anion is a poorer leaving group from sulfur than is chloride. The results obtained with o-nitrophenol would appear to support this hypothesis. Provided that the rationale given above is correct, the mechanistic route to **23** cannot involve a displacement on sulfur to produce an oxasulfonium salt. A likely route to **23** would involve a fragmentation of the S-(N-succinimido)sulfonium salt, **15,** to give the enol form of succinimide (**25**) and the sulfonium cation **26.** Addition of the o-nitrophenol to the highly reactive intermediate **26** would be expected to yield the observed product **23.** Ample precedent for this mechanistic speculation existed in the postulation of Vilsmaier and Sprügel,[25] who proposed that the formation of chloromethyl methyl sulfide from **15** arose from the fragmentation of **15** to **25** and **26,** followed by attack of chloride on **26.**

substituent on phenol	R	Cl Cl⁻ S⁺ R′	% yield of ortho-alkylthioalkylated phenol[a]	% yield of o-alkylphenol obtained on desulfurization
H	CH₃	CH₃	62	95[c]
p-CH₃	CH₃	CH₃	69	93[c]
p-OCH₃	CH₃	CH₃	58	98[c]
p-Cl	CH₃	CH₃	70	94[c]
o-CH₃	CH₃	CH₃	73	93[c]
o-CH₃	CH₃CH₂	CH₃CH₂	70[b]	100[d]
o-CH₃	(CH₂)₄		65	92[e]
o-NO₂ (**21**)	CH₃	CH₃	72 (**22**)	f

[a] All yields are based on unrecovered phenol. Products are at least 97% pure unless otherwise specified. [b] 92% purity as determined by VPC analysis. [c] Ortho methylation. [d] Ortho ethylation. [e] Ortho n-butylation. [f] The reduction of **22** was not attempted.
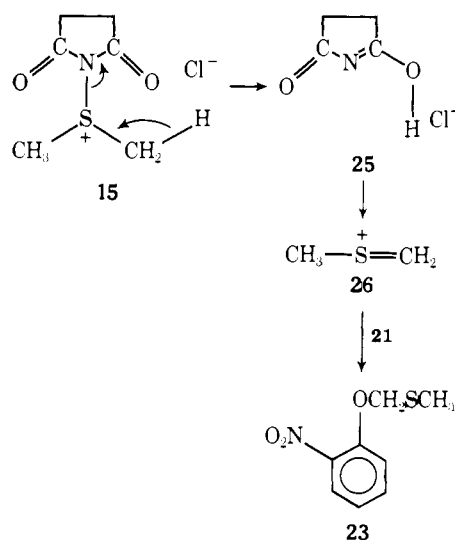
The last mechanistic detail which merits discussion concerns the significant difference between our results and those reported by Claus[19] and Vilsmaier.[21] Two factors differentiate these studies. Our work was carried out at a lower temperature, and base in the form of triethylamine was added. It seems probable that both our work and that of Claus and Vilsmaier involve the initial formation of an oxasulfonium salt. At the lower temperatures which characterize our reaction conditions, the oxasulfonium salt should have reasonable stability. The addition of base at these temperatures would be expected to generate the desired ylide. It is our feeling that, once generated, the ylide should rapidly rearrange. Since the studies of Claus and Vilsmaier did not involve base addition, it was unlikely that any ylide would be formed. Thus, when they "warmed" their reaction mixtures, the relatively weak sulfur-oxygen bond of the oxasulfonium salt probably should have been cleaved either heterolytically to form an oxenium ion and dimethyl sulfide, or homolytically to form a phenoxide radical and a dimethylsulfonium radical cation. Either of these combinations could recombine to produce the observed sulfonium compounds.

Table II provides data on the reductive desulfurization of the ortho-alkylthioalkylated phenols with W-2 Raney nickel. As shown, yields for this step ranged from 92 to 100%. Since the reductive cleavage of the carbon-sulfur bond leaves behind a hydrocarbon moiety, the two-step process constitutes an excellent method for the selective ortho alkylation of phenols.

Table III. Yields Obtained in the Formylation of Phenols with **28** and Triethylamine

substituent on phenol	% yield of **32**[a]	% yield of **33** from **32**	overall % yield of **33** from phenol
H	30	67	20
p-CH₃	46	76	35
p-OCH₃	39	78	30
p-Cl	42	79	33

[a] The percent yield of **32** was based on unrecovered phenol. The percent conversion ranged from 64 to 74%.

Ortho Formylation

Our success with the ortho alkylation of phenols prompted us to explore the possibility of extending our methodology to include the ortho formylation of phenols. Of the many methods available for the formylation of the aromatic nucleus, none is without complications. Most either occur in low yield, lack specificity, or are restricted to electron-rich aromatic compounds. Each of the most widely used variants (Gattermann,[26] Gattermann-Koch,[27] Reimer-Tiemann,[28] Vilsmaier-Haack,[29] Duff[30,31]) has one or more of these limitations associated with it. Thus, the application of methods used in our ortho formylation of anilines seemed attractive.

In principle, several approaches were possible. Among the most attractive possibilities was the use of either **27** or **28** as


27

28
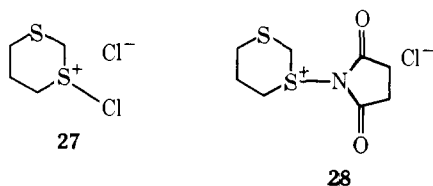
the active reagent. These reagents were readily available through the reaction of either chlorine or N-chlorosuccinimide with dithiane.[7] In practice, **28** gave the best results. Addition of the phenol to a methylene chloride solution of **28** at −70 °C gave **29** which was not isolated, but was treated immediately

29

30   **31**

32   **33**
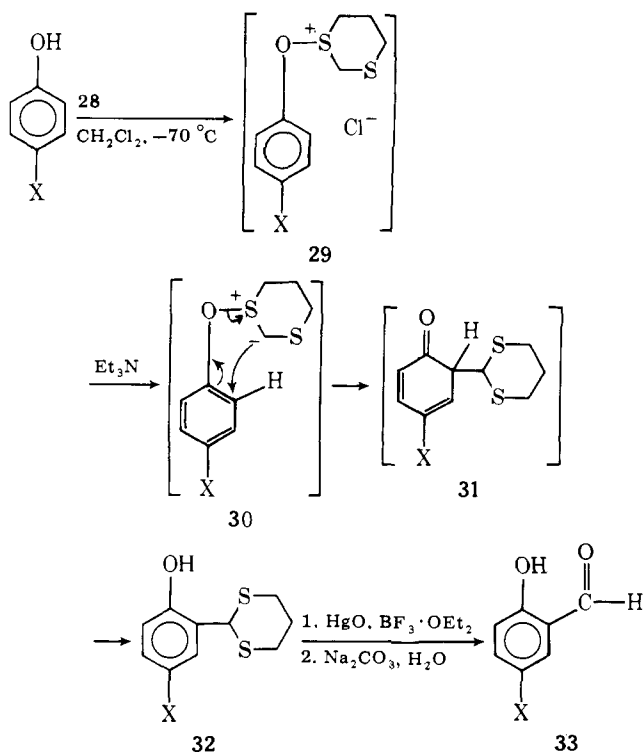
with triethylamine. This produced the ylide **30**, which spontaneously rearranged to give the dienone **31**. Hydrogen transfer and accompanying rearomatization then gave **32**. The hydrolysis of **32** to the corresponding salicylaldehyde **33** was readily accomplished according to a modification of the Vedejs-Fuchs procedure for hydrolysis of dithiane derivatives.[32] Table III lists the yields of **32** obtained when **28** was used as the active reagent. Also listed in Table III are the yields of aldehydes obtained in the hydrolysis of **32** with mercuric oxide and boron trifluoride etherate followed by neutralization with aqueous sodium carbonate, and the overall yields of salicylaldehydes based on starting phenols. Although the overall yields are only 20–35%, the specificity of the process and resultant ease of purification of the final product make this method a superior one for the synthesis of salicylaldehydes.

Having a series of o-methylthiomethylated phenols readily available as a result of our alkylation studies, we decided to explore the possibility of oxidizing the methylthiomethyl side chain to the aldehyde function. Oxidation of the methylene which separates the sulfur atom from the aromatic ring should be easily accomplished since this position can be considered to be activated by both of the groups attached to it. Prior to any type of oxidation, it seemed judicious to protect the hydroxyl function of **14**. Acetylation of **14** with sodium hydroxide and acetic anhydride gave **34**. The oxidation of the methylene

14   **34**

33   **35**
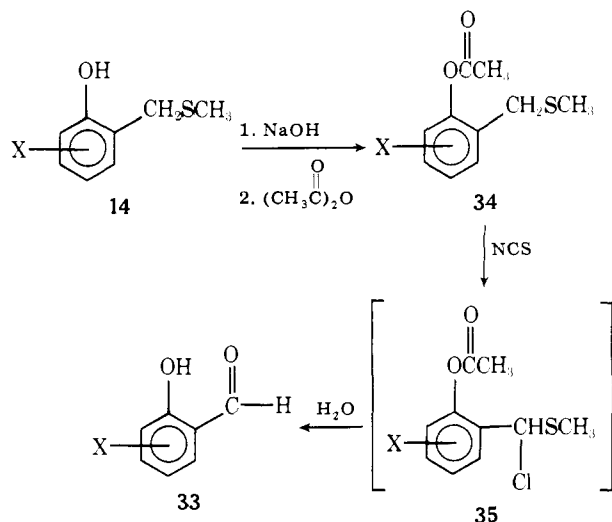
group of **34** was accomplished with N-chlorosuccinimide. The oxidation product, **35**, was not purified, but was hydrolyzed directly to the corresponding salicylaldehyde (**33**) by refluxing with water. Table IV gives the yields for the conversion of **14** into the acetate and from there into the corresponding salicylaldehydes. The overall yields for the conversion of o-methylthiomethylated phenols into salicylaldehydes ranged from 43 to 60%.

In summary, we have developed highly specific methods for the synthesis of ortho-alkylated phenols and for the ortho formylation of phenols. Both of these transformations depend on a [2,3]-sigmatropic rearrangement for the critical step in the ortho-substitution procedure. As a result of the cyclic nature of the rearrangement step, the ortho substitution is relatively insensitive to substituents on the ring. Thus, phenols bearing substituents ranging from strongly electron withdrawing to strongly electron donating can be tolerated.

Experimental Section

o-Methylthiomethylation of Phenol. General Procedure A. To a rapidly stirred mixture of 64.0 g (0.48 mol) of N-chlorosuccinimide in 2 L of dry methylene chloride was added 48.0 mL (0.656 mol) of dimethyl sulfide over a 15-min period at a temperature of from 0 to −5 °C. After an additional 10 min, the temperature was lowered to

−25 °C and 37.6 g (0.40 mol) of phenol in 100 mL of methylene chloride was added over a 15-min period. After an additional 30 min, 68.5 mL (0.492 mol) of triethylamine was added at −25 °C, and the reaction mixture was allowed to warm to room temperature. The solution was concentrated in vacuo and the salts were dissolved in 2 L of ether and extracted with 1.5 L of water. The water was back-extracted with 1.5 L of ether, and the ethereal solutions were combined and concentrated to 2 L. The ether solution was successively washed with 1 L of 3% hydrochloric acid, 1 L of 3% aqueous sodium bicarbonate, and two 500-mL portions of water, dried over anhydrous sodium sulfate, filtered, and concentrated to give a yellow liquid. Fractional distillation of the residue afforded 11.42 g (0.122 mol) of unreacted phenol, bp 53 °C (1.5 mm), as the most volatile component.

The second fraction afforded 19.66 g (0.128 mol, 46% yield based on unrecovered starting phenol) of 2-thiomethoxymethylphenol, bp 81 °C (0.025 mm) [lit.[11] bp 70 °C (10⁻² mm)]. The NMR agreed with that reported in the literature;[11] IR (neat) 2.92, 5.14, 5.25, 5.62, 5.85, 6.27, and 13.32 μ.

The third fraction provided 13.53 g (0.063 mol) of 2,6-di(thiomethoxymethyl)phenol (16), bp 140 °C (0.025 mm) [lit.[11] bp 80 °C (10⁻³ mm)], in 23% yield (based on unrecovered starting phenol). The NMR agreed with that reported in the literature;[11] IR (neat) 2.97, 5.20, 5.36, 5.51, 6.28, 12.60, and 13.37 μ.

o-Methylthiomethylation of *p*-Cresol. General procedure A was followed using 64.0 g (0.48 mol) of *N*-chlorosuccinimide, 48.0 mL (0.66 mol) of dimethyl sulfide, 43.2 g (0.40 mol) of *p*-cresol, and 68.5 mL (0.49 mol) of triethylamine. After workup, fractional distillation of the product mixture gave 16.05 g (0.15 mol) of unreacted *p*-cresol, bp 52 °C (0.6 mm), as the most volatile component.

The second fraction afforded 18.99 g (0.113 mol, 46% yield based on unrecovered starting *p*-cresol) of 4-methyl-2-thiomethoxymethylphenol, bp 75 °C (0.05 mm). The NMR agreed with that reported in the literature;[12] IR (neat) 2.93 (OH), 5.30, 5.70, 6.19, 11.30, and 12.26 μ.

The third fraction provided 15.31 g (0.067 mol, 28% yield based on unrecovered starting *p*-cresol) of 4-methyl-2,6-di(thiomethoxymethyl)phenol, bp 122 °C (0.05 mm). The NMR agreed with that reported in the literature;[12] IR (neat) 2.97 (OH), 5.70, 6.20, and 11.60 μ.

o-Methylthiomethylation of *p*-Methoxyphenol. General procedure A was followed using 64.0 g (0.48 mol) of *N*-chlorosuccinimide, 48.0 mL (0.66 mol) of dimethyl sulfide, 49.6 g (0.40 mol) of *p*-methoxyphenol, and 68.5 mL (0.49 mol) of triethylamine. After workup, fractional distillation of the product mixture gave 11.80 g (0.095 mol) of unreacted *p*-methoxyphenol, bp 85 °C (0.2 mm), as the most volatile component.

The second fraction afforded 23.45 g (0.128 mol, 42% yield based on unrecovered starting *p*-methoxyphenol) of 4-methoxy-2-thiomethoxymethylphenol, bp 116 °C (0.01 mm) [lit.[13] bp 120–130 °C (0.03 mm)]. The NMR agreed with that reported in the literature;[13] IR (neat) 2.90 (OH), 5.42, 5.87, 6.23, 11.64, and 12.33 μ.

The third fraction provided 6.45 g (26.4 mmol, 9% yield based on unrecovered starting *p*-methoxyphenol) of 4-methoxy-2,6-di-(thiomethoxymethyl)phenol, bp 171 °C (0.01 mm) [lit.[13] bp 170–180 °C (0.04 mm)]. The NMR agreed with that reported in the literature;[13] IR (neat) 2.95 (OH), 5.82, 6.21, and 11.67 μ.

o-Methylthiomethylation of *o*-Cresol. General procedure A was followed using 64.0 g (0.48 mol) of *N*-chlorosuccinimide, 48.0 mL (0.66 mol) of dimethyl sulfide, 43.2 g (0.40 mol) of *o*-cresol, and 68.5 mL (0.49 mol) of triethylamine. After workup, fractional distillation of the product mixture gave 1.01 g (9.40 mmol) of dithiomethoxymethane,[12] bp 34 °C (2.5 mm), as the most volatile component.

The second fraction afforded 17.53 g (0.162 mol) of unreacted *o*-cresol, bp 66 °C (2.75 mm).

The third fraction provided 21.09 g (0.126 mol, 53% yield based on unrecovered starting *o*-cresol) of 2-methyl-6-thiomethoxymethylphenol, bp 86 °C (0.03 mm) [lit.[11] bp 70 °C (10⁻³ mm)]. The NMR agreed with that reported in the literature;[11] IR (neat) 2.97 (OH), 5.21, 5.37, 5.58, 6.27, 12.87, and 13.38 μ.

Ortho Alkylation of *o*-Cresol Using Tetrahydrothiophene. General procedure A was followed using 64.0 g (0.48 mol) of *N*-chlorosuccinimide, 46.5 g (0.528 mol) of tetrahydrothiophene, 43.2 g (0.40 mol) of *o*-cresol, and 68.5 mL (0.49 mol) of triethylamine. After workup, fractional distillation of the product mixture gave 8.07 g (0.075 mol) of unreacted *o*-cresol as the most volatile component.

Table IV. Yields Obtained in the Oxidation of **14** to Salicylaldehydes

substituent on **14** (X)	% yield of **34** from **14**	% yield of **33** from **34**	overall % yield of **33** from **14**
H	90	54	49
p-CH₃	86	52	45
p-OCH₃	93	62	58
p-Cl	92	65	60
o-NO₂	90	48	43

The second fraction afforded 36.37 g (0.187 mol, 58% yield based on unrecovered starting *o*-cresol) of 2-methyl-6-(2-tetrahydrothienyl)phenol, bp 123 °C (0.01 mm) [lit.[11] bp 80 °C (10⁻³ mm)]. The NMR agreed with that reported in the literature;[11] IR (neat) 3.05 (OH), 5.22, 5.40, 5.55, 6.27, 12.85, and 13.45 μ.

o-Methylthiomethylation of *p*-Chlorophenol. General Procedure B. To a rapidly stirred mixture of 53.3 g (0.40 mol) of *N*-chlorosuccinimide in 2 L of dry methylene chloride was added 36.7 mL (0.50 mol) of dimethyl sulfide over a 15-min period at a temperature of 0–5 °C. After an additional 10 min the temperature was lowered to −25 °C and 103.0 g (0.80 mol) of *p*-chlorophenol in 100 mL of methylene chloride was added over a 15-min period. After an additional 30 min, 57.0 mL (0.41 mol) of triethylamine was added at −25 °C and the reaction mixture was allowed to warm to room temperature slowly. The solution was concentrated in vacuo and the salts were taken up in 2 L of ether and extracted with 1.5 L of water. The water was extracted with 1.5 L of ether and the ethereal solutions were combined and concentrated to 2 L. The ether solution was successively washed with 1 L of 3% hydrochloric acid, 1 L of 3% aqueous sodium bicarbonate, and 1 L of water, dried over anhydrous sodium sulfate, and concentrated to give a yellow liquid. Fractional distillation of this residue afforded 64.27 g (0.495 mol) of unreacted *p*-chlorophenol as the most volatile component.

The second fraction gave 36.09 g (0.191 mol, 63% yield based on unrecovered starting *p*-chlorophenol) of 4-chloro-2-thiomethoxymethylphenol, bp 107 °C (0.005 mm), mp 64.0–64.5 °C (recrystallized from hexane) (lit.[13] mp 63–65 °C). The NMR agreed with that reported in the literature;[13] IR (KBr) 3.02 (OH), 5.39, 5.76, 6.26, 11.35, and 12.32 μ.

The third fraction provided 2.78 g (0.011 mol, 3.6% yield based on unrecovered starting *p*-chlorophenol) of 4-chloro-2,6-di(thiomethoxymethyl)phenol, bp 142 °C (0.005 mm). The NMR agreed with that reported in the literature;[13] IR (neat) 2.91 (OH), 5.82, 6.32, and 11.31 μ.

o-Methylthiomethylation of Phenol. General procedure B was followed using 53.3 g (0.40 mol) of *N*-chlorosuccinimide, 36.7 mL (0.50 mol) of dimethyl sulfide, 75.2 g (0.80 mol) of phenol, and 57.0 mL (0.41 mol) of triethylamine. Fractional distillation afforded 45.0 g (0.479 mol) of unreacted phenol, 28.60 g (0.186 mol) of 2-thiomethoxymethylphenol (58% yield), and 2.82 g (0.013 mol) of 2,6-di(thiomethoxymethyl)phenol (4% yield; both yields were based on unrecovered starting phenol). The thiomethoxymethylated products were identical in all respects with those described above.

o-Methylthiomethylation of *p*-Cresol. General procedure B was followed using 53.3 g (0.40 mol) of *N*-chlorosuccinimide, 36.7 mL (0.50 mol) of dimethyl sulfide, 86.5 g (0.80 mol) of *p*-cresol, and 57.0 mL (0.41 mol) of triethylamine. Fractional distillation afforded 53.81 g (0.503 mol) of unreacted *p*-cresol, 31.03 g (0.185 mol) of 4-methyl-2-thiomethoxymethylphenol (62% yield), and 3.03 g (13.3 mmol) of 4-methyl-2,6-di(thiomethoxymethyl)phenol (4.5% yield; both yields were based on unrecovered starting *p*-cresol). The thiomethoxymethylated products were identical in all respects with those described above.

o-Methylthiomethylation of *p*-Methoxyphenol. General procedure B was followed using 53.3 g (0.40 mol) of *N*-chlorosuccinimide, 36.7 mL (0.50 mol) of dimethyl sulfide, 99.2 g (0.80 mol) of *p*-methoxyphenol, and 57.0 mL (0.41 mol) of triethylamine. Fractional distillation afforded 58.63 g (0.472 mol) of unreacted *p*-methoxyphenol, 29.74 g (0.328 mol) of 4-methoxy-2-thiomethoxymethylphenol (49% yield), and 2.23 g (9.0 mmol) of 4-methoxy-2,6-di(thiomethoxymethyl)phenol (3% yield; both yields are based on unrecovered starting *p*-methoxyphenol). The thiomethoxymethylated products were identical in all respects with those described above.

o-Methylthiomethylation of *o*-Cresol. General procedure B was followed using 53.3 g (0.40 mol) of *N*-chlorosuccinimide, 36.7 mL (0.50 mol) of dimethyl sulfide, 86.5 g (0.80 mol) of *o*-cresol, and 57.0 mL (0.41 mol) of triethylamine. Fractional distillation afforded 55.95 g (0.517 mol) of unreacted *o*-cresol and 29.72 g (0.177 mol) of 2-methyl-6-thiomethoxymethylphenol (63% yield based on unrecovered starting *o*-cresol), which was identical in all respects with an authentic sample.

o-Alkylthioalkylation of *o*-Cresol Using Tetrahydrothiophene. General procedure B was followed using 53.3 g (0.40 mol) of *N*-chlorosuccinimide, 39.6 g (0.45 mol) of tetrahydrothiophene, 86.5 g (0.80 mol) of *o*-cresol, and 57.0 mL (0.41 mol) of triethylamine. Fractional distillation afforded 50.72 g (0.469 mol) of unreacted *o*-cresol and 46.69 g (0.241 mol) of 2-methyl-6-(2-tetrahydrothienyl)-phenol (73% yield based on unrecovered starting *o*-cresol), which was identical in all respects with an authentic sample.

Use of Chlorosulfonium Chloride in the *o*-Alkylthioalkylation of Phenols. General Procedure C. The following is a general procedure for *o*-thiomethoxymethylating phenols using a twofold excess of the phenol relative to the chlorosulfonium chloride salt formed by reaction of dimethyl sulfide with chlorine.[33]

o-Methylthiomethylation of *o*-Cresol. General Procedure C. To a mechanically stirred solution of 18.2 mL (0.40 mol) of chlorine in 1500 mL of methylene chloride, cooled to −70 °C, was added 36.7 mL (0.50 mol) of dimethyl sulfide at a rate that maintained the temperature below −60 °C. When the yellow solution decolorized (after about 5 min), a solution of 86.5 g (0.80 mol) of *o*-cresol dissolved in 100 mL of methylene chloride was added over a 10-min period, while the temperature was maintained below −60 °C. After 20 min, 114.0 mL (0.82 mol) of triethylamine was added while keeping the temperature below −60 °C. The cooling bath was removed and the reaction mixture was allowed to warm gradually to room temperature. The reaction mixture was successively extracted with 1.5 L of water, 1 L of 3% sodium bicarbonate, and 1 L of water. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to yield a yellow liquid. Fractional distillation afforded 47.34 g (0.438 mol) of unreacted *o*-cresol, followed by 44.24 g (0.264 mol) of 2-methyl-6-methylthiomethylphenol (73% yield relative to unrecovered starting *o*-cresol).

o-Methylthiomethylation of *p*-Methoxyphenol. General procedure C was followed using 18.2 mL (0.40 mol) of chlorine, 36.7 mL (0.50 mol) of dimethyl sulfide, 99.2 g (0.80 mol) of *p*-methoxyphenol, and 114.0 mL (0.82 mol) of triethylamine. Fractional distillation afforded 48.21 g (0.390 mol) of unreacted *p*-methoxyphenol, followed by 44.05 g (0.239 mol) of 4-methoxy-2-methylthiomethylphenol (58% yield relative to unrecovered starting *p*-methoxyphenol).

o-Methylthiomethylation of *p*-Chlorophenol. General procedure C was followed using 18.2 mL (0.40 mol) of chlorine, 36.7 mL (0.50 mol) of dimethyl sulfide, 103.0 g (0.80 mol) of *p*-chlorophenol, and 114.0 mL (0.82 mol) of triethylamine. Fractional distillation afforded 56.98 g (0.442 mol) of unreacted *p*-chlorophenol, followed by 47.37 g (0.251 mol) of 4-chloro-2-methylthiomethylphenol (70% yield relative to unrecovered starting *p*-chlorophenol).

o-Methylthiomethylation of Phenol. General procedure C was followed using 18.2 mL (0.40 mol) of chlorine, 36.7 mL (0.50 mol) of dimethyl sulfide, 75.2 g (0.80 mol) of phenol, and 114.0 mL (0.82 mol) of triethylamine. Fractional distillation afforded 36.38 g (0.386 mol) of unreacted phenol, followed by 39.36 g (0.256 mol) of 2-methylthiomethylphenol (62% yield relative to unrecovered starting phenol).

o-Alkylthioalkylation of *o*-Cresol Using Tetrahydrothiophene. General procedure C was followed using 18.3 mL (0.40 mol) of chlorine, 39.6 mL (0.45 mol) of tetrahydrothiophene, 86.5 g (0.80 mol) of *o*-cresol, and 114.0 mL (0.82 mol) of triethylamine. Fractional distillation afforded 47.54 g (0.438 mol) of unreacted *o*-cresol, followed by 45.89 g (0.236 mol) of 2-methyl-6-(2-tetrahydrothienyl)-phenol (65% yield relative to unrecovered starting *o*-cresol).

o-Methylthiomethylation of *p*-Cresol. General procedure C was followed using 18.2 mL (0.40 mol) of chlorine, 36.7 mL (0.50 mol) of dimethyl sulfide, 86.5 g (0.80 mol) of *p*-cresol, and 114.0 mL (0.82 mol) of triethylamine. Fractional distillation afforded 50.40 g (0.466 mol) of unreacted *p*-cresol, followed by 38.81 g (0.231 mol) of 4-methyl-2-methylthiomethylphenol (69% yield relative to unrecovered starting *p*-cresol).

o-Alkylthioalkylation of *o*-Cresol Using Diethyl Sulfide. General procedure C was followed using 18.2 mL (0.40 mol) of chlorine, 48.5

mL (0.45 mol) of diethyl sulfide, 86.5 g (0.80 mol) of *o*-cresol, and 114.0 mL (0.82 mol) of triethylamine. Fractional distillation afforded 46.97 g (0.434 mol) of unreacted *o*-cresol ($\geq$95% pure by GC), followed by 50.08 g (0.256 mol, $\geq$92% pure by GC) of 2-(α-diethyl sulfide)-6-methylphenol, bp 133 °C (0.01 mm), which was identified by spectral analysis: ir (neat) 3.03 (OH), 5.23, 5.40, 5.60, 6.30, 12.86, and 13.41 μ; NMR (CDCl$_3$) τ 2.73 (1 H, s, OH), 2.90–3.54 (3 H, m, aromatic), 5.92 (1 H, q, J = 7.0 Hz, methine), 7.72 (2 H, q, J = 7.5 Hz, SCH_2CH$_3$), 7.80 (3 H, s, ArCH_3), 8.46 (3 H, d, J = 7.0 Hz, SCHArCH_3), and 8.90 (3 H, t, J = 7.5 Hz, SCH$_2$CH_3); exact mass mol wt 196.0924 (calcd for C$_{11}$H$_{16}$OS, 196.0922).

o-Methylthiomethylation of *o*-Nitrophenol. To a mechanically stirred solution of 4.55 mL (0.10 mol) of chlorine in 500 mL of methylene chloride, cooled to −70 °C, was added 9.2 mL (0.125 mol) of dimethyl sulfide at a rate that maintained the temperature below −60 °C. After 5 min, a solution of 27.82 g (0.20 mol) of *o*-nitrophenol dissolved in 50 mL of methylene chloride was added over a 10-min period. After 20 min, 28.5 mL (0.20 mol) of triethylamine was added, keeping the temperature below −60 °C. The cooling bath was removed and the reaction mixture was allowed to warm gradually to room temperature. The solvent was removed in vacuo and the residue was dissolved in 500 mL of ethyl acetate, extracted once with 500 mL of water, and dried over anhydrous sodium sulfate. The solution was filtered and concentrated. Column chromatography of 5% of the reaction mixture on 125 g of silica gel, using 20% methylene chloride-hexane as eluant, gave 0.60 g (4.3 mmol) of unreacted *o*-nitrophenol as the faster moving component. This was followed by 0.81 g (4.05 mmol) of the desired 2-nitro-6-methylthiomethylphenol (72% yield based on unrecovered starting *o*-nitrophenol). Recrystallization from 25% benzene-hexane gave yellow needles, mp 77–78 °C (lit.[11] mp 78–79 °C). The NMR agreed with that reported in the literature;[11] IR (KBr) 3.07 (OH), 6.22 and 13.52 (aromatic), 6.54 and 7.55 (NO$_2$), and 11.61 (C–N) μ.

2-Nitro-*o*-(methylthiomethyl)phenol (23). To a mechanically stirred mixture of 1.33 g (0.01 mol) of *N*-chlorosuccinimide in 50 mL of methylene chloride, cooled to −70 °C, was added 1.17 mL (0.016 mol) of dimethyl sulfide. After 15 min, a solution of 2.78 g (0.02 mol) of *o*-nitrophenol in 20 mL of methylene chloride was added. After 30 min, 1.06 g (0.01 mol) of triethylamine was added, and the reaction mixture was allowed to warm gradually to room temperature. The solvent was removed in vacuo, and the residue was dissolved in 150 mL of ethyl acetate, extracted with 150 mL of water, and dried over anhydrous magnesium sulfate. The solution was filtered and concentrated. Column chromatography of one-half of the reaction mixture on 125 g of silica gel, using 20% methylene chloride-hexane as eluant, gave 0.78 g (5.63 mmol) of *o*-nitrophenol as the faster moving component. This was followed by 0.42 g (2.10 mmol) of 2-nitro-*o*-(thiomethoxymethyl)phenol (48% yield based on unrecovered starting *o*-nitrophenol). The NMR spectrum agreed with that reported in the literature.[11]

Raney-Nickel Reduction of 4-Methyl-2-methylthiomethylphenol. A General Procedure. To a tenfold excess of W-2 Raney nickel in 200 mL of absolute methanol was added 3.26 g (19.4 mmol) of 4-methyl-2-methylthiomethylphenol. The mixture was stirred for 1 h at room temperature. The solution was decanted and the Raney nickel was washed twice with 150-mL portions of absolute methanol and then with two 150-mL portions of methylene chloride. The solutions were combined, filtered through a Celite pad, and concentrated in vacuo. The residue was dissolved in 75 mL of methylene chloride and dried over anhydrous sodium sulfate. Filtration, followed by concentration, afforded 2.18 g (17.9 mmol) of 2,4-dimethylphenol (93% yield). The structure of the reduced product was confirmed through comparison of the spectra with "The Sadtler Standard Spectra", IR No. 521 and NMR No. 6016 M.

Raney-Nickel Reduction of 4-Chloro-2-methylthiomethylphenol. Raney-nickel reduction (as above) of 3.77 g (0.02 mol) of 4-chloro-2-methylthiomethylphenol afforded 2.68 g (18.8 mmol) of 4-chloro-*o*-cresol (94% yield). The structure of the reduced product was confirmed through comparison of its IR spectrum with Spectrum No. C 5520-8 from "The Aldrich Library of Infrared Spectra".[40]

Raney-Nickel Reduction of 2-Methylthiomethylphenol. Raney-nickel reduction, according to the general procedure, of 1.49 g (9.7 mmol) of 2-methylthiomethylphenol afforded 1.0 g (9.3 mmol) of *o*-cresol (95% yield). The structure of the product was confirmed through comparison of the spectra with "The Sadtler Standard Spectra", IR No. 844 and NMR No. 3153 M.

Raney-Nickel Reduction of 2-Methyl-6-methylthiomethylphenol.
Raney-nickel reduction (as above) of 3.20 g (19.0 mmol) of 2-methyl-6-methylthiomethylphenol afforded 2.16 g (17.7 mmol) of 2,6-dimethylphenol (93% yield). The structure of the reduced product was confirmed through comparison of the spectra with "The Sadtler Standard Spectra", IR No. 294 and NMR No. 36 M.

Raney-Nickel Reduction of 4-Methoxy-2-methylthiomethylphenol.
Raney-nickel reduction (as above) of 3.68 g (0.02 mol) of 4-methoxy-2-methylthiomethylphenol afforded 2.70 g (19.6 mmol) of 4-methoxy-*o*-cresol (98% yield): mp 70-71 °C (lit.[34] 70-71 °C); IR (film) 3.00 (OH), 5.46, 5.81, 6.24, 11.61, and 12.36 μ (all aromatic); NMR (CDCl$_3$) τ 3.17-3.64 (3 H, m, aromatic), 4.35 (1 H, s, OH), 6.33 (3 H, s, OCH$_3$), 7.83 (3 H, s, ArCH$_3$).

Raney-Nickel Reduction of 2-Methyl-6-(2-tetrahydrothienyl)phenol.
Raney-nickel reduction (as above) of 3.88 g (20 mmol) of 2-methyl-6-(2-tetrahydrothienyl)phenol afforded 3.0 g (18.3 mmol) of 2-*n*-butyl-6-methylphenol in 92% yield. The structure of the reduced product was confirmed through comparison of the IR spectrum with that reported in the literature;[35] NMR (CDCl$_3$) τ 2.84-3.50 (3 H, m, aromatic), 5.05 (1 H, s, OH), 7.44 (2 H, t, J = 7.0 Hz, ArCH$_2$-), 7.84 (3 H, s, ArCH$_3$), and 8.08-9.33 (7 H, m, ArCH$_2$CH$_2$-CH$_2$CH$_3$).

Raney-Nickel Reduction of 6-Methyl-2-(α-diethyl sulfide)phenol.
Raney-nickel reduction (as above) of 2.66 g (13.6 mmol) of 6-methyl-2-(α-diethyl sulfide)phenol afforded 1.88 g (13.8 mmol) of 6-ethyl-*o*-cresol (quantitatively). The IR spectrum of the reduced product agreed with that reported in the literature;[36] NMR (CDCl$_3$) τ 2.85-3.52 (3 H, m, aromatic), 5.48 (1 H, s, OH), 7.45 (2 H, q, J = 7.0 Hz, ArCH$_2$CH$_3$), 7.88 (3 H, s, ArCH$_3$), and 8.83 (3 H, t, J = 7.0 Hz, ArCH$_2$CH$_3$).

Salicylaldehyde Trimethylene Mercaptal. General Procedure. To a slurry of 1.33 g (0.010 mol) of *N*-chlorosuccinimide in 50 mL of methylene chloride at −70 °C was added 1.20 g (0.010 mol) of dithiane in 5 mL of methylene chloride over a 5-min period. After an additional 15 min, 1.60 g (0.017 mol) of phenol in 5 mL of methylene chloride was added, dropwise. After another 15 min, 1.06 g (10.5 mmol) of triethylamine was added at a rate that maintained the temperature below −60 °C. The cooling bath was removed and the reaction mixture was allowed to warm gradually to room temperature. Successive extractions with 150 mL of water and 150 mL of saturated sodium chloride solution, followed by drying (anhydrous magnesium sulfate), filtration, and concentration, afforded a yellow oil. The oil was seeded and refrigerated at 0 °C for 9 days. The crystalline precipitate collected by filtration was triturated with carbon tetachloride and then hexane, and dried in vacuo to afford 0.314 g of white solid, mp 117-125 °C. The filtrate was concentrated and submitted to preparative thick layer chromatography on silica gel to give 0.414 g of phenol (4.4 mmol, 25.9%) as the faster moving component, and 0.484 g of the desired product, mp 118-124 °C. Overall, there was obtained 0.798 g (3.76 mmol) of salicylaldehyde trimethylene mercaptal in 30% yield based on unrecovered starting phenol. An analytical sample was prepared by additional thick layer chromatography followed by recrystallization from carbon tetrachloride: mp 123-126 °C; IR (KBr) 3.01, 6.28, 6.69, 6.92, 7.03, 7.45, 7.88, 8.02, 8.39, 9.22, 9.71, 11.79, and 13.29 μ; NMR (CDCl$_3$) τ 2.50-3.40 (5 H, m, -OH and aromatic), 4.57 (1 H, s, benzylic H), 6.8-7.2 (4 H, m, two SCH$_2$), and 7.7-8.3 (2 H, m, -SCH$_2$CH$_2$CH$_2$S-); exact *m/e* 212.0331 (calcd for C$_{10}$H$_{12}$OS$_2$, *m/e* 212.0330). Anal. Calcd for C$_{10}$H$_{12}$OS$_2$: C, 56.57; H, 5.70. Found: C, 56.46; H, 5.72.

5-Methoxysalicylaldehyde Trimethylene Mercaptal. The general procedure was followed using 1.33 g (0.010 mol) of *N*-chlorosuccinimide, 1.20 g (0.010 mol) of dithiane, 2.48 g (0.020 mol) of *p*-methoxyphenol, and 1.06 g (0.011 mol) of triethylamine. Seeding led to no precipitate, so the entire reaction mixture was submitted to thick layer chromatography on silica gel using 25% ether-hexane as eluant. The faster moving band gave 0.897 g of *p*-methoxyphenol (7.30 mmol, 36%); this was followed by 1.199 g (4.95 mmol) of the desired 5-methoxysalicylaldehyde trimethylene mercaptal (39% yield based on unrecovered starting *p*-methoxyphenol), mp 115-121 °C. An analytical sample was prepared by trituration with carbon tetrachloride followed by recrystallization from carbon tetrachloride: mp 123-124 °C; IR (KBr) 2.92, 3.46, 6.26, 6.69, 7.02, 7.51, 7.71, 7.90, 8.25, 8.51, 8.65, 9.15, 9.70, 9.98, 10.70, 11.06, 11.54, 12.13, 12.42, 13.03, 13.45, and 14.39 μ; NMR (CDCl$_3$) τ 2.95-3.26 (3 H, m, aromatic), 3.80-4.20 (1 H, br s, OH), 4.56 (1 H, s, benzylic H), 6.23 (3 H, s, OCH$_3$), 6.80-7.16 (4 H, m, -SCH$_2$-), and 7.66-8.33 (2 H, m,

-SCH$_2$CH$_2$CH$_2$S-); exact *m/e* 242.0439 (calcd for C$_{11}$H$_{14}$O$_2$S$_2$, *m/e* 242.0435). Anal. Calcd for C$_{11}$H$_{14}$O$_2$S$_2$: C, 54.51; H, 5.82; S, 26.46. Found: C, 54.54; H, 5.76; S, 26.59.

5-Methylsalicylaldehyde Trimethylene Mercaptal. The general procedure was followed using 1.33 g (0.010 mol) of *N*-chlorosuccinimide, 1.20 g (0.010 mol) of dithiane, 1.84 g (0.017 mol) of *p*-cresol, and 1.06 g (0.011 mol) of triethylamine. Removal of residual solvent in vacuo from the reaction mixture led to the formation of a precipitate which was collected by filtration, triturated with carbon tetrachloride and then hexane, and dried in vacuo to afford 0.409 g of white solid, mp 136.0-137.5 °C. The combined filtrates were refrigerated for 2 h and the resulting solid was collected by filtration and cleaned as above to afford an additional 0.267 g of white solid, mp 136.5-137.5 °C. All of the filtrates were combined, concentrated, and submitted to thick layer chromatography on silica gel using 25% ether-hexane as eluant. The faster moving band gave 0.65 g of *p*-cresol (6.0 mmol, 35%); this was followed by 0.463 g of the desired product, mp 136.5-137.5 °C (recrystallized from carbon tetrachloride). Overall, there was obtained 1.14 g (5.05 mmol) of 5-methylsalicylaldehyde trimethylene mercaptal (46% yield based on unrecovered starting *p*-cresol). Additional thick layer chromatography increased the melting point to 137.5-138.5 °C; IR (KBr) 2.97, 3.42, 6.20, 6.65, 7.01, 7.47, 7.90, 8.32, 8.41, 8.71, 9.16, 11.05, 11.52, 12.10, 12.38, 12.60, 12.75, and 13.40 μ; NMR (CDCl$_3$) τ 2.60-3.30 (3 H, m, aromatic), 3.7-4.1 (1 H, br s, -OH), 4.58 (1 H, s, benzylic H), 6.83-7.25 (4 H, m, -SCH$_2$-), 7.75 (3 H, s, ArCH$_3$), and 7.60-8.30 (2 H, m, -SCH$_2$CH$_2$CH$_2$S-); exact *m/e* 226.0490 (calcd for C$_{11}$H$_{14}$OS$_2$, *m/e* 226.0486) Anal. Calcd for C$_{11}$H$_{14}$OS$_2$: C, 58.37; H, 6.23. Found: C, 58.24; H, 6.33.

5-Chlorosalicyladehyde Trimethylene Mercaptal. The general procedure was followed using 1.33 g (0.010 mol) of *N*-chlorosuccinimide, 1.20 g (0.010 mol) of dithiane, 2.18 g (0.017 mol) of *p*-chlorophenol, and 1.06 g (11.5 mmol) of triethylamine. Cooling and scratching of the resulting orange oil caused crystal formation. The crystals were collected by filtration and triturated with carbon tetrachloride and then hexane to afford 0.574 g of a white solid, mp 127-128 °C. The combined filtrates were refrigerated overnight and the resulting solid was collected by filtration and cleaned as above to afford an additional 0.132 g of white solid, mp 126-128 °C. All of the filtrates were now combined, concentrated, and submitted to thick layer chromatography on silica gel using 25% ether-hexane as eluant. The faster moving band gave 0.793 g of *p*-chlorophenol (6.15 mmol, 36%); this was followed by 0.405 g of white solid, mp 125-128 °C (recrystallized from carbon tetrachloride). Overall, there was obtained 1.11 g (4.50 mmol) of 5-chlorosalicyladehyde trimethylene mercaptal (42% yield based on unrecovered starting *p*-chlorophenol). Another recrystallization from carbon tetrachloride raised the melting point to 128-129 °C; IR (KBr) 3.00, 3.41, 6.27, 6.72, 7.08, 7.51, 7.88, 8.17, 8.41, 9.05, 10.90, 12.10, 12.35, 12.56, and 12.81 μ; NMR (CDCl$_3$) τ 2.60-3.30 (3 H, m, aromatic), 3.60 (1 H, s, -OH), 4.64 (1 H, s, benzylic H), 6.80-7.15 (4 H, m, two -SCH$_2$-), and 7.70-8.25 (2 H, m, -SCH$_2$CH$_2$CH$_2$S-); exact *m/e* 245.9942 (calcd for C$_{10}$H$_{11}$ClOS$_2$, *m/e* 245.9939). Anal. Calcd for C$_{10}$H$_{11}$ClOS$_2$: C, 48.67; H, 4.49; S, 25.99. Found: C, 48.58; H, 4.46; S, 25.65.

Salicylaldehyde. General Procedure for Trimethylene Mercaptal Hydrolysis. To a magnetically stirred mixture of 0.433 g (2.0 mmol) of red mercuric oxide and 0.284 g (2.0 mmol) of boron trifluoride etherate in 6.7 mL of water was added 0.212 g (1.0 mmol) of salicylaldehyde trimethylene mercaptal in 1.0 mL of tetrahydrofuran. After stirring at room temperature for 2 h, the reaction mixture was added to 50 mL of 5% sodium carbonate solution and the resulting yellow precipitate was removed by suction filtration through a Celite pad. The filtrate was cooled and acidified to neutrality with hydrochloric acid, and then extracted with two 75-mL portions of methylene chloride. The combined organic phases were washed with 150 mL of saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated. Chromatography of the resulting yellow liquid on 20 g of silica gel using 15% ether-hexane as eluant afforded 0.082 g (0.67 mmol, 67% yield) of salicylaldehyde; the structure of the product was confirmed through comparison of the infrared spectrum with "The Sadtler Standard Spectra", IR No. 9989.

5-Methoxysalicylaldehyde. The general procedure was followed using 0.433 g (2.0 mmol) of red mercuric oxide, 0.284 g (2.0 mmol) of boron trifluoride etherate, and 0.242 g (1.0 mmol) of 5-methoxysalicylaldehyde trimethylene mercaptal. Chromatography afforded

0.119 g (0.78 mmol, 78% yield) of 5-methoxysalicylaldehyde; the structure of the product was confirmed through comparison of the infrared spectrum with "The Sadtler Standard Spectra", IR No. 36414.

5-Chlorosalicylaldehyde. The general procedure was followed using 0.649 g (3.0 mmol) of red mercuric oxide, 0.426 g (3.0 mmol) of boron trifluoride etherate, and 0.370 g (1.5 mmol) of 5-chlorosalicylaldehyde trimethylene mercaptal. Chromatography afforded 0.185 g (1.18 mmol, 79% yield) of 5-chlorosalicylaldehyde, mp 96–99 °C (lit.[37] mp 100 °C). The structure of the product was further confirmed through comparison of the infrared spectrum with the "Aldrich Library of Infrared Spectra", IR No. 330.

5-Methylsalicylaldehyde. To a magnetically stirred mixture of 1.299 g (6.0 mmol) of red mercuric oxide and 0.852 g (6.0 mmol) of boron trifluoride etherate in 20 mL of water, was added 0.678 g (3.0 mmol) of 5-methylsalicylaldehyde trimethylene mercaptal in 3.0 mL of tetrahydrofuran. After stirring at room temperature for 2 h, the reaction mixture was added to 100 mL of 5% sodium carbonate solution and the resulting yellow precipitate was removed by suction filtration through a Celite pad. The filtrate was cooled and acidified to neutrality with hydrochloric acid, and then extracted with two 150-mL portions of methylene chloride. The combined organic phases were washed with 300 mL of saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated. Chromatography of the resulting yellow liquid on 60 g of silica gel (60–200 mesh) using 20% ether-hexane as eluant afforded 0.309 g (2.27 mmol, 76% yield) of 5-methylsalicylaldehyde, mp 52–54 °C (lit.[38] mp 55.8 °C). Sublimation increased the melting point to 54–55 °C. The structure of the product was further confirmed through comparison of the infrared spectrum with "The Sadtler Standard Spectra", IR No. 32911.

O-Acyl-2-methylthiomethylphenol. General Procedure. To a stirred solution of 7.70 g (50.0 mmol) of 2-methylthiomethylphenol in 5 mL of tetrahydrofuran at −5 °C, was added a solution of 4.20 g (75.0 mmol) of potassium hydroxide in 40 mL of water at 0 °C. Acetic anhydride (6.83 g, 67.0 mmol) was added at a rate that maintained the temperature at or below 0 °C. After an additional 5 min, the cold reaction mixture was extracted with two 75-mL portions of ether. The combined ethereal layers were washed successively with 75 mL of 2% aqueous potassium hydroxide, 75 mL of water, and 75 mL of saturated sodium chloride, dried over anhydrous magnesium sulfate, filtered, and concentrated to afford 8.78 g (44.8 mmol, 90%) of O-acyl-2-methylthiomethylphenol, bp 70 °C (0.01 mm), $n^{26.2}$D 1.5437; IR 5.65 (C=O), 8.30, 8.52, and 9.20 (ν C-O-C), and 13.54 μ (ortho substitution); NMR (CDCl$_3$) τ 2.50–3.10 (4 H, m, aryl H), 6.43 (2 H, s, ArCH_2S), 7.77 (3 H, s, COCH$_3$), and 8.08 (3 H, s, SCH$_3$); exact m/e 196.0561 (calcd for C$_{10}$H$_{12}$O$_2$S, m/e 196.0558). Anal. Calcd for C$_{10}$H$_{12}$O$_2$S: C, 61.20; H, 6.16; S, 16.34. Found: C, 61.19; H, 6.22; S, 16.49.

O-Acyl-4-chloro-2-methylthiomethylphenol. Following the general procedure outlined above, 9.43 g (50.0 mmol) of 4-chloro-2-methylthiomethylphenol was reacted to give 10.53 g (45.7 mmol, 92%) of O-acyl-4-chloro-2-methylthiomethylphenol: bp 88 °C (0.01 mm); $n^{25.2}$D 1.5564; IR 5.65 (C=O), 8.30, 8.52, and 9.03 (ν C-O-C), 11.34 and 12.17 μ (1,2,4-trisubstituted benzene); NMR (CDCl$_3$) τ 2.50–3.10 (3 H, m, aryl H), 6.46 (2 H, s, ArCH_2S), 7.73 (3 H, s, COCH$_3$), and 8.05 (3 H, s, SCH$_3$); exact m/e 230.0172 (calcd for C$_{10}$H$_{11}$ClO$_2$S, m/e 230.0168). Anal. Calcd for C$_{10}$H$_{11}$ClO$_2$S: C, 52.06; H, 4.81; S, 13.90. Found: C, 51.95; H, 4.85; S, 14.10.

O-Acyl-4-methyl-2-methylthiomethylphenol. Following the general procedure outlined above, 8.40 g (50.0 mmol) of 4-methyl-2-methylthiomethylphenol was reacted to give 9.06 g (43.2 mmol, 86%) of O-acyl-4-methyl-2-methylthiomethylphenol: bp 75 °C (0.01 mm); $n^{26.4}$D 1.5398; IR 5.67 (C=O), 8.23, 8.43, and 9.12 (ν C-O-C), 11.05 and 12.13 μ (1,2,4-trisubstituted benzene); NMR (CDCl$_3$) τ 2.75–3.10 (3 H, m, aryl H), 6.46 (2 H, s, ArCH_2S), 7.72 (3 H, s, ArCH_3), 7.77 (3 H, s, COCH$_3$), and 8.14 (3 H, s, SCH$_3$); exact m/e 210.0717 (calcd for C$_{11}$H$_{14}$O$_2$S, m/e 210.0714). Anal. Calcd for C$_{11}$H$_{14}$O$_2$S: C, 62.83; H, 6.71; S, 15.25. Found: C, 62.78; H, 6.79; S, 15.22.

O-Acyl-4-methoxy-2-methylthiomethylphenol. Following the general procedure outlined above, 9.20 g (50.0 mmol) of 4-methoxy-2-methylthiomethylphenol was reacted to give 10.49 g (46.4 mmol, 93%) of O-acyl-4-methoxy-2-methylthiomethylphenol: bp 103 °C (0.01 mm); $n^{25.6}$D 1.5462; IR 5.67 (C=O), 8.23, 8.46, and 9.10 (ν C-O-C), 8.34 and 9.65 (aromatic ether), 11.11 and 12.20 μ (1,2,4-trisubstituted benzene); NMR (CDCl$_3$) τ 2.82–3.34 (3 H, m,

aryl H), 6.26 (3 H, s, OCH$_3$), 6.45 (2 H, s, ArCH$_2$S), 7.74 (3 H, s, COCH$_3$), and 8.04 (3 H, s, SCH$_3$); exact m/e 226.0667 (calcd for C$_{11}$H$_{14}$O$_3$S, m/e 226.0664). Anal. Calcd for C$_{11}$H$_{14}$O$_3$S: C, 58.38; H, 6.24; S, 14.17. Found: C, 58.50; H, 6.24; S, 14.27.

O-Acyl-2-methylthiomethyl-6-nitrophenol. To a stirred solution of 1.99 g (10.0 mmol) of 2-methylthiomethyl-6-nitrophenol in 2 mL of tetrahydrofuran at 0 °C was added a solution of 0.84 g (15.0 mmol) of potassium hydroxide in 10 mL of water at 0 °C. Acetic anhydride (1.35 g, 13.3 mmol) was then added to the red solution at a rate that maintained the temperature at or below 0 °C. After an additional 5 min, the cold reaction mixture was extracted with two 25-mL portions of ether. The combined ethereal layers were washed with 75 mL of saturated sodium chloride, dried over anhydrous magnesium sulfate, filtered, and concentrated to give a solid yellow residue. Recrystallization from hexane gave 1.71 g of O-acyl-2-methylthiomethyl-6-nitrophenol as almost colorless needles, mp 73.5–75.0 °C. The supernatant liquid was concentrated and purified by thick layer chromatography on silica gel, GF 254 (15% methylene chloride-hexane as eluant) to afford 0.452 g of additional product, mp 72.0–74.0 °C. Overall there was obtained 2.16 g (8.98 mmol, 90%) of the desired product. A second recrystallization from hexane gave colorless needles: mp 74.7–75.0 °C; IR (KBr) 5.66 (C=O), 6.52, 7.39, and 11.03 (-NO$_2$), 8.31, 8.51, and 9.25 (ν C-O-C), 12.47 and 13.53 μ (1,2,3-trisubstituted benzene); NMR (CDCl$_3$) τ 1.80–2.80 (3 H, m, aryl H), 6.32 (2 H, s, ArCH$_2$S), 7.61 (3 H, s, COCH$_3$), and 8.00 (3 H, s, SCH$_3$); exact m/e 241.0412 (calcd for C$_{10}$H$_{11}$NO$_4$S, m/e 241.0409). Anal. Calcd for C$_{10}$H$_{11}$NO$_4$S: C, 49.78; H, 4.59; S, 13.29. Found: C, 49.72; H, 4.61; S, 13.29.

Salicylaldehyde. General Procedure. To a rapidly stirred solution of 0.980 g (5.0 mmol) of O-acyl-2-methylthiomethylphenol in 20 mL of carbon tetrachloride at room temperature was added 0.70 g (5.25 mmol) of N-chlorosuccinimide in one portion. After 1 h the succinimide was removed by filtration and the filtrate was concentrated in vacuo. To the residue was added 25 mL of water and 3 mL of tetrahydrofuran, and the mixture was stirred and heated at 100 °C for 16 h. The reaction mixture was cooled to 25 °C and extracted with two 75-mL portions of ether. The ether extracts were combined, washed with 100 mL of saturated sodium chloride, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on a 75 × 25 cm column of 60–200 mesh silica gel (15% ether-hexane as eluant). The 375–575-mL fraction contained 0.327 g (2.68 mmol, 54%) of the desired salicylaldehyde; the structure of the product was confirmed through comparison of the infrared spectrum with "The Sadtler Standard Spectra", IR No. 9989.

5-Methylsalicylaldehyde. Following the general procedure outlined above, 0.969 g (4.61 mmol) of O-acyl-4-methyl-2-methylthiomethylphenol was reacted with 0.645 g (4.84 mmol) of N-chlorosuccinimide to give (in the 300–430-mL column fraction) 0.327 g (2.4 mmol, 52%) of the desired 5-methylsalicylaldehyde, mp 52–54 °C (lit.[38] mp 55.8 °C). The structure of the product was confirmed through comparison of the infrared spectrum with "The Sadtler Standard Spectra", IR No. 32911.

5-Methoxysalicylaldehyde. Following the general procedure outlined above (with the exception that the chlorinated intermediate was refluxed in aqueous tetrahydrofuran for 24 h to complete cleavage of the acetate function) 1.13 g (5.0 mmol) of O-acyl-4-methoxy-2-methylthiomethylphenol was reacted with 0.70 g (5.25 mmol) of N-chlorosuccinimide to give (in the 500–800-mL column fraction) 0.472 g (3.11 mmol, 62%) of the desired 5-methoxysalicylaldehyde; the structure of the product was confirmed through comparison of the infrared spectrum with "The Sadtler Standard Spectra", IR No. 36414.

5-Chlorosalicylaldehyde. To a rapidly stirred solution of 1.153 g (5.0 mmol) of O-acyl-4-chloro-2-methylthiomethylphenol in 20 mL of carbon tetrachloride at room temperature was added 0.70 g (5.25 mmol) of N-chlorosuccinimide in one portion. After 1 h, the succinimide was removed by filtration and the filtrate was concentrated in vacuo. To the residue were added 25 mL of water and 3 mL of tetrahydrofuran, and the mixture was stirred and heated at 100 °C for 16 h. The reaction mixture was cooled to 25 °C and extracted with two 75-mL portions of ether. The ethereal extracts were combined, washed with 100 mL of saturated sodium chloride, dried over anhydrous magnesium sulfate, filtered, and concentrated to give a white solid. The white solid was triturated with 10 mL of 15% ether-hexane and filtered to afford 0.336 g of the desired aldehyde, mp 99–100 °C

(lit.[37] mp 100 °C). The filtrate was concentrated and purified by thick layer chromatography on silica gel GF 254 (15% ether–hexane as eluant) to give an additional 0.169 g of the aldehyde, mp 90–93 °C (trituration with 1.0 mL of 5% ether–hexane raised the melting point to 98.0–99.5 °C). Overall there was obtained 0.505 g (3.24 mmol, 65%) of the desired 5-chlorosalicylaldehyde; the structure of the product was further confirmed through comparison of the infrared spectrum with "The Sadtler Standard Spectra", IR No. 330.

3-Nitrosalicylaldehyde. To a rapidly stirred solution of 1.205 g (5.0 mmol) of *O*-acyl-2-methylthiomethyl-6-nitrophenol in 20 mL of carbon tetrachloride at room temperature was added 0.70 g (5.25 mmol) of *N*-chlorosuccinimide in one portion. After 1 h the succinimide was removed by filtration and the filtrate was concentrated in vacuo. To the residue were added 25 mL of water and 3 mL of tetrahydrofuran and the mixture was stirred and heated at 100 °C for 16 h. The reaction mixture was cooled to 25 °C and extracted with two 75-mL portions of ethyl acetate. The extracts were combined and washed with 100 mL of saturated sodium chloride, dried over anhydrous magnesium sulfate, filtered, and concentrated to give a yellow solid. The solid was triturated with 10 mL of ether and filtered to give 0.249 g of the desired 3-nitrosalicylaldehyde, mp 108–109 °C (lit.[39] mp 109–110 °C). Concentration of the filtrate and refrigeration of the residue for 3 days afforded a second crop of yellow solid which was collected by filtration and triturated with 2 mL of ether to give an additional 0.152 g of product, mp 107–109 °C. Overall there was obtained 0.401 g (2.42 mmol, 48%) of the desired 3-nitrosalicylaldehyde: IR (KBr) 3.30 (–OH), 6.08 (CHO), 6.64, 7.48, and 11.66 (NO_2) μ; NMR (Me_2SO-d_6) τ −1.55 (1 H, s, CHO), 0.50 (1 H, d of d, aryl H adjacent to nitro, $J = 8.0$ and 2.0 Hz), 0.71 (1 H, d of d, aryl H adjacent to aldehyde, $J = 8.0$ and 2.0 Hz), 1.57 (1 H, t, aryl H para to hydroxyl, $J = 8.0$ Hz), and 0.33 (1 H, br s, –OH).

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