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Reaction of Sulfinate Esters with Grignard and Organocopper Lithium Reagents. A Useful Route to Chiral Sulfoxides[1]

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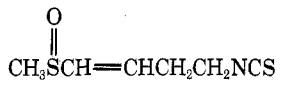
The reaction of sulfinate esters with various Grignard reagents was found to give a complex mixture of sulfoxide and sulfides. The use of organocopper lithium reagents in place of the Grignard effects the conversion of sulfinate esters to sulfoxides in higher yields and cleaner product mixtures. (−)-Menthyl (−)-(*S*)-*p*-toluenesulfinate and (−)-menthyl (−)-(*S*)-benzenesulfinate were treated with organocopper lithium reagents. The reactions were found to proceed with inversion of configuration at sulfur to give sulfoxides of high optical purity.

The sulfoxide moiety, because of its pyramidal structure, can give rise to asymmetry in a molecule. The first known natural product in which optical activity results from chirality of an atom other than carbon is sulforaphen (**1**),[2] isolated from the black radish.



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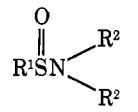
Sulfoxides can be prepared in various states of optical purity by a number of techniques. Asymmetric oxidation of sulfides with several reagents (optically active peracids,[3a-h] iodine in the presence of a chiral catalyst,[3i] or microbes[4]) provides sulfoxides, usually of low optical purity. Alternatively, sulfoxides can be optically enriched by incorporation into inclusion compounds with a chiral host molecule,[5] or by partial oxidation[6] or reduction[7a,b] with chiral reagents. In addition, the use of special techniques such as circularly polarized light[7c] and "chiral" electrodes[7d] have also produced respectable optical yields of chiral sulfoxides. Finally, sulfoxides of high optical purity can be prepared in variable yields by reaction of a variety of sulfinyl compounds (e.g., sulfinamides **2**,[8] heterocycles **3**,[9] or sulfinate esters **4**[10]) with organometallic reagents.



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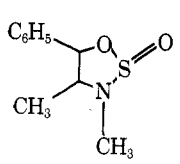

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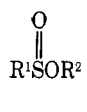

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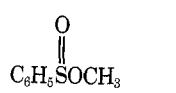
The most widely used synthetic procedure, dating from 1924,[10a] involves the reaction of a sulfinate ester **4** with a Grignard reagent. This reaction was later employed by Andersen[10b,c] to prepare optically active aryl sulfoxides; Mislow subsequently confirmed[10d,e] that the reaction was highly stereospecific, furnishing products of high optical purity.

While this valuable synthetic technique in certain instances can give sulfoxides in high yield, close scrutiny of the literature reveals that yields depend greatly on the structure of the target sulfoxide.[11] It appeared that careful examination of the reaction of a simple sulfinate ester such as methyl phenylsulfinate[12] (**5**) might provide some insight to the causes of this problem. Thus **5** and two cyclic sulfinate esters [1,2-oxathiolane 2-oxide (**6**) and 1,2-oxathiane 2-oxide (**7**)[13]] were treated with a number of Grignard reagents. The reaction of sulfinate esters with organocopper lithium reagents was also examined to evaluate their utility for sulfoxide formation.



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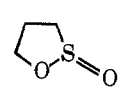

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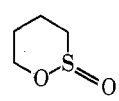

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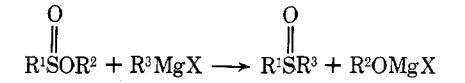
Results and Discussion

It was found that these compounds can react with Grignard reagents to give sulfoxides, but the conditions must be very carefully selected, otherwise considerable quantities of sulfides and other impurities are produced. These impurities can often remain tenaciously with the sulfoxide making separation difficult and thus severely limiting the synthetic utility of the reaction. The results obtained are summarized in Table I.

Reduction of Sulfinates to Sulfoxides by Grignard Reagents. In each case it was possible to characterize some sulfoxide in the reaction mixture, but the yields varied greatly with the structure of both sulfinate ester and Grignard reagent.



From the results of Table I, it is obvious that the sulfoxide, once generated, can react further. In the case where an equivalent amount of Grignard reagent was used, care was

Table I. Reaction of Grignard Reagents with Sulfinate Esters

Sulfinate (1 equiv)	CH_3MgBr (75-16-1)[k]			CH_3CH_2MgBr (925-90-6)			C_6H_5MgBr (100-58-3)		
	Equiv of Grignard	Products	Yield, %	Equiv of Grignard	Products	Yield, %	Equiv of Grignard	Products	Yield, %
5 (670-98-4)[k]	1.0	$C_6H_5S(=O)CH_3$[a]	27	1.0	$C_6H_5S(=O)CH_2CH_3$[a,h]	32	1.0	$C_6H_5S(=O)C_6H_5$[b,g]	55
		$C_6H_5SCH_3$[a]	24		$C_6H_5SCH_2CH_3$[a,h]	29			
6 (24308-28-9)	3.3	$C_6H_5SCH_3$[b]	50	3.3	$C_6H_5SCH_2CH_3$[b,d]	60	6.0	$C_6H_5S(=O)C_6H_5$[a]	73
								$C_6H_5SC_6H_5$[a]	10
	1.0	$CH_3S(=O)(CH_2)_3OH$[c,j] (8a)	33				1.0	$C_6H_5S(=O)(CH_2)_3OH$[f] (8b)	57
		$CH_3CH_2S(CH_2)_3OH$[c] (11a)	33						
	2.0	$CH_3CH_2S(CH_2)_3OH$[b] (11a)	70				2.0	$C_6H_5S(CH_2)_3OH$[a] (11b)	65
7 (24308-29-0)	1.0	$CH_3S(=O)(CH_2)_4OH$[c] (9a)	40				1.0	$C_6H_5S(=O)(CH_2)_4OH$[e] (9b)	50
		$CH_3CH_2S(CH_2)_4OH$[c,j] (10b)	20				2.0	$C_6H_5S(=O)(CH_2)_4OH$[a] (9b)	24
	2.0	$CH_3CH_2S(CH_2)_4OH$[b,d] (10b)	60					$C_6H_5S(CH_2)_4OH$[a] (10c)	6
								$C_6H_5SCH(C_6H_5)(CH_2)_3OH$[a] (10d)	30
							4.0	$C_6H_5SCH(C_6H_5)(CH_2)_3OH$[b] (10d)	54

[a] Separated by chromatography on silica (eluent benzene–ethyl acetate, 5:1). [b] Separated by distillation. [c] Separated by washing crude product with ether. [d] Purified by preparative VPC (Carbowax 20M at 190–195 °C). [e] Purified by preparative TLC (silica, benzene–methanol 3:1). [f] Purified by preparative TLC (silica, benzene–methanol, 5:1). [g] Purified by crystallization (ether–hexanes). [h] Estimated by NMR. [i] Obtained ~90% pure characterized by NMR, MS, and reaction with MeMgI to give $CH_3CH_2S(CH_2)_3OH$. [j] Obtained ~80% pure characterized by NMR, MS, and reaction with MeMgI to give $CH_3CH_2S(CH_2)_3OH$. [k] Registry no.

taken to prevent excess reagent in the reaction mixture. A dilute solution of the organomagnesium compound was added very slowly to a vigorously stirred solution of the sulfinate ester. Even under these conditions, considerable amounts of sulfides were found in some of the product mixtures.

When **5** reacted with 1 equiv of phenylmagnesium bromide the sole product isolated is diphenyl sulfoxide; it has been shown[14] that this compound is insensitive to reduction by Grignard reagents. Cyclic sulfinates **6** and **7** can be made to yield pure sulfoxides in their reaction with phenylmagnesium bromide if the conditions of the reaction are carefully controlled.

Sulfinate esters **5–7** react with alkyl Grignard reagents to give mixtures of sulfoxide and sulfides which are sometimes very difficult to separate; the mixture formed by reaction of **5** with ethylmagnesium bromide proved to be especially recalcitrant.

Reduction of Sulfoxides to Sulfides. The nature of the sulfide formed depends on the structure of the intermediate sulfoxide and the quantity of Grignard reagent present. If the sulfoxide contains a phenyl group and a twofold (or greater) excess of organomagnesium reagent is used, the sulfide is generally that corresponding in structure to the sulfoxide; however, when **7** reacts with phenylmagnesium bromide, the sulfide **10d** (corresponding to double addition of the Grignard reagent) is the predominant product.

7 **10c** **10d**

Although the reaction of sulfoxides with Grignard reagents is exceedingly complex,[15,16] Manya and co-workers suggested routes to the two types of sulfides.[16] The formation of sulfide corresponding in structure to the sulfoxide is rationalized in terms of a sulfenic acid precursor, formed by decomposition of **12**. The formation of sulfides of the type **10d** was also explained by a process involving the intermediate sulfonium methylide **12**, but through a rearrangement process (Scheme I).

Scheme I

When R^3 is phenyl we detected benzene in the reaction mixture, corroborating the above proposal.

Organocopper Compounds. Because of the complexity encountered in the reaction of sulfinate esters with Grignard reagents, we decided to explore the reaction with organocopper reagents. Reagents of the type **14** have been known for some time to be more specific in many of their reactions than Grignard reagents.[17]

R_2CuLi

14

It was thought that perhaps the selectivity might extend to their reaction with sulfinate esters. It was found that treatment of **5** with lithium dimethylcuprate yielded methyl phenyl sulfoxide in 59% yield. Treatment of sulfinate esters **6**, **7**, and methyl *n*-butylsulfinate (**15**) with organocopper lithium reagents yielded sulfoxides in moderate yields (Table II).

In most cases, the yield of isolated sulfoxide was greater than that of sulfoxide from the parallel Grignard reaction. In addition, the quantity of sulfide corresponding in structure to the target sulfoxide was considerably less. Furthermore, sulfide corresponding to double addition (vide supra, **13**) was not found in any of these reactions.

A notable exception was provided by the reactions of sulfinate esters **5** and **15** with lithium di-*n*-butylcuprate and lithium diphenylcuprate, respectively. In both cases *n*-butyl phenyl sulfide was formed; no sulfoxide was detected.[18]

In contrast to the Grignard reagents, in most cases, an excess of the organocopper reagent can be tolerated in the reaction mixture. Thus treatment of **5** with a four molar excess of lithium dimethylcuprate gave methyl phenyl sulfoxide in 43% yield. The best yield of sulfoxide obtained with the corresponding Grignard reagent was 27%; treatment of **5** with 3.3 mol of Grignard yielded only sulfide.

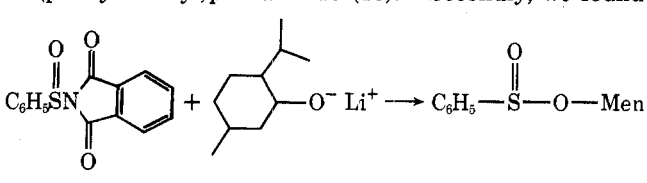
In these reactions considerable quantities of starting material remained unaccounted for. Despite our ability to regain 94% of a sample of diphenyl sulfoxide which had been treated for an extended period of time with lithium diphenylcuprate (Table III), it proved impossible to isolate the sulfoxide in greater than 50% yield by the reaction of **5** with lithium diphenylcuprate. The only other organic material isolated in this reaction was biphenyl, a compound often found as a contaminant in the phenyllithium used in the reaction. *n*-Butyl phenyl sulfoxide was reduced by excess lithium di-*n*-butylcuprate at −40 °C to the corresponding sulfide (Table III). This may account in part for the absence of sulfoxide in the reaction of **5** with lithium di-*n*-butylcuprate (Table II).[18]

The low yield of methyl phenyl sulfoxide in the reaction of *p*-tolyl phenylsulfinate (**4**, $R^1 = C_6H_5$; $R^2 = p\text{-}CH_3C_6H_4$) with lithium dimethylcuprate may be due to the instability of aryloxy sulfinate esters.[19]

Stereochemistry. From the above results it has been shown that organocopper reagents give higher yields of sulfoxides on reaction with sulfinate esters. If the reactions are stereospecific, they would be the preferred reagents for the synthesis of chiral sulfoxides.

(−)-Menthyl (−)-(*S*)-*p*-toluenesulfinate and (−)-menthyl (−)-(*S*)-benzenesulfinate were treated with lithium organocuprates. The reactions were found to proceed with inversion of configuration at sulfur to give sulfoxides of high optical purity (Table IV).

There are two noteworthy features to our modified procedures for the preparation of optically active sulfoxides. The first is that we were able to effect the preparation of menthyl benzenesulfinate by the reaction of lithium menthoxide with *N*-(phenylsulfinyl)phthalimide (**16**).[22] Secondly, we found



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that high-pressure liquid chromatography (HPLC) is the method of choice in the purification of these sulfoxides, giving compounds of high purity with little loss of material.

In conclusion, the reaction of organocopper lithium reagents with menthyl sulfinates provides a viable route to optically active sulfoxides.

Table II. Reaction of Diorganocopper Lithium Reagents with Sulfinate Esters

	$C_6H_5S(=O)OCH_3$ (5)		$n\text{-}C_4H_9S(=O)OCH_3$ (15)[h]		6		7		$C_6H_5S(=O)OC_6H_4CH_3\text{-}p$[i]	
R_2CuLi, R	Temp, °C	Products (% yield)	Temp, °C	Products (% yield)	Temp, °C	Products (% yield)	Temp, °C	Products (% yield)	Temp, °C	Products (% yield)
CH_3 (15681-48-8)[g]	0	$C_6H_5S(=O)CH_3$ (59)	0	$n\text{-}C_4H_9S(=O)CH_3$[a] (50)	0	$CH_3S(=O)(CH_2)_4OH$[b] (59)			0	$C_6H_5S(=O)CH_3$[c] (22) $C_6H_5SCH_3$[c] (53)
C_2H_5 (38297-20-0)	−78	$C_6H_5S(=O)CH_2CH_3$[d] (36)								
$n\text{-}C_4H_9$ (24406-16-4)	−40	$C_6H_5S\text{-}n\text{-}C_4H_9$[a] (36)	0	No isolable products						
			−30	$(n\text{-}C_4H_9)_2S(=O)$[c] (15)						
			−78	$(n\text{-}C_4H_9)_2S(=O)$[d] (52)						
C_6H_5 (2402-69-9)	0	$C_6H_5S(=O)C_6H_5$[e] (50)								
	−78	$C_6H_5S(=O)C_6H_5$[e] (48)	−78	$C_6H_5S\text{-}n\text{-}C_4H_9$[a] (64)	0	$C_6H_5S(=O)(CH_2)_4OH$[f] (32)	0	$C_6H_5S(=O)(CH_2)_3OH$[f] (52)		

[a] Purified by distillation. [b] Purified by preparative TLC (silica, chloroform). [c] Purified by column chromatography (silica, ethyl acetate), then Kugelrohr distillation at 100 °C (1 mmHg). [d] Purified by column chromatography (silica, ethyl acetate), distillation, then rechromatographed (dry column alumina) with benzene–pyridine (19:1) or 1,4-dioxane. [e] Purified by column chromatography (silica, hexanes then chloroform). [f] Purified by column chromatography [silica, ethyl acetate–cyclohexane (4:1), then methanol]. [g] Registry no., 673-80-3. [i] Registry no., 60270-05-5.

Table III. Reaction of Organocopper Lithium Reagents with Sulfoxides

Registry no.	Sulfoxide (1 mol)	$(R^3)_2CuLi$ R^3	Mol	Temp, °C	Time, h	Products, % yield $R^1-\overset{O}{\overset{\|}{S}}-R^3$	Others (% yield)
945-51-7	$C_6H_5\overset{O}{\overset{\|}{S}}C_6H_5$	C_6H_5	2	0	3	94	
13153-10-1	n-$C_4H_9\overset{O}{\overset{\|}{S}}C_6H_5$	n-C_4H_9	2	−40	1	11	n-$C_4H_9SC_6H_5$ (80)
1193-82-4	$CH_3\overset{O}{\overset{\|}{S}}C_6H_5$	CH_3	2	0	3	49[a]	$CH_3SC_6H_5$ (11) $C_6H_5\overset{O}{\overset{\|}{S}}CH_2CH_2\overset{O}{\overset{\|}{S}}C_6H_5$[a] (10) $C_6H_5SCH_2CH_2SC_6H_5$ (3)
2976-98-9	n-$C_4H_9\overset{O}{\overset{\|}{S}}CH_3$	CH_3	2	0	3	88	

[a] Isolated as sulfone.

Table IV. Synthesis of Chiral Sulfoxides

$$R^1\overset{O}{\overset{\|}{S}}\text{—OMen} + R_2{}^3CuLi \rightarrow R^1\overset{O}{\overset{\|}{S}}R^3$$

Registry no.	R^1	R^3	Yield, %	$[\alpha]_D$	$[\alpha]_D{}^{lit.}$	Optical purity, %
34513-32-1	C_6H_5	CH_3	16	+133.9°	+146°[a]	96
1517-82-4	p-$CH_3C_6H_4$	CH_3	55	+143.2°	+145.5°[b]	99
	p-$CH_3C_6H_4$	C_6H_5	59	+21.8°	+22°[a]	100

[a] Highest value in the same solvent. [b] For literature values see Experimental Section.

Experimental Section[21]

Preparation of Sulfinate Esters. Methyl phenylsulfinate (5) and methyl n-butylsulfinate (15) were prepared by the method of Douglass;[12] 1,2-oxathiane 2-oxide (6) and 1,2-oxathiolane 2-oxide (7) were prepared by the method of Harpp and Gleason.[13]

***p*-Tolyl Phenylsulfinate (4, $R^1 = C_6H_5$; $R^2 = p$-$CH_3C_6H_4$).** p-Cresol (2.16 g, 2.0 mmol) was added to a stirred suspension of sodium hydride [0.824 g of a 58% suspension in paraffin oil (2.0 mmol) in pentane (100 ml)]. The salt was washed well (pentane), then suspended in carbon tetrachloride. Phenyl sulfinylphthalimide (16,[22] 5.42 g, 2.0 mmol) was added and the mixture was stirred for 1 h. The mixture was filtered and the solvent removed to give p-tolyl phenylsulfinate as a colorless oil (4.30 g, 93%) pure by TLC (silica, benzene R_f 0.6); NMR ($CDCl_3$) gave signals at δ 8.8–7.5 (multiplet, 5 H), 7.3 (singlet, 4 H), and 2.22 (singlet, 3 H). The compound decomposed exothermically to give a red polymeric tar when distillation was attempted; decomposition also occurred when the compound was stored overnight at −20 °C.

Preparation of Grignard Reagents. Stock solutions of methylmagnesium iodide, ethylmagnesium bromide (in ether), and phenylmagnesium bromide (in ether–tetrahydrofuran, 50:50) were prepared in the usual manner. They were standardized by addition of the solution (1 ml) to a solution of iodine (4 ml) in benzene (100 ml). After stirring with water (50 ml), excess iodine was titrated with 0.1 N sodium thiosulfate. After standardization of the iodine solution the concentration of organomagnesium compound was calculated.

Reaction of Grignard Reagents with Sulfinate Esters. The sulfinate ester (5 g) in anhydrous ether (50 ml) was placed in a 500-ml three-necked flask fitted with a dropping funnel, a mercury sealed stirrer, and a condenser with a drying tube attached. The stirred solution was cooled to 5–10 °C, then the Grignard reagent was added dropwise. When addition was complete the stirred mixture was refluxed (50–60 °C) for 5 h and then cooled in an ice bath and hydrolyzed with water (100 ml, C_6H_5MgBr) or saturated aqueous sodium thiosulfate solution (C_2H_5MgBr and CH_3MgBr). The magnesium salts were removed by filtration or centrifugation, and the aqueous layer was extracted several times with chloroform–tetrahydrofuran (1:1). The organic extracts were dried ($MgSO_4$) and the solvent was flash evaporated. The resulting oil was analyzed as indicated in Table I. Products were characterized by comparison with authentic samples.

Preparation of Organocopper Reagents.[23] Purified cuprous iodide[23,24] (1.9 g, 10 mmol) was placed in a three-necked flask fitted with two dropping funnels with equilibrating side arm, and a magnetic stirrer. The apparatus was flame dried under a stream of prepurified nitrogen, anhydrous ether (10 ml) was added, and the stirred suspension was cooled to the required temperature. Two equivalents of alkyl- or aryllithium were then added dropwise, at 0 °C for methyl- or phenyllithium and at −30 °C for ethyl- or n-butyllithium.

Reaction of Lithium Organocopper Reagents with Sulfinate Esters. The sulfinate (10 mmol) in anhydrous ether (40 ml) was added dropwise to the organocopper reagent under a stream of prepurified nitrogen. The mixture was stirred (~15 min) and then hydrolyzed with saturated aqueous ammonium chloride (50 ml). After stirring for 15 min at room temperature, the mixture was filtered and both the copper salts and the aqueous layer were washed well with chloroform–tetrahydrofuran (1:1). The organic extracts were dried ($MgSO_4$) and evaporated to give an oil that was worked up as indicated in Table II. All products were identified by comparison with authentic samples.

Synthesis of Sulfides. n-Butyl methyl sulfide, diphenyl sulfide, and methyl phenyl sulfide were all available from commercial sources. Ethyl phenyl sulfide, ethyl propan-3-ol sulfide, butan-4-ol ethyl sulfide, phenyl propan-3-ol sulfide, and butan-4-ol phenyl sulfide were prepared by the method of McMurdy and Prager.[25]

Di-n-butyl sulfide was prepared by reduction of the sulfoxide with sodium bisulfite.[26] n-Butyl phenyl sulfide and butan-4-ol methyl sulfide were prepared by slight modifications of the method of Windus and Shildneck.[27] Phenyl 1-phenylbutan-4-ol sulfide (**10d**) was prepared by the method of Lehto and Shirley.[28] All sulfides were pure by TLC and gave NMR spectra consistent with their structures. They showed the following properties.

Di-*n*-butyl Sulfide: bp 70–72 °C (12 mm) [lit. 187 °C (1 atm),[29] 91.0–91.5 °C (10 mm)[30]]; $n^{25}D$ 1.4509 (lit. $n^{20}D$ 1.45297,[29] $n^{30}D$ 1.4532[30]).

Ethyl Phenyl Sulfide: bp 92–96 °C (0.5 mm) [lit. 123 °C (12 mm),[31] 90 °C (10 mm),[32] 98 °C (22 mm),[33] 102–104 °C (15 mm)[34]].

***n*-Butyl Phenyl Sulfide:** bp 120–122 °C (18 mm) [lit. 117 °C (15 mm),[33] 78–83 °C (2.3 mm),[35] 123–129 °C (25 mm)[36]], $n^{25}D$ 1.5423 [lit. $n^{21}D$ 1.5472,[33] $n^{28}D$ 1.5432,[35] $n^{25}D$ 1.5312[36]].

Ethyl Propan-3-ol Sulfide (11a): bp 132 °C (15 mm) [lit. 85–86 °C (5 mm)[25]]; ir ν_{max} (film) 3340, 2910, 2810 and 1060 cm^{-1}; MS m/e 120 (P^+) and 87 ($CH_3CH_2SCH_2^+$; base peak). Anal. Calcd for

$C_5H_{12}OS$: C, 50.00; H, 10.00, S, 26.66. Found: C, 50.21; H, 10.21; S, 26.47.

Phenyl Propan-3-ol Sulfide (11b): bp 105 °C (0.1 mm) [lit. 134–135 °C (2 mm)[37]], 155–159 °C (8 mm);[38] ir ν_{max} (film) 3350, 2940, 2880, 1060, and 1030 cm^{-1}; MS *m/e* 168 (P^+), 150 ($P^+ - H_2O$), 123 ($C_6H_5SCH_2^+$), 110 ($C_6H_6S^+$), 91 ($C_7H_7^+$), and 77 ($C_6H_5^+$). Anal. Calcd for $C_9H_{12}OS$: C, 64.28; H, 7.14; S, 19.04. Found: C, 64.53; H, 7.19; S, 18.78.

Butan-4-ol Methyl Sulfide (10a): bp 103–105 °C (10 mm) [lit. 81–85 °C (3 mm)[25]]; ir ν_{max} (film) 3340, 2910, 2850, 1055, and 1030 cm^{-1}; MS *m/e* 120 (P^+), 102 ($P^+ - H_2O$), and 61 ($CH_3SCH_2^+$).

Butan-4-ol Ethyl Sulfide (10b): bp 132 °C (15 mm), 71–73 °C (0.75 mm) [lit. 81–85 °C (3 mm)[25]]; ir ν_{max} (film) 3340, 2910, 2810, and 1060 cm^{-1}; MS *m/e* 134 (P^+), 87 ($CH_3CH_2SCH{=}CH^+$), and 75 ($CH_3CH_2SCH_2^+$). Anal. Calcd for $C_6H_{14}OS$: C, 53.73; H, 10.44; S, 23.88. Found: C, 53.89; H, 10.36, S, 23.61.

Butan-4-ol Phenyl Sulfide (10c): bp 112 °C (0.1 mm) [lit. 150 °C (6 mm),[39] needles, mp 24 °C [40]]; ir ν_{max} (film) 3380, 2950, 2870, 1060, and 1030 cm^{-1}; MS *m/e* 182 (P^+), 164 ($P^+ - H_2O$), 123 ($C_6H_5SCH_2^+$), 110 ($C_6H_5SH^+$, base peak), 91 ($C_7H_7^+$), and 77 ($C_6H_5^+$). Anal. Calcd for $C_{10}H_{14}OS$: C, 70.07; H, 6.58; S, 23.35. Found: C, 70.24; H, 6.67; S, 23.36.

Phenyl 1-Phenylbutan-4-ol Sulfide (10d): bp 190 °C (1 mm), 180 °C (0.5 mm); ir ν_{max} (film) 3350, 3050, 3030, 2940, 2870, 1060, and 1030 cm^{-1}; MS *m/e* 258 (P^+), 240 ($P^+ - H_2O$), 199 ($C_6H_5SCHC_6H_5^+$), 149 ($C_6H_5CHCH_2CH_2CH_2OH^+$), 131 ($CH_2{=}CHCH_2CHC_6H_5^+$, base peak), 117 ($CH_2{=}CHC_6H_5^+$), 110 ($C_6H_5SH^+$), 91 ($C_7H_7^+$), and 77 ($C_6H_5^+$). Anal. Calcd for $C_{16}H_{18}OS$: C, 74.41; H, 6.97; S, 12.40. Found: C, 74.14; H, 6.94; S, 12.70.

Synthesis of Sulfoxides. Di-*n*-butyl sulfoxide was commercially available. All other sulfoxides were identified by comparison (TLC, VPC, NMR, ir) with authentic samples prepared by oxidation of the corresponding sulfide with sodium metaperiodate ($NaIO_4$)[41] or *m*-chloroperbenzoic acid. They showed the following properties.

***n*-Butyl Methyl Sulfoxide:** bp 101 °C (8 mm), $n^{25}D$ 1.4679.

Methyl Phenyl Sulfoxide: bp 95–97 °C (0.1 mm) [lit. 78–79 °C (0.1 mm),[41] 115 °C (2 mm)[42]], $n^{25}D$ 1.5762 (lit. $n^{25}D$ 1.5880[42]).

Ethyl Phenyl Sulfoxide: bp 80–82 °C (0.15 mm) [lit. 146 °C (13 mm)[43]], $n^{22}D$ 1.4679.

***n*-Butyl Phenyl Sulfoxide:** bp 99–99.5 °C (0.4 mm), $n^{26.5}D$ 1.5433, $d^{26.5}$ 1.0652, $[R_L]D^{exp}$ 53.99 (calcd, 53.88).

Methyl Propan-3-ol Sulfoxide (8a): decomposes before boiling; NMR (CCl_4) δ ~2.00 (m, 2 H, CCH_2C), 2.20 (s, 3 H, $CH_3S{=}O$), 2.7 (m, 2 H, $CH_2S{=}O$), 3.90 (m, 2 H, CH_2O–), and 4.20 (s, 1 H, OH).

Phenyl Propan-3-ol Sulfoxide (8b): decomposition before boiling; MS *m/e* 184 (P^+), 166 ($P^+ - H_2O$), 126 ($C_6H_5OH^+$, base peak), 107 [$O{=}S(CH_2)_3OH^+$], 91 ($C_7H_7^+$), and 77 ($C_6H_5^+$); ir ν_{max} (film) 3340, 2900, 2815, and 1010 cm^{-1}. Anal. Calcd for $C_9H_{12}O_2S$: C, 58.69; H, 6.52; S, 17.39. Found: C, 58.01, H, 6.64; S, 16.87.

Butan-4-ol Methyl Sulfoxide (9a): decomposes before boiling; MS *m/e* 136 (P^+), 119 ($P^+ - OH$), and 64 ($P^+ - CH_3SOH$); NMR ($CDCl_3$) δ 1.68 (m, 4 H, $-CH_2CH_2-$), 2.60 (s, 3 H, $CH_3S{=}O$), 2.80 (t, 2 H, $-CH_2S{=}O$), 3.50 (t, 2 H, $-CH_2O$–), and 4.25 (s, 1 H, OH).

Butan-4-ol Phenyl Sulfoxide (9b): decomposes before boiling; MS *m/e* 198 (P^+), 180 ($P^+ - H_2O$), 166 ($C_6H_5SCH{=}CH_2^+$), 107 ($HOCH_2CH_2CH_2CH_2SH_2^+$, base peak), 91 ($C_7H_7^+$), and 77 ($C_6H_5^+$); ir ν_{max} (film) 3340, 2900, 2815, 1040, and 1010 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O_2S$: C, 60.60; H, 7.07; S, 16.16. Found: C, 60.84; H, 7.24; S, 15.86.

Preparation of Methyl Phenylsulfenate (17, $R^1 = C_6H_6$; $R^2 = CH_3$). Freshly prepared phenylsulfenyl chloride, bp 43–48 °C (1.5 mm) [lit.[44] 58–60 °C (3 mm)] (19.8 g, 0.14 mol), was added to a solution of sodium methoxide [prepared from 3.5 g, (0.15 g-atom) of sodium] in methanol (200 ml) at 0 °C. The mixture was allowed to warm up to room temperature, filtered, and evaporated to give methyl phenylsulfenate (5.3 g), pure by VPC: bp 95 °C (6 mm) [lit. 88–89 °C (0.4 mm)[44]]; $n^{26}D$ 1.5508; d^{26} 1.1081; $[R_L]D^{exp}$ 40.75 (calcd, 40.89).

Reaction of Methyl Phenylsulfenate (17, $R^1 = C_6H_5$; $R^2 = CH_3$) with Lithium Dimethylcuprate. The sulfenate ester (1.4 g, 10 mmol) was treated with lithium dimethylcuprate (20 mmol) at 0 °C for 1 h. Distillation afforded a sample of methyl phenyl sulfide (1.08 g, 87%), pure by VPC, TLC (silica, hexanes, or CCl_4), identical with an authentic sample (NMR, ir).

Synthesis of Chiral Sulfoxides. Menthyl Sulfinate Esters. (−)-Menthyl (−)-(*S*)-benzenesulfinate was prepared from lithium menthoxide [obtained from menthol (15.6 g, 100 mmol) and *n*-butyllithium] and *N*-(phenylsulfinyl)phthalimide (**16**,[22] 27.1 g, 100 mmol) in a similar manner to that described for *p*-tolyl phenylsulfinate. The resultant oil (20 g), containing one major component (TLC, silica, chloroform R_f 0.77), was purified by filtration through silica (60 g), followed by crystallization from methanol (−78 °C) to give a colorless solid (4.0 g). This was recrystallized twice from pentane to give (−)-menthyl (−)-(*S*)-benzenesulfinate as colorless needles, mp 51–52 °C (lit.[47] 49–51 °C), $[\alpha]D$ −205.5° (*c* 2.4, acetone) (lit.[47] −205.5°).

(−)-Menthyl (−)-(*S*)-*p*-toluenesulfinate was prepared by the method of Estep and Tavares[48] (71%), mp 102–104.5 °C (lit.[48] 108–109 °C), $[\alpha]D$ −210° (*c* 2.0, acetone) (lit.[48] −210°).

Chiral Sulfoxides. The sulfinate ester was treated with the lithium organocuprate as described previously. The resulting organic materials were chromatographed on silica to give several fractions that were monitored by TLC and VPC. Methyl phenyl (+)-(*R*)-sulfoxide was purified by Kugelrohr distillation, preparative TLC (silica, ethyl acetate), and a final Kugelrohr distillation to give material 95.2% pure (VPC), $[\alpha]D$ +133.9° (lit.[45] 128–149°).

The *p*-tolyl sulfoxides were purified by HPLC. After the initial separation on a silica column to remove the starting material and menthol, the sulfoxide fraction was separated from high molecular weight material on a μ-styragel column (tetrahydrofuran as eluent). Reversed phase chromatography on a C_{18}-Porasil column (3:1 tetrahydrofuran–water as eluent) gave methyl *p*-tolyl (+)-(*R*)-sulfoxide[10] and phenyl *p*-tolyl (+)-(*R*)-sulfoxide,[10] pure by TLC and NMR.

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Registry No.—**8a,** 15163-71-0; **8b,** 49639-22-7; **9a,** 60270-06-6; **9b,** 49639-23-8; **10a,** 20582-85-8; **10b,** 18721-62-5; **10c,** 5851-37-6; **10d,** 60270-07-7; **11a,** 18721-61-4; **11b,** 24536-40-1; **16,** 40167-15-5; **17** ($R^1 = C_6H_5$; $R^2 = CH_3$), 26905-22-6; *p*-cresol, 106-44-5; CH_3Li, 917-54-4; C_2H_5Li, 811-49-4; n-C_4H_9Li, 109-72-8; C_6H_5Li, 591-51-5; cuprous iodide, 7681-65-4; di-*n*-butyl sulfide, 544-40-1; ethyl phenyl sulfide, 622-38-8; *n*-butyl phenyl sulfide, 1126-80-3; ethyl phenyl sulfoxide, 4170-80-3; phenylsulfinyl chloride, 931-59-9; lithium menthoxide, 25531-51-5; methyl phenyl (+)-(*R*)-sulfoxide, 4850-71-9; methyl *p*-tolyl (+)-(*R*)-sulfoxide, 1519-39-7; phenyl *p*-tolyl (+)-(*R*)-sulfoxide, 16491-20-6.

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$$R^1\overset{\overset{O}{\|}}{S}OR^2 \xrightarrow{(R^3)_2CuLi} R^1SOR^2 \xrightarrow{(R^3)_2CuLi} R^1SR^3$$

17

then react with the organometallic reagent. We are able to show that methyl phenylsulfenate (**17**, $R^1 = C_6H_5$; $R^2 = CH_3$) reacts rapidly and smoothly with $(CH_3)_2CuLi$ to give methyl phenyl sulfide in good yield. This, however, does not allow us to explain the anomous reactions that produce *n*-butyl phenyl sulfide.
(19) Phenyl *p*-tolylsulfinate ester could be prepared in good yield, as a colorless liquid which decomposed on standing overnight (at −20 °C) to give a brown tar. This observation is corroborated by Baarschers and Krupay, who attempted to obtain phenyl methylsulfinate (**4**, $R^1 = CH_3$; $R^2 = C_6H_5$).[20]
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Enzymic-Like Aromatic Oxidations. Metal-Catalyzed Peracetic Acid Oxidation of Phenol and Catechol to *cis,cis*-Muconic Acid[1]

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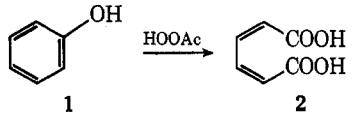
Phenol is oxidized to *cis,cis*-muconic acid (CCMA) by peracetic acid in the presence of catalytic quantities of Cu(II) and Fe(III). No CCMA is formed in the absence of these metals or in the presence of other specified metals. The yield of CCMA depends on the kind and quantity of metal ion used, being higher for oxidations with Fe(III) than Cu(II). Trace quantities of Fe(III) are effective at catalyzing the formation of CCMA. Catechol has been identified as an intermediate in the reaction. Kinetic studies indicate that the rate of disappearance of phenol is independent of metal and first order in both phenol and peracetic acid. The results are accommodated by a scheme which involves hydroxylation of phenol to give a mixture of catechol and *p*-hydroquinone followed by the formation of a metal–catechol complex which is rapidly and cleanly oxidized to CCMA.

In 1931 Boeseken and Engelberts[2] reported the oxidative cleavage of phenol (**1**) to *cis,cis*-muconic acid (CCMA, **2**)[3]



1 **2**

using peracetic acid (HOOAc). The carbon–carbon bond adjacent to the OH is cleaved leaving the stereochemistry about the two remaining double bonds unchanged. This reaction represents a rare example of a specific, nonenzymatic oxidative cleavage of an aromatic system. Other workers have since reported the peracetic acid oxidation of catechol[4] (**3**) to CCMA