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# Metalation of sulfur-containing organic compounds

Frederick Jarvis Webb  
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14

METALATION OF SULFUR-CONTAINING ORGANIC COMPOUNDS

by

Frederick Jarvis Webb

A Thesis Submitted to the Graduate Faculty  
for the Degree of

DOCTOR OF PHILOSOPHY

Major Subject Organic Chemistry

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METALATION OF SULFUR-CONTAINING ORGANIC COMPOUNDS

INTRODUCTION

The interest in sulfur-containing organic compounds has increased in recent years, partly because of their unusual and valuable physiological properties, and partly because of their significance to theoretical and practical organic chemistry.

Prior to the inception of the work embodied in this thesis, no attempt had been made to study the metalation of a variety of sulfur compounds. Because of the multivalent character of sulfur, there are available for study more types of compounds than is the case in the oxygen series. For instance, in addition to the sulfide and thiophenol types, the counterparts of the ethers and the phenols, there is a variety of disulfides, sulfoxides, and sulfones from which to choose. In this investigation it was proposed to limit the types of compounds studied to representative thiophenols, sulfides, disulfides, sulfoxides, and sulfones.

The interest in the investigation lay chiefly in determining the positions involved in the various metalations. In a few sulfur compounds metalations had been observed which were unusual in that the

position in the molecule substituted by the metalating agent differed from the position substituted by the same reagent in the corresponding oxygen compound. In addition to the theoretical significance of such reactions, there is the practical importance that a reaction of this type may make available a compound or a series of compounds otherwise quite inaccessible. Furthermore, it was proposed to study the role, in these transformations, of temperature, of solvents, and of metalating agents, and to investigate metalation rates as determined by these factors and by the structures of the sulfur compounds.

HISTORICAL

Reactions of Alkyl Alkyl and Alkyl Aryl Sulfoxides

1. Reactions with sodium

If alkyl sulfides are analogous to alkyl halides, it might be expected that both classes of compounds would undergo the Wurtz-Fittig reaction with metallic sodium. However, the action of sodium on alkyl sulfides in ether was found to be very slow; after three months only a trifling amount of an indefinite reaction product was obtained (1).

The important influence of the solvent is illustrated by experiments on the cleavage of sulfides in liquid ammonia (2, 3). The reaction of phenyl sulfide with sodium in liquid ammonia yielded only benzene and sodium sulfide (2). Incidentally, the introduction of thiophenol into liquid ammonia resulted in the immediate precipitation of the ammonium salt. Treatment with sodium converted the ammonium salt to the sodium salt:



Later investigators (3) were unable to repeat the work of Kraus

(1) Moses and Reid, *J. Am. Chem. Soc.*, **48**, 776 (1926).

(2) Kraus and White, *Ibid.*, **45**, 775 (1923).

(3) Williams and Gebauer-Fuelnegg, *Ibid.*, **53**, 352 (1931).

and White. In spite of a very careful search, no benzene or sodium sulfide could be isolated from the action of sodium on phenyl sulfide in liquid ammonia. A deep red solution formed when the reaction was complete. Evaporation of the solvent left a brown powder, which ignited on exposure to moist air. Only thiophenol and aniline were identified. Corresponding experiments with aliphatic sulfides gave no amines; the products were mercaptides, hydrocarbons, and sodamide:



## 2. Reactions with mercuric salts

The reactions of heavy metal salts with aliphatic sulfides have been the subject of many investigations since 1853, when Loir (4) first observed this chemical transformation. Mercuric salts coördinate rapidly with alkyl sulfides to form crystalline solids, which are used frequently as derivatives. A paper containing an excellent bibliography is that of Faragher, Morrell, and Comay (5). More recently, methods of derivatizing alkyl phenyl sulfides have been studied by Ipatieff and Friedman (6). Since this class of compounds coördinates very slowly or not at all with mercuric chloride, other methods of derivatization were sought and found in the palladous chloride complexes (7), which form rapidly

(4) Loir, Ann., 87, 369 (1853).

(5) Faragher, Morrell, and Comay, J. Am. Chem. Soc., 51, 2774 (1929).

(6) Ipatieff and Friedman, ibid., 61, 684 (1939).

(7) Mann and Purdie, J. Chem. Soc., 1549 (1935).

and in good yield. Apparently, mercuration of alkyl phenyl sulfides does not occur under the conditions used to form coordination compounds. Possibly this indicates that coordination precedes mercuration.

The mercuration of alkyl phenyl sulfides has been little investigated. Broad generalizations cannot be made at present; because too few compounds have been studied. However, in the most extensive study so far reported (8), the sulfur compounds appeared to mercurate less readily and give less pure products than the corresponding oxygen compounds.

The behavior of thiophenol toward mercuric salts is very different from that of phenol under corresponding conditions. At ordinary temperatures thiophenol gave a mercaptide, which on heating decomposed to yield mercury, diphenyl disulfide, mercuric sulfide, and phenyl sulfide. Phenol scarcely formed a mercury-oxygen linkage at all. Instead, the mercury entered the ring (9). To avoid the interaction of mercuric salts with the sulfhydryl group, Sachs and Ott attempted to mercurate *o*-methylmercaptobenzoic acid. They used a general method for mercurating aromatic carboxylic acids, but were unable to isolate a definite product. In contrast, *o*-methoxybenzoic acid is readily mercurated in boiling water to give a para-substituted mercurial (10).

Phenyl sulfide was also mercurated by Sachs and Ott. After experimenting with various conditions, they successfully obtained, by

(8) Sachs and Ott, *Ber.*, 59, 171 (1926).

(9) Dimroth, *Ber.*, 31, 2154 (1898).

(10) Lajoux, *J. Pharm. Chim.*, [7], 11, 279 (1915).

heating phenyl sulfide and mercuric acetate in amyl acetate at 150°, a soluble crystalline substance. This was mainly di- and triacetoxymercury derivatives, from which there was separated a 10% yield of *p*-acetoxymercuriphenyl phenyl sulfide. Treatment with nitric acid gave *p*-nitrophenyl phenyl sulfone, thus establishing that mercuration had taken place in the para position.

A monochloromercury compound was precipitated in the course of a week from a mixture of 2-ethylmercaptothiophene, sodium acetate, and mercuric chloride in alcohol (11). The position of the entering substituent was not determined; but, owing to the ease with which thiophene is substituted in the  $\alpha$ -positions as compared to the  $\beta$ -positions, there can be little doubt that 2-ethylmercapto-5-thienylmercuric chloride was produced in this reaction.

Methyl-2-thienyl sulfide was metalated in the same way to yield a monomercurial, but the reaction time was shortened to two days. Again, the chloromercury group was assumed to have entered the 5-position.

### 3. Reactions with organomagnesium compounds

Like diethyl ether, the corresponding sulfur, selenium, and tellurium compounds also promote the formation of methylmagnesium iodide, but to a lesser extent (12). It would be expected that the

(11) Steinkopf and Leonhardt, Ann., 495, 166 (1932).

(12) Hepworth, J. Chem. Soc., 119, 1249 (1921).

dialkyl sulfides, selenides, and tellurides would catalyze the reaction in ascending order of magnitude, if the tendency of the central atom to become tetravalent and the stability of the resultant "onium" compound were essential factors in the reaction. Since the experimental facts are otherwise, Hepworth concluded that the ability to form compounds of higher valency may be the initial cause of the catalyzing action, but it can have only a very slight effect on the speed of the reaction.

Double compounds containing alkyl sulfide and methylmagnesium iodide were formed, but not obtained in a crystalline condition.

The sulfur compounds, ethyl *n*-propyl sulfide, pentamethylene sulfide, and 1,4-dithian were compared with their oxygen analogues to determine the relative catalyzing action on the formation of methylmagnesium iodide. The oxygen compounds were the more effective catalysts. Structure was shown to have an important bearing on the promotion of the reaction, since the open-chained compounds had a greater activating effect than the cyclic compounds. Of the cyclic compounds, those with two coördinating elements had greater activity than those with but one such element.

Allyl sulfide was, apparently, unattacked by ethyl- or phenylmagnesium bromide in boiling ether. During a thirty-minute reflux period, 1,2-di-*p*-tolylmercaptoethylene destroyed scarcely any of a standard ethylmagnesium bromide solution (13). Refluxing with an

(13) Gilman and Peterson, J. Am. Chem. Soc., 48, 423 (1926).

etheral solution of phenylmagnesium bromide for fifteen hours cleaved allyl *p*-tolyl sulfide to a slight extent. Less cleavage occurred with allyl phenyl sulfide under corresponding conditions (14). The stability of sulfides toward Grignard reagents, under these mild conditions, is further exemplified by the fact that the use of aliphatic sulfides as a medium for Grignard reactions is the subject of a French patent (15).

#### 4. Reactions with organoalkali compounds

At ordinary temperatures phenyl sulfide was cleaved to a very slight extent by phenylsodium in benzene. Furthermore, splitting began only after the reactants were heated for several hours at 70-80°. Even with an excess of phenylsodium, large amounts of phenyl sulfide were recovered (16). Undoubtedly, metalation occurred in these reactions but went unobserved because of failure to derivatize the metalation product. Bebb (17) found that phenylsodium in benzene metalated phenyl sulfide to the extent of 56% in forty-eight hours at room temperature. Derivatization with gaseous carbon dioxide gave *o*-phenylmercaptobenzoic acid. When phenyl sulfide was refluxed with *n*-butyllithium in ether for twenty hours, 30% of *o*-phenylmercaptobenzoic acid was obtained subsequent

(14) McKenna, M. H., Unpublished master's thesis, Iowa State College (1929).

(15) French patent, 744,545 (1933) [*C.A.*, 27, 4240 (1933)].

(16) Fuchs and Breuer, *Monatsh.*, 53, 438 (1929).

(17) Bebb, R. L., Doctoral Dissertation, Iowa State College (1938); Gilman and Bebb, *J. Am. Chem. Soc.*, 61, 109 (1939).



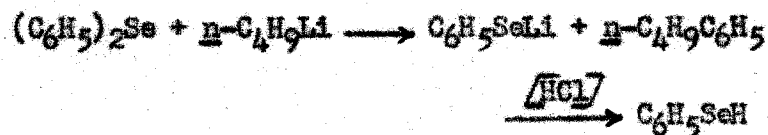
to carbonation by powdered dry-ice. Some cleavage occurred in this reaction, since the odor of thiophenol was noticed when the mixture was acidified. However, the amount of mercaptan was too small to permit isolation. No cleavage was noted when the reaction time was shortened to six hours. In this case the yield of metalation acid decreased to 24%. An ethereal solution of phenylcalcium iodide was refluxed with phenyl sulfide for forty-eight hours, but no metalation products were isolated upon carbonation. The resulting acidic material was exclusively benzoic acid. In addition, 96% of the starting material was recovered from the neutral fraction.

Phenyl ether, the oxygen analogue of phenyl sulfide, was metalated by *n*-butyllithium in ether to the extent of 60% in twenty hours and 51% in six hours, as determined by the yield of *o*-phenoxybenzoic acid obtained.

Under corresponding conditions *n*-butyllithium cleaved phenyl selenide with the formation of phenyllithium and butyl phenyl selenide:



The formation of phenyllithium is somewhat unusual. One would expect the lithium to combine with the more "negative" selenium rather than with the less "negative" carbon:



This reaction actually took place, as evidenced by the isolation of a

small quantity of selenophenol. No butylbenzene was reported. In contrast, the yield of phenyllithium was relatively large; 19% according to the yield of benzoic acid obtained subsequent to carbonation.

A comparison of the products resulting from the action of *n*-butyllithium on phenyl ether, phenyl sulfide, and phenyl selenide indicates two divergent phenomena. First, the extent of metalation decreases markedly as the central element is changed from oxygen to sulfur to selenium; the yields being 51%, 24%, and 0%, respectively, under the same conditions. Secondly, the cleavage of the bridge linkage increases from none at all with oxygen and only a trace with sulfur to 19% with selenium.

Unlike mercuration, which attacked the para position of phenyl sulfide, metalation with organoalkali compounds involved the hydrogen situated ortho to the hetero element. This statement is illustrative of a general rule which has been developed from metalation studies of a great variety of ethers, including aryl alkyl ethers, diaryl ethers, and cyclic ethers. Thus, mercuration generally replaces the same hydrogen that is replaced in the ordinary nuclear substitution reactions such as bromination, nitration, or sulfonation (18). On the other hand, metalation with organometallic compounds almost invariably acts on the hydrogen ortho to oxygen, sulfur (19), or nitrogen (20). An unusual

(18) Dibenzofuran is a notable exception. Page 26 of this thesis.

(19) Compare the metalation of dibenzothiophene with phenylcalcium iodide. Page 32 of this thesis.

(20) Diphenylamine is metalated meta to the nitrogen; Gilman and Brown, *J. Am. Chem. Soc.*, **62**, 3208 (1940).

metalation by n-butyllithium was observed with methyl phenyl sulfide. This reaction proceeded quite unlike the related anisole and, instead of giving an ortho nuclear metalation product, gave exclusively a lateral metalation product (21):



The metalation of ethyl phenyl sulfide by n-butyllithium results in an ortho nuclear substitution product (21), as is the case with the corresponding oxygen compound, phenetole.

A long-chained alkyl phenyl sulfide has been studied by Hoyt (22). Equimolecular quantities of n-butyllithium and phenyl n-tetradecyl sulfide were refluxed for fifty-two hours in ether solution. At the end of this time the failure to obtain a Michler's ketone color test indicated the absence of metalating agent and the probable absence of metalation products. On carbonation, 5-10 mg. of benzoic acid were isolated, and 64% of the starting material was recovered.

When the same reaction was performed in petroleum ether (b.p. 28-38°) at reflux temperature, 92.1% of phenyl n-tetradecyl sulfide was recovered. The only acidic material found was a trace of valeric acid.

(21) Gilman and Webb, *J. Am. Chem. Soc.*, **62**, 987 (1940).

(22) Hoyt, F. W., Doctoral Dissertation, Iowa State College (1940).

### Grignard Reagents from Sulfur-containing Organic Halides

In experiments with the Grignard reagents from *p*-bromophenyl phenyl ether and its sulfur and selenium analogues, Dilthey (23) found that the ease of formation of the organomagnesium halides increased as the bridge element was changed from oxygen to sulfur to selenium. This observation appears to be an exception to the general rule, inasmuch as the oxygen compounds usually form Grignard reagents more readily and in higher yields than the corresponding sulfur compounds. For example, Brand and his co-workers (24) experienced considerable difficulty in preparing Grignard reagents from *p*-bromophenyl methyl sulfide and from *o*-bromophenyl ethyl sulfide. In contrast, *p*-bromoanisole and *o*-bromophenetole react with magnesium to give almost quantitative yields of the corresponding organometallic compounds (25). 2-Bromodibenzothiophene reacts very sluggishly with magnesium to yield only 17% of the corresponding carboxylic acid on carbonation (26); whereas 2-dibenzofurancarboxylic acid is prepared by a similar reaction in 70% yields (27).

Somewhat surprising is the relative inertness of 2-bromofuran toward ordinary magnesium or toward magnesium activated with iodine. A

- (23) Dilthey, *J. prakt. Chem.*, 136, 71 (1933).
- (24) Brand and Stallmann, *Ber.*, 54, 1578 (1921); *J. prakt. Chem.*, 107, 358 (1924); Brand and Stein, *ibid.*, 108, 19 (1924).
- (25) Zoellner, E. A., Doctoral Dissertation, Iowa State College (1933).
- (26) Jacoby, A. L., Doctoral Dissertation, Iowa State College (1938); Gilman and Jacoby, *J. Org. Chem.*, 3, 108 (1938).
- (27) Bywater, W. G., Doctoral Dissertation, Iowa State College (1934).

reaction was effected, however, by the use of a magnesium-copper alloy; but only after activating it for one-half hour with iodine (28). The preparation of 2-thienylmagnesium bromide also presented difficulties. A three-hour period of refluxing was required to complete the reaction (29).

From this survey of representative sulfur and oxygen types, it is apparent that, in general, the Grignard reagents form more readily from the oxygen-containing organic halides than from the corresponding sulfur compounds.

#### Reactions of Disulfides

##### 1. Reactions with metals

The aliphatic disulfides were cleaved to mercaptides by sodium in boiling ethyl ether (1). The extent of the reaction was hindered by the formation of an insoluble coating of the mercaptide on the metal. The ease of cleavage increased from methyl to butyl, and in the case of the higher disulfides was apparently quantitative. In ether, the reaction of dibenzyl disulfide was extremely sluggish, whereas in ethanol at reflux temperatures, bibenzyl and hydrogen sulfide were formed. Di-*p*-nitrobenzyl disulfide underwent a complex decomposition when treated with sodium in ether at 34°, since the odor of ammonia was apparent.

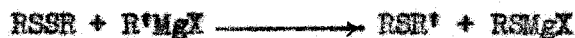
(28) Shepard, Winslow, and Johnson, *J. Am. Chem. Soc.*, **52**, 2083 (1930).  
(29) Krause and Benwanz, *Ber.*, **62**, 1710 (1929).

Magnesium had no action on these disulfides when refluxed in ether, in benzene, or in xylene.

Disulfides undergo a very ready scission by sodium in liquid ammonia (3).

## 2. Reactions with organometallic compounds

Disulfides are cleaved by organomagnesium compounds with the formation of a sulfide and a mercaptides



Ethyl phenyl sulfide,  $\alpha$ -naphthyl phenyl sulfide, and ethyl isobutyl sulfide have been prepared in this way (30).

Phenyllithium and triphenylmethylsodium react with disulfides in a manner entirely analogous to the scission with Grignard reagents. The reaction appears to be a very rapid one, as evidenced by the instantaneous decolorization of a red ether solution of triphenylmethylsodium when added dropwise to an ether solution of diphenyl disulfide. As the RSR\* compounds are obtained in good yields, the reaction may be used for preparative purposes.

Since phenyllithium has been shown to metalate phenyl sulfide (17), it is probable that g-phenylmercaptophenyllithium was formed when phenyllithium was reacted with diphenyl disulfide (31). However, as

(30) Wuyts, Bull. soc. chim., 37, 35, 166 (1906).

(31) Schönberg, Stephenson, Kaltschmitt, Petersen, and Schulten, Ber., 66, 237 (1933).

has often been the case, metalation was not observed through failure to use a "tagging reaction."

Diphenyl diselenide was cleaved by phenyllithium and by *p*-methoxyphenyllithium to give phenyl selenide and *p*-methoxyphenyl phenyl selenide.

Schönberg and his co-workers (32) have observed the effect of organolithium compounds on some thioacetals and related derivatives. Cleavage of the carbon-sulfur bond was the main reaction.

### Reactions of Cyclic Sulfides

#### 1. Reactions with sodium

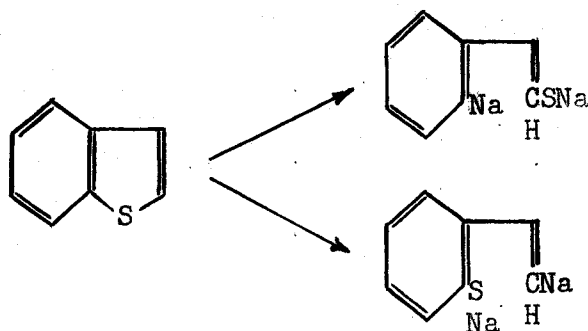
Thianaphthene is the only thiophene derivative which has been metalated by sodium metal (33, 34). In a first attempt (33) the reactants were heated together at 114-120°. Under these drastic conditions the thiophene ring was cleaved, very little thianaphthene was recovered, and most of the sulfur appeared as sodium sulfide. Under milder conditions (34) the nucleus was apparently not cleaved, and metalation was effected in good yields. When thianaphthene, in ether solution, was shaken with sodium sand, a red-colored solution formed in four hours. Later a violet-red precipitate separated. After a few days

(32) Schönberg, Kaltschmitt, and Schulten, Ber., 66, 245 (1933).

(33) Weissgerber and Kruber, Ber., 53, 1551 (1920).

(34) Schönberg, Peterson, and Kaltschmitt, Ber., 66, 233 (1933).

the precipitate no longer increased in size, and the reaction was terminated by carbonation to yield 56% of 2-thianaphthenecarboxylic acid. The high yield precludes the possibility that the metalating agent was an organosodium compound produced by cleavage of the carbon-sulfur bond by sodium.



## 2. Reactions with sodamide (33)

Sodamide in the absence of solvent does not cleave thianaphthene, in marked contrast to the behavior of sodium under these conditions. The reaction began even at 50-60° with the evolution of ammonia and was complete at 120°. Hydrolysis of the resulting yellowish-brown powder gave an almost complete recovery of thianaphthene. Carbonation yielded a mixture of 2-carboxy- and 2,3-dicarboxythianaphthene, of which approximately two-thirds was mono- and one-third dicarboxylic acid. Sodium metal in an atmosphere of ammonia behaved similarly.

In a large batch, thianaphthene (400 g.) was metalated with finely pulverized sodamide in xylene. The reaction was allowed to proceed for six hours with vigorous stirring, first at 100° and then at 145°. Carbonation was effected at 100-110° for twelve hours. The acidic fraction



was esterified and separated by fractional distillation into 10.5% methyl 2-thianaphthenecarboxylate and 7.8% dimethyl 2,3-thianaphthenedicarboxylate.

### 3. Reactions with mercuric salts

The mercuration of thiophene and its derivatives has been studied extensively since the discovery of this reaction by Volhard (35) in 1892. The parent compound and its alkyl and halogen derivatives are metalated readily at room temperature with a mixture of mercuric chloride and sodium acetate in alcohol. Volhard, using this procedure, prepared the mono- and dichloromercury derivatives of thiophene,  $\beta$ -methylthiophene, and  $\beta$ -isopropylthiophene. Only a monochloromercury compound was obtained from  $\alpha$ -methylthiophene. This fact indicates that substitution under these very mild conditions was occurring preferentially in the active alpha positions. Methyl 2-thienyl ketone was not mercurated by this procedure but formed a double compound with one molecule of mercuric chloride. Meta-directing groups appear to hinder mercuration, since Steinkopf (36) reports the failure to obtain mercuration under the above conditions with 2-nitrothiophene, and the reaction with 2-thenoic acid proceeds very slowly. Phenyl thienyl ketone (37) is not mercurated

(35) Volhard, Ann., 267, 172 (1892).

(36) Steinkopf and Bauermeister, Ann., 403, 50 (1914); Steinkopf, Ann., 413, 310 (1917); Steinkopf, Augestad-Jensen, and Donat, Ann., 430, 78 (1922).

(37) Weitkamp and Hamilton, J. Am. Chem. Soc., 59, 2699 (1937).

under these mild conditions. However, more drastic treatment gave a monomercurial, a dimercurial, and a double compound, consisting of one molecule of the monomercurial and one of the dimercurial.

The monomercurial was formed in almost quantitative yield when benzothienone was refluxed with a mercuric chloride-mercuric acetate mixture in glacial acetic acid. Conversion to the known 2-iodo-5-benzothienone proved that the chloromercury group had entered the expected 2-position.

Fusion of mercuric acetate with benzothienone gave the double compound, which was converted to the dimercurial by refluxing with excess mercuric acetate in methyl "cellesolve" solution. Cleavage of the resultant diacetoxymercury compound with bromine and potassium bromide gave the known 2,3-dibromo-5-benzothienone and located the acetoxymercury groups in the 2- and 3-positions.

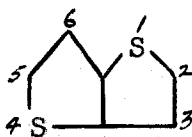
Thiophene was tetramercurated in a few hours with a cold saturated aqueous solution of mercuric acetate (38).

3-Bromothiophene was dimercurated (39) with mercuric acetate in 50% acetic acid at 50° to give the expected 2,5-diacetoxymercuri-3-bromothiophene. In order to introduce a third acetoxymercury group into the remaining  $\beta$ -position, the temperature of boiling glacial acetic acid was necessary. This illustrates the relative activity of the  $\alpha$ -hydrogens as compared with those in the  $\beta$ -positions.

(38) Paolini and Silbermann, Gazz. chim. ital., 45, II, 385 (1915).

(39) Steinkopf, Ann., 543, 128 (1940). This paper contains references to his earlier and extensive studies of the mercuration of thiophene.

Thieno[3,2-b]thiophene was monomercurated (40)



Thieno[3,2-b]thiophene

by shaking overnight with a mercuric chloride-sodium acetate mixture. The structure of the resulting mercurial was not elucidated. However, by analogy to the mercuration of thiophene, it is probable that the chloromercury group entered the 2- (or 5-) position. That this is only a probability can be readily understood by referring to the mode of mercuration of thianaphthene, which is substituted in the 3-position, rather than in the 2- or ortho position (41).

Thienothiophene has been separated from thianaphthene by fractional mercuration (42).

The metalation of that highly reactive compound, thianaphthene, has been extensively studied. "One or more" mercuriacetates were obtained when thianaphthene was warmed with mercuric acetate in acetic acid or alcohol (43). The composition of one of these agreed with a monoacetoxy-mercury derivative. Weissgerber and Kruber (33) studied the mercuration

(40) Challenger and Gibson, *J. Chem. Soc.*, 305 (1940).

(41) See page 26 of this thesis.

(42) Challenger and Miller, *J. Chem. Soc.*, 1006 (1939).

(43) Bezdzik, Friedländer, and Koeniger, *Ber.*, 41, 227 (1907).

of thianaphthene as a means of separating it from the naphthalene fraction of coal tar. A coal tar fraction was mercurated, and pure thianaphthene obtained on acidification of the resulting mercurial. Studies of this type were also pursued by Challenger (42), who detected thianaphthene in shale oil by mercuration.

None of these earlier workers (33, 43) determined the structures of the mercury compounds, and the problem has been solved only recently (42). Because of the ease with which thianaphthene is substituted, it was found very difficult to prepare a monomercurated product. A variety of conditions yielded only disubstituted derivatives. A monomercurial was finally obtained by treating thianaphthene with mercuric acetate in very dilute alcohol for two or three days. Propionyl chloride converted the monomercurial to an ethyl ketone identical with the known 3-propionylthianaphthene, thus proving that the mercurial was a 3-substituted derivative. In thianaphthene, therefore, mercuration corresponds to bromination, nitration, and acylation.

Mercuration of dibenzofuran (44) and N-ethylcarbazole (45) with mercuric acetate resulted in the formation of the 4- and 2-acetoxymercury derivatives, respectively. Oddly enough, no mercurial was isolated when mercuric acetate was allowed to react with dibenzothiophene in boiling alcohol (26). However, the slow addition of mercuric acetate to a melt of dibenzothiophene at 140-145° did effect a reaction as acetic acid

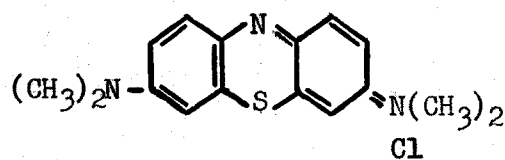
(44) Gilman and Young, *J. Am. Chem. Soc.*, **56**, 1415 (1934).

(45) Gilman and Kirby, *J. Org. Chem.*, **1**, 146 (1936).

distilled from the mixture. Difficulty was experienced in purifying the product, and as a result analysis showed a content of mercury which was 2% too high for a dibenzothienylmercuric acetate. It was suggested that the mono-derivative was contaminated with a small quantity of a dimercurial.

Like dibenzothiophene, neither N-phenyl- nor N-benzylphenothiazine was metalated by boiling alcoholic mercuric acetate (46). Instead, the solution turned an intense wine-red color, and mercury and mercurous acetate were precipitated. However, N-methylphenothiazine was mercurated rapidly in this manner to give both 3-acetoxymercuri- and 3,7-diacetoxymercuri-N-methylphenothiazine. Further mercuration of the mono-derivative gave the dimercurial. The corresponding N-ethyl compounds were obtained by the same procedure.

The mercuration of methylene blue was the subject of an investigation by Chalkley (47).



Methylene Blue

Inorganic salts of mercury exert a toxic effect on tubercle bacilli but show weak penetration of the cells. It appeared probable that the

(46) Finzi, Gazz. chim. ital., 62, 175 (1932).

(47) Chalkley, J. Am. Chem. Soc., 47, 2055 (1925).

penetrating action could be increased by combining the inorganic salt with an organic dye, such as methylene blue, which readily stained the organism. Earlier attempts to mercurate methylene blue had been unsuccessful, because complex formation largely suppressed the concentration of mercuric ion. Only in the presence of a large excess of mercuric acetate could mercuration be effected. Two compounds were obtained. One, believed to be a bismercurial, was not isolated in a pure form because of the readiness with which it passed into a colloidal condition. The other was a monoacetoxymercury derivative, whose structure was not determined. Somewhat better yields of a monoacetoxymercury compound were obtained from the benzoyl derivative of methylene blue. Again, the structure was not elucidated.

#### 4. Reactions with organomagnesium compounds

The number of nuclei which have been metalated by means of the Grignard reagent was recently extended to include thiophene (40). Heating in dimethylaniline with excess ethylmagnesium bromide gave, on carbonation, 9.1% of  $\alpha$ -thenoic acid with the complete absence of the  $\beta$ -isomer.

Like thiophene, thieno [3,2-b]thiophene (40) has been metalated with ethylmagnesium bromide. The reaction, carried out in dimethylaniline at 160-170°, followed by carbonation overnight, yielded 12% of a monocarboxylic acid. The same acid resulted in 14% yield when amyl ether was used as solvent. A dicarboxylic acid was formed when the

reaction in amyl ether was repeated with a one mole excess of Grignard reagent. The structures of the metalation acids were not determined; but, from analogy to substitutions in thiophene derivatives, and more particularly to metalations by organometallic compounds, it is almost certain that 2-carboxy- and 2,5-dicarboxythienothiophene were produced.

Ethylmagnesium bromide began to act on thianaphthene even at room temperature. Completion of the reaction in dimethylaniline at the boiling point for an hour gave 24% of 2-thianaphthene-carboxylic acid subsequent to carbonation (33).

Inasmuch as these three heterocycles were metalated under very similar conditions, the yields of monocarboxylic acids may be significant in determining the relative aromaticities of the three compounds. On the basis, then, of the relative ease of metalation with ethylmagnesium bromide, the order of increasing aromaticity is thioephene, thienothiophene, and thianaphthene.

#### 5. Reactions with organoalkali compounds

According to the hydrogen chloride scission of organolead compounds, furan appears to be more aromatic than thiophene (48). However, metalation experiments do not clearly substantiate this concept (49). Furan was metalated by 2-thienylsodium to yield 2-furylsodium, since carbona-

(48) Gilman and Tome, Rec. trav. chim., **51**, 1054 (1932).

(49) Gilman and Breuer, J. Am. Chem. Soc., **56**, 1123 (1934).

tion of the mixture gave 2-furoic acid and no thenoic acid (49). This experiment indicates the greater aromaticity of furan as compared to thiophene. On the other hand, when thiophene was reacted with 2-furylsodium, 2-thenoic acid resulted on carbonation of the mixture. Although no 2-furoic acid was detected in the latter reaction, it cannot be concluded that none was present. The method of mixed melting points was found to be unreliable with a mixture of these two compounds, nor was there available any method for quantitatively separating 2-furoic acid from 2-thenoic acid. In the two experiments, the yield of 2-furoic acid from furan and 2-thienylsodium was almost the same as the yield of 2-thenoic acid from thiophene and 2-furylsodium.

These workers also metalated 2-methylthiophene with benzylsodium in heptane. After 144 hours at 60° there was isolated 21% of 2-methyl-5-thenoic acid subsequent to carbonation. This is but another illustration of the slow rate at which metalations proceed in aliphatic hydrocarbon solvents (17). Only a trace of 2-methyl-5-furoic acid was obtained when a mixture of ethylsodium and 2-methylfuran was heated at 60° for ten hours.

Thiophene itself appeared to be more readily metalated by ethylsodium, since 30% of 2-thenoic acid was obtained following derivatization of the metalation product with carbon dioxide (50).

As with dibenzofuran, the metalation of dibenzothiophene with

(50) Schorigin, Ber., 43, 1938 (1910)



organolithium compounds affects the 4-position. This follows from a comparison of authentic 4-methyldibenzothiophene, prepared by ring closure, with the methyl derivative obtained from the metalation product and dimethyl sulfate (26).

Dibenzothiophene has been metalated by a series of organolithium compounds, under comparable conditions (26). The yields of 4-dibenzothiophenecarboxylic acid, isolated subsequent to carbonation, made possible the arrangement of the various R groups in order of decreasing effectiveness: n-butyl, phenyl,  $\alpha$ -naphthyl, and p-methoxyphenyl.

An investigation of the effect of solvent on the metalation of dibenzothiophene has been made by Bebb (17). For purposes of comparison, all reactions were allowed to proceed for twenty hours with n-butyllithium as the metalating agent. At the end of the specified time, the mixtures were carbonated and the yields of acid determined. Of the various solvents tested, only n-butyl ether was found to be suitable for metalations with n-butyllithium. In this solvent 61% of 4-dibenzothiophenecarboxylic acid was obtained at room temperature and 90% of the same product at 80°. No metalation occurred in benzene at room temperature or in dioxane at 40-45°, nor were any acidic products isolated from similar reactions at reflux temperatures in two fractions of petroleum ether (b.p. 30-35° and 60-68°). In only six hours at room temperature, n-amylsodium gave a 37% yield of the 4-acid when the solvent was petroleum ether (b.p. 60-68°).

In this connection it is interesting to correlate the effects of

solvents on halogen-metal, metal-metal, and hydrogen-metal interconversions (51). As well as being an excellent solvent for metalations, n-butyl ether has been shown to be an excellent solvent for halogen-metal interconversions (52). On the other hand, petroleum ether has been shown to be a poor solvent for metalations (17) and the least active of a series of solvents for the promotion of halogen-metal interconversions (52). Similarly, no metal-metal interconversion occurred between n-butyllithium and tetraphenyllead in petroleum ether (b.p. 60-68°). In benzene, under the same conditions, a reaction occurred but to an extremely slight extent (53).

In a number of reactions (54, 55, 56) phenylcalcium iodide has been shown to correspond to the phenyl alkali compounds in its activity toward certain functional groups. However, unlike phenyllithium, which metalated dibenzothiophene in the 4-position, phenylcalcium iodide effected a substitution in the 3-position (26). This constituted the first reported case in which an organometallic compound metalated a position meta to a hetero element in preference to an unhindered ortho position. That the metalation involved the 3-position of dibenzothiophene was shown by two indirect procedures (57). First, the metalation acid

- (51) Hydrogen-metal interconversion and metalation are synonymous.
- (52) Gilman and Moore, J. Am. Chem. Soc., 62, 1843 (1940).
- (53) Gilman and Moore, ibid., 62, 3206 (1940).
- (54) Kirby, R. H., Doctoral Dissertation, Iowa State College (1937).
- (55) Gilman, Kirby, Lichtenwalter, and Young, Reg. trav. chim., 55, 79 (1936).
- (56) Gilman and Bailie, J. Org. Chem., 2, 84 (1937).
- (57) Gilman, Jacoby, and Pacevitz, ibid., 3, 120 (1938).

was shown to be unlike the known 2- and 4-dibenzothiophenecarboxylic acids. Hence, it could be either a 1- or a 3-substituted compound. 1-Dibenzothiophenecarboxylic acid was then synthesized and shown to differ from the metalation acid. Therefore, since three of the four possible acids had been prepared by known methods, the remaining one must have been the 3-acid. Second, any doubt concerning the position of the bromine atom in the bromodibenzothiophene from which the "1-acid" was prepared, was removed by synthesizing 3-bromodibenzothiophene 5-dioxide and showing that it was unlike the sulfone obtained by oxidizing 1-bromodibenzothiophene.

Since the symmetrical phenoxathiin (58) was metalated preferentially ortho to oxygen rather than ortho to sulfur, it might be expected that dibenzofuran would metalate more rapidly than dibenzothiophene. This was actually found to be the case, as determined by three different procedures (59). In the first of these, one mole of n-butyllithium was refluxed with one mole of dibenzofuran and one of dibenzothiophene in ether solution for six hours. Following carbonation, there was isolated 39% of 4-dibenzofurancarboxylate, which contained no sulfur, as shown by a sodium fusion test. In a check run, which was refluxed twelve hours, 35% of sulfur-free 4-dibenzofurancarboxylic acid was found. When a similar reaction mixture was carbonated after refluxing only two hours, a trace of 4-dibenzothiophenecarboxylic acid was

(58) See page 35 of this thesis.

(59) Gilman, Van Ess, Willis, and Stuckwisch, J. Am. Chem. Soc., 62, 2606 (1940).

separated.

In the second method of establishing the greater rate at which dibenzofuran is metalated as compared to dibenzothiophene, an ethereal solution of 4-dibenzothieryllithium was used to metalate dibenzofuran. After a reflux period of six hours, there was isolated, subsequent to carbonation, a mixture of 4-dibenzofurancarboxylic acid and 4-dibenzothiophenecarboxylic acid. This mixture was oxidized, and the resulting 4-dibenzothiophenecarboxylic acid 5-dioxide was separated from the unchanged 4-dibenzofurancarboxylic acid by extraction with ether, the sulfone being essentially insoluble.

Under duplicate conditions, it was shown that 4-dibenzofuryllithium did not metalate dibenzothiophene, since the acidic product, isolated on carbonation, contained no sulfur and was identified as 4-dibenzofurancarboxylic acid.

Third, separate metalations showed dibenzofuran to be metalated more readily.

A corresponding set of experiments, in which N-ethylcarbazole was compared with dibenzofuran and with dibenzothiophene, demonstrated that the relative rates of metalation of these three compounds by n-butyllithium were as follows (60):

dibenzofuran > dibenzothiophene > N-ethylcarbazole

When 1,4-dihydrodibenzothiophene (26) was treated with phenyllithium at ordinary temperatures, a rapid dehydrogenation took place,

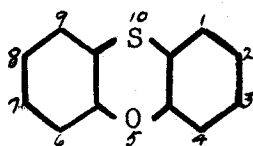
(60) Unpublished studies by Mr. C. G. Stuckwisch.

for there was isolated, after carbonation, a 90% yield of dibenzothiophene. Other products found were benzene and benzoic acid.

A similar reaction, in which phenylisopropylpotassium was added to the dihydro compound, yielded some dibenzothiophene, together with what appeared to be a mixture of mono- and dicarboxydibenzothiophenes. No definite compounds were identified in the acidic fraction.

By analogy with the work of Bradley (61) on the metalation of 1,4-dihydronaphthalene and 1,4-dihydrodibenzofuran, it is probable that had more moderate conditions been used in the reactions of 1,4-dihydrodibenzothiophene mentioned above, 1,2-dihydrodibenzothiophene-2-carboxylic acid would have been isolated.

The metalation of phenoxathiin (59) has been investigated with a view to determining the relative orienting effects of sulfur and oxygen.



After refluxing for twenty-four hours with *n*-butyllithium in ether, there was isolated subsequent to carbonation 53-61% of a monophenoxathiin-carboxylic acid. The melting point of this acid differentiated it from the known 2- and 3-phenoxathiincarboxylic acids. Evidently, then, it was a 1- or a 4-substituted compound. Identification was finally

(61) Bradley, C. W., Doctoral Dissertation, Iowa State College (1937); Gilman and Bradley, *J. Am. Chem. Soc.*, **60**, 2333 (1938).

completed by converting the metalation acid to the known 4-chloro-phenoxathiin 10-dioxide.

Inasmuch as some unusual orientations have been obtained in metalations of sulfur compounds (62), it was not surprising that the acid obtained on refluxing phenoxathiin with phenylcalcium iodide in ether solution, followed by carbonation, differed from the acid produced in a similar reaction with n-butyllithium. Although the melting point of the metalation acid from phenylcalcium iodide agreed with that of the known 2-phenoxathiincarboxylic acid, a mixed melting point determination showed a depression. The compound may be the as yet unknown 1-acid, or it might be 4,6-dicarboxyphenoxathiin. The latter suggestion did not appear to be very probable, in view of the fact that no disubstituted products were reported from phenoxathiin and n-butyllithium, a more reactive (63) metalating agent than phenylcalcium iodide. Recently a dibasic acid was isolated (64) from a metalation of phenoxathiin with n-butyllithium according to the usual procedure (59) and shown to be identical with the acid from phenylcalcium iodide and phenoxathiin by a mixed melting point determination.

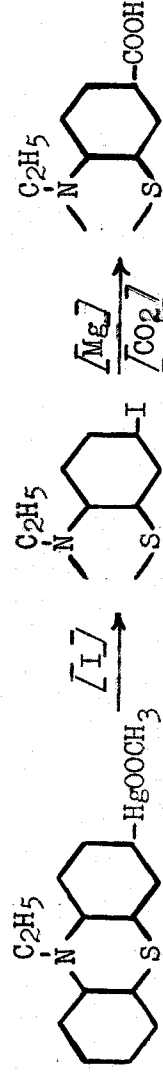
Treatment of n-ethylphenothiazine with n-butyllithium for a twenty hour reflux period yielded, on carbonation, 36.6% of a gummy

(62) See pages 17 and 32 of this thesis.

(63) n-Butyllithium is considered to be more reactive than phenylcalcium iodide because higher yields of metalation products are obtained with dibenzofuran, dibenzothiophene, and phenyl sulfide.

(64) Unpublished studies by Mr. Souran Avakian.

acidic product (65). Owing to the difficulty of purifying this substance, the yield of pure monocarboxylic acid was less than 6%. The structure of the compound was not proved, but the possibility of a substituent in the 3-position was excluded by preparation of 10-ethylphenothiazine-3-carboxylic acid in the following sequence of reactions:



Van Ess believed that metalation occurred in the 1-position, but the recent work of Stuckwisch (60) on the relative rates of metalation of dibenzothiofene and *p*-ethylcarbazole show conclusively that sulfur has a greater activating effect than nitrogen. Consequently, it now appears more likely that the metalation product is a 4-derivative.

The greater activating effect of oxygen as compared with nitrogen is shown by the yields of metalation acids from phenoxathin, 53-61%, and *p*-ethylphenothiazine, 36.6%, under essentially the same conditions.

That oxygen compounds are more readily metalated than the corresponding sulfur compounds is further exemplified by a comparison of dibenzo-*p*-dioxin with thianthrene (60). The sulfur compound, when

(65) Van Ess, P. R., Doctoral Dissertation, Iowa State College (1936).

treated with n-butyllithium, gave mostly monometalation together with a small amount of dimetalation. The oxygen compound, on the other hand, gave only dimetalation under the same conditions and therefore must be more readily substituted.

### Reactions of Sulfoxides

#### 1. Reactions with sodium

A study was made of the behavior of several sulfoxides toward reagents which would indicate the influence exerted by the sulfoxide linkage on adjacent methylene groups (66). Benzyl phenyl sulfoxide, dibenzyl sulfoxide, and bis(phenylsulfinyl)methane were tested. The sulfoxide groups apparently had no activating effect, since none of these compounds reacted with sodium in cold benzene. The effect of sodium on diphenyl sulfoxide under these conditions was determined also to guard against addition reactions. Here again, no reaction was observed. A similar observation had been made somewhat earlier by Fuchs and Gross (67). However, at 80-90° a reaction took place between sodium and diphenyl sulfoxide when the reactants were heated with benzene in a sealed tube. The reaction was very slow, for sodium was present even after the mixture had been kept for a year. Carbonation gave phenyl sulfide (53%), a little recovered diphenyl sulfoxide,

(66) Shriner, Struck, and Jorison, J. Am. Chem. Soc., 52, 2060 (1930).  
(67) Fuchs and Gross, Ber., 63, 1009 (1930).



sodium carbonate, and a trace of thiophenol.

Di-*p*-tolyl sulfoxide, under the same conditions, with sodium or potassium, formed dark red partially soluble compounds. Filtration of this mixture, followed by decomposition with water, gave a basic solution. Another mixture of this kind was kept for one year, filtered, and then carbonated; but no carboxylic acid was obtained. Only a trace of dimethyldibenzothiophene was isolated (68).

The formation of the above products was explained by assuming that the colored substances were analogous to metal ketyls, and that carbon dioxide abstracted oxygen and sodium to form sodium carbonate and organic sulfides. The sodium was evidently not attached to carbon, since no carboxylic acids were found. Cleavage of the sulfides would yield thiophenols, and the abstraction of water from the sulfoxide would lead to cyclization.

## 2. Reactions with sodamide

Sodamide was shown to convert diphenyl sulfoxide to dibenzothiophene in a reaction first discovered by Schonberg (69). By a study of the conditions of this reaction, Courtot (70) and his co-workers were able to increase the yield of dibenzothiophene from 25% to 32%. In addition to dibenzothiophene, there was obtained in smaller amounts,

(68) Breuer, Dissertation, Vienna (1929).

(69) Schönberg, Ber., 56, 2275 (1923).

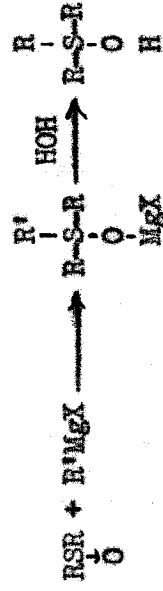
(70) Courtot, Chaix, and Nicolas, Compt. rend., 194, 1660 (1932).

phenyl sulfide, diphenyl disulfide, aniline, and benzenesulfonic acid. Further study of this reaction (71) indicated that it had a limited application, since no cyclization was observed with di-*p*-bromophenyl sulfoxide. According to these investigators, the cyclization occurred through a simple dehydration.

### 3. Reactions with organomagnesium compounds

In addition to his studies on the catalyzing action of sulfides on the formation of Grignard reagents, Hepworth (12) also determined the effect of sulfoxides. Both diphenyl sulfoxide and diisocanyl sulfoxide initiated the formation of methylmagnesium iodide and to a greater extent than some simple sulfides. The amorphous double compounds which separated from benzene solution apparently had the structure  $2R_2SO \cdot CH_3MgI$  according to analyses for magnesium and iodine. Inasmuch as the double compounds could not be obtained in crystalline form, the results were not very convincing.

Unsuccessful attempts were made to produce sulfonium compounds by the addition of Grignard reagents to the sulfur-oxygen bond of sulfonides (72):



(71) Courtot, Chaix, and Kelner, Compt. rend., 194, 1837 (1932).  
(72) Hepworth and Clapham, J. Chem. Soc., 119, 1188 (1921).

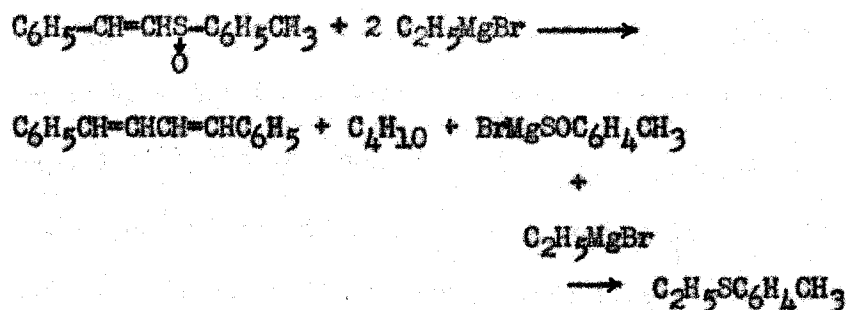
Experiments of this type were carried out under the impression, since shown to be false (66), that the sulfur-oxygen bond of a sulfoxide is identical with the carbon-oxygen bond of a ketone.

No apparent reaction occurred when methylmagnesium iodide in ether was refluxed with diphenyl sulfoxide. Accordingly, the ether was replaced with toluene and the heating continued for twelve hours. On hydrolysis, 44% of the sulfoxide was recovered together with 54.5% of phenyl sulfide. A similar reduction occurred with phenylmagnesium bromide, but at a slower rate, since only 33% of phenyl sulfide was obtained after fifteen hours in toluene. Diisooamyl sulfide was reduced to the extent of 70% by methylmagnesium iodide under these conditions; whereas benzyl phenyl sulfoxide gave only 43% reduction with the same reagent. No cleavage products were noted in any of these reactions.

To determine whether benzyl phenyl sulfoxide and trimethylene trisulfoxide contained active hydrogen atoms, the two compounds were heated with methylmagnesium iodide in anisole solution at 70° for one hour. No gas was evolved under these conditions.

In contrast to the saturated sulfoxides, styryl *p*-tolyl sulfoxide was cleaved by an excess of ethylmagnesium bromide at room temperature (73). The products isolated were ethyl *p*-tolyl sulfide and 1,4-diphenylbutadiene.

(73) Kohler and Potter, *J. Am. Chem. Soc.*, 57, 1320 (1935).



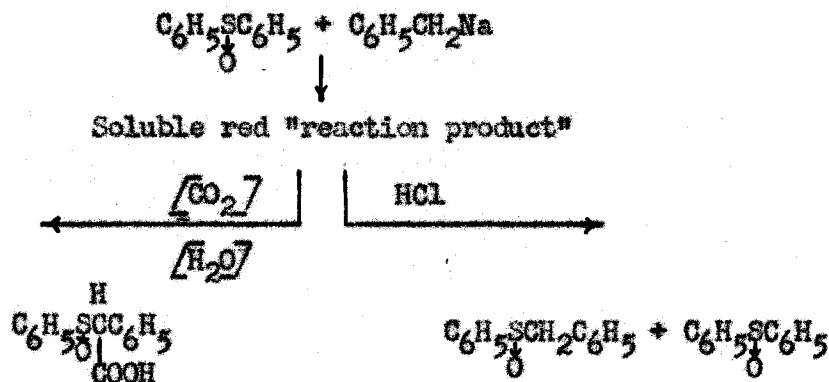
The corresponding reaction with phenylmagnesium bromide gave biphenyl, phenyl *p*-tolyl sulfide, and 1,4-diphenylbutadiene. In both reactions the cleavage of the carbon-sulfur linkage apparently preceded the reductive formation of the sulfide, because the Grignard reagents were without action on styryl *p*-tolylsulfide.

In addition to the above products from the reaction with phenylmagnesium bromide, these investigators isolated an oil which was oxidized and subsequently identified as  $\beta, \beta, \beta$ -triphenylethyl *p*-tolyl sulfone. They were unable to account for the formation of this compound.

#### 4. Reactions with organoalkali compounds

Although sulfonium compounds were not formed from organomagnesium halides and sulfoxides (72), it appeared possible that the more reactive organoalkali compounds might add to the sulfur-oxygen linkage to yield sulfonium hydroxides on hydrolysis. This hope was not realized for the reaction of aromatic sulfoxides with organosodium compounds followed an entirely different course (74):

(74) Fuchs and Breuer, Monatsh., 53, 438 (1929).



Possibly this reaction proceeds through a primary scission of diphenyl sulfoxide by benzylna to form benzyl phenyl sulfoxide and phenylsodium. The phenylsodium produced in this way, as well as any unreacted benzylna, would then be expected to metalate benzyl phenyl sulfoxide. A measure of support is given to this mechanism by the fact that phenylsodium in benzene does metalate benzyl phenyl sulfoxide.

In addition to the unexpected rearrangement, an unusual solvent effect was observed in the reaction of benzylna with diphenyl sulfoxide. In benzene, very little benzyl phenyl sulfoxide was found when the mixture was hydrolyzed, and only 1-3% yields of  $\alpha$ -carboxybenzyl phenyl sulfoxide were obtained when the reaction was terminated by carbonation. On the other hand, the same reaction in toluene gave 30-35% of benzyl phenyl sulfoxide on hydrolysis and 35-40% yields of  $\alpha$ -carboxybenzyl phenyl sulfoxide on carbonation. The latter reaction yielded, as an additional acidic product, an unstated quantity of *p*-benzylbenzoic acid. The remarkable difference in yields brought about by the two different solvents cannot be attributed to a temperature effect since room temperature was maintained throughout.

Benzylsodium and di-*p*-tolyl sulfoxide behaved similarly in toluene solution, benzyl *p*-tolyl sulfoxide being obtained after hydrolysis. Oddly enough, benzyl phenyl sulfoxide and benzylsodium gave only recovered starting material. The most careful search revealed no dibenyl sulfoxide.

Diphenyl sulfoxide reacted with phenylsodium in benzene to form a red, difficultly soluble compound. On carbonation, an acidic substance was obtained, but all attempts to crystallize or purify it were fruitless.

At higher temperatures the reactions of aromatic sulfoxides with organoalkali compounds followed a different course, for 50% of dibenzothiophene was obtained when phenylsodium and diphenyl sulfoxide were heated in a sealed tube. Di-*p*-tolyl sulfoxide reacted similarly. Benzylsodium also converted diphenyl sulfoxide to dibenzothiophene but the yield was less than when phenylsodium was used.

When a dilute ethereal solution of triphenylmethylsodium and diphenyl sulfoxide was cooled to  $-60^{\circ}$  or  $-70^{\circ}$  a violet red precipitate appeared. This compound was purified by crystallization and analyzed for sulfur and sodium from which the following composition was calculated:



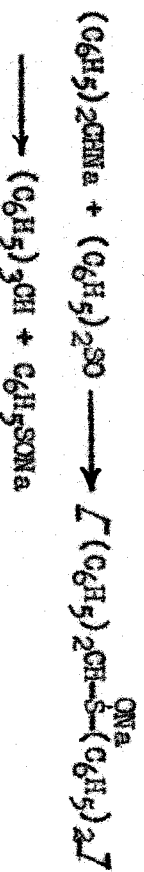
Attempts to determine the structure did not lead to any definite conclusions. Decomposition with hydrogen chloride gave sodium chloride, diphenyl sulfoxide, and triphenylmethane in approximately stoichiometrical amounts; whereas carbonation yielded diphenyl sulfoxide and

triphenylacetic acid.

A similar reaction took place between diphenyl sulfoxide and 9,10-dihydroanthracene-9,10-disodium, but unlike the previous case, no definite compound could be isolated. However, the sodium in the reaction mixture had evidently entered into a state of combination which differed from that in the original anthracene compound; because the sodium could not be removed entirely by shaking with mercury.

Almost all the sodium can be removed from 9,10-dihydroanthracene-9,10-disodium by the action of mercury. A black greasy precipitate formed when benzohydrilsodium reacted with diphenyl sulfide (75). Large amounts of triphenylmethane, smaller quantities of diphenyl disulfide, and a trace of thiophenol were isolated. Later this experiment was repeated with a view to investigating the mechanism of the reaction (76). The reactants were shaken for two days in ether solution. The solid phase which formed during this period was identified as sodium benzene-sulfonate,  $C_6H_5SO_3Na$ . In addition, only triphenylmethane was found and it was shown that triphenylmethylsodium was not its precursor. The

reaction was believed to occur by a primary addition of diphenylmethylsodium to the sulfur-oxygen linkage followed by a migration of the phenyl group from sulfur to oxygen with a subsequent cleavage:



(75) Bergmann and Tschudnowsky, Ber., **65**, 457 (1932).

(76) Schönberg and Stephenson, Ber., **66**, 250 (1933).

## Reactions of Sulfones

### 1. Reactions with sodium

The sulfone group activates to a considerable extent the hydrogen of an adjacent methylene group. Thus, hydrogen was slowly liberated when sodium was added to a benzene solution of benzyl phenyl sulfone. Dibenzyl sulfone and bis(phenylsulfonyl)methane behaved similarly (66, 77). Diphenyl sulfone was cleaved by sodium metal in xylene at 140° (78).

### 2. Reactions with inorganic compounds

The hydrogen of a methylene group may become very acid when adjacent to both a sulfone group and some other activating atomic linkage, or when adjacent to two or more sulfone groups. For example, dibenzyl sulfone was slightly soluble in 10% sodium hydroxide solution, but insoluble in 10% sodium carbonate solution; whereas bis(phenylsulfonyl)methane dissolved in both of these solutions. Salt formation in compounds of this type occurs more readily with sodium and potassium alkoxides. Long years ago, Baumann and his co-workers (79) examined the

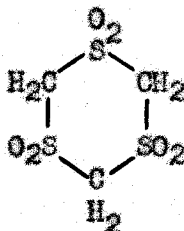
(77) Shriner and Greenlee, J. Org. Chem., 4, 242 (1939).

(78) Kraft and Vorster, Ber., 26, 2813 (1893).

(79) Baumann and Fromm, Ber., 22, 2600 (1889); Baumann and Camps, Ber., 23, 69, 1874 (1890); Camps, Ber., 25, 233, 248 (1892); Laves, Ber., 25, 347 (1892); Baumann, Ber., 26, 2074 (1893); Lomnitz, Ber., 27, 1667 (1894); Peters, Ber., 38, 2565 (1905).



cyclic compound trimethylene trisulfone and some of its derivatives.



Trimethylene Trisulfone

Sodium, potassium, barium, magnesium, and silver salts of trimethylene trisulfone were readily prepared.

### 3. Reactions with organomagnesium compounds

Neither dimethyl sulfone nor diphenyl sulfone promoted the formation of methylmagnesium iodide (12).

Diphenyl sulfone, benzyl phenyl sulfone and trimethylene trisulfone were largely recovered, subsequent to hydrolysis, after long periods of heating with methylmagnesium iodide in toluene or anisole solution (72). From this experiment one would be led to believe that Grignard reagents do not add to, cleave, or reduce sulfones. However, since anisole at the boiling point can be metalated nuclearly by ethylmagnesium bromide (80), it seems highly probable that the more active hydrogen of the methylene group of benzyl phenyl sulfone would be metalated also under these conditions. As the reaction mixtures were hydrolyzed, the starting

(80) Challenger and Miller, J. Chem. Soc., 894 (1938).

materials in each case were recovered and no metalation was observed. Metalation of sulfones by methylmagnesium iodide has been demonstrated by measuring the volume of methane liberated (81). Thus,  $\beta$ -phenylethyl *p*-tolyl sulfone and  $\beta, \beta$ -diphenylethyl *p*-tolyl sulfone liberated at least one mole of methane when heated at 50-75° with methylmagnesium iodide. Methane was evolved slowly at room temperature when methyl *p*-tolyl sulfone was treated with methylmagnesium iodide. In this reaction *p*-tolylsulfonylmethylmagnesium iodide was formed. The -MgI group may be replaced by reagents typical for the carbon-magnesium linkage (82). The failure of Gibson (83) to observe an evolution of methane, when methyl phenyl sulfone was refluxed in ether with methylmagnesium iodide, may be attributed to the fact that the sulfone is almost insoluble in the solvent employed.

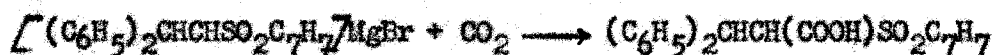
The great activity of unsaturated sulfones toward Grignard reagents became apparent when it was shown that ethylmagnesium bromide reacted completely with  $\alpha, \beta$ -bis(*p*-tolylsulfonyl)ethylene on refluxing thirty minutes (13). The nature of the reaction product was not determined. A more complete study of organomagnesium halides with alpha beta unsaturated sulfones has been made by Kohler (81). On addition of benzalmethyl phenyl sulfone to phenylmagnesium bromide, there was produced a yellow intermediate which disappeared in an excess of the Grignard reagent. A

(81) Kohler and Potter, *J. Am. Chem. Soc.*, 57, 1319 (1935).

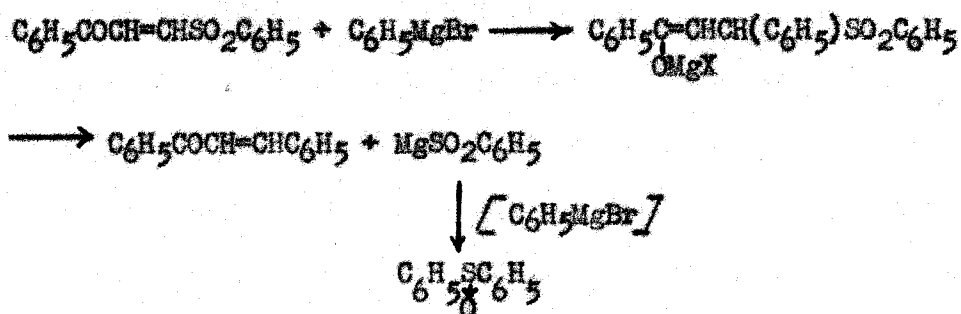
(82) Connor and Ziegler, *ibid.*, 62, 2596 (1940).

(83) Gibson, *J. prakt. Chem.*, 142, 218 (1934).

colorless magnesium compound was finally obtained, which on hydrolysis gave a saturated sulfone,  $(C_6H_5)_2CHCH_2SO_2C_7H_7$ . The intermediate magnesium derivative behaved like the corresponding compounds obtained by adding a Grignard reagent to an alpha beta unsaturated ketone (84). With bromine it formed an  $\alpha$ -bromosulfone and with acid chlorides and carbon dioxide, the corresponding ketones and carboxylic acid.



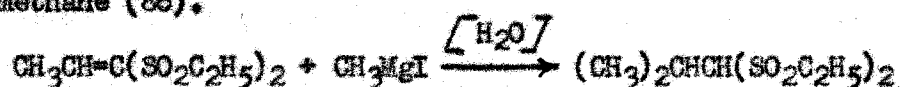
The investigation of unsaturated sulfur compounds was extended to include  $\beta$ -benzoyl- $\alpha$ -benzenesulfonylethylene (85). The main reaction with phenylmagnesium bromide was addition to the conjugated system,  $-C=C-C=O$ ; but complications ensued, owing to cleavage of the addition product and further reaction of the cleavage products:



Addition of the reagent to the carbonyl group also occurred to a slight extent.

- (84) Kohler and co-workers, *J. Am. Chem. Soc.*, 54, 4667 (1932); 55, 690 (1933); 55, 1073 (1933); 57, 2517 (1935).  
 (85) Kohler and Larsen, *ibid.*, 57, 1448 (1935); 58, 1518 (1936).

Inasmuch as each of the above unsaturated compounds contains a benzene ring, the formation of the addition products may be due to or influenced by conjugation of the aromatic unsaturation with that of the side chain. That this type of unsaturation is nonessential has been shown recently by the addition of methylmagnesium iodide to 1,1-bis-(ethylsulfonyl)propene-1 with the formation of bis(ethylsulfonyl)-isopropylmethane (86).



#### 4. Reactions with organosodium compounds

Diphenyl sulfone formed a red air-sensitive solution when treated with benzylna in toluene. On decolorization with dry hydrogen chloride at  $-60^\circ$ , a crystalline compound was obtained. Analysis indicated the formula,  $\text{C}_6\text{H}_5\text{SO}_2\cdot\text{CH}(\text{C}_6\text{H}_5)_2$ , but no proof of structure was presented (74).

#### Benzenesulfonyl Fluoride with Grignard Reagents

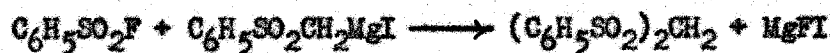
Phenylmagnesium bromide and benzenesulfonyl fluoride gave diphenyl sulfone and a little biphenyl. However, in addition to the expected methyl phenyl sulfone, methylmagnesium iodide yielded another product

(86) Rothstein, J. Chem. Soc., 1565 (1940).

which was believed to be benzenesulfonylmethylphenylsulfonic acid (87),  $C_6H_5SO_2(CH_3)(C_6H_5)SOOH$ . Later, this "acid" was correctly identified (88) as bis(phenylsulfonyl)methane, the acidic properties being due to the activating effect of the two sulfone groups on the methylene group between them. The mechanism of the formation of the disulfone has not been established. It is probable that in the first reaction methyl phenyl sulfone is formed:



A lateral metalation of methyl phenyl sulfone may then take place, to be followed by coupling of the metalation product with unchanged benzenesulfonyl fluoride.



- (87) Steinkopf and Jaeger, J. prakt. Chem., 128, 63 (1930).  
(88) Cowie and Gibson, J. Chem. Soc., 46 (1934).

## EXPERIMENTAL

### General Procedure

#### 1. Preparation of organometallic compounds

The procedures used in the experimental portion of this thesis adhere closely to the procedures described in earlier metalation studies from this laboratory (17, 26). However, as some differences inevitably arise, a rather detailed description of method will be given here and any deviations will be noted as they occur.

All reactions involving organometallic compounds were carried out in an atmosphere of nitrogen purified by passage through three wash bottles of alkaline pyrogallol, two of concentrated sulfuric acid, and finally through a drying tower containing phosphorous pentoxide on glass wool. A little soda lime was introduced before the phosphorous pentoxide to remove any acid vapors from the sulfuric acid.

The conventional apparatus, consisting of a three-necked flask, a Hopkins condenser, and a dropping funnel, was cleaned in an acid bath and carefully rinsed, first with tap water and finally with distilled water, before drying in an oven at approximately 130°.

When an experiment was to be started, the required glassware was removed from the oven and connected directly to the outlet from the

nitrogen purification train. In this way the setting up and the flushing of the apparatus was accomplished simultaneously. Mercury- or rubber-sealed stirrers were used when agitation was necessary. If no precipitate formed in a reaction, refluxing was found to provide sufficient mixing, and mechanical stirring was eliminated.

Grignard reagents were prepared, whenever listed, according to the best conditions described by Zoellner (25). Organolithium compounds were prepared according to the literature with particular attention to the latest contribution (89), which contains an excellent summary of previous work in this field. Other organometallic compounds were less frequently used, so their preparations will be described in detail as they are used.

Solutions of organometallic compounds, prepared from the reaction of a halide with a metal, usually require filtration, since excess metal is generally employed. In the first work reported in this thesis, solutions of organolithium compounds were filtered by decantation through a loose plug of glass wool. As this type of filtration removes only coarse particles, the filtrate always contains a considerable quantity of finely divided black solid, which apparently consists of lithium metal and lithium oxides and nitrides. Earlier workers studying metalations apparently found no discordant results from the use of these turbid solutions. Early in the course of this research, however, it was

(89) Gilman, Langham, and Moore, *J. Am. Chem. Soc.*, **62**, 2327 (1940).

observed that when turbid solutions of organolithium compounds were reacted with sulfides, more cleavage resulted than when the same reaction was carried out with an organolithium solution which had been filtered perfectly clear. An excellent method for the filtration of solutions of organometallic compounds has been described (89). This, however, requires a special apparatus and considerable attention in its manipulation. It was found more convenient to allow the solid particles to settle, and then to force the clear supernatant liquid by means of nitrogen pressure from one three-necked flask to another through a glass tube containing a plug of glass wool. Obviously, all manipulations were performed in an atmosphere of nitrogen. The small loss entailed in this method of filtration is unimportant, since an excess of the metalating agent was always present.

## 2. Metalation procedures

Whenever feasible, the metalation procedures of Bebb (17) were followed in order that a wider correlation of data might be made. Reactions were generally terminated by carbonation on crushed, solid carbon dioxide.

## 3. Separation of reaction products

The frequently encountered cleavages of carbon-sulfur linkages by organometallic compounds necessitated a general procedure for the



separation of carboxylic acids from thiophenols. The following method will be referred to later as "the usual procedure," or "the usual method," etc. Isolation of the reaction products was most conveniently begun, after carbonation, by acidification of the cooled mixture with ice-dilute (5-10%) hydrochloric acid solution. Separation of the ether layer was followed by thorough extraction of the aqueous layer with four or five fresh portions of ether. The combined ether layer was filtered into a clean separatory funnel and extracted with portions of 5% sodium bicarbonate solution, 100 ml. of solution being used for a one-tenth mole run. The bicarbonate solution containing the carboxylic acid or acids was separated, washed with ether, and warmed on a steam bath to remove dissolved ether. If the solution at this point was dark colored or turbid, it was treated with bone-black and filtered before cooling in an ice bath and acidifying with hydrochloric acid. The precipitated acid, if solid, was collected on a suction filter, dried, and weighed. The filtrate was next extracted with several small quantities of ether, dried over anhydrous sodium sulfate, filtered, and the ether evaporated to recover any dissolved acid. This last step was found to be an important one, for occasionally, the acid precipitated differed from the acid extracted. If acidification of the bicarbonate solution precipitated a liquid or no acid, extraction with ether was again resorted to and the acid recovered from the ether solution in the manner described above for the filtrate.

The original ether solution, now freed of carboxylic acids, was

next extracted with 10%-20% potassium hydroxide solution. Any thiophenols were isolated from this basic aqueous extract exactly as in the manner described above for carboxylic acids.

The remaining neutral fraction was dried over sodium sulfate, filtered, the ether distilled, and the residue either distilled or crystallized, depending on its state.

#### Metalation of Thiophenol

A solution of 11.0 g. (0.10 mole) of freshly distilled thiophenol in 25 ml. of ether was refluxed nineteen hours with a solution of *n*-butyllithium prepared from 54.8 g. (0.40 mole) of *n*-butyl bromide and 5.52 g. (0.80 g. atom) of lithium in 400 ml. of ether. Carbonation was effected by pouring on crushed solid carbon dioxide. Acidification of the bicarbonate extract gave 0.45 g. (2.94%) of *o,o'*-dicarboxydiphenyl disulfide, melting at 280° or at 286° (90) after three crystallizations from ethanol.

Anal. Calcd. for  $C_{14}H_{10}O_4S_2$ : neut. equiv., 153. Found: neut. equiv., 154.

Reaction with excess diazomethane yielded the dimethyl ester; m.p., 128-129°. One crystallization from ethanol raised the m. p. to 131-132° (91).

(90) Gattermann, *Ber.*, 32, 1151 (1899).

(91) List and Stein, *Ber.*, 31, 1670 (1898) report a melting point of 130.5° and Gattermann, ref. 90, gives a melting point of 134°.

As 74.5% of the thiophenol was recovered, the yield of acid based on thiophenol reacted was 11.6%.

#### Metalation of Diphenyl Disulfide

A filtered solution of *n*-butyllithium, prepared from 0.2 mole of *n*-butyl bromide and 0.4 g. atom of lithium in 200 ml. of ether, was treated with 10.9 g. (0.05 mole) of diphenyl disulfide. The mixture was refluxed for twenty hours, carbonated by solid carbon dioxide, and worked up in the customary manner to yield 0.65 g. (4.25%) of *o,o'*-dicarboxydiphenyl disulfide melting over the range 235-245° (dec.). After several crystallizations from ethanol and from acetic acid-water mixtures the pure white compound was obtained; m. p., 302-305° (microscope stage).

Anal. Calcd. for  $C_{14}H_{10}O_4S_2$ : neut. equiv., 153. Found: neut. equiv., 156.

The methyl ester, prepared from the acid and diazomethane, melted at 131-132° after one crystallization from ethanol (91).

Distillation of the neutral fraction gave 5.2 g. (31.4%) of *n*-butyl phenyl sulfide; b. p., 96-98° (4 mm.);  $n_D^{20}$  1.5458 (92). The residue was crystallized from ethanol to yield 1.95 g. or 17.9% of diphenyl disulfide identified by a mixed melting point determination. The yield of metalation acid was 5.18% on the basis of diphenyl

(92) Ipatieff, Pines, and Friedman, J. Am. Chem. Soc., 60, 273 (1938).

disulfide not recovered.

### Metalation of Methyl Phenyl Sulfide

The methyl phenyl sulfide used in the following experiments was prepared from thiophenol and dimethyl sulfate in aqueous sodium hydroxide solution. The yields from four preparations, 75%, 61%, 67%, and 79%, did not equal the theoretical yield obtained by Baker and Moffitt (93) in a similar methylation. The boiling point in each case was 84-85° (18 mm.). The last preparation had  $n^{26.5} 1.5826$  in agreement with the value reported by Taboury (94). The other preparations had  $n^{26.5} 1.5830$ .

#### 1. Metalation of methyl phenyl sulfide by sodium in diethyl ether

This experiment was performed in an attempt to metalate methyl phenyl sulfide with sodium in accordance with the procedure used to metalate thianaphthene (34). A mixture of 12.4 g. (0.1 mole) of methyl phenyl sulfide and 2.5 g. (0.11 g. atom) of sodium sand in 75 ml. of diethyl ether was stirred for eighteen hours at room temperature (25-28°) prior to carbonation on dry-ice. A faint Color Test I (95), obtained after the reaction had proceeded for only two hours, indicated either

(93) Baker and Moffitt, J. Chem. Soc., 1722 (1930).

(94) Taboury, Ann. chim. phys. 87, 15, 60 (1908).

(95) Gilman and Schulze, J. Am. Chem. Soc., 47, 2002 (1925).

metalation or cleavage. The reaction was worked up in the usual way to give 0.40 g. of phenylmercaptoacetic acid by precipitation and 0.25 g. of the same acid by extraction of the filtrate. The total yield of acid melting at 61-63° was 3.87%. Identification was completed by a mixed melting point determination (96).

By extraction with potassium hydroxide solution there was isolated 2.3 g. (20.9%) of thiophenol; b. p., 84-85° (50 mm.);  $n_{D}^{23} 1.5850$ . The recovered methyl phenyl sulfide amounted to 6.5 g. or 52.4%. This recovery, together with the yield of thiophenol, accounts for 73.3% of the starting material. The yield of acid, therefore, on the basis of sulfide not recovered is 14.5%.

## 2. Metalation of methyl phenyl sulfide by sodium in benzene

The procedure in this experiment differed from the foregoing one in that benzene was employed as the solvent, and the reaction time was increased to twenty-four hours. The amounts of reactants were the same. When the reaction was worked up in the usual manner, only a trace of acidic material was isolated. It was not identified. Some cleavage occurred, as evidenced by the odor of thiophenol, which was noted after the potassium hydroxide extract was acidified. An attempt to derivatize the thiophenol with 2,4-dinitrochlorobenzene was unsuccessful. Inasmuch as 87.5% of the starting material was recovered, very little reaction

(96) Gabriel, Ber., 12, 1639 (1879).

could have occurred.

3. Metalation of methyl phenyl sulfide by mercuric acetate

The reaction was carried out under the conditions used to prepare p-acetoxymercuriphenyl methyl ether (97). One-tenth mole of methyl phenyl sulfide and 15.0 g. (0.05 mole) of mercuric acetate were stirred and heated on a steam bath for nine and one-half hours, and then let stand overnight. In the morning, the reaction mixture contained a white solid, which was crystallized from ethanol to give 6.67 g. of p-acetoxymercuriphenyl methyl sulfide; m. p., 183-184°; yield, 36%. The constant melting point from ethanol was 184°.

Anal. Calcd. for  $C_9H_{10}O_2SHg$ : Hg, 52.40. Found: Hg, 52.84; 52.78.

The structure of the acetoxymercury derivative was proved by converting it to the corresponding bromomercury compound, which was then compared with an authentic specimen of p-methylmercaptophenylmercuric bromide prepared from p-methylmercaptophenylmagnesium bromide and mercuric bromide.

To a solution of 1 g. (0.0027 mole) of p-acetoxymercuriphenyl methyl sulfide was added a solution of 0.32 g. (0.0027 mole) of potassium bromide in 100 ml. of aqueous ethanol. The finely-divided white solid which separated was allowed to settle overnight, filtered, and washed

(97) Dimroth, Ber., 35, 2867 (1902).

with water and ethanol before drying; weight, 0.93 g.; yield, 85.5%. The mercurial was purified by extraction with chloroform in a Soxhlet apparatus. By this method the pure compound was obtained in the form of white needles; m. p., 268-269°; yield, 68.8%. The loss on purification may be due to incomplete extraction, as the process is slow, and sufficient time may not have been allowed.

Ten and eight-tenths grams (0.03 mole) of mercuric bromide were added gradually to the Grignard reagent from 6.09 g. (0.03 mole) of p-bromophenyl methyl sulfide and 7.9 g. (0.033 g. atom) of magnesium turnings in 40 ml. of ether. The mixture was hydrolyzed with 10% ammonium chloride solution, after standing overnight. The grey-colored solid which formed was triturated twice with 10% ammonium chloride solution, and then washed successively with ether, ethanol, water, and ethanol before drying. The crude yield was 8.75 g. (71.5%). The compound was purified, as in the first preparation, by extraction with chloroform to yield 6.65 g. (55%); m. p., 265-268°. For analysis, the compound was crystallized from chloroform; m. p., 268-269°. A mixed melting point determination with the above compound showed no depression.

Anal. Calcd. for  $C_7H_7SHgBr$ : Hg, 49.68. Found: Hg, 49.64.

#### 4. Metalation of methyl phenyl sulfide by n-butylmagnesium bromide

Since anisole can be metalated with Grignard reagents (80), it appeared likely that methyl phenyl sulfide could also be metalated under similar conditions.

The Grignard reagent was prepared from 0.15 g. atom of magnesium turnings and 0.12 mole of *n*-butyl bromide in 75 ml. of ether. One-tenth mole (67.2 ml. of a 1.49 normal solution) was pipetted into a clean 250 ml. three-necked flask in the usual arrangement of apparatus, and the ether distilled. After cooling, 12.4 g. (0.1 mole) of methyl phenyl sulfide was added, and the mixture heated at 135-140° (thermometer in the liquid). While being heated the apparatus was contained in a safety glass enclosure, as Challenger and co-workers report an explosion in a similar reaction (40). White fumes were formed, and a gas was evolved. A white precipitate formed on the sides of the flask after about one-half hour of heating. After two hours, the mixture was cooled and carbonated by crushed solid carbon dioxide. There was then isolated, in the usual manner, 42% of *n*-valeric acid. Any other carboxylic acid must have been present only in traces. Sixty-three per cent of the methyl phenyl sulfide was recovered. By extraction with potassium hydroxide solution there was separated 0.13 g. of an oil, having the odor of thiophenol, but an attempt to derivatize this with chloroacetic acid met with no success.

In a check experiment, the Grignard reagent was prepared in the same way, but all of it was utilized. After filtration, the ether was distilled from the *n*-butylmagnesium bromide until the temperature of the liquid reached 140°. One-tenth mole of methyl phenyl sulfide was added after cooling, and the mixture was refluxed for five hours at 150-155° (thermometer in liquid). Carbonation was effected by solid



carbon dioxide. The acidic fraction yielded 0.05 g. of o-methylmercapto-benzoic acid, which, after recrystallization from water, weighed 0.03 g. (0.2%) and melted at 163.5-164.5°. The mixed melting point determination with an authentic specimen of the acid was 164.5-165.5°.

Sixty-seven per cent of the starting material was recovered. Accordingly, the yield of acid was 5.4%, based on methyl phenyl sulfide not recovered.

5. Metalation of methyl phenyl sulfide by methyllithium

The filtered solution of methyllithium prepared from 25 g. (0.176 mole) of methyl iodide and 2.42 g. (0.35 g. atom) of lithium in 150 ml. of ether was treated with 12.4 g. (0.1 mole) of methyl phenyl sulfide. The mixture was refluxed for twenty hours, carbonated in the usual way, and worked up in the customary manner to give 0.02 g. of phenylmercapto-acetic acid, m. p., 60-62°, alone or mixed with an authentic specimen (96). The yield based on the starting material was 0.12%, but the yield based on the sulfide reacted was 1.48%, since 84% was recovered.

6. Metalation of methyl phenyl sulfide by n-butyllithium in petroleum ether

To a solution containing 0.07 mole (by acid titration) of n-butyllithium in 85 ml. of petroleum ether (b. p. 28-38°) was added

0.065 mole of methyl phenyl sulfide. After a reflux period of twenty hours, a 20 ml. aliquot was removed, carbonated, and worked up in the usual manner. The acid was obtained in the form of a dark brown oil, which resisted attempts at solidification. The neutral fraction was lost because of a flask breakage. The remainder of the reaction mixture was boiled for forty-five hours before it was carbonated by dry-ice. Again, the acid isolated was an oil, which was not solidified. Very little metalation could have occurred, however, since 91.5% of the original sulfide was recovered.

Owing to the slow rate of metalation in petroleum ether, it was decided to repeat the experiment and allow a longer time for the reaction to take place. *n*-Butyllithium was prepared in the usual way (89) from 27.4 g. (0.2 mole) of *n*-butyl bromide and 2.76 g. (0.4 g. atom) of lithium in 150 ml. of petroleum ether (b. p. 28-38°). Following a reflux period of two hours, the mixture was filtered by means of a dry asbestos filter under nitrogen pressure. The resulting solution was one normal by acid titration and had a volume of 90-95 ml. After the addition of 12.4 g. (0.1 mole) of methyl phenyl sulfide in 10 ml. of petroleum ether (b. p. 28-38°), the mixture was refluxed seven days and carbonated by solid carbon dioxide. The acidic material isolated in the usual manner weighed 1.02 g. and melted at 58-60°. When an attempt was made to recrystallize this acid from petroleum ether (b. p. 60-68°), a portion did not dissolve. The soluble material was identified as phenylmercaptoacetic acid; m. p. and m. m. p., 60-62°; weight, 0.6 g.;

yield, 3.58%. The material which was insoluble in petroleum ether melted at 190-195° after softening at 184°. After one recrystallization from ethanol and water, it melted between 200-230° (35 mg.). Further crystallizations from benzene gave a constant melting point of 203-204° without decomposition. The compound was soluble in sodium bicarbonate solution, and contained no sulfur as shown by a sodium fusion. It has not been identified.

By extraction with potassium hydroxide solution, there was obtained 0.25 g. (2.27%) of thiophenol; b. p., 70-80° (50 mm.);  $n_{D}^{23.5}$  1.5822.

Thirty-four per cent of the starting material was accounted for since 31.7% of methyl phenyl sulfide was recovered and 2.27% of thiophenol was isolated. This raises the yield of phenylmercaptoacetic acid to 5.4% on the basis of methyl phenyl sulfide not reacted.

#### 7. Metalation of methyl phenyl sulfide by *n*-butyllithium in the absence of solvent

The metalating agent was obtained in the customary manner from 27.4 g. (0.2 mole) of *n*-butyl bromide and 2.76 g. (0.4 g. atom) of lithium in 200 ml. of ether. The clear filtered solution was concentrated by distillation to a small volume. After the addition of one-tenth mole of methyl phenyl sulfide, the distillation was continued to remove the small quantity of diethyl ether remaining. The mixture was heated at 130-150° for three hours. During this time the contents of

the flask became almost entirely solid and turned brown. After the mixture had cooled, it was taken up in ether and carbonated by dry-ice. By means of the customary procedure a trace of an acidic material was isolated but not identified. The potassium hydroxide extraction yielded 2.5 g. (22.7%) of thiophenol; b. p., 99-100° (50 mm.);  $n_{D}^{23.5}$  1.5850. Owing to the fact that the compound had a much higher boiling point than that reported in the literature (b. p. 84-86°, 50 mm.), identification was completed by the preparation of 2,4-dinitrophenyl phenyl sulfide, m. p. 120-121° without crystallization (98). Inasmuch as the yield of the derivative was 80%, the thiophenol must have had a high degree of purity. Only 29% of the original methyl phenyl sulfide was recovered.

The foregoing experiment was repeated in order to obtain sufficient carboxylic acid for identification purposes. Milder conditions were used in an effort to decrease the cleavage of the sulfide.

*n*-Butyllithium was prepared from 27.4 g. (0.2 mole) of *n*-butyl bromide and 2.76 g. (0.4 g. atom) of lithium in 100 ml. of ether. After concentration of the clear filtered solution to a small volume, the reaction vessel contained a white solid and a yellow liquid. Fifteen-hundredths of a mole of methyl phenyl sulfide was added, and heat applied until the inside temperature reached 70°. At this point, a little excess ether was allowed to escape by opening the reaction

(98) Post, Turner, and Norton, *J. Am. Chem. Soc.*, **54**, 1985 (1932).

vessel momentarily. No test was made to determine whether all the ether had been removed, but in view of the high temperature used later in this experiment, it is probable that little, if any, free ether remained. The heating was continued for fifteen minutes, after which a vigorous evolution of gas began, and in a few minutes the mixture solidified completely. The heating was continued for one-half hour until the inside temperature reached  $150^{\circ}$ . Heating was discontinued, and the mixture was cooled slowly during approximately one-half hour. The solid reaction mixture was taken up in ether and carbonated by the customary procedure. By acidification of the bicarbonate extract there was obtained 3.25 g. (19.4%) of phenylmercaptoacetic acid; m. p. and m. m. p.,  $61-63^{\circ}$  (96). As an additional 0.3 g. of the same acid was isolated from the filtrate, the total yield was 3.55 g., or 21.2%. Less cleavage occurred in this reaction, since only 1.1 g. (10%) of pure thiophenol was isolated. From the neutral fraction, 9.5 g. (52.2%) of the starting material was recovered. The yield of phenylmercaptoacetic acid based on the unreacted methyl phenyl sulfide was 51.2%.

#### 8. Metalation of methyl phenyl sulfide by phenyllithium

Phenyllithium was prepared from 18.8 g (0.12 mole) of bromobenzene and 1.72 g. (0.25 g. atom) of lithium in 80 ml. of ether. After filtration and addition of 12.4 g. (0.1 mole) of methyl phenyl sulfide, the mixture was refluxed sixteen hours prior to carbonation by crushed solid

carbon dioxide. Extraction with sodium bicarbonate solution, followed by acidification, gave 2.15 g. of acidic material melting over the range 105-115°. This was identified as benzoic acid, after recrystallization from water. The filtrate from the original precipitation was extracted with ether. Evaporation of the ether left 2.15 g. of acidic material; m. p., 50-53°. One crystallization from petroleum ether (b. p. 60-68°) gave 1.75 g.; m. p., 58-60° (12.8%). An additional crystallization from the same solvent produced 1.55 g. melting at 61-63° alone or mixed with an authentic specimen of phenylmercaptoacetic acid (96). The yield of acid was 16.5% based on the methyl phenyl sulfide not recovered as 4.6 g. (37%) was recovered.

#### 9. Metalation of methyl phenyl sulfide by phenylsodium

Phenylsodium was prepared in 100 ml. of benzene from 12.4 g. (0.11 mole) of chlorobenzene and 5.06 g. (0.22 g. atom) of sodium sand (17). When the reaction was completed, the mixture was cooled in ice, and 12.4 g. (0.1 mole) of methyl phenyl sulfide was added dropwise in 20 ml. of benzene. The metalation was terminated by carbonation by solid carbon dioxide after five hours of stirring at room temperature. Acidification of the bicarbonate extract gave 5.95 g. of a yellow acid, m. p. 95-105°, which yielded 4.05 g. of pure benzoic acid after treatment with "Norite" and crystallization from water. The filtrate from the original precipitation was neutralized, concentrated, acidified, and

extracted with ether. Evaporation of the ether gave 2.65 g. (15.8%) of acidic material melting at 50-53°. This was recrystallized from water and from petroleum ether (b. p. 60-68°) to give 1.5 g. (8.95%) of pure phenylmercaptoacetic acid; m. p., 61-63°. Identification was completed by a mixed melting point determination with an authentic specimen (96). The recovery of starting material from the neutral fraction amounted to 5.5 g. or 44.4%. This raises the yield of phenylmercaptoacetic acid to 28.4% based on unrecovered methyl phenyl sulfide.

The following experiment was carried out in an attempt to prepare phenylmercaptomalonic acid by slow carbonation (99) of the reaction product of phenylsodium and methyl phenyl sulfide.

The reaction was carried out as in the previous experiment, but the reactants were stirred at room temperature for thirteen and one-half hours. Carbonation was then effected by passing a slow stream (less than one bubble per second) of dry carbon dioxide over the surface of the stirred mixture for thirteen hours. The reaction was worked up entirely in the cold to avoid decomposing any substituted malonic acid which might be present; but only benzoic acid (24.8%) was found. No phenylmercaptoacetic acid was isolated. Fifty-eight per cent of the starting material was recovered.

(99) Callman and Pacevitz, *J. Am. Chem. Soc.*, **62**, 1301 (1940).

10. Metalation of methyl phenyl sulfide by phenylcalcium iodide in diethyl ether.

Phenylcalcium iodide was prepared from 61.2 g. (0.3 mole) of iodobenzene and 16 g. (0.4 g. atom) of calcium turnings in 200 ml. of ether. All of the calcium was placed in a 500 ml. three-necked flask, in the usual arrangement of apparatus together with 25% of the iodobenzene, 50 ml. of ether, and a crystal of iodine. The mixture was then refluxed with a micro burner until the iodine color disappeared and the reaction started, as evidenced by the appearance of a red color. The remainder of the iodobenzene, in 50 ml. of ether, was added dropwise with stirring. When the reaction became vigorous, 100 ml. of ether was added quickly by raising the condenser. After the addition of the iodobenzene, the mixture was refluxed for one and one-half hours and allowed to stand overnight in an atmosphere of nitrogen. The solution was filtered through glass wool under nitrogen pressure, and the residue extracted with 250 ml. of ether in several portions (100). The red filtrate was concentrated to 250 ml. and treated with 12.4 g. (0.1 mole) of methyl phenyl sulfide in 40 ml. of ether. The mixture was carbonated by solid carbon dioxide after refluxing forty-six hours. The only acidic product found was benzoic acid. From the neutral fraction there

(100) A similar preparation (0.1 mole of iodobenzene) gave, on carbonation, 35.6% of benzoic acid. The extracted residue was carbonated separately, but yielded only a trace of acidic material.



was recovered 9.75 g., or 78.5% of the starting material.

11. Metalation of methyl phenyl sulfide by phenylcalcium iodide in the absence of solvent

Inasmuch as *n*-butylmagnesium bromide metalated methyl phenyl sulfide at an elevated temperature and in the absence of solvent, it seemed possible that phenylcalcium iodide would also bring about a substitution under these conditions.

Phenylcalcium iodide was prepared as in the preceding experiment, but 300 ml. of ether were employed. The ether solution, after filtration and extraction, was concentrated by distillation until the inside temperature reached 100°. One-tenth mole of methyl phenyl sulfide was added at this point and the distillation continued until the inside temperature reached 150°. The distillation was stopped and the mixture refluxed at 150-160° for three and one-half hours prior to carbonation. This was not very successful, since the mixture was a solid which was insoluble in ether. The main products of the reaction were recovered methyl phenyl sulfide (58.8%) and thiophenol (12.95%); b. p., 84-86° (50 mm.);  $n_{D}^{23.5}$  1.5870.

Relative Rates of Metalation of Methyl Phenyl Sulfide  
and Methyl Phenyl Ether

A cyclic ether, dibenzofuran, was metalated more rapidly by n-butyllithium than a cyclic sulfide, dibenzothiophene, under corresponding conditions (59). It appeared interesting to determine whether the same relations would hold when an alkyl aryl ether was compared with an alkyl aryl sulfide.

n-Butyllithium was prepared from 27.4 g. (0.1 mole) of n-butyl bromide and 2.76 g. (0.4 g. atom) of lithium in 200 ml. of ether. The clear filtered solution was divided into two parts by means of a 100 ml. pipette. To one portion was added 6.2 g. (0.05 mole) of methyl phenyl sulfide; and to the other portion was added 5.4 g. (0.05 mole) of anisole. Both mixtures were refluxed five hours, then carbonated and worked up in the customary manner.

From the reaction with methyl phenyl sulfide there was obtained 3.16 g. (37.6%) of phenylmercaptoacetic acid; m. p., 61-63°. Since 36.2% of the sulfide was recovered, the yield of acid was 59.4%, based on sulfide not recovered.

The reaction with anisole gave 32.4% of o-methoxybenzoic acid; 1.82% of 2,2'-dimethoxybenzophenone; and 32.6% of recovered anisole. In this case the total metalation (acid + ketone) was 50.5%, based on anisole not recovered.

A repeat experiment was refluxed for 4.5 hours. All other conditions

were the same.

The reaction with methyl phenyl sulfide yielded 39.7% of phenyl-mercaptoacetic acid and 48.4% of recovered sulfide. The yield, based on methyl phenyl sulfide not recovered, was 77.0%.

From the reaction with anisole, there was isolated 30.8% of o-methoxybenzoic acid, 1.24% of 2,2'-dimethoxybenzophenone, and 47.2% of anisole. Here the total metalation was 60.3%, based on anisole not recovered.

#### Metalation of Methyl Aryl Sulfides by n-Butyllithium

##### 1. Metalation of methyl p-tolyl sulfide

Methyl p-tolyl sulfide was prepared in 85.5% yield from p-tolyl mercaptan and dimethyl sulfate in aqueous potassium hydroxide solution. The preparation had the following physical properties: b. p., 100-101° (18 mm.);  $n^{16}$  1.5750 (101).

For the metalation, 13.8 g. (0.1 mole) of the sulfide was added to the solution of n-butyllithium from 27.4 g. (0.2 mole) of n-butyl bromide and 2.78 g. (0.4 g. atom) of lithium in 200 ml. of ether. After sixteen hours at the boiling point, the mixture was carbonated in the usual way. By means of the customary procedures there was isolated 6.94 g. (38.2%)

(101) Auwers and Arndt, Ber., 42, 540 (1909) reported  $n^{16}$  1.5754. The yield is not stated in their paper.

of *p*-tolylmercaptoacetic acid; m. p., 93-94°. Identification was made by a mixed melting point determination with an authentic specimen (102). Also, there was recovered 51% of the starting material, b. p., 100-102° (18 mm.), which raises the yield of acid to 77.8% based on unrecovered methyl *p*-tolyl sulfide.

## 2. Metalation of *p*-chlorophenyl methyl sulfide

The sulfide was prepared in 65% yield by the action of dimethyl sulfate on *p*-chlorothiophenol, which in turn, was prepared by reacting sulfur with *p*-chlorophenylmagnesium bromide. The sulfide was difficult to purify, and even after several distillations (b. p. 107-108°, 12 mm.) the refractive index,  $n^{25}$  1.5952, was lower than that reported in the literature;  $n^{25}$  1.6023 (103).

The metalating agent, obtained from 8.22 g. (0.06 mole) of *n*-butyl bromide and 0.74 g. (0.12 g. atom) of lithium in 40 ml. of ether, was filtered perfectly clear and treated with 4.8 g. (0.03 mole) of *p*-chlorophenyl methyl sulfide in 25 ml. of ether. The resulting solution immediately became yellow, and after one-half hour at room temperature, was brown in color. The mixture was refluxed five hours and kept for one-half hour. At this time, Color Test I (95) was strongly positive,

(102) Fummerer, Ber., 42, 2279 (1909).

(103) Brand and Stein, J. prakt. Chem., 108, 18 (1924) prepared the compound by another method.

and Color Test III (104) was weakly positive. Following carbonation by crushed solid carbon dioxide, the mixture was worked up in the usual manner. On acidification of the bicarbonate extract, a gummy red solid precipitated. This material was dried in ether solution over sodium sulfate, recovered from the ether solution, and crystallized from petroleum ether (b. p. 60-68°) to yield 0.35 g. (5.75%) of p-chlorophenylmercaptoacetic acid. Two recrystallizations from the same solvent gave the pure compound; m. p., 105°. Identification was completed by a mixed melting point determination with an authentic specimen (105).

### 3. Metalation of p-dimethylaminophenyl methyl sulfide

The sulfide (b. p. 159-160°, 20 mm.) was prepared in 79% yield from sodium p-dimethylaminophenyl mercaptide and methyl iodide in liquid ammonia (106). The mercaptide was prepared by adding bis(p-dimethylaminophenyl) disulfide to a solution of sodium in liquid ammonia.

The metalation was carried out by refluxing for nineteen hours a mixture of 16.7 g. (0.1 mole) of the sulfide with a solution of n-butyllithium prepared from 27.4 g. (0.1 mole) of n-butyl bromide and 2.76 g. (0.4 g. atom) of lithium in 200 ml. of ether. The reaction was worked up in the usual way, after carbonation, to yield 2.65 g. of p-dimethyl-

(104) Gilman and Yablunsky, J. Am. Chem. Soc., 63, 839 (1941).

(105) Friedländer and Chwala, Monatsh., 28, 273 (1907)

(106) Zincke and Jörg, Ber., 42, 3374 (1909) previously prepared this compound but by another method.

aminophenylmercaptoacetic acid; m. p., 75-80°. The aqueous filtrate was neutralized, evaporated to dryness, the salts taken up in a small volume of water, the solution made barely acid with hydrochloric acid, and extracted exhaustively with ether. In this way an additional 2.07 g. of the acid was obtained; m. p., 75-80°. The total yield was 4.72 g. or 22.4%. The compound was purified by recrystallization from benzene (m. p., 85-86°) and identified by a mixed melting point determination with an authentic specimen prepared from chloroacetic acid and sodium *p*-dimethylaminophenyl mercaptide.

Anal. Calcd. for  $C_{10}H_{13}O_2NS$ : N, 6.63. Found: N, 6.66.

From the neutral fraction there was recovered 52.1% of the starting material, which increases the yield of acid to 46.7% on the basis of sulfide not recovered.

In a check experiment there was isolated 15.2% of *p*-dimethylamino-phenylmercaptoacetic acid, m. p., 84-85°, and 43.1% of the starting material was recovered. In this case the yield of acid based on unrecovered sulfide was 25.6%. A portion of this reaction mixture gave a positive Color Test III. No purple color was observed when the reactants were mixed, but a yellow color was obtained on hydrolysis. The positive test indicated only a trace of an aryllithium compound, since no acid corresponding to it was obtained, in spite of a careful search.

4. Metalation of methyl  $\alpha$ -naphthyl sulfide

The filtered solution of n-butyllithium, prepared from 13.7 g (0.1 mole) of n-butyl bromide and 1.4 g. (0.2 g. atom) of lithium in 85 ml. of ether, was treated with 8.7 g. (0.05 mole) of methyl  $\alpha$ -naphthyl sulfide (107). The mixture immediately began to darken, and after one-half hour had a deep brown color. Carbonation was effected in the usual manner, after a five-hour reflux period. The  $\alpha$ -naphthylmercaptoacetic acid, isolated by the customary procedures, weighed 3.85 g. (35.4%); m. p., 99-100°. Several recrystallizations from ethanol-water and glacial acetic acid-water mixtures gave a constant melting point of 101-102°. Identification was completed by a mixed melting point determination with a specimen prepared from  $\alpha$ -thionaphthol and chloroacetic acid, which also melted at 101-102° (108).

5. Metalation of methyl  $\beta$ -naphthyl sulfide

The sulfide was prepared in 40% yield from  $\beta$ -thionaphthol and dimethyl sulfate in the usual way (109). The properties of the preparation agreed with those reported. No yield was given, however.

For the metalation, 6.96 g. (0.04 mole) of methyl  $\beta$ -naphthyl

(107) Kindly prepared by Mr. J. L. Rendall.

(108) German patent, 414,853 [Chem. Zentr., II, 774 (1925)]. The melting point reported here is 111-112°.

(109) Staudinger, Goldstein, and Schlenker, Helv. Chim. Acta, 4, 342 (1921).

sulfide was added to a solution of *n*-butyllithium prepared from 10.96 g. (0.08 mole) of *n*-butyl bromide and 1.10 g. (0.16 g. atom) of lithium in 80 ml. of ether. After a twenty-hour reflux period, there was isolated in the customary manner, subsequent to carbonation, 1.5 g. (17.2%) of  $\beta$ -naphthylmercaptoacetic acid melting at 88-90°. One crystallization from benzene gave 1.02 g. of long needles, melting at 91-92° alone or mixed with an authentic specimen of  $\beta$ -naphthylmercaptoacetic acid (110). The yield of pure acid was 11.7%.

A substance (0.02 g.) melting in the range 115-120°, and as yet unidentified, was separated by extraction with sodium hydroxide solution.

The neutral fraction yielded 5.9 g. (8%) of the starting material (m. p. 55-57°) which was identified by oxidation to the corresponding sulfone; m. p., 142-143°. On the basis of the sulfide not recovered the yield of acid is increased to 43.2%.

#### Metalation of Alkyl Aryl Sulfides

##### 1. Metalation of ethyl phenyl sulfide by *n*-butyllithium

Ethyl phenyl sulfide was prepared in 94% yield from thiophenol and dimethyl sulfate in aqueous sodium hydroxide solution (111). The yield was not reported in this paper. The preparation had  $n_D^{22.5}$  1.5650 whereas

(110) Friedländer and Woroshzow, Ann., 388, 14 (1912).

(111) Pollak, Deutscher, and Krauss, Monatsh., 48, 103 (1927).



Taboury (94) found  $n_{D}^{22.5}$  1.5662.

To the solution of n-butyllithium prepared from 2.8 g. (0.4 g. atom) of lithium and 27.4 g. (0.2 mole) of n-butyl bromide in 200 ml. of ether was added 13.8 g. (0.1 mole) of ethyl phenyl sulfide in 40 ml. of ether. The mixture was stirred and refluxed for fifteen hours prior to carbonation. There was then isolated 2.3 g. (12.6%) of o-ethylmercaptobenzoic acid, melting in the range 115-120°. After three crystallizations from ethanol and water, there was obtained 1.4 g. (7.7%) of the pure acid, melting at 134-135° alone or mixed with an authentic specimen (112). Extraction of the acid filtrate gave 0.6 g. of acidic material melting at 100°. It was not identified. Distillation of the neutral fraction yielded 7.1 g. (51.5%) of unreacted starting material. The yield of metalation product on the basis of unrecovered ethyl phenyl sulfide was 26% crude and 15.8% pure.

The experiment was repeated in order to ascertain whether any benzoic acid was formed by cleavage of the sulfide. The crude acid melted between 105-110° and weighed 2.70 g. (14.7%). Recrystallization from a mixture of benzene and petroleum ether (b. p. 60-68°) yielded 1.52 g. (8.4%) of o-ethylmercaptobenzoic acid; m. p., 131-132°. After recrystallization from the same mixture of solvents, the melting point and mixed melting point agreed with that of the pure compound, 134-135°. The aqueous solution, from which the crude acid had been precipitated, was extracted with ether. The ethereal solution was

(112) German patent, 203,388 Chem. Zentr., II, 1752 (1908).7

dried, filtered, and distilled to yield 0.42 g. of crude benzoic acid; m. p., 112-115°. One recrystallization from petroleum ether (b. p. 60-68°), preceded by a treatment with "Norite," gave 0.27 g.; m. p., 120-121°; m. m. p., 121-122°. Since 0.13 g. (m. p. 118-119°) was obtained by sublimation of the filtrate, the total yield of benzoic acid was 3.26%. It is interesting to note that the acid which sublimed toward the end of the process melted at 102-110°. A mixture of equal parts of benzoic and *o*-ethylmercaptobenzoic acids melted in the range 105-110°.

Recovery was made to the extent of 59.4% of the sulfide used. Accordingly, 62.7% of the starting material is accounted for since 3.26% of benzoic acid was formed. The yield of *o*-ethylmercaptobenzoic acid on the basis of ethyl phenyl sulfide not reacted is 39.9% crude and 22.4% pure.

## 2. Metalation of ethyl phenyl sulfide by phenylcalcium iodide

A solution of 250 ml. of phenylcalcium iodide (prepared as on p. 70) was treated with 13.8 g. (0.1 mole) of ethyl phenyl sulfide in 40 ml. of ether. The reaction was terminated by pouring on dry-ice after a sixty-hour reflux period. The crude acid weighed 9.7 g. and was identified as benzoic acid by a mixed melting point determination, following recrystallization; yield, 26.5% based on iodobenzene employed. The neutral fraction was distilled to give 8.4 g. or 61% of ethyl phenyl sulfide.

### 3. Metalation of n-propyl phenyl sulfide by n-butyllithium

This sulfide was prepared from n-propyl bromide and thiophenol (92) in 71% yield. In general, this method gives yields which vary from 60% to 85%. The refractive index,  $n_D^{20}$  1.5548, was slightly lower than that reported, 1.5571.

One-tenth mole of n-propyl phenyl sulfide was refluxed for twenty hours with a solution of n-butyllithium prepared from n-butyl bromide (0.2 mole) and lithium (0.4 g. atom) in 200 ml. of ether. Following carbonation, there was obtained by acidification of the bicarbonate extract 3.2 g. of acidic material melting from 101° to 105°. Recrystallization from petroleum ether (b. p. 60-68°) gave 1.35 g. of  $\alpha$ -(n-propylmercapto)benzoic acid (113); m. p., 118-120°; yield, 6.9%. Extraction of the filtrate gave 0.42 g. of benzoic acid melting at 117-119° or at 120-121° after one recrystallization from petroleum ether (b. p. 60-68°); yield, 3.47% crude, 2.48% pure. Both acids were identified by mixed melting point determinations.

The recovery of the starting material from the neutral fraction amounted to 54.5% which, together with the yield of benzoic acid, accounts for 58% of the n-propyl phenyl sulfide originally employed. On the basis of sulfide not recovered, the yield of sulfur acid is 16.4%. The ether layer in which the sulfide had been dissolved, was

(113) Donleavy and English, J. Am. Chem. Soc., **62**, 220 (1940).

concentrated to a small volume through a column having approximately ten theoretical plates and a reflux ratio of one to ten. Attempts to derive n-propyl mercaptan in the residue with 2,4-dinitrochlorobenzene met with failure.

#### 4. Metalation of isopropyl phenyl sulfide by n-butyllithium

The sulfide was prepared in 87% yield from thiophenol and isopropyl bromide in alcoholic potassium hydroxide solution (92). The properties of the preparation agreed with those reported in the literature (92).

The sulfide (0.1 mole) was refluxed for twenty hours with a filtered solution of n-butyllithium prepared from n-butyl bromide (0.2 mole) and lithium (0.4 g. atom) in 200 ml. of ether. The crude acid, isolated by the usual procedures after carbonation, weighed 3.25 g.; melting range, 100-105°. One recrystallization from petroleum ether (b. p. 60-68°) gave 2.24 g.; m. p., 114-116°; yield, 11.4% as g-isopropylmercaptobenzoic acid. The pure acid was obtained after an additional crystallization from the same solvent; m. p., 116-117°. The acid was identified by comparison with a sample prepared from methyl thio-salicylate and isopropyl bromide in alcoholic potassium hydroxide solution.

Anal. Calcd. for  $C_{10}H_{12}O_2S$ : S, 16.33. Found: S, 16.53.

From the petroleum ether filtrates there was obtained, in addition to five-tenths of a gram of g-isopropylmercaptobenzoic acid, twenty

milligrams of an acid melting at 154-155°. The melting point was not raised by further crystallization from petroleum ether (b. p. 60-68°). As yet, this compound has not been identified.

No benzoic acid was found after a thorough examination of the aqueous layer from which the original acid had been precipitated. Instead, a trace of o-isopropylmercaptobenzoic was isolated.

Distillation of the neutral fraction resulted in a recovery of 65% of the original sulfide which raises the yield of o-isopropylmercaptobenzoic acid to 32.7% on the basis of sulfide not recovered.

A check experiment carried out under the same conditions and with the same quantities gave 2.7 g. (13.8%) of crude acid, melting range, 105-114°. One crystallization from petroleum ether (b. p. 60-68°) yielded pure o-isopropylmercaptobenzoic acid (11.0%); m. p., 116-117°. By concentration of the filtrate, there was obtained 0.06 g. of o-isopropylmercaptobenzoic acid, together with approximately 4 mg. of the higher melting acid; m. p., 154-156°.

The recovery of the starting material amounted to 67.8%. In this case the yield of o-isopropylmercaptobenzoic acid based on sulfide not recovered is 34.2%. In addition, 1.25 g. of an oil, boiling at 172-174° (5-6 mm.) was separated from the neutral portion. This fraction is, as yet, unresolved.

##### 5. Metalation of n-butyl phenyl sulfide by n-butyllithium

The sulfide was prepared according to the recent directions of

Ipatieff and his co-workers (92). The yield and physical properties agreed with the values reported.

The metalating agent was prepared from n-butyl bromide (0.2 mole) and lithium (0.4 g. atom) in 200 ml. of ether. The filtration was performed by pouring the solution through a porous plug of glass wool into a clean three-necked flask, previously swept with nitrogen. The filtrate contained no large pieces of lithium, but did contain some black solid. One-tenth mole of n-butyl phenyl sulfide in 25 ml. of ether was added dropwise during a ten-minute period. No heat developed. The mixture was refluxed nineteen hours and carbonated by solid carbon dioxide. The reaction mixture was worked up in the customary manner to yield, by acidification, 2.1 g. (10%) of o-(n-butylmercapto)benzoic acid, melting over the range 85-90°. Two recrystallizations from petroleum ether (b. p. 60-68°) raised the melting point to 97-98°, where it remained unaltered after recrystallization from ethanol. Identification was made by comparison with an authentic specimen prepared from methyl thiosalicylate and n-butyl bromide (113). Concentration of the petroleum ether filtrates gave 0.3 g. of acidic material, melting at 75-77° or at 79-80° after recrystallization from petroleum ether (b. p. 60-68°). The melting point was unchanged by another crystallization from petroleum ether or by two crystallizations from ethanol-water mixtures. This substance has not been identified.

The aqueous filtrate, from which the o-(n-butylmercapto)benzoic acid had been filtered, was extracted with ether to yield 0.5 g. of

benzoic acid; m. p., 115-117°. Two crystallizations from petroleum ether (b. p. 60-68°) gave the pure compound which was identified by a mixed melting point determination; yield, pure, 2.86%; crude, 4.1%.

Extraction with sodium hydroxide solution gave 0.42 g. of a dark brown crystalline solid, which melted at 102-103° after crystallization from ethanol. It was not further examined.

From the neutral fraction there was recovered 52% of the starting material which raises the yield of  $\alpha$ -( $\eta$ -butylmercapto)benzoic acid to 22.6% on the basis of sulfide not reacted.

In a check experiment there was isolated, 1.55 g. of  $\alpha$ -( $\eta$ -butylmercapto)benzoic acid; melting range, 85-90°; yield, 7.38%. One-tenth gram of the lower melting compound (74-77°) was found. The yield of crude benzoic acid, m. p. 117-119°, was 4.5%. By extraction with sodium hydroxide there was isolated only 0.17 g. of the product melting at 101-103°, after crystallization from ethanol. A more careful distillation of the neutral fraction gave, in addition to 63% of recovered  $\eta$ -butyl phenyl sulfide, 1.3% of  $\eta$ -butyl mercaptan which was isolated and identified as the lead salt; m. p. and m. m. p., 80-81° (11A). In this case the yield of  $\alpha$ -( $\eta$ -butylmercapto)benzoic acid, based on unreacted sulfide, was 23.6%.

In the following experiment the solution of  $\eta$ -butyllithium contained no suspended solid, in contrast to the preceding experiments. The reflux period was eighteen hours, otherwise all conditions were the same

(11A) Wertheim, J. Am. Chem. Soc., 51, 3661 (1929).

as before. There was isolated 6.5% of *o*-(*n*-butylmercapto)benzoic acid, 1.23% of benzoic acid, and 1.04% of *n*-butyl mercaptan (as the lead salt). Sixty-four per cent of *n*-butyl phenyl sulfide was recovered. The yield of *o*-(*n*-butylmercapto)benzoic acid on the basis of sulfide not reacted was 19.4%.

#### 6. Metalation of *n*-butyl phenyl sulfide by lithium

These cleavage experiments were performed to ascertain whether the benzoic acid formed in some metalation reactions was due to cleavage of the sulfide by lithium metal.



To a solution of 7.3 g. (0.05 mole) of *n*-butyl phenyl sulfide in 50 ml. of ether was added 0.69 g. (0.1 g. atom) of lithium cut in small pieces (1-2 mm. square). The mixture was stirred and refluxed for seventeen and one-half hours prior to carbonation by dry-ice. A 17.2% yield of benzoic acid was isolated by the usual procedures and identified by a mixed melting point determination. Cleavage of the linkage between the sulfur atom and the butyl group also occurred, as evidenced by the isolation of 18.2% of thiophenol which was identified as 2,4-dinitrochlorophenyl phenyl sulfide (98).

No *n*-butyl mercaptan was present in the neutral fraction, since no reaction was observed when portions of it were treated with lead acetate or with 2,4-dinitrochlorobenzene. Only *n*-butyl phenyl sulfide



(10%) was recovered from this fraction of the reaction mixture.

The failure to isolate any n-butyl mercaptan in the preceding experiment may have been due to the small quantities of reactants employed or to the use of too short a reaction time. Hence, a larger run was made, and the reaction time was extended.

To a suspension of 1.38 g. (0.2 g. atom) of lithium in 50 ml. of ether was added 16.6 g. (0.1 mole) of n-butyl phenyl sulfide in 25 ml. of ether. A faint positive color test (95) was obtained after the mixture had been stirred for seven hours at room temperature, but very little change in the appearance of the mixture had occurred. However, after thirty-six hours of stirring and refluxing, a heavy yellow precipitate was present in the yellow ether solution. At this time a positive Color Test III (104) was obtained, indicating the presence of an aryl lithium compound or compounds. After carbonation by dry-ice, the reaction mixture was worked up in the customary manner. On acidification of the sodium bicarbonate extract, hydrogen sulfide was evolved, and there was precipitated 2.72 g. of an acidic material melting over the range 90-100°. This acidic material was separated into two fractions by extraction with petroleum ether (b. p. 60-68°). The insoluble portion weighed 0.03 g. and decomposed at 170°. On recrystallization from ethanol and water, it melted at 270° after darkening at 250°. This substance is as yet unidentified. The soluble portion was separated by fractional crystallization into 1.3 g. (10.6%) of benzoic acid and 0.05 g. (0.24%) of g-(n-butylmercapto)benzoic acid. The latter

two acids were identified by mixed melting point determinations. The total yield of benzoic acid was 11.9%, since 0.15 g. (1.3%) was obtained by extraction of the filtrate from the original precipitation. The distinctive odors of n-butyl mercaptan and valeric acid were not noticed possibly because of the masking effect of the odor of thiophenol.

Acidification of the potassium hydroxide extract gave 2.25 g. (20.5%) of thiophenol. Three grams (18.1%) of the starting material was recovered.

#### 7. Metalation of cyclohexyl phenyl sulfide by n-butyllithium

The sulfide, prepared in 39% yield from thiophenol and bromocyclohexane in alcoholic potassium hydroxide solution, had b. p. 138-139° (8 mm.) and  $n^{25}$  1.5558 (115). Gilman and Heck report  $n^{25}$  1.5663. No yield is given in their paper.

The filtered solution of n-butyllithium, from 13.7 g. (0.1 mole) of n-butyl bromide and 1.38 g. (0.2 g. atom) of lithium in 100 ml. of ether, was refluxed for forty-eight hours with 9.6 g. (0.05 mole) of cyclohexyl phenyl sulfide. The mixture was carbonated and worked up in the usual way to yield 11.4% of a monocarboxy cyclohexyl phenyl sulfide; melting range, 75-80°. Benzoic acid (10 mg.) was also isolated. The pure sulfur acid, obtained by recrystallizations from petroleum ether (b. p. 60-68°), melted at 80-81°.

(115) Gilman and Heck, J. Am. Chem. Soc., 50, 2223 (1928).

Anal. Calcd. for  $C_{13}H_{16}O_2S$ : S, 13.56. Found: S, 13.71.

The identification of this compound was not completed, but it is probably p-cyclohexylmercaptobenzoic acid.

From the neutral fraction there was recovered 58.4% of the starting material. As a result, the yield of sulfur acid is increased to 27.6% on the basis of unrecovered sulfide.

A check experiment, which was refluxed for twenty-two hours, yielded 8.5% of the same sulfur acid and 60.5% of unreacted starting material. Here the yield of sulfur acid is 21.6% calculated on the basis of sulfide not recovered.

### 8. Metalation of ethyl $\beta$ -naphthyl sulfide by n-butyllithium

The sulfide (116) was obtained from  $\beta$ -thionaphthol and diethyl sulfate in 55% yield; b. p.,  $170^\circ$  (15 mm.); b. p.,  $130^\circ$  (3 mm.).

To the filtered solution of n-butyllithium prepared from 8.22 g. (0.06 mole) of n-butyl bromide, 0.83 g. (0.12 g. atom) of lithium in 40 ml. of ether, was added 5.64 g. (0.03 mole) of ethyl  $\beta$ -naphthyl sulfide in 10 ml. of ether. The mixture, which rapidly developed a brown color, was refluxed twenty hours and then carbonated by dry-ice. The yellow acidic material, isolated by the customary procedures, melted from  $130^\circ$  to  $135^\circ$  and weighed 1.42 g. After one treatment with "Norite"

(116) Kraft and Schönherr, Ber., 22, 824 (1889) previously obtained this compound by another method.

and two crystallizations from benzene, the melting point was 157-158°, but the yellow color of the material persisted. A further treatment with "Norite," followed by recrystallization from an acetic acid-water mixture, changed neither the melting point nor the color. The neutral equivalent was 195, whereas the value calculated for ethyl monocarboxynaphthyl sulfide is 232. This acidic substance was not identified, but from the high melting point, it is probably an impure  $\beta$ -ethylmercaptanaphthoic acid.

Two and one-tenth grams (37.5%) of the starting material was recovered.

#### Attempted Preparation of p-Methylmercaptophenyllithium

The p-bromophenyl methyl sulfide used in the experiments was prepared by brominating methyl phenyl sulfide (117). The compound boiled at 148-149°, (40 mm.); 103-104°, (4 mm.), and melted at 37-38°, after crystallization from ethanol. The yield and constants agreed with the values given in the literature.

The purpose of this experiment was to metalate p-bromophenyl methyl sulfide with p-methylmercaptophenyllithium, a reaction which would correspond to the metalation of p-bromoanisole with p-anisyllithium (118).

To 0.42 g. (0.06 g. atom) of lithium, cut in small pieces and

(117) Van Hove, Bull. sci. acad. roy. Belg., [5], 12, 929 (1926).

(118) Gilman, Langham, and Jacoby, J. Am. Chem. Soc., 61, 106 (1939).

suspended in 15 ml. of ether, was added dropwise with stirring, 6.09 g. (0.03 mole) of p-bromophenyl methyl sulfide in 15 ml. of ether. No reaction occurred, as shown by the failure to obtain a Color Test I (95), in spite of vigorous stirring and refluxing. An almost quantitative recovery of the starting material was effected by filtering and evaporating the ether.

The experiment was repeated, after the starting material had been recrystallized from ethanol; but the result was the same.

#### Attempted Metalation of p-Bromophenyl Methyl Sulfide

##### 1. Attempted metalation of p-bromophenyl methyl sulfide by n-butyl-lithium

The conditions of this experiment correspond with those used to metalate p-bromoanisole with n-butyllithium (118). To the filtered solution of n-butyllithium, prepared from 6.85 g. (0.05 mole) of n-butyl bromide and 0.70 g. (0.1 g. atom) of lithium in 100 ml. of ether, was added rapidly 5.08 g. (0.025 mole) of p-bromophenyl methyl sulfide in 50 ml. of ether. After fifteen minutes, a 50 ml. aliquot was removed and carbonated by pouring on dry-ice. By means of the usual procedures, there was isolated 1.23 g. (88%) of p-methylmercaptobenzoic acid; m. p., 189.5-190° (119). The remainder of the reaction mixture was refluxed for seventeen hours. Before termination of the reaction by carbonation, (119) Zincke and Jörg, Ber., 43, 3443 (1910).

Color Test III (104) was positive (120). This portion of the reaction mixture gave only 6.1% of *p*-methylmercaptobenzoic acid. The neutral fraction yielded 0.93 g. of an oil; b. p., 148-155° (40 mm.). From the boiling point, this fraction was probably unreacted starting material (18.3%). A forerun of 0.67 g. was not identified.

2. Attempted metalation of *p*-bromophenyl methyl sulfide by methyllithium

Methyllithium has been shown to be a poor reagent for halogen-metal interconversions (52), but a somewhat better reagent for hydrogen-metal interconversions (121). Inasmuch as some halogen-substituted methoxybenzenes underwent H-M, rather than X-M interconversion with methyllithium (121), it was hoped that a similar reaction would occur with *p*-bromophenyl methyl sulfide.

Methyllithium was prepared from 14.2 g. (0.1 mole) of methyl iodide and 1.38 g. (0.2 g. atom) of lithium in 100 ml. of ether. The filtered solution was concentrated and then treated with 10.2 g. (0.05 mole) of *p*-bromophenyl methyl sulfide in 20 ml. of ether. The total volume was 85 ml. After fifteen minutes, a 5 ml. aliquot was removed and carbonated in the usual way. The remainder was refluxed for twenty-two hours before carbonation. Both fractions were worked up in the same

(120) On standing after hydrolysis, the mixture slowly developed a green color.

(121) Langham, Brewster, and Gilman, J. Am. Chem. Soc., 63, 545 (1941).

manner. The aliquot yielded only a trace of acidic material, which was insufficient for examination. The main portion gave 5-10 mg. of *p*-methylmercaptobenzoic acid, identified by a mixed melting point determination. Distillation separated the neutral fraction into three fractions. The first of these, boiling over the range 80-87° (18 mm.), was identified as methyl phenyl sulfide (10.3%) by oxidation to the corresponding sulfone and determination of the mixed melting point with an authentic specimen. The second fraction, boiling from 96 to 100° (18 mm.), was identified as methyl *p*-tolyl sulfide (14.1%) by means of the same procedure. The third fraction boiled between 115 to 120° (10 mm.) and was identified in the above manner as *p*-bromophenyl methyl sulfide (5.88%).

The experiment was repeated with a larger excess of methyllithium and in a more concentrated solution. The filtered solution of the metalating agent, prepared from 21.3 g. (0.15 mole) of methyl iodide and 2.07 g. (0.3 g. atom) of lithium in 100 ml. of ether, was concentrated to 35 ml. before treatment with 10.2 g. (0.05 mole) of *p*-bromophenyl methyl sulfide. The mixture was refluxed for twenty hours, then carbonated and worked up in the usual way. A trace of a gummy acid was isolated, but not identified. The neutral fraction yielded 2.4 g. (28.2%) of methyl *p*-tolyl sulfide, which was identified by oxidation to the corresponding sulfone (m. m. p.).

## Metalation of Sulfones

### 1. Metalation of methyl phenyl sulfone by n-butyllithium

The sulfone was prepared by oxidizing methyl phenyl sulfide with hydrogen peroxide in glacial acetic acid (122). The melting point, 87-88°, agreed with the literature reports.

The experiment was performed to determine whether an organolithium compound had any action on the sulfone linkage.

To an ice-cold solution of n-butyllithium prepared from 13.7 g. (0.1 mole) of n-butyl bromide and 1.38 g. (0.2 g. atom) of lithium in 100 ml. of ether was added, dropwise with stirring, 7.80 g. (0.05 mole) of methyl phenyl sulfone in 300 ml. of ether during thirty minutes. The ice bath was removed, the reaction allowed to warm to room temperature during a period of one and one-half hours, and was then refluxed for one hour. The mixture was carbonated and worked up in the customary manner to yield 4.70 g. (47%) of pure benzenesulfonylacetic acid; m. p., 111-112°. Identification was made by a mixed melting point determination with a specimen prepared by hydrogen peroxide oxidation of phenylmercaptoacetic acid (123).

Since 45.5% of methyl phenyl sulfone was recovered, the yield of acid, based on methyl phenyl sulfone not recovered, was 86.5%.

(122) Hinsberg, Ber., 43, 289 (1910).

(123) Claesson, Bull. soc. chim., [2], 23, 446 (1875).



2. Metalation of ethyl phenyl sulfone by ethylmagnesium bromide

Ethyl phenyl sulfone was prepared by oxidizing the corresponding sulfide with hydrogen peroxide in glacial acetic acid (122). The melting point was 41-42° in agreement with the literature.

Eight and five-tenths grams (0.05 mole) of ethyl phenyl sulfone in 50 ml. of ether was added during five minutes to a stirred solution of 0.05 mole of ethylmagnesium bromide (1.65 N) in 30.3 ml. of ether. When most of the sulfone had been added, a white precipitate appeared and a vigorous reaction set in which caused rapid refluxing for ten minutes, and more gentle refluxing for about an hour. If the stirring was stopped and the precipitate allowed to settle, no color test (95) could be obtained from the clear supernatant liquid, but a strong positive test could be obtained if some of the solid were used. After five hours at room temperature, the mixture was carbonated and worked up in the customary way. Acidification of the bicarbonate extract gave a gummy oil which was not identified. Extraction with potassium hydroxide, followed by acidification, gave 0.07 g. of a compound which crystallized in colorless, flat plates from ethanol; m. p., 156°. This compound may be a methylene disulfone (88). It was not a carboxylic acid, since it was insoluble in sodium bicarbonate solution. The neutral fraction yielded 61% of the starting material.

3. Metalation of ethyl phenyl sulfone by n-butyllithium

To the stirred, ice-cold solution of n-butyllithium prepared from 6.85 g. (0.05 mole) of n-butyl bromide and 0.69 g. (0.10 g. atom) of lithium in 50 ml. of ether was added, during twenty minutes, 4.25 g. (0.025 mole) of ethyl phenyl sulfone in 60 ml. of ether. A very slight precipitate formed. The mixture was stirred at room temperature for one and one-half hours, and refluxed for the same period before carbonation. On acidification of the bicarbonate extract, there was obtained 1.5 g. of an oil which contained no valeric acid. This substance could not be solidified or crystallized, and underwent further changes on standing, as it turned black.

The reaction mixture apparently contained no constituent that was soluble in potassium hydroxide solution but insoluble in sodium bicarbonate solution.

Only 30.6% of ethyl phenyl sulfone was recovered.

4. Metalation of diphenyl sulfone by n-butyllithium

To the filtered solution of n-butyllithium from 8.22 g. (0.06 mole) of n-butyl bromide and 0.83 g. (0.12 g. atom) of lithium in 60 ml. of ether was added during fifteen minutes 6.54 g. (0.03 mole) of diphenyl sulfone in 200 ml. of an ether-benzene mixture (125 ml. of ether and 75 ml. of benzene). The reaction mixture rapidly became brown in color, and as it began to reflux, was cooled in an ice bath. When the vigorous

reaction ceased, the cooling bath was removed and the mixture was stirred at room temperature for two hours and then refluxed for two hours before carbonation. The mixture was worked up in the usual way, but considerable benzene was required to dissolve the solids. The acid fraction weighed 0.25 g. and melted at 200° after gradually darkening from 130°. Attempts to purify this substance by crystallization from a variety of solvents was unsuccessful. A portion of it was apparently decarboxylated by successive attempts to dissolve it in petroleum ether (b. p. 60-68°), benzene, and ethanol, since it was only partially soluble in sodium bicarbonate solution after this treatment.

The neutral fraction yielded 34.4% of diphenyl sulfone.

5. Metalation of dibenzothiophene 5-dioxide by n-butyllithium

The metalating agent, prepared from 2.74 g. (0.02 mole) of n-butyl bromide and 0.28 g. (0.04 g. atom) of lithium in 30 ml. of ether, was treated with 2.1 g. (0.01 mole) of dibenzothiophene 5-dioxide (124) in 100 ml. of ether. A pink color, produced immediately, gradually deepened to purple when all the dioxide was added. After a twelve-hour reflux period, Color Test III (104) was positive, indicating the presence of an aryllithium compound. The mixture was worked up in the usual way, after carbonation, to give an acidic gum, but all efforts to purify or crystallize the compound were unsuccessful.

(124) Kindly provided by Mr. H. A. Pacevitz.

Attempted Metalation of Methyl Phenyl Selenide

1. Attempted metalation of methyl phenyl selenide by *n*-butyllithium in diethyl ether

Methyl phenyl selenide was prepared from selenophenol and dimethyl sulfate (93). The compound, obtained in 80% yield, had b. p. 89-90° (15 mm.) and  $n_{25}^{25}$  1.6060.

For the metalation, *n*-butyllithium was prepared from 13.7 g. (0.1 mole) of *n*-butyl bromide and 1.40 g. (0.2 g. atom) of lithium in 100 ml. of ether. To the clear filtered solution was added 8.35 g. (0.05 mole) of methyl phenyl selenide in 25 ml. of ether. After being stirred at room temperature for one-half hour there was no pronounced change in the appearance of the reaction mixture other than the production of a yellow color. The mixture was then refluxed for nineteen hours, carbonated by dry-ice, and worked up in the usual way. Only benzoic acid was isolated; yield, 28.4%. The neutral fraction was distilled to give 25.6% of *n*-butyl methyl selenide (125) and 13.8% of recovered methyl phenyl selenide. Both liquids were identified by boiling point and refractive index.

In an effort to minimize the cleavage reaction, a second experiment was performed, in which all quantities of materials were the same as in the first reaction, but the reflux time was shortened to four hours. At

(125) Tschugaeff, Ber., 42, 52 (1909).

the end of this period Color Test III (104) was negative (126), yet 1.27 g. or 21% of benzoic acid was isolated subsequent to carbonation.

2. Attempted metalation of methyl phenyl selenide by *n*-amylsodium in petroleum ether

Petroleum ether was chosen because it has been shown to be a poor solvent for cleavage reactions (53). However, as the aliphatic hydrocarbons are also poor solvents for metalations with organolithium compounds, it was necessary to employ an organometallic compound which is active in petroleum ether; namely, *n*-amylsodium (17).

The metalating agent was prepared (99) at ice bath temperature from 10.6 g. (0.1 mole) of *n*-amyl chloride and 5.7 g. (0.25 g. atom) of sodium in 100 ml. of petroleum ether (b. p. 28-38°). Without removing the ice bath, 8.35 g. (0.05 mole) of methyl phenyl sulfide was added rapidly. No change was observed for about fifteen minutes. Then the mixture changed from a black to a gray color and became so warm that it refluxed for a few minutes. When the refluxing ceased, the ice bath was removed, and stirring continued for four hours at room temperature. The thick brown mixture was then carbonated as usual. Great care was necessary in performing this operation, since the solid was inflammable in air.

(126) The failure to obtain a color test in this case was unexpected in view of the high concentration of phenyllithium (approx. 0.1 molar) which was present.

The mixture was worked up by use of the customary procedures to yield 31.8% of crude benzoic acid; m. p., 117-119°. In an attempt to recrystallize the acid from water, 0.15 g. remained undissolved, and was filtered off. The filtrate deposited 1.5 g. of benzoic acid; m. p., 120-121°; yield, 25%. The acidic material which was insoluble in water was organic in nature, but did not melt at 280°. It was not identified.

3. Attempted metalation of methyl phenyl selenide by sodium in petroleum ether

Inasmuch as the anylsodium in the foregoing experiment contained excess sodium metal, it seemed advisable to test the action of sodium on methyl phenyl selenide.

A mixture of 3.4 g. (0.02 mole) of methyl phenyl selenide and 1.05 g. (0.045 g. atom) of sodium sand in petroleum ether (b. p. 28-38°) was stirred for four hours and carbonated by solid carbon dioxide. Only a trace of reddish oil was isolated by extraction with sodium bicarbonate solution. Hence, very little cleavage could have occurred between the phenyl group and the selenium atom with the formation of phenylsodium.

## DISCUSSION

Thiophenol was metalated ortho to the sulfur linkage by *n*-butyllithium, as evidenced by the isolation of *o,o'*-dicarboxydiphenyl disulfide subsequent to carbonation. The orientation in this case corresponds to that previously observed with phenol,  $\beta$ -naphthol (127), resorcinol (128), some hydroxydibenzofurans (128), and hydroxyphenanthrenes (129). The formation of the disulfide probably resulted from the action of atmospheric oxygen on first formed thiosalicylic acid. This postulate is supported by several observations. No *n*-butyl phenyl sulfide was found, as would have been the case if diphenyl disulfide had formed first and then reacted with butyllithium (30, 31). On the other hand, 31.4% of this sulfide was produced when diphenyl disulfide was metalated by *n*-butyllithium. Moreover, in the latter reaction a higher yield of *o,o'*-dicarboxydiphenyl disulfide was obtained, but rather surprising was the failure to isolate any *o*-(*n*-butylmercapto)benzoic acid from this mixture, inasmuch as *n*-butyl phenyl sulfide is metalated by *n*-butyllithium. Possibly this result indicates that diphenyl disulfide is metalated more rapidly than *n*-butyl phenyl sulfide under the same conditions.

(127) Unpublished studies by Mr. C. E. Arntzen.

(128) Gilman, Willis, Cook, Webb, and Meals, *J. Am. Chem. Soc.*, **62**, 667 (1940).

(129) Gilman and Cook, *ibid.*, **62**, 2813 (1940).

TABLE I

Metalation of Methyl Phenyl Sulfide

Metalating Agent :	Time : hrs.	Temp. : °C.	Solvent :	Acid <sup>a</sup> : Yield, %	Thiophenol : Yield, %	Recovered Sulfide, %
Sodium	18	25-28	ether	3.46	20.9	52.4
Sodium	18	25-28	benzene	trace <sup>b</sup>	trace	87.5
Mercuric acetate	9.5	95-100		e		
<u>n</u> -Butylmagnesium bromide	2	135-140	none	42.0 <sup>f</sup>	trace	63
<u>n</u> -Butylmagnesium bromide	5	150-155	none	0.2 <sup>d</sup>		67
Methylithium	20	34	ether	0.12		84
<u>n</u> -Butyllithium	20	28-38	pet. ether	trace		91.5
<u>n</u> -Butyllithium	168	28-38	pet. ether	3.67	2.27	31.7
<u>n</u> -Butyllithium	3	130-150	none	trace	22.7	29
<u>n</u> -Butyllithium	1	70-150	none	21.2	10	52.2
Phenyllithium	16	34	ether	12.8		37.0
Phenylsodium	5	r. t.	benzene	15.8		44.4
Phenylcalcium iodide	46	34	none	e		78.5
Phenylcalcium iodide	3.5	150-160	none	e	12.95	58.8

<sup>a</sup>The acid was phenylmercaptoacetic acid, unless otherwise specified. The yields were based on starting material employed.

<sup>b</sup>Traces were not identified.

<sup>c</sup>The product in this case was p-acetoxymercuriphenyl methyl sulfide (36.6%).

<sup>d</sup>m-Methylmercaptobenzoic acid was isolated.

<sup>e</sup>Benzoic acid was the only carboxylic acid separated.

<sup>f</sup>Valeric acid only was isolated in this case.



The formation of phenylmercaptoacetic acid by the reaction of sodium with methyl phenyl sulfide (Table I) cannot be unequivocally attributed to a metalation by sodium. It is probable that the metalating agent was methylsodium, inasmuch as a relatively high yield of thiophenol was obtained subsequent to carbonation and hydrolysis.



Apparently, cleavage of the sulfur-phenyl linkage did not occur to any perceptible extent, as no benzoic acid was isolated.

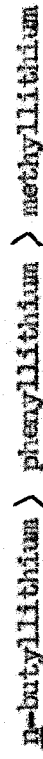


The failure to observe even the odor of acetic acid, on carbonation, indicated the absence of methylsodium. This may have been the result of two competitive reactions which destroyed the methylsodium. The first of these probably resulted in the cleavage of diethyl ether and the second in the metalation of methyl phenyl sulfide. Phenylmercaptomethylsodium apparently does not cleave ether very rapidly. This observation is not surprising, inasmuch as some complex organosodium compounds are known to be relatively stable in ether solution; for example, 4-dibenzofurylsodium (130). The very slight cleavage of methyl phenyl sulfide by sodium in benzene agrees with other cleavage reactions in this solvent (16, 53).

The metalation of methyl phenyl sulfide by mercuric acetate, by n-butylmagnesium bromide, by phenylsodium, and by a variety of organo- (130) Young, R. V., Doctoral Dissertation, Iowa State College (1936).

lithium compounds brought about substitutions in three different positions of the molecule. Mercuric acetate introduced an acetoxymercury group into the para position. This orientation appears to be rather general for alkyl aryl and aryl aryl ether types, as both phenyl sulfide (8) and methyl phenyl ether (96) undergo mercuration in the para position. Such is not the case with some cyclic ether types, however (131). Mercuration, therefore, corresponds to bromination in methyl phenyl sulfide. This is also true of thianaphthene (42). The metalation of methyl phenyl sulfide by *n*-butylmagnesium bromide resulted in an ortho nuclear substitution, as evidenced by the isolation of *o*-methylmercaptobenzoic acid subsequent to carbonation and hydrolysis. This substitution corresponds to that effected by the action of Grignard reagents on anisole (80). It was shown earlier (21) that *n*-butyllithium in diethyl ether metalated methyl phenyl sulfide laterally. Results have now been obtained which show that methyllithium and phenyllithium in diethyl ether, *n*-butyllithium in petroleum ether (b. p. 28-38°), and phenylsodium in benzene also give a lateral metalation product, for phenylmercaptacetic acid was isolated in each case following carbonation.

Arrangement of the organolithium compounds in order of decreasing effectiveness gives the following series:



It was shown earlier (26) that *n*-butyllithium, under comparable conditions, metalates dibenzothiophene approximately five times more rapidly than

(131) See page 26 of this thesis.

phenyllithium. *n*-Butyllithium metalates methyl phenyl sulfide approximately three times more rapidly than phenyllithium (Table I).

Phenyl sulfide was metalated to a much greater extent (56%) than was methyl phenyl sulfide (12.8%) by phenylsodium in benzene. This may be explained by the fact that the reaction time was forty-eight hours in the first case but only five hours in the second. It is probable that the reaction period is very important when a metalation is performed in a hydrocarbon solvent. This conception is substantiated by the observation that *n*-butyllithium with methyl phenyl sulfide in petroleum ether gave only a trace of metalation in twenty hours and 3.67% of phenylmercaptoacetic acid after one week. Dibenzothiophene was not metalated by *n*-butyllithium after twenty-hour reflux periods in petroleum ether or in benzene (17). It is probable that longer reflux periods would have brought about metalation.

From the evidence at hand, it appears that the position substituted in the methyl phenyl sulfide molecule is conditioned by the metalating agent employed, rather than by such factors as temperature or solvent. Thus, the same position was substituted by *n*-butyllithium in diethyl ether or in petroleum ether, and by phenylsodium in benzene. As might be expected, the rate of the reaction differed in the various solvents, and was especially slow in petroleum ether when *n*-butyllithium was the metalating agent.

Essentially the same conditions which brought about a nuclear metalation with *n*-butylmagnesium bromide gave a lateral substitution

with n-butyllithium. The fact that the same product is obtained with n-butyllithium at both high and low temperatures leads to the conclusion that the lateral metalation product is the result of a direct replacement of hydrogen by lithium and not the result of a rearrangement of a first formed nuclear metalation product. This follows from a study of the lateral metalation of hydrocarbons where it was found "that metalation of the side chain was always enhanced by elevating the temperature of the reaction mixture" (132). Moreover, the migration of a lithium atom from the nucleus to the side chain of an organolithium compound is, as yet, unknown, in spite of attempts to bring about such a transformation (132, 133). As yet, there is no evidence to decide whether the nuclear metalation with the Grignard reagent is the result of a direct replacement of nuclear hydrogen or the result of the rearrangement of a first formed lateral metalation product. As dibenzofuran and methyl phenyl sulfide are metalated to approximately the same extent by n-butyllithium, the activities of the hydrogens replaced appear to be approximately equal. Hence, it was somewhat surprising that phenylcalcium iodide metalated dibenzofuran (55), but not methyl phenyl sulfide. Phenyl sulfide was also metalated by n-butyllithium, but not by phenylcalcium iodide (17). The explanation may lie in the unusual character of phenylcalcium iodide which metalated dibenzothiophene in

- (132) Pacevitz, H. A., Doctoral Dissertation, Iowa State College (1940).  
(133) Gilman, Pacevitz, and Baine, J. Am. Chem. Soc., 62, 1514 (1940).

the 3-position rather than in the expected 4-position (26, 57). Thus, it may be that phenylcalcium iodide will not metalate the same hydrogen atoms in methyl phenyl sulfide and phenyl sulfide that are metalated by n-butyllithium. However, the same hydrogens appear to be replaced in phenoxathiin by n-butyllithium and phenylcalcium iodide (64).

TABLE II

Metalation of Methyl Phenyl Sulfide and Methyl Phenyl Ether  
by n-Butyllithium

Run	Compound	Time hrs.	Yield, %; based on Reactants Introduced	Reactants Not Recovered
1 <sup>a</sup>	C <sub>6</sub> H <sub>5</sub> SCH <sub>3</sub>	15	43.5	62.0
	C <sub>6</sub> H <sub>5</sub> OCH <sub>3</sub>	15	37.8	45.9
2	C <sub>6</sub> H <sub>5</sub> SCH <sub>3</sub>	5.0	37.6	59.4
	C <sub>6</sub> H <sub>5</sub> OCH <sub>3</sub>	5.0	34.2	50.5
3	C <sub>6</sub> H <sub>5</sub> SCH <sub>3</sub>	4.5	39.7	77.0
	C <sub>6</sub> H <sub>5</sub> OCH <sub>3</sub>	4.5	32.0	60.3

<sup>a</sup>This data from ref. 21 is included for comparison.

A cyclic ether, dibenzofuran, was metalated considerably more rapidly than a cyclic sulfide, dibenzothiophene (59). However, this

relationship did not appear to be true when methyl phenyl ether was compared with methyl phenyl sulfide. In each of three experiments (Table II) methyl phenyl sulfide gave a higher yield of metalation product than methyl phenyl ether. This difference may be the result of two factors. First, the hydrogens involved in the metalation of these two compounds are not of the same type since one is aliphatic and the other aromatic. Second, only one compound is obtained on carbonation of the metalation product of the sulfide whereas two products (acid and ketone) are found on carbonation of the ether. In each case the acid can be isolated easily and quantitatively but the ketone is isolated with greater difficulty. The yield of ketone from the reaction with anisole was never more than a few per cent, whereas Bebb obtained a forty per cent yield from the same reaction (17). The effect of the reaction time on the yield of metalation products does not appear to be very significant inasmuch as there was no great difference in the yields (Table II) when the reactants were refluxed five hours or fifteen hours.

TABLE III

Metalation of Methyl Aryl Sulfides by n-Butyllithium

Aryl Group	Time hrs.	Acid <sup>a</sup> , Yield, %		Recovered Sulfide, %
		A	B	
<u>p</u> -Tolyl	16	38.2	77.8	51.0
<u>p</u> -Chlorophenyl	5	5.75	—	b
<u>p</u> -Dimethylaminophenyl	19	22.4	46.7	52.1
<u>p</u> -Dimethylaminophenyl	19	15.2	25.6	43.1
$\alpha$ -Naphthyl	5	35.4	—	b
$\beta$ -Naphthyl	20	11.7	43.2	85.0

<sup>a</sup>The acid in each case was a substituted acetic acid. The yields were based on sulfide introduced, A, and on sulfide not recovered, B.

<sup>b</sup>The neutral fraction was not investigated.

When a series of aryl methyl sulfides (Table III) was metalated by n-butyllithium in ether solutions under comparable conditions, lateral metalation occurred in each case. No nuclear metalation was observed, and cleavage of the carbon-sulfur linkage did not occur to any marked extent. Arrangement of the aryl radicals in order of decreasing yield (Column A, Table III) of metalation product gives the following series: Phenyl, p-tolyl,  $\alpha$ -naphthyl > p-dimethylaminophenyl,  $\beta$ -naphthyl >

p-chlorophenyl. Within the experimental limits, there is no appreciable difference between the first three. It is probable that a higher yield of p-dimethylaminophenylmercaptoacetic acid would have been obtained but for the amphoteric character of the compound, which made its isolation difficult. The rather low yield obtained from methyl  $\beta$ -naphthyl sulfide and the high yield from methyl  $\alpha$ -naphthyl sulfide is somewhat surprising, in view of the results with the corresponding hydrocarbons. When  $\alpha$ - and  $\beta$ -methylnaphthalene were metalated by organosodium compounds, the higher yield of lateral metalation product was obtained with the  $\beta$ -compound (132). The low yield obtained from p-chlorophenyl methyl sulfide was in agreement with the results obtained with p-bromophenyl methyl sulfide. The bromo compound was not metalated under the conditions employed for the metalation of p-bromoanisole by n-butyllithium (118) or by methyllithium (121). In the case of the sulfur compound, the former reagent gave mainly interconversion, whereas the latter gave mainly coupling. The halogen of p-bromophenyl methyl sulfide was inactive toward lithium, as shown by the failure to obtain an organolithium compound from these reagents. However, the corresponding Grignard reagent formed readily and in a yield of approximately 70%. This compound was previously prepared, with difficulty, by Brand and his co-workers (24). In general, sulfur-containing organic halides form Grignard reagents more readily than the corresponding oxygen compounds. The reverse is true of p-bromophenyl phenyl ether and p-bromophenyl phenyl sulfide (23). It is interesting to note that the



corresponding selenium compound gave a Grignard reagent more readily than the sulfide (23).

TABLE IV

Metalation of Alkyl Aryl Sulfides by *n*-Butyllithium

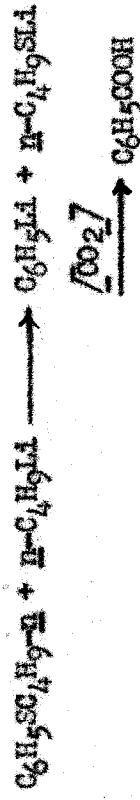
Sulfide	Time hrs.	Metalation Acid <sup>a</sup> , %		Benzoic Acid, %	Recovered Sulfide, %
		A	B		
Ethyl phenyl	15	7.7	15.8	b	51.5
	15	8.4	22.4	3.5	59.4
<i>n</i> -Propyl phenyl	20	6.9	16.4	3.5	54.5
Isopropyl phenyl	20	11.4	32.7	0	65.0
	20	11.0	34.2	0	67.8
<i>n</i> -Butyl phenyl	19	10.0	22.8	4.1	52.0
	19	7.38	23.6	4.5	63.0
	18	6.5	19.4	1.2	64.0
Cyclohexyl phenyl <sup>c</sup>	48	11.4	27.6	(10 mg.)	58.4
	24	8.5	21.6	0	60.5
Ethyl $\beta$ -naphthyl <sup>c</sup>	20	20.4	32.7	-	37.5

<sup>a</sup>The yields were based on sulfide introduced, A, and on sulfide not recovered, B.

<sup>b</sup>A small quantity (0.6 g.) of a crude acid isolated in this experiment probably contained benzoic acid.

<sup>c</sup>The acid isolated was not identified.

In marked contrast to the series of aryl methyl sulfides which were metalated only in the side chain, the alkyl aryl sulfides listed above (Table IV) were metalated only in the aromatic nucleus, ortho to the sulfide linkage. In this respect they correspond to the similar oxygen compounds. Another significant difference between the two series is found in the yields of metalation products. In general, the lateral metalations proceeded to a greater extent than the nuclear metalations. All the alkyl phenyl sulfides, which underwent nuclear metalations, did so to approximately the same extent. The differences in the yields do not appear to be significant. The high yield reported from ethyl  $\beta$ -naphthyl sulfide was based on an impure acid which was not identified. The high melting point of this material, however, precludes the possibility that the compound was a substituted acetic acid. The behavior of the methyl phenyl sulfides contrasts with that of the higher alkyl phenyl sulfides in another respect. The former were not cleaved appreciably by the metalating agents, whereas the latter yielded small quantities of cleavage products, with the possible exception of isopropyl phenyl sulfide. From the metalation of this compound with *n*-butyllithium, there was obtained, in addition to *o*-isopropylmercaptobenzoic acid, a trace of another sulfur-containing acid. The other sulfides (Table IV) gave, in addition to an *o*-alkylmercaptobenzoic acid, 1-5% yields of benzoic acid, possibly produced in the following manner:



The formation of a trace of benzoic acid was also observed when n-butyllithium reacted with phenyl n-tetradecyl sulfide (22). The lower alkylmercapto groups are apparently cleaved more readily than the higher members of this series. n-Butyl mercaptan was isolated only in the reaction expressed in the above equation. An attempt to isolate alkylmercaptans in the other reactions met with failure. Cleavage to yield what may have been an aromatic thiol was also observed in the case of n-butyl phenyl sulfide when the metalating agent contained a small quantity of lithium metal, but was not observed in the absence of lithium. The organolithium compounds appeared to cleave the alkyl phenyl sulfides only at the phenyl-sulfur linkage. Lithium metal, however, cleaved n-butyl phenyl sulfide in two ways to yield both benzoic acid and thiophenol, subsequent to carbonation.



The fate of the butyl group was not disclosed, but it did not appear as n-butyl mercaptan, because negative tests for mercaptans were obtained with lead acetate and with 2,4-dinitrochlorobenzene. In one experiment lithium and n-butyl phenyl sulfide were stirred for seven hours at room temperature, and then refluxed for thirty-six hours to yield 20.5% of thiophenol, 11.9% of benzoic acid, and 0.24% of o-(n-butylmercapto)benzoic acid. The sulfur acid was probably the result of a metalation of n-butyl phenyl sulfide by phenyllithium. This reaction is akin to that of sodium with methyl phenyl sulfide, as mentioned earlier in this discussion.

The experimental portion of this thesis does not include the

metalation of any sulfoxides. A review of this field was given in the historical section (134).

The activating effect of a sulfone group on an adjacent methyl or methylene group has been described in the historical section of this thesis. It was found that a reactive organometallic compound, n-butyllithium, had no effect on the sulfone group of methyl phenyl sulfone. Instead, a lateral metalation occurred to the extent of 86.5% based on methyl phenyl sulfone not recovered. Ethyl phenyl sulfone reacted quite vigorously with ethylmagnesium bromide at room temperature. A gas was evolved and, on carbonation, a product soluble in sodium bicarbonate solution was isolated but not identified owing to the fact that it could not be crystallized or solidified. A crystalline compound was obtained by extraction with potassium hydroxide solution. This compound, which was insoluble in sodium bicarbonate solution, may be a methylene disulfone. n-Butyllithium metalated ethyl phenyl sulfone at ice bath temperature. Again, the carboxylic acid fraction, isolated on carbonation, was a gum which could not be crystallized and which underwent further changes on keeping as it turned black. Diphenyl sulfone reacted vigorously with n-butyllithium in ether-benzene solution and metalation occurred as evidenced by the isolation of a carboxylic acid fraction after carbonation. This acidic substance proved difficult to crystallize and was apparently partially decarboxylated by successive attempts to

(134) See pages 38-44 of this thesis.

dissolve it in boiling petroleum ether (b. p. 60-68°), in ethanol, and in benzene. When an ether solution of dibenzothiophene 5-dioxide was added to a solution of n-butyllithium in the same solvent, there was produced a pink color which gradually deepened to purple when all the dioxide was added. At the end of a twelve-hour reflux period, the mixture evidently contained an aryllithium compound as Color Test III (104) was positive. After carbonation, a carboxylic acid fraction was isolated in the form of a gum which was not crystallized or identified. Further metalation studies on sulfones are indicated. Possibly some interesting orientations might be obtained with aryl sulfones, as the sulfone group is a meta-directing group. Practically all metalation studies have been made with compounds containing ortho-para directing substituents.

Bebb (17) found that phenyl selenide was readily cleaved by n-butyllithium to the extent of 19%, according to the yield of benzoic acid obtained subsequent to carbonation. Phenyl sulfide was also cleaved under the same conditions, but to only a slight extent. In view of the fact that various methyl phenyl sulfides were quite stable to organolithium compounds, it was thought that methyl phenyl selenide would also be fairly stable under the same conditions, or at least more stable than phenyl selenide. However, methyl phenyl selenide was cleaved to approximately the same extent as phenyl selenide, since 28.4% of benzoic acid was obtained on carbonation following a nineteen-hour reflux period. From the neutral fraction there was isolated, in addition to a 13.8%

recovery of the starting material, a 25.6% yield of *n*-butyl methyl selenide.



Bebb isolated *n*-butyl phenyl selenide in his reaction with phenyl selenide. A 21% yield of benzoic acid resulted when *n*-butyllithium and methyl phenyl selenide were refluxed for only four hours. Another experiment was performed using amylsodium in petroleum ether (b. p. 23-36°). The hydrocarbon solvent was employed in an effort to minimize the cleavage reaction, but this was unsuccessful, since 25% of benzoic acid was obtained after four hours at room temperature. In a separate experiment, sodium sand was stirred with methyl phenyl selenide for four hours at room temperature in low boiling petroleum ether. On carbonation, only a trace of an acidic material was isolated. Hence, the excess sodium present in the reaction with amylsodium had scarcely any effect.

SUMMARY

A review has been made of the reactions of sulfides, disulfides, sulfoxides, and sulfones with sodium, sodamide, mercuric salts, organomagnesium compounds, and organoalkali compounds.

Thiophenol and diphenyl disulfide have been metalated by *n*-butyllithium.

The metalation of methyl phenyl sulfide by a variety of metalating agents in different solvents has been studied with a view of determining the effect on the position involved in the metalation.

The relative rates of metalation of methyl phenyl sulfide and methyl phenyl ether have been studied.

A series of methyl aryl sulfides has been metalated by *n*-butyllithium to ascertain the effect on the metalation of varying the aryl group.

Several alkyl phenyl sulfides were metalated by *n*-butyllithium to learn the type of orientation involved.

The reactions of *p*-bromophenyl methyl sulfide with lithium, *n*-butyllithium, and methylolithium have been studied.

A number of sulfones have been metalated by means of organometallic compounds.

The metalation of methyl phenyl selenide was attempted.