Summary.

Emphasis is placed on the necessity of carefully observing certain precautions in the distillation of chenopodium oil from the plant, in order to avoid the decomposition of the ascaridole by prolonged contact with steam or boiling water.

An examination of 7 authentic samples of chenopodium oil collected during the season of 1919 shows them to comply with the requirements of the United States Pharmacopeia and to contain from 60 to 77% of ascaridole.

The examination of a sample of chenopodium oil distilled in Java shows it to be very similar to the oils of American origin, and the analysis of 5 American oils returned from Brazil, and over a year old, shows them to be normal in character.

Chenopodium oil distilled from wild plants collected in Florida was found to contain less ascaridole than the oil distilled from cultivated plants in Maryland. The same constituents were found in it that were found in the Maryland oil.

The terpenes of chenopodium oil were found to contain *p*-cymene, *l*-limonene and probably α-terpinene.

WASHINGTON, D. C.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF JOHNS HOPKINS UNIVERSITY.]

REACTIONS AND DERIVATIVES OF β,β′-DICHLORO-ETHYL SULFIDE.

BY OREGON B. HELFRICH[1] AND E. EMMET REID.

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Introduction.

In view of the prominence into which β,β′-dichloro-ethyl sulfide has been recently brought by reason of its use in the war as "mustard gas," it was thought that an investigation of the chemistry of this substance would be of particular interest. While mustard gas on the battle field was the most permanent of the gases used in large quantity and was apparently inert, it has been found that it can take part in quite a variety of reactions. The purpose of this work[2] has been to make a study of certain of these reactions. The study has been limited to the reactions which involve the sulfur atom and the 2 chlorine atoms. Since the reactions involving the chlorine atoms always removed them, generally as sodium

[1] From dissertation of Oregon B. Helfrich.

[2] The mustard gas used in this investigation consisted of crude material obtained from both the American University Experiment Station and the Edgewood Arsenal, and of some of the redistilled product from the first mentioned place. The crude material was used as a source of the dichloro-ethyl sulfoxide and sulfone while the redistilled product was used in the condensations.

chloride or hydrochloric acid, while those reactions involving the sulfur atom merely raised it to a higher state of oxidation, there exists in common among all the derivatives prepared what might be called the "mustard residue," $-CH_2CH_2SCH_2CH_2-$. The feasibility of giving this group a special name such as "mustarene" and calling its derivatives "mustarides," etc., was abandoned[1] in favor of names conforming with the system of nomenclature now being used in *Chemical Abstracts*.

Historical.

The only derivatives of this class that have previously been prepared, aside from the substances thiodiglycol,[1] $S(CH_2CH_2OH)_2$, and ethylene disulfide,[2] $S(CH_2CH_2)_2S$, which have been known for a long time, are the 4-alkyl-14,-thiazans which Clarke[3] synthesized by the condensation of aliphatic amines with dichloro-ethyl sulfide, and the dichloro-ethyl sulfoxide and sulfone which were obtained during the war investigations.

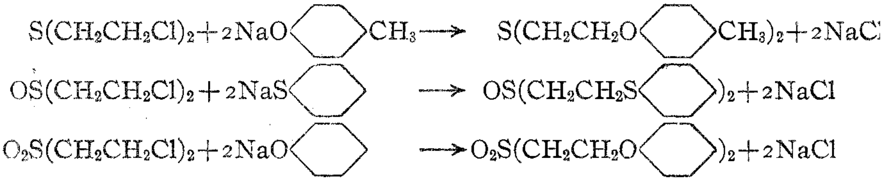
Outline of Present Study.

I. Products obtained by the oxidation of dichloro-ethyl sulfide:

$$(ClCH_2CH_2)_2S \longrightarrow (ClCH_2CH_2)_2SO \longrightarrow (ClCH_2CH_2)_2SO_2$$

Dichloro-ethyl sulfide. Dichloro-ethyl sulfoxide. Dichloro-ethyl sulfone.

II. Products obtained by the condensation of dichloro-ethyl sulfide, sulfoxide, and sulfone with sodium thiophenate and phenates:



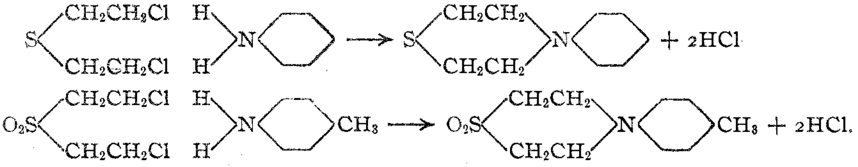
III. Products obtained by the reaction of dichloro-ethyl sulfide, sulfoxide, and sulfone with sodium mercaptides and alcoholates:

$$S(CH_2CH_2Cl)_2 + 2\,NaSBu \longrightarrow S(CH_2CH_2SBu)_2 + 2NaCl$$

$$O_2S(CH_2CH_2Cl)_2 + 2NaSEt \longrightarrow O_2S(CH_2CH_2SEt)_2 + 2NaCl$$

$$S(CH_2CH_2Cl)_2 + 2NaOEt \longrightarrow S(CH = CH_2)_2 + 2EtOH + 2NaCl$$

IV. Products obtained by the condensation of dichloro-ethyl sulfide, sulfoxide, and sulfone with the aromatic amines.[4]



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[1] Communication with Dr. E. J. Crane on this point led to the adoption of the names to be found in the following pages.

[2] V. Meyer, *Ber.*, 19, 3259 (1886); Crafts, *Ann.*, 124, 110 (1862).

[3] *J. Chem. Soc.*, 101, 1583 (1912).

[4] Similar to Clarke's synthesis of the 4-alkyl-1,4-thiazans.

V. Products obtained by other reactions.

$$S(CH_2CH_2Cl)_2 + 2NaOOCCH_3 \longrightarrow S(CH_2CH_2OOCCH_3)_2 + 2NaCl$$

$$OS(CH_2CH_2Cl)_2 + 2NaI \longrightarrow OS(CH_2CH_2I)_2 + 2NaCl$$

$$\begin{matrix}ClCH_2CH_2\\ ClCH_2CH_2\end{matrix}\!>\!S + MeI \longrightarrow \begin{matrix}ClCH_2CH_2\\ ClCH_2CH_2\end{matrix}\!>\!S\!<\!\begin{matrix}I\\ Me\end{matrix}$$

In order to confirm the formulas of the derivatives prepared analyses were carried out in practically every case, usually the sulfur only being determined. The sulfur analyses were made by the sodium peroxide fusion, carried out in the Parr bomb,[1] with subsequent precipitation and determination of the sulfur as barium sulfate. This method was found very convenient and gave good results with all the crystalline derivatives, but with the few oily derivatives the results were hardly satisfactory, the analytical figures quoted in these cases being usually the best pair out of about 5 analyses. As the composition of these oils was rather definitely fixed by their method of preparation and by their oxidation products, little time was spent in the development of the method of analysis. In the few cases where analyses for halogen were made, the method used was to decompose the substance with sodium in absolute alcohol and then to determine the halogen, in the usual way, as silver halide.

I. Oxidation Products.

(a) **β,β′-Dichloro-ethyl Sulfoxide, (bis(β-chloro-ethyl)Sulfoxide),** $(ClCH_2CH_2)_2SO$.—In a report of war gas investigations there is a statement to the effect that dichloro-ethyl sulfide is oxidized by conc. nitric acid to the corresponding sulfoxide[2] melting at 109.5°. No further information regarding the preparation or the substance itself is vouchsafed. Since in the present work a detailed study of the substance has been made, the results are herein set forth.

When pure dichloro-ethyl sulfide is dropped into conc. nitric acid at room temperature, there is energetic reaction with evolution of heat and formation of a light green solution. From this solution, after diluting with water, the sulfoxide separates as white crystal plates. These melt constant at 109.5° (corr.) which agrees with the melting point given in the war gas report.

So far as one can judge by handling this substance it is entirely without effect upon the human skin.

Dichloro-ethyl sulfoxide is soluble in a variety of solvents, *e. g.*, water, conc. mineral acids (especially), alcohol, ether, benzene, carbon disulfide, and acetone. At 20°, 100 cc. of water dissolves 1.2 g. of sulfoxide; and

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[1] *J. Ind. Eng. Chem.*, 11, 230 (1919).

[2] For brevity dichloro-ethyl sulfoxide will be referred to as the *sulfoxide* wherever clearness will permit.

at 100°, more than its own weight, in fact no limit could be found. At 20°, 100 cc. of alcohol[1] dissolves 4.3 g. of sulfoxide; at 80°, the solubility seems infinite. A large temperature coefficient of solubility is at once apparent for the sulfoxide in these 2 solvents. In conc. mineral acids the sulfoxide is quite soluble even at room temperature, due, no doubt, to the basic nature of the sulfoxide.

Dichloro-ethyl sulfoxide can not be distilled without partial decomposition even at reduced pressure. The chief decomposition product is dichloro-ethyl sulfide. No dichloro-ethyl sulfone can be detected in the distillate. It seems that during the distillation the sulfoxide dissociates into the sulfide and oxygen, the former appearing in the distillate and the latter either escaping as such or effecting a destructive oxidation of some of the sulfoxide.

Hydrolysis of the Sulfoxide.—Although dichloro-ethyl sulfide is hydrolyzed fairly rapidly by hot water according to the equation.

$$S(CH_2CH_2Cl)_2 + 2HOH \longrightarrow S(CH_2CH_2OH)_2 + 2HCl,$$

dichloro-ethyl sulfoxide is practically unchanged even in boiling water, the solution giving no precipitate with silver nitrate solution. The dichloro-ethyl sulfone in boiling water gives a precipitate of silver chloride with silver nitrate solution, thus showing a greater hydrolysis than the sulfoxide. Conductivity measurements also confirm the greater hydrolysis of the sulfone. Dichloro-ethyl sulfoxide is completely hydrolyzed by alcoholic sodium hydroxide, dihydroxyethyl sulfoxide ($(HOCH_2CH_2)_2SO$), a viscous oily liquid, easily soluble in water, alcohol, and ether, being obtained.

Reactions.—Dichloro-ethyl sulfoxide is oxidized by various reagents, best by chromic acid, to the corresponding sulfone which is described below. By virtue of the presence of the two halogen atoms, dichloro-ethyl sulfoxide is able to participate in many reactions analogously to the dichloro-ethyl sulfide. The derivatives so obtained will be considered in connection with the corresponding derivatives from the sulfide.

Experimental.

Preparation.—50 g. of pure dichloro-ethyl sulfide was dropped slowly into 100 g. of conc. nitric acid in a small balloon flask. The temperature was kept below 50 to 55° in order to avoid loss. After the addition was complete, the acid solution was filtered through asbestos (when the sulfide used was not pure there always separated considerable sulfur) and poured into 250 cc. water. Upon standing the sulfoxide came out as a beautiful white crystalline product. After several hours it was filtered with suction and the product dried. Yield, 80–85%. This was quite pure and generally melted about 106–7°. Recrystallization out of alcohol or water

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[1] Unless otherwise specified "alcohol" means the usual 95% material.

gave the pure substance, melting at 109.5° (corr.). When crude dichloroethyl sulfide was used, care had to be taken in the addition to the acid, as the reaction was considerably more violent. A sample of crude mustard gas from the American University gave on oxidation a light brown product (melting at 105° ±) in about 55% yield. A sample of the crude material from the Edgewood Arsenal, of slightly better grade, gave an almost white product in about the same yield. The sulfoxide obtained from either source melted at 109.5°, after one recrystallization out of hot water. Sulfur analysis gave: S; 18.50 and 18.26%., calc. 18.30%.

Distillation.—50 g. of dichloro-ethyl sulfoxide was distilled *in vacuo.* The distillate came over between 105–145° under 18 mm. pressure. It was composed of a white solid and 2 apparently immiscible liquids. Some of the white solid was separated and treated in alcohol solution with sodium thiophenate and the resulting product recrystallized out of alcohol to constant melting point. It melted at 121.0° showing it to be bis(β-phenyl-mercapto-ethyl) sulfoxide (described below) which proves that the white solid was unchanged dichloro-ethyl sulfoxide. The oily portion of the distillate was shaken with water, becoming in this operation one homogeneous oil, no doubt by solution of the other liquid (perhaps a water solution of the sulfoxide), then the oil separated and was distilled *in vacuo.* The main portion came over between 95° and 107° under 12 mm. pressure. This was further fractionated and came over nearly constant at 105–8° under 18 mm. pressure. As this boiling point was rather indicative of mustard gas, care was exercised in handling it. The distillate was a pale yellow oil of faint odor similar to that of mustard gas. On treatment in alcohol solution with sodium thiophenate and recrystallization of the product out of alcohol, it yielded bis(β-phenyl-mercapto-ethyl) sulfide melting at 57.5°. Together with the other data this clearly showed the main decomposition product during the distillation to have been dichloro-ethyl sulfide. After finding the sulfide as a product of decomposition it was thought probable that some sulfone might be present also if decomposition had taken place according to the reaction:

$$2(ClCH_2CH_2)_2SO \longrightarrow (ClCH_2CH_2)_2S + (ClCH_2CH_2)_2SO_2.$$

But no sulfone was found. Indeed the amount of actual sulfide isolated practically excluded any such possibility. It seems probable that the formation of the sulfide was due to the dissociation of the sulfoxide thus:

$$(ClCH_2CH_2)_2SO \longrightarrow (ClCH_2CH_2)_2S + O$$

the oxygen being consumed in some oxidation-decomposition reaction.

Solubilities.—The sulfoxide was shaken with water and with alcohol for 2 days at 20° and assuming saturation at the end of that time, samples of the solutions were weighed (or measured), evaporated to dryness and the residues weighed.

Sulfoxide in water at 20°.

Sample of Solution No. 1 weighed 13.48 g. — residue 0.15 g. ≎ 1.1 g. per 100 cc.
Sample of Solution No. 2 weighed 11.09 g. — residue 0.13 g. ≎ 1.2 g. per 100 cc.

Sulfoxide in alcohol at 20°.

Sample of Solution No. 1, 10 cc. — residue 0.42 g. ≎ 4.2 g. per 100 cc.
Sample of Solution No. 2, 10 cc. — residue 0.44 g. ≎ 4.4 g. per 100 cc.

Hydrolysis of the Sulfoxide.—I. Information furnished by treatment with silver nitrate as to the presence of the chlorine ion in the water solution of dichloro-ethyl sulfoxide.

100 cc. of a boiling 1% solution of the sulfoxide gave no precipitate on the addition of 20 cc. of 5% silver nitrate solution. Hydrolysis must be very low.

On the other hand 100 cc. of a boiling 1% solution of the sulfone did give a definite precipitate of silver chloride on the addition of 20 cc. of a 5% silver nitrate solution. Whence hydrolysis is greater than with the sulfoxide.

II. Conductivity measurements relative to hydrolysis.

Dilute aqueous solutions of the sulfoxide and sulfone were made, their initial conductances measured and after 10 days the conductances again determined. It was found that at 20° there was no change in the conductance of the sulfoxide solution while, under identical conditions, the conductance of the sulfone solution increased about 20%. This clearly demonstrates the greater hydrolysis in the latter solution. Measurements were also made keeping the solutions at 100° but the results were worthless because a blank showed that the solubility of the glass in the tubes used was more than sufficient to produce the effects noted.

III. Preparation of the hydrolysis product.

Fifteen g. of sulfoxide was added to a hot solution of 8 g. of sodium hydroxide in 100 cc. of alcohol. The separation of sodium chloride was rapid. Most of the alcohol was evaporated off on the steam bath, the product treated with water, and extracted with ether. The extract was separated off, dried, and evaporated, yielding the dihydroxyethyl sulfoxide as a light brown syrup. This was somewhat deliquescent and easily soluble in water, alcohol, and ether.

(b) **Dichloro-ethyl Sulfone (Bis(β-chloro-ethyl)sulfone), ($ClCH_2CH_2)_2SO_2$.**—When dichloro-ethyl sulfoxide is further oxidized by the use of fuming nitric acid, potassium permanganate, or chromic acid, the chief product is the corresponding sulfone.[1] When this step is carried out by a hot aqueous solution containing 5–10% chromic acid and 15–18% sulfuric acid the yield is nearly quantitative. By the use of the other 2 oxidizing agents the yield of sulfone is not so good since considerable amounts of the sulfoxide are either completely oxidized or converted into other products not easily isolated. In the report previously referred to,

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[1] Whenever clearness permits, dichloro-ethyl sulfone will be called "the sulfone."

it was stated that dichloro-ethyl sulfone is obtained by oxidation with fuming nitric acid and that it melts at 54.0°. No further details were given. In the present study dichloro-ethyl sulfone has been studied in some detail, as was the sulfoxide, and is presented accordingly.

Dichloro-ethyl sulfone crystallizes out of alcohol or water in beautiful thin white leaflets melting at 56.0° (corr.), or 2° higher than figure given above. Upon distillation at atmospheric pressure it undergoes partial decomposition, boiling at about 230°, with evolution of hydrogen chloride and sulfur dioxide, yielding as distillate a yellow oil containing much unchanged sulfone and as residue a considerable amount of carbonized matter. Under 20 mm. pressure, however, it boils without decomposition at 183° the distillate solidifying easily and melting at 55–6°. The solubility of the sulfone in water and dil. acids is much less than that of the sulfoxide, probably because of the lack of the basic properties in the sulfone. At 20° 100 cc. of water dissolves 0.6 g. of sulfone, at 100° 2.4 g. When it is recalled that the sulfoxide is practically infinitely soluble in water at 100° the difference between these compounds in their relation toward water is at once apparent. In alcohol, which may be taken as representative of the organic solvents, the sulfone is slightly more soluble than the sulfoxide; at 20°, 100 cc. of alcohol dissolves 7.1 g. of sulfone and at 80° the solubility is very great.

Physiological Action of the Sulfone.[1]—Dichloro-ethyl sulfone produces on contact with the skin blisters and persistent sores. Its vapors are lachrymatory, causing soreness of the eyes, and somewhat sternutatory, causing a slight burning in the nostrils, but as its vapor pressure is so low at ordinary temperatures that no inconvenience is experienced in handling it. That these unpleasant properties should reoccur in the sulfone after disappearing in the sulfoxide is peculiar. The theory[2] has been advanced that hydrolysis is one of the main factors entering into the action of dichloro-ethyl sulfide on the human body. It is of interest to note here that the hydrolysis of the sulfide by water is greatest, the sulfone next and the sulfoxide least. These facts are in accordance with the theory mentioned as applied to the observed physiological effects of the sulfoxide and sulfone.

Hydrolysis of the Sulfone.—In regard to the actual hydrolysis of the dichloro-ethyl sulfone the following calculation is of interest. A 1% solution of the sulfone in water at 100° gives a partial precipitation of its chlorine as silver chloride when treated with 20 cc. of 5% silver nitrate solution. The 5% silver nitrate solution = 0.3 *M* whence the concentration of $AgNO_3 (= Ag^+)$ after addition to the 100 cc. of sulfone solution is 0.05 *M*. For calculation take the solubility of silver chloride at 100°

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[1] Unpublished report of Dr. E. K. Marshall.

[2] E. K. Marshall, *J. Am. Med. Assoc.*, **73**, 684 (1919); *C. A.*, **13**, 2929 (1919).

$= 1.0 \times 10^{-5}$. That is $K_{AgCl} = 1.0 \times 10^{-10}$. Since there was some precipitation of silver chloride, we know that $(Ag^+ \times Cl^-) = K_{AgCl}$ or $(0.05) \times (Cl^-) = 1.0 \times 10^{-10}$. That is $Cl^- > 2.0 \times 10^{-9}$ in the boiling sulfone solution. Since, however, precipitation is incomplete we know further that the Cl^- concentration only exceeded the value 2.0×10^{-9} by a small amount. These figures give a fair idea of the hydrolysis of the sulfone in boiling water. In cold water it is, of course, much less, as no precipitate of silver chloride is obtained in the cold. It is regretted that time was not available to make a more exact study of these relations.

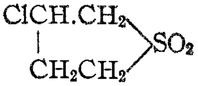
β,β'-Dihydroxy-ethyl sulfone is prepared by the hydrolysis of the dichloro-ethyl sulfone by alcoholic sodium hydroxide. It is a thick syrup, somewhat deliquescent, and in general similar to the sulfoxide analogue. It is difficult to obtain entirely free from water. The best product obtained boiled under 15 mm. pressure evenly distributed over the range 140–165°.

Reactions.—When an alcohol solution of dichloro-ethyl sulfone is treated with an alcohol solution of sodium sulfide, reaction is very rapid. The product is an amorphous white solid (probably $S<(CH_2CH_2)_2>SO_2$), which does not melt at 200°, and is insoluble in the ordinary solvents.

The other products obtained from the sulfone by the replacement of its chlorine atoms will be taken up in connection with the similar derivatives of dichloro-ethyl sulfide.

Experimental.

Preparation.—50 g. of dichloro-ethyl sulfoxide was heated in 350 cc. of water, containing 25 g. of chromic acid (or the equivalent amount of sodium dichromate) and 40 cc. of conc. sulfuric acid, for a period of 4 to 6 hours. The reaction mixture was then allowed to cool and to stand several hours before filtering. The crude product as filtered off was quite dark from chromium salts and was digested with 100 cc. of boiling water. After the sulfone had solidified by cooling the water was poured off and the product dissolved in 100 cc. of hot alcohol. The solution was filtered hot and after cooling the white, or pale-greenish, product filtered off and dried. A second crop of good material was obtained by adding an equal volume of water to the alcohol mother liquor. Yield, 50 g.; m. p., 55–6°. On recrystallization the pure substance melted at 56.0°.

Distillation.—100 g. of sulfone distilled at ordinary pressure at about 230° with considerable decomposition, yielding a clear yellow oil as distillate, while giving off hydrogen chloride and sulfur dioxide. About $^1/_3$ of the original material remained in the distilling bulb as a carbonized residue. The yellow oil distilled over again at 230° with evolution of more hydrogen chloride and sulfur dioxide. Again there was a carbonized residue. The distillate now weighed 35 g. Determination of the chlorine content showed 14.5%, a proportion which did not indicate any simple decomposition product. $(ClCH_2CH_2)_2SO_2$ contains 36.6%,  $\left.\begin{array}{l} ClCH.CH_2 \\ | \\ CH_2CH_2 \end{array}\right\rangle SO_2$ contains 22.9%. A sample of the oil treated with sodium thiophenate in hot alcohol solution gave a separation of sodium chloride and, on diluting with water, an oily crystal pulp was obtained. By recrystallization out of alcohol crystals melting at 104.5° were isolated. This melting point corresponds exactly with that of bis(β-phenyl-mercapto-ethyl) sulfone, obtained by the condensation of sodium thiophenate with dichloro-ethyl sulfone. Thus it appears that there was some unchanged sulfone still in the oil after 2 distillations at atmospheric pressure. From the chlorine content it seems that the oil in question contained about 40% of the sulfone dissolved in some oily chlorine-free sulfur compound. The nature of the oily constituent was not determined. The fact that the decomposition took place practically constantly at 230° should be noted. When the final yellow oil was distilled *in vacuo* there was practically no decomposition but the distillation took place over quite a range of temperature ($^2/_3$ of the total came over between 125–150° under 23 mm. pressure), showing clearly that this oil was not a single substance, as the constant boiling point (with decomposition) at atmospheric pressure might have led one to believe.

The pure dichloro-ethyl sulfone distils *in vacuo* without any decomposition at 183° under 20 mm. pressure.

II. Products by Condensation with Sodium Thiophenate and Phenates.

The fundamental reaction in the preparation of these derivatives is the formation of sodium chloride with the simultaneous condensation of the organic residues.

$$2C_6H_5SNa + (ClCH_2CH_2)_2S \longrightarrow 2NaCl + (C_6H_5SCH_2CH_2)_2S$$

$$2C_6H_5ONa + (ClCH_2CH_2)_2S \longrightarrow 2NaCl + (C_6H_5OCH_2CH_2)_2S$$

It is seen that the condensation with sodium thiophenate gives complex trisulfides or related bodies, while with the phenates it produces various mixed sulfide-ethers. All of these substances which have been prepared are white (or nearly so) crystalline bodies. Most of them can be recrystallized out of alcohol but those from the more complex phenols (α- and β-naphthol, eugenol, vanillin, tribromo-phenol) are only slightly soluble. None of the derivatives is soluble in water. So far as has been ascertained none of them is dangerous to work with. The yields in general are good. For those products obtained from sodium thiophenate the yields are nearly quantitative.

The stability of the multiple-sulfides and their oxidation products, together with the quantitative nature of the condensation of sodium thiophenate with dichloro-ethyl sulfide, -sulfoxide, or -sulfone are among the outstanding features of this field. While the reactions

$$2C_6H_5SNa + (ClCH_2CH_2)_2S \longrightarrow 2NaCl + (C_6H_5SCH_2CH_2)_2S \quad (1)$$
$$2C_6H_5SNa + (ClCH_2CH_2)_2SO \longrightarrow 2NaCl + (C_6H_5SCH_2CH_2)_2SO \quad (2)$$
$$2C_6H_5SNa + (ClCH_2CH_2)_2SO \longrightarrow 2NaCl + (C_6H_5SCH_2CH_2)_2SO_2 \quad (3)$$

with thiophenate all take place nearly quantitatively, the corresponding ones with sodium phenate give smaller and varying yields. Thus the reaction corresponding to (1) gives a good yield, the reaction corresponding to (2) gives none of the desired product, while the reaction corresponding to (3) gives the expected product but only in poor yield. These relations hold in general also for the other phenols which condense readily with only the dichloro-ethyl sulfide. With regard to oxidation the sulfide-ethers function entirely differently from the multiple-sulfides. Thus it has been found that the former are entirely broken down by nitric or chromic acid (giving in several cases quinone), while in the latter the sulfur atoms alone are oxidized to the quadrivalent or hexavalent condition, the chain of sulfur and carbon atoms remaining unbroken. In general nitric acid oxidizes the sulfide groups to sulfoxide groups, while chromic acid or permanganate oxidizes either of these to sulfone groups.

A systematic study of the oxidation products of bis(β-phenyl-mercapto-ethyl) sulfide, $(C_6H_5SCH_2CH_2)_2S$, has been made and the following series developed:

Name. (Formula.)	Sulfur.		M. p. (corr.). °C.	Sol. in 100 cc. Alc.		Remarks.
	Calc.	Found.		Cold. (18° ±).	Hot. (75° ±).	
Bis(β-phenyl-mercapto-ethyl) sulfide $(C_6H_5SCH_2CH_2)_2S$	31.40	31.66 31.43	57.5	0.65 g.	10 g.	Lustrous white leaflets
Bis(β-phenyl-mercapto-ethyl) sulfoxide $(C_6H_5SCH_2CH_2)_2SO$	29.81	29.98 29.67	121.0	1.0 g.	sol.	Lustrous white leaflets
Bis(β-phenyl-sulfinyl-ethyl) sulfoxide $(C_6H_5SOCH_2CH_2)_2SO$	27.12	26.90 27.04	161.0	s. sol.	sol.	Small white crystals
Bis(β-phenyl-mercapto-ethyl)sulfone $(C_6H_5SCH_2CH_2)_2SO_2$	28.40	28.40 28.27	104.5	s. sol.	sol.	Lustrous white leaflets
Bis(β-phenyl-sulfinyl-ethyl) sulfone $(C_6H_5SOCH_2CH_2)_2SO_2$	25.95	25.84 26.07	164.0	insol.	s. sol.	Small white plates
Bis(β-phenyl-sulfonyl-ethyl) sulfone $(C_6H_5SO_2CH_2CH_2)_2SO_2$	23.83	23.80 23.74	235.0	insol.	insol.	White needles

Attention is here called to the fact that these oxidation products of the multiple-sulfides should furnish excellent material for a study of the relation between certain physical properties, especially melting points and solubilities, and the chemical composition and structure. These compounds form a series of closely related derivatives, differing only by slight degrees of oxidation of the sulfur atoms and not by any changes in the main skeleton. Consideration of the table shows what a large influence the oxidation of the sulfur atoms has upon the melting point in these trisulfides. The stabilizing influence of raising the sulfur atom to its higher valences is therein apparent. When one considers that in a molecule containing bivalent sulfur atoms there must exist in consequence of the higher valence possibilities of the sulfur atom not only reactive tendencies toward certain classes of substances but also within the molecule itself a certain flexibility of structure, it is easy to conceive that the oxidation (*i. e.*, saturation) of these sulfur atoms should exert a large influence on the rigidity of the structure of the molecule and thereby effect the melting point and other properties. That the trisulfone which contains completely saturated sulfur atoms should be at the top of the series with regard to melting point, difficulty of solution in organic solvents, etc., is at once obvious.

Such reasoning apparently fails in the case of the simpler series but it

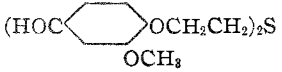
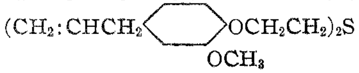
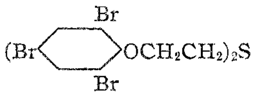
$(ClCH_2CH_2)_2S$.	$Cl(CH_2CH_2)_2SO$.	$Cl(CH_2CH_2)_2SO_2$.
14.4°	109.5°	56.0°

should be recalled that the present work has already pointed out that dichloro-ethyl sulfoxide lies out of line with the sulfide and sulfone in physiological properties and in hydrolysis. It is probable that there is a specific effect exerted by the presence of the sulfoxide group together with 2 chlorine atoms in the β-positions. Any such specific effect would of course prevent the successful application of the above reasoning with regard to physical properties.

Condensation with Phenols.—The sulfide-ethers, already referred to, now come up for specific discussion. Since the condensation between the phenates and dichloro-ethyl sulfoxide does not take place at all, and with dichloro-ethyl sulfone the yield is rather poor, most of the derivatives prepared are of the structure $(ROCH_2CH_2)_2S$ where "R" is an aromatic residue. Further, since these sulfide-ethers are unstable towards oxidation it has been impossible to complete the series of oxidation products.

The sulfide-ethers and sulfone-ethers are nicely crystallized substances, insoluble in water, the simpler ones easily soluble in hot alcohol, the more complex ones rather difficultly. So far as known they have no effect on the human skin.

A number of aromatic phenols was tried unsuccessfully in this work. Those which failed to give the condensation were *p*-chlorophenol, *p*-nitrophenol, thymol, resorcine, methyl salicylate, and ethyl salicylate. No explanation for the discrepancy in the action of the phenol group in these compounds has been developed. In these cases where the condensation does not take place the sodium hydroxide present hydrolyzes the dichloroethyl sulfide with separation of sodium chloride from the alcohol solution

Name. (Formula.)	Sulfur.		M. p. (Corr.) °C.	Sol. in 100 cc. Alc.		Remarks.
	Calc.	Found.		Cold. (18.0.)	Hot. (75.0.)	
Bis(β-phenoxy-ethyl) sulfide....	11.68	11.67	54.2	1.4 g.	20 g.	Fine white needles
$(C_6H_5OCH_2CH_2)_2S$		11.70				
Bis(β-phenoxy-ethyl) sulfone....	10.46	10.30	108.0	s. sol.	sol.	Pinkish leaflets
$(C_6H_5OCH_2CH_2)_2SO_2$		10.41				
Bis(β-*p*-cresoxy-ethyl) sulfide...	10.60	10.55	78.0	0.2 g.	sol.	Lustrous needles
$(p\text{-}CH_3.C_6H_4.OCH_2CH_2)_2S$		10.68				
Bis(β-*p*-cresoxy-ethyl) sulfone...	9.58	9.64	120.0	s. sol.	sol.	Small pink leaflets
$(p\text{-}CH_3.C_6H_4.OCH_2CH_2)_2SO_2$		9.58				
Bis(β-*o*-cresoxy-ethyl) sulfide...	10.60	10.47	46.5	0.3 g.[a]	sol.	White needles
$(o\text{-}CH_3C_6H_4OCH_2CH_2)_2S$		10.51				
Bis(β-α-naphthoxy-ethyl) sulfide	8.55	8.60	94.5	insol.	s. sol.	Light brown crystals
$(\alpha\text{-}C_{10}H_7OCH_2CH_2)_2S$		8.46				
Bis(β-β-naphthoxy-ethyl) sulfide	8.55	8.48	129.0	insol.	0.6 g.	Small crystals
$(\beta\text{-}C_{10}H_7OCH_2CH_2)_2S$		8.51				
Bis(β - β - naphthoxy - ethyl) sulfone....................	7.88	7.90	151.0	s. sol.	sol.	Small shining plates
$(\beta\text{-}C_{10}H_7OCH_2CH_2)_2S$		7.76				
Bis(β-vanilloxy-ethyl) sulfide...	8.25	8.22	131.5	insol.	2 g.	Gray needles
 $(HOC\underset{OCH_3}{\langle\quad\rangle}OCH_2CH_2)_2S$		8.24				
Bis(β-eugenoxy-ethyl) sulfide...	7.73	7.80	113.5	0.1 g.	2 g.	Yellow powder
 $(CH_2{:}CHCH_2\underset{OCH_3}{\langle\quad\rangle}OCH_2CH_2)_2S$						
Bis(β - tribromo-phenoxy-ethyl) sulfide....................	4.29	4.29	118.5	insol.	0.5 g.	White powder
 $(Br\overset{Br}{\underset{Br}{\langle\quad\rangle}}OCH_2CH_2)_2S$		4.26				

[a] Solubility in 70% alcohol.

as usual, the reaction going for the most part according to the equation

$$S(CH_2CH_2Cl)_2 + 2NaOH \longrightarrow S(CH_2CH_2OH)_2 + 2NaCl.$$

This hydrolysis takes place to some extent also even in the cases where the condensation takes place but it is exceeded by the more rapid condensation. In the case of the thiophenol condensation the hydrolysis reaction is entirely negligible on account of the rapidity of the condensation. It is probable that both reactions go on simultaneously, their relative velocities depending on the properties of the reactants.

Another reaction which probably takes place to some extent is the formation of vinyl sulfide. If dichloro-ethyl sulfide is treated with

$$S(CH_2CH_2Cl)_2 + 2NaOH \longrightarrow S(CH = CH_2)_2 + 2NaCl + 2H_2O$$

sodium ethylate, vinyl sulfide seems the main product. The slow hydrolysis of dichloro-ethyl sulfide by alkali in 50% alcohol in the cold gives a rather high-boiling oil, insoluble in water and heavier than water. This is certainly not thiodiglycol and from its odor and properties may be a polymer of vinyl sulfide. Investigation of this point was cut short by an accident.

Experimental.

It would be useless repetition to give in detail the preparation of each of these derivatives. With the exception of the 3 products obtained by oxidation, which will be considered briefly below, they were all prepared by the following procedure.

0.01 Mole of dichloro-ethyl sulfide (-sulfoxide, or -sulfone) was added to a solution of 0.02 mole of the phenol (or thiophenol) in 20 cc. of *N* alcoholic sodium hydroxide, plus 25 cc. of alcohol and heated on the steam bath one hour. Then 20 cc. of water was added to dissolve the sodium chloride and cause the separation of the product, if this had not already taken place. The product was then filtered off and recrystallized to constant melting point and analyzed. The solubility figures given in the table are based on the weights of the crystals crop in successive recrystallizations. The figures thus make no claim for exactness yet give a fair idea of the solubility.

An example of the calculation of solubility is given:

Bis(β-phenyl-mercapto-ethyl) sulfide recrystallized from 50 cc. portions of alcohol.	1st 1st, m. p. 57.0°; wt. 3.91 g.; 1st 2nd, oil 2nd 1st, m. p. 57.5°; wt. 3.63 g.; 2nd 2nd, m. p. 57° 3rd 1st, m. p. 57.5°; wt. 3.28 g.; 3rd 2nd, m. p. 57.5°

The difference in weight between the 1st 1st and 2nd 1st is 0.28 g., and between the 2nd 1st and 3rd 1st is 0.35 g. The average is 0.32 g. and assuming this to represent the amount dissolved in the 50 cc. alcohol at the temperature of filtration (18°), we find 0.65 g. per 100 cc. as an estimate of the solubility at that temperature. In those cases where the solubility in cold alcohol was extremely low, there has been given as an estimate of the solubility at 75° the weight of the substance separating on cooling from 100 cc. alcohol which had been boiled with an excess of the substance and then very rapidly filtered while boiling hot.

Oxidation of Products.—The preparation of the 3 products obtained by oxidation methods will now be given.

1. Bis(β-phenyl-sulfinyl-ethyl) sulfoxide ($(PhSOCH_2CH_2)_2SO$) was prepared by the oxidation of bis(β-phenyl-mercapto-ethyl) sulfide ($(PhSCH_2CH_2)_2S$) by conc. nitric acid. The preparation was difficult and the yield poor. Nitric acid was added very slowly drop by drop to the sulfide until the first energetic reaction was over and the oil barely dissolved to form a clear yellow solution. On diluting a yellowish white product separated in small amount and was recrystallized out of alcohol. If an excess of nitric is used no crystal product is obtained.

2. Bis(β-phenyl-sulfinyl-ethyl) sulfone ($(PhSOCH_2CH_2)_2SO_2$) was

prepared similarly by the oxidation of bis(β-phenyl-mercapto-ethyl) sulfone ($(PhSCH_2CH_2)_2SO_2$) by nitric acid. The preparation in this case was not difficult and the yield satisfactory. On account of its low solubility even in boiling alcohol the product was recrystallized from nitric acid.

3. Bis(β-phenyl-sulfonyl-ethyl) sulfone ($(PhSO_2CH_2CH_2)_2SO_2$) was prepared by the oxidation of any of the lower oxidized substances of the same skeleton by either permanganate or chromic acid. The product was recrystallized out of nitric acid, being practically insoluble in alcohol.

(*a*) Three g. of bis(β-phenyl-mercapto-ethyl) sulfide (or sulfone, etc.), was heated in a solution of 5 g. of chromic acid and 10 cc. of conc. sulfuric acid in 100 cc. of water for $^1/_2$ hour on a steam bath. After cooling the crude product was filtered off.

(*b*) Three g. of bis(β-phenyl-mercapto-ethyl) sulfide (or sulfone, etc.), was dissolved in 10 cc. of conc. nitric acid, 100 cc. water added, and the boiling acid solution treated with potassium permanganate solution as long as the latter was decolorized and the white precipitate of the product continued to form. The crude product was filtered off.

The purified products were identical.

III. Products by Condensation with Sodium Mercaptides (and Alcoholates).

The condensation of dichloro-ethyl sulfide (-sulfoxide, or -sulfone) with sodium mercaptides is quite similar to that with sodium thiophenolate already considered.

$$S(CH_2CH_2Cl)_2 + 2NaSBu \longrightarrow S(CH_2CH_2SBu)_2 + 2NaCl.$$

$$S(CH_2CH_2Cl)_2 + 2NaSPh \longrightarrow S(CH_2CH_2SPh)_2 + 2NaCl.$$

The reaction is rapid in the hot alcohol solution and the yields nearly quantitative. The stability of these multiple-sulfides and their oxidation products is again an outstanding feature.

(Formula.)	Sulfur. Calc.	Sulfur. Found.	B. p. °C.	M. p. (corr.) °C.	Remarks.
Bis(β-butyl-mercapto-ethyl) sulfide... $(BuSCH_2CH_2)_2S$	36.09	35.53 35.31	222–3	17.5	Oil, unpleasant persistent odor
Bis(β-butyl-mercapto-ethyl) sulfoxide. $(BuSCH_2CH_2)_2SO$	34.04	[a]	...	25.0	Oil, very slight odor
Bis(β-butyl-sulfinyl-ethyl) sulfoxide.. $(BuSOCH_2CH_2)_2SO$	30.57	30.36 30.42	...	196.0	Brilliant small white crystals
Bis(β-butyl-mercapto-ethyl) sulfone.. $(BuSCH_2CH_2)_2SO_2$	32.21	32.10 32.14	...	73.7	Shining white needles
Bis(β-butyl-sulfinyl-ethyl) sulfone.... $(BuSOCH_2CH_2)_2SO_2$	29.09	29.05 28.98	...	101.0	Very small gray-white crystals
Bis(β-butyl-sulfonyl-ethyl) sulfone... $(BuSO_2CH_2CH_2)_2SO_2$	26.52	26.36 26.52	...	266.5	Glittering gray crystal plates

[a] Analysis not run on account of nature and small quantity of material.

From the condensation products obtained by the use of butyl mercaptan a series of oxidation products has been prepared analogous to that obtained from the thiophenol derivatives.

Just as with the similar phenyl derivatives the last 2 compounds of the table are only slightly soluble in organic solvents. For purification it is necessary to recrystallize bis(β-butyl-sulfonyl-ethyl) sulfone out of nitric acid; bis(β-butyl-sulfinyl-ethyl) sulfone may be recrystallized out of either alcohol or nitric acid. In general these butyl derivatives are slightly more soluble than the corresponding phenyl derivatives. In this (butyl) series the trisulfoxide (bis(β-butyl-sulfinyl-ethyl) sulfoxide) is prepared with greater ease though the yield is still poor. On comparing the melting points of the compounds it is seen that the trisulfoxide, trisulfone, and disulfoxide-sulfone of the butyl series melt higher than those of the phenyl series, while the other 3 members of the butyl series melt lower. This is a rather interesting point because it indicates that the oxidation of all 3 sulfur atoms in the butyl compounds must cause a considerably greater internal disturbance and rearrangement (in the direction of rendering the molecule more rigid in structure) than in the case of the phenyl compounds

From the alkyl mercaptans lower than butyl such complete series have not been prepared. Various attempts to prepare the derivatives containing 2 and 3 sulfoxide groups have failed. The oxidation of the lower alkyl trisulfides with nitric acid neither breaks down the carbon-sulfur chain nor furnishes the desired sulfoxide. Thus bis(β-ethyl-mercapto-ethyl) sulfide, on oxidation with conc. nitric acid and subsequent dilution, furnishes no crystals of the trisulfoxide. However, the original skeleton has not been destroyed, for the addition of potassium permanganate to the nitric acid gives in fair yield the trisulfone (bis(β-ethyl-sulfonyl-ethyl) sulfone) which can be easily isolated.

The derivatives which have been prepared and investigated are contained in the following table. As might be surmised from what has just preceded, these fall into 3 classes (the sulfoxide types being missing), of which bis(β-butyl-mercapto-ethyl) sulfide and -sulfone and bis(β-butyl-sulfonyl-ethyl) sulfone are typical. The table is divided horizontally into 3 sections, one for each type of derivatives. The derivative in the first section (trisulfides) are all oils, freezing at about room temperature, immiscible in water, but soluble in the ordinary organic solvents. The members of the second section (disulfide-sulfones) are with one exception crystalline substances of sharp melting point, very slightly soluble in hot water, somewhat more so in hot dilute nitric acid, and easily soluble in hot alcohol. The members of the third section (ti-sulfones) are high melting substances, insoluble in water and nearly so in alcohol, but easily crystallized from hot nitric acid. In the case of isobutyl-, secondary butyl-, and amyl mercaptans, the supply on hand was so small that no attempt was made to develop the full series possible with them.

Name. (Formula.)	Sulfur. Calc.	 Found.	B. p. ° C.	M. p. (corr.) ° C.	Remarks.
Bis(β-ethyl-mercapto-ethyl) sulfide $(EtSCH_2CH_2)_2S$	45.71	45.43 45.31	173–5	17.0	$n^{22.5}$. = 1.5150, odor rather unpleasant, and persistent
Bis(β-propyl-mercapto-ethyl) sulfide. $(PrSCH_2CH_2)_2S$	40.33	40.12 39.96	193–5	27.5	
Bis(β-butyl-mercapto-ethyl) sulfide $(BuSCH_2CH_2)_2S$	36.09	35.53 35.31	222–3	17.5	d^{20} 1.102, $n^{22.5}$ = 1.5455
Bis(β-amyl-mercapto-ethyl) sulfide $(i\text{-}AmSCH_2CH_2)_2S$	32.65	32.41 32.01	170	20.0	
Bis(β-methyl-mercapto-ethyl) sulfone $(MeSCH_2CH_2)_2SO_2$	44.86	44.59 44.61	...	77.0	Brilliant white leaflets
Bis(β-ethyl-mercapto-ethyl) sulfone. $(EtSCH_2CH_2)_2SO_2$	39.67	39.51 39.44	...	64.0 64.0	Long thin white plates
Bis(β-propyl-mercapto-ethyl) sulfone $(PrSCH_2CH_2)_2SO_2$	35.55	35.51 35.44	...	75.5	Thin white waxy plates
Bis(β-butyl-mercapto-ethyl) sulfone.. $(BuSCH_2CH_2)_2SO_2$	32.31	32.10 32.14	...	73.7	Shining white needles
Bis(β-*i*-butyl-mercapto-ethyl) sulfone $(i\text{-}BuSCH_2CH_2)_2SO_2$	32.21	32.20 32.11	...	94.2	Shining white needles (broader)
Bis(β - (*sec.*)butyl - mercapto-ethyl) sulfone $((sec.)BuSCH_2CH_2)_2SO_2$	32.21	32.18 32.07	...	15.0	Oil
Bis(β-amyl-mercapto-ethyl) sulfone. $(i\text{-}AmSCH_2CH_2)_2SO_2$	29.45	29.33 29.51	...	91.0	Small white needles
Bis(β-ethyl-sulfonyl-ethyl) sulfone $(EtSO_2CH_2CH_2)_2SO_2$	31.37	31.21 31.29	...	223.0	Shining small thin white plates
Bis(β-propyl-sulfonyl-ethyl) sulfone. $(PrSO_2CH_2CH_2)_2SO_2$	28.73	28.70 28.62	...	254.0	Thin white plates
Bis(β-butyl-sulfonyl-ethyl) sulfone $(BuSO_2CH_2CH_2)_2SO_2$	26.52	26.52	...	266.5	Very small white (gray) plates

The normal butyl derivatives are repeated for comparison.

A consideration of the table brings out several interesting points with regard to the melting points of these substances. Among the trisulfides the propyl derivatives stands out by reason of its melting higher than any of the others (ethyl-, butyl-, isoamyl-). Among the disulfide-sulfones the derivatives from the normal mercaptans show a definite alternation in their melting points, resembling the series with aliphatic acids, glycol, and amines. The derivatives from mercaptans containing an odd number of carbon atoms melt higher than the adjacent derivatives from mercaptans of even number of carbon atoms. Thus the methyl-derivative melts higher than the ethyl- while the propyl-derivative melts higher than all the normal derivatives below isoamyl-. The effect of the position of the carbon atoms is strikingly brought out in the butyl derivatives.

The *n*-butyl compound melts at 73.7°, the isobutyl- at 94.2°, and the secondary-butyl- at 15.0°.

Reaction with Alcoholates.—The reaction between dichloro-ethyl sulfide and sodium alcoholates now comes under consideration. Just as the phenols gave products similar to those obtained with thiophenol it was expected that the alcoholates would furnish derivatives similar to those of the mercaptides. Such, however, is not the case. The reaction

$$S(CH_2CH_2Cl)_2 + 2NaOEt \longrightarrow S(CH_2CH_2OEt)_2 + 2NaCl \qquad (1)$$

does not take place, or if it does the product indicated undergoes rapid decomposition. It seems that the chief product of the reaction is vinyl sulfide. This is easily understood, for alcoholic caustic soda frequently eliminates hydrochloric acid from aliphatic-halogen compounds forming unsaturated derivatives. The reaction here would be:

$$S(CH_2CH_2Cl)_2 + 2NaOEt \longrightarrow S(CH = CH_2)_2 + 2NaCl + 2EtOH \quad (2)$$

It might be considered that the mechanism of the reaction is bettered by a combination of (1) with the reaction

$$S(CH_2CH_2OEt)_2 \longrightarrow S(CH = CH_2)_2 + 2EtOH.$$

Experimental.

The trisulfides were prepared by adding 0.1 mole of dichloro-ethyl sulfide to an absolute alcohol (it was later found that 95% alcohol and sodium hydroxide acted as well) solution of 0.2 mole of sodium mercaptide, prepared by dropping 0.25 atom of sodium into 100 cc. of absolute alcohol and then adding 0.2 mole of mercaptan. The reaction mixture was warmed on a steam bath under a reflux condenser for $^1/_2$ hour to cause the separation of sodium chloride, and then poured out into water. The product separated as an oil sinking to the bottom. The oil was separated, dried and distilled *in vacuo*. The yield was very good when pure mercaptans were used. Considerable difficulty was encountered in obtaining the pure isoamyl derivative because, as later found out, the original mercaptan (Kahlbaum's) was less than 70% pure, introducing considerable impurities difficult to separate. The distillation of these oils *in vacuo* proceeded very smoothly, no bumping or decomposition being observed.

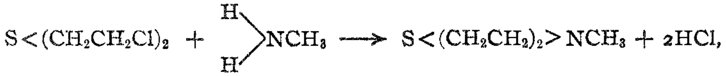
The disulfide-sulfones were obtained in an analogous fashion from dichloro-ethyl sulfone and the mercaptides. These substances all separated as crystalline bodies on pouring the reaction mixture into water and were then recrystallized to constant melting point out of alcohol. Their solubilities in cold alcohol (18 ± °) ranged from 1 to 4 g. while in hot alcohol they were all quite soluble.

The preparation of the other compounds discussed was exactly analogous to the methods outlined for the corresponding phenyl derivatives.

Reaction with Alcoholates.—In the reaction between dichloro-ethyl sulfide and the sodium alcoholates the product was apparently the same independent of nature of the alcoholate used. The reaction gave a separation of sodium chloride from the alcohol solution just as usual but the oil obtained on pouring into water was low boiling and had an odor resembling that described for vinyl sulfide. An unpurified lot of the oil distilled over at 60–70° with polymerization. Vinyl sulfide[1] boils at 102° but the lot distilled, no doubt, contained water and this together with the recognized abnormally high vapor pressures of vinyl sulfide at temperatures down towards room temperature could easily cause distillation at 60–70°. The products continually polymerized on redistillation and could not be obtained pure. This polymerization of vinyl sulfide has been previously observed.[1]

IV. Products by Condensation with Aromatic Amines.

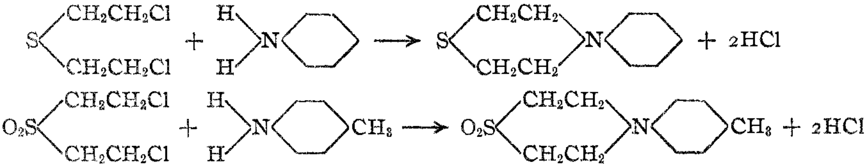
Attention has already been called to the preparation by Clarke of several of the 4-alkyl-1,4-thiazans by the condensation of aliphatic amines with dichloro-ethyl sulfides. In his work the condensation



$$\mathrm{S{<}(CH_2CH_2Cl)_2} + \left.\begin{matrix}\mathrm{H}\\ \mathrm{H}\end{matrix}\right\rangle \mathrm{NCH_3} \longrightarrow \mathrm{S{<}(CH_2CH_2)_2{>}NCH_3} + 2\mathrm{HCl},$$

was carried out in absolute alcohol in the presence of dry sodium acetate at 100° (sealed tube).

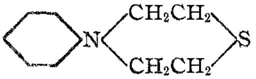
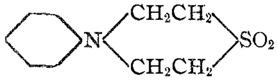
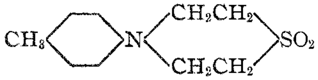
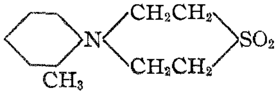
In the present investigation the *aromatic amines* have been condensed with dichloro-ethyl sulfide and sulfone, yielding respectively 4-aryl-1,4-thiazans and 4-aryl-1,4-sulfonazans



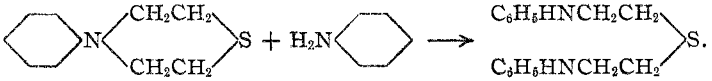
The sulfonazans are especially easy to prepare and work with. Thus, refluxing dichloro-ethyl sulfone with the desired amine in absolute alcohol solution in the presence of anhydrous sodium acetate gives the condensation readily. The thiazans can not be made thus. However, if dichloro-ethyl sulfide and aniline are mixed in the proper proportions and allowed to stand overnight the liquid becomes a mass of light brown crystals. From such a product the 4-phenyl-1,4-thiazan can be obtained in fairly pure condition. The sulfonazans are more easily prepared in a similar way, *i. e.*, dichloro-ethyl sulfone and aniline (or other aromatic amine) are heated to 130°, the condensation being then quite rapid, and from the cooled product the pure 4-phenyl-1,4-sulfonazan is obtained by recrystallization out of alcohol or dil. hydrochloric acid.

[1] Semmler, *Ann.*, 241, 92 (1887).

THE DERIVATIVES PREPARED.

Name. (Formula.)	Sulfur.		M. p. (corr.) °C.	Remarks.
	Calc.	Found.		
4-Phenyl-1,4-thiazan.......... 	17.87	16.58 16.40	108–111	Dull white product, not pure. Sol. in hot toluene
4-Phenyl-1,4-sulfanazan....... 	15.16	14.97 15.09	123.5	Clear gran. crystals
4-*p*-Cresyl-1,4-sulfonazan...... 	14.22	14.18 14.06	136.5	White plates out of aq. HCl. Small gran. crystals from alcohol
4-*o*-Cresyl-1,4-sulfonazan...... 	14.22	14.31 14.12	135.0	Fernlike crystal aggregates out of alcohol

Only one of the 4-aryl-1,4-thiazans was prepared because of the difficulty of obtaining these derivatives. The difficulty encountered was based on 2 facts, (1) their insolubility (causing inconvenience in purification), and (2) their secondary reaction with excess aromatic amine, apparently to break open the heterocyclic ring



The compound resulting from the secondary reaction is easily soluble in dil. hydrochloric acid (quite in contrast with the thiazan), yielding in alkaline solution an oil heavier than water, which is only slightly volatile in steam. The composition of this substance has not been determined but there seems little reason to doubt that it is of the nature indicated in the equation.

The only method that has been found to yield the phenyl thiazan is to let the aniline and dichloro-ethyl sulfide mixture stand several days. Actually 2 moles of aniline are used for one mole of dichloro-ethyl sulfide in order that the liberated hydrochloric acid may be taken care of. Thus there is present one mole of excess aniline, and care must be exercised in order that the secondary reaction does not gain headway. The secondary reaction goes to completion if the reaction product is heated on the steam bath, giving an amber-colored clear solid (when cold) which dissolves completely in hot water. In the cold, however, the secondary reaction is negligible and the aniline hydrochloride may be leached out by water without harming a product which has been allowed to condense for several days at room temperature.

Dichloro-ethyl sulfide heated with 2 moles of *o*- or *p*-toluidine also gives water-soluble products. The reaction in the cold has not been studied.

In the condensation to form the sulfonazans the secondary reaction is not so important. Thus condensation at 130° gives 4-phenyl-1,4-sulfonazan in about 50% yield. It is, however, hardly to be doubted that some of reactants here also take part in a similar secondary reaction. Several attempts to prepare the sulfonazans from α- and β-amino-anthraquinone failed completely.

The alkyl thiazans prepared by Clarke are basic compounds of which the hydrochlorides and picrates are easily obtained. The lower members are very strong bases, very soluble in water and organic solvents and fuming in the presence of acids. The properties of the 4-phenyl-1,4-thiazan present a sharp contrast. It is insoluble in water and most organic solvents and its basic tendencies are almost negligible, it being only slightly soluble in hot hydrochloric acid.

The aryl sulfonazans present an interesting class of substances. They are easily obtained by the method outlined in this paper but can not be obtained by the oxidation of the aryl thiazans as one might conjecture from a comparison of the formulae. Not only from the point of view of a new heterocyclic type but also regarded as another group of tertiary aromatic amines they abound with possibilities. It is hoped that work may soon be carried out to ascertain their adaptability to the various condensations effected with the ordinary tertiary aromatic amines. Particular reference is had to the condensations resulting in the production of various dyes, *i. e.*, malachite green, crystal violet, etc.

Experimental.

Preparation of (4)-Phenyl-(1,4)-thiazan.—50 g. of dichloro-ethyl sulfide was mixed with 60 g. of aniline and let stand 3 days or more (solidification took place overnight). The brown crystal mass was leached twice with boiling water and once with very dilute hydrochloric acid to remove the last of the aniline. The residue was dissolved in hot 10% hydrochloric acid and poured into a large volume of cold water. The product separated first as gummy drops but on boiling the water these became completely solid. This grayish white product was filtered off, leached 3 times with 100 cc. portions of boiling alcohol and finally recrystallized from toluene. Even then it did not give a sharp melting point (108–111°) showing the purification to be still incomplete.

Preparation of the (4)-Aryl-(1,4)-sulfonazans.—0.2 mole of aromatic amine was mixed with 0.1 mole of dichloro-ethyl sulfone and heated to 130° for 10–15 minutes. The condensation was rapid with resultant solidification of the product. This was dissolved in conc. sulfuric acid and poured into water. The crude crystal product separated and was recrystallized out of alcohol or dil. hydrochloric acid to constant melting point.

V. Products by Other Reactions.

In this section, on account of its miscellaneous character, the experimental matter is included in the discussion of each particular reaction.

Di-iodo-ethyl Sulfide, -sulfoxide, and -sulfone.—The replacing of the chlorine atoms is easily carried out in each case by refluxing for 2 hours with an alcoholic solution of sodium iodide. The iodo compounds are obtained in good yields. They are much less soluble in water and alcohol than the corresponding chloro compounds. It is reported that Grignard used the di-iodo-ethyl sulfide as the basis of a test for mustard gas. He passed air supposed to contain the latter through a solution of potassium iodide in water and a resultant yellowish precipitate showed a dangerous concentration of mustard gas.

The reactions involved in the preparation of the iodo derivatives are evidently

$$S(CH_2CH_2Cl)_2 + 2NaI \longrightarrow S(CH_2CH_2I)_2 + 2NaCl$$
$$OS(CH_2CH_2Cl)_2 + 2NaI \longrightarrow OS(CH_2CH_2I)_2 + 2NaCl$$
$$O_2S(CH_2CH_2Cl)_2 + 2NaI \longrightarrow O_2S(CH_2CH_2I)_2 + 2NaCl$$

After the refluxing was over the alcohol solution and the separated crystals were poured into cold water. The di-iodo-ethyl sulfide separated in brown solid lumps, becoming yellowish white on shaking with sodium sulfite solution. Recrystallized twice out of alcohol the melting point remained at 55–60°. This substance darkened slowly at room temperature and at elevated temperatures rapidly became black. It is insoluble in water, very slowly hydrolyzed by alkali, only slightly soluble in cold and moderately in hot alcohol. The determination of iodine by decomposition with sodium ethylate and weighing as silver iodide gave 75.09% and 74.83%, calc. 74.27%.

The di-iodo-ethyl sulfoxide was obtained first as brown crystal product but after recrystallization out of alcohol became almost white and melted constant at 104.5° (corr.). It is easily soluble in hot alcohol but only moderately so in hot water. It crystallizes from water in small needles. Analysis gave 70.45% and 70.81% iodine, calc. 70.95%.

Di-iodo-ethyl sulfone was obtained as a white crystal product, recrystallizing out of alcohol in beautiful fine needles melting at 203° after softening at 198°. It was practically insoluble in water and cold alcohol and only moderately soluble in hot alcohol. It was the most stable of the iodo-derivatives. Analysis gave 68.46 and 68.14% iodine, calc., 67.91%.

Bis-β-thio-ethyl Acetate,[1] $S(CH_2CH_2OOCCH_3)_2$.—This compound,

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[1] It is impossible that the oil which Clarke (*J. Chem. Soc.*, 101, 1586 (1912)), observed could have been this diacetate, for it would have been completely hydrolyzed in his procedure.

which is the diacetate of the "mustard residue," $S(CH_2CH_2)_2$, was obtained only with considerable difficulty. Several attempts to prepare it by the reaction of sodium acetate on dichloro-ethyl sulfide in alcohol solution failed, owing to hydrolysis and alcoholysis. The sodium chloride separated and the odor of ethyl acetate was distinct but none of the desired product was obtained. It was found that the desired reaction took place smoothly and in good yield if carried out in glacial acetic acid solution:

$$S(CH_2CH_2Cl)_2 + 2NaOOCCH_3 \longrightarrow S(CH_2CH_2OOCCH_3)_2 + 2NaCl$$

Thus 15 g. of anhydrous sodium acetate was heated with 13 g. of dichloroethyl sulfide in 50 g. of glacial acetic acid on a steam bath for 6 hours. The sodium chloride was filtered off and the oil distilled *in vacuo*. After taking off the acetic acid up to 100° at 30 mm. the rest came over practically constant at 155–6° at 20 mm. d^{20}, 1.132; $n^{22.5}$ 1.4720. This did not freeze at —20°. It is rapidly hydrolyzed by water. Advantage was taken of this in checking the composition.

1.4492 g. of diacetate was heated on a steam bath with 150 cc. of 0.1124 *N* potassium hydroxide solution for 2 hours. The excess of alkali was found by titration to be 25.0 cc.; whence the alkali used was 0.01405 mole. Theory requires 0.01407 mole according to the equation

$$S(CH_2CH_2OOCCH_3)_2 + 2KOH \longrightarrow S(CH_2CH_2OH)_2 + 2KOOCCH_3.$$

Miscellaneous Reactions.

Finally there have been a number of other reactions more or less superficially investigated but, on account of lack of time, without isolating the derivatives which are assumed.

Satisfactory evidence has been obtained to show that dichloro-ethyl sulfide forms sulfonium compounds. Thus a solution of 0.2 g. of the sulfide with 0.7 g. of methyl iodide in 20 cc. of 70% alcohol had originally at 50° in a certain cell a resistance of 2100 ohms but after 4 hours at this temperature the resistance had dropped to 8 ohms. This great rise in conductivity can only be explained by the formation of a strong electrolyte, such as a sulfonium iodide, in the solution. Neither the rapidity of the rise in conductance nor the actual amount of the rise could be explained by hydrolysis. This was apparent from parallel experiments in which the dichloro-ethyl sulfide was hydrolyzed not by water, as would have to be the case above, but by alcoholic sodium hydroxide.

The Friedel-Craft's reaction between dichloro-ethyl sulfide and benzene or toluene in the presence of aluminum chloride has been found to proceed smoothly and to yield waxy solids. Several attempts to prepare the Grignard reagent from dichloro-ethyl sulfide failed, as did also an attempt to remove the chlorine by sodium in absolute ether as in the Wurtz synthesis.

In closing it is desired to direct attention to the manifold variations among these derivatives, their interesting possibilities and the wide opportunities for further research in this field.

Conclusions.

The reactivity of the chlorine atoms in dichloro-ethyl sulfide and its oxidation products has been demonstrated. The study of this reactivity has led to several new types of derivatives. Compounds of the type, $RSCH_2CH_2SCH_2CH_2SR$, were investigated where "R" was either aromatic or aliphatic. The remarkable stability of the sulfur-carbon chains has appeared of general nature. Of the structure, $(ROCH_2CH_2)_2S$ it was found that only those products could be obtained where "R" is an aromatic radical. Thus it seems that the stability of this structure is quite dependent on the nature of the radical "R." The tendency towards the formation of a heterocyclic 6-membered ring seems especially strong. This is brought out not only in the thiazan and sulfonazan condensations, but also in the formation of the substances diethylene disulfide, $S<(CH_2CH_2)_2>S$ and diethylene sulfide-sulfone $S<(CH_2CH_2)_2>SO_2$. The rapidity of hydrolysis of the diacetate, $(CH_3COOCH_2CH_2)_2S$, which may be regarded as 2 molecules of ethyl acetate linked together by the replacement of a β-hydrogen atom in each ethyl group by one sulfur atom, points out clearly the decrease in esterifying power effected by such substitution.

Physiological Effects.

A large number of the compounds prepared have been submitted to Dr. E. K. Marshall, Jr., and Mr. J. W. Williams, Jr., for study in the Pharmacological Laboratory of Washington University, St. Louis. We are indebted to them for the following brief summary of their findings. They will publish a more complete report in the *Journal of Pharmacology and Experimental Therapeutics*.

"In view of the related structure of these compounds to the highly physiologically active *dichloro-ethyl sulfide*, it is interesting to examine their physiological properties. The slight solubility of most of the compounds in water, and sometimes even in alcohol or olive oil has rendered this extremely difficult. A number of the compounds have had to be omitted entirely on account of their being so nearly insoluble in water and in olive oil.

"*Mustard gas* is a very active skin irritant, but the susceptibility of different individuals varies widely. *Dichloro-ethyl sulfoxide* produced mild erythema in one susceptible individual only, and does not appear to possess the typical skin irritant action of *mustard gas*. *Dichloro-ethyl sulfone* in aqueous alcoholic, or olive oil solution, produces an effect on the skin which appears to be similar in all respects to that produced by *mustard gas*. Typical vesicles with edema, and erythema were produced with a 5% alcoholic solution. A 1% solution in olive oil produced a positive reaction in only one out of four individuals tried. It appears, therefore, to be less active than the sulfide. The *di-iodo-ethyl sulfoxide* resembled the corresponding chlorine compound, giving a slight erythema in one individual. *Di-iodo-ethyl sulfoxide* is very insoluble but a 0.5% solution in alcohol produced positive reactions in two out of four individuals tried. The di-acetate derivative applied as the pure oil produced mild reactions in all individuals tried. It is much less active than mustard gas. The following compounds in 1% solution in olive oil produced no reaction when applied to the skin of two individuals who were very susceptible to mustard gas, and the other compounds mentioned above:

$$(EtSCH_2CH_2)_2SO_2 \text{ and } p\text{-}H_3CC_6H_4N<(CH_2CH_2)_2>SO_2.$$

"The following produced no effect in 2% solution in olive oil:

$(EtSCH_2CH_2)_2S$, $(PrSCH_2CH_2)_2SO_2$, $(BuSCH_2CH_2)_2SO_2$, $(i\text{-}BuSCH_2CH_2)_2SO_2$, $(PhOCH_2CH_2)_2S$, $(PhOCH_2CH_2)_2SO_2$, $(PhSCH_2CH_2)_2S$ and $PhN<(CH_2CH_2)_2>SO_2$.

"All substances were tested in saturated aqueous solution for antiseptic or bactericidal properties against *bacillus coli* and *staphylococcus aureus.* The great majority showed absolutely no indication of any antiseptic or bactericidal power, a few showed some slight antiseptic power; and $(ClCH_2CH_2)_2SO_2$ and $(ICH_2CH_2)_2SO_2$ killed the organisms in 24 hours, but not in one hour. Further investigation revealed that the antiseptic properties of these substances were not of a high order. Incidentally these are among the most toxic of the derivatives for animals, and both irritate the skin.

"The compounds were dissolved in olive oil and the toxicity tested by subcutaneous injection into white mice. The *di-iodo-ethyl sulfone* and *dichloro-ethyl sulfone* are the most toxic of the compounds investigated, the former being considerably more toxic than the latter. The other compounds can be arranged in the order of their toxicity as follows:

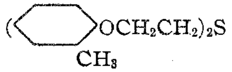
$(ClCH_2CH_2)_2SO$, $(ICH_2CH_2)_2SO$, $(EtSCH_2CH_2)_2SO_2$, $(PrSCH_2CH_2)_2SO_2$, $(BuSCH_2CH_2)_2SO_2$, $(i\text{-}BuSCH_2CH_2)_2S$.

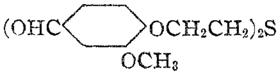
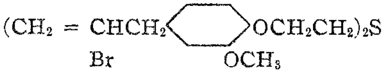
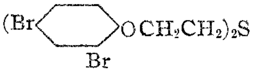
The following compounds are all less toxic than the above, but the fatal dose was not determined:

$(EtSCH_2CH_2)_2S$, $(CH_3CO_2CH_2CH_2)_2S$, $(PhOCH_2CH_2)_2S$, $(PhOCH_2CH_2)_2SO_2$, $(PhSCH_2CH_2)_2S$, $PhN<(CH_2CH_2)_2>SO_2$ and $p\text{-}CH_3C_6H_4N<(CH_2CH_2)_2>SO_2$."

Summary.

The following new compounds have been prepared:—

Name.	Formula.	M. p.
Bis(β-chloro-ethyl) sulfoxide...........	$(ClCH_2CH_2)_2SO$	109.5°
Bis(β-chloro-ethyl) sulfone............	$(ClCH_2CH_2)_2SO_2$	56.0°
Bis(β-iodo-ethyl) sulfide...............	$(ICH_2CH_2)_2S$	55–60°
Bis(β-iodo-ethyl) sulfoxide............	$(ICH_2CH_2)_2SO$	104.5°
Bis(β-iodo-ethyl) sulfone..............	$(ICH_2CH_2)_2SO_2$	203°.0
Bis(β-phenyl-mercapto-ethyl) sulfide....	$(PhSCH_2CH_2)_2S$	57.5°
Bis(β-phenyl-mercapto-ethyl) sulfoxide..	$(PhSCH_2CH_2)_2SO$	121.0°
Bis(β-phenyl-mercapto-ethyl) sulfone...	$(PhSCH_2CH_2)_2SO_2$	104.5°
Bis(β-phenyl-sulfinyl-ethyl) sulfoxide...	$(PhSOCH_2CH_2)_2SO$	161°.0
Bis(β-phenyl-sulfinyl-ethyl) sulfone....	$(PhSOCH_2CH_2)_2SO_2$	164°.0
Bis(β-phenyl-sulfonyl-ethyl) sulfone....	$(PhSO_2CH_2CH_2)_2SO_2$	235°.0
Bis(β-phenoxy-ethyl) sulfide............	$(PhOCH_2CH_2)_2S$	54.2°
Bis(β-phenoxy-ethyl) sulfone...........	$(PhOCH_2CH_2)_2SO_2$	108.0°
Bis(β-*p*-cresoxy-ethyl) sulfide..........	$(p\text{-}CH_3.C_6H_4.OCH_2CH_2)_2S$	78.0°
Bis(β-*p*-cresoxy-ethyl) sulfone..........	$(p\text{-}CH_3.C_6H_4.OCH_2CH_2)_2SO_2$	120.0°
Bis(β-*o*-cresoxy-ethyl) sulfide..........	 $(\underset{CH_3}{C_6H_4}OCH_2CH_2)_2S$	46.5°
Bis(β,α-naphthoxy-ethyl) sulfide.......	$(\alpha\text{-}C_{10}H_7.OCH_2CH_2)_2S$	94.5°

Name.	Formula.		M. p.
Bis(β,β-naphthoxy-ethyl) sulfide	$(\beta\text{-}C_{10}H_7.OCH_2CH_2)_2S$		129.0°
Bis(β,β-naphthoxy-ethyl) sulfone	$(\beta\text{-}C_{10}H_7.OCH_2CH_2)_2SO_2$		151.0°
Bis(β-vanilloxy-ethyl) sulfide			131.5°
Bis(β-eugenoxy-ethyl) sulfide			113.5°
Bis(β-tribromo-phenoxy-ethyl) sulfide			118.5°
Bis(β-butyl-mercapto-ethyl) sulfide	$(BuSCH_2CH_2)_2S$	b. p. 222–3°	17.5°
Bis(β-butyl-mercapto-ethyl) sulfoxide	$(BuSCH_2CH_2)_2SO$		25.0°
Bis(β-butyl-mercapto-ethyl) sulfone	$(BuSCH_2CH_2)_2SO_2$		73.7°
Bis(β-butyl-sulfinyl-ethyl) sulfoxide	$(BuSOCH_2CH_2)_2SO$		196°.0
Bis(β-butyl-sulfinyl-ethyl) sulfone	$(BuSOCH_2CH_2)_2SO_2$		171.0°
Bis(β-butyl-sulfonyl-ethyl) sulfone	$(BuSO_2CH_2CH_2)_2SO_2$		266.5°
Bis(β-ethyl-mercapto-ethyl) sulfide	$(EtSCH_2CH_2)_2S$	b. p. 173–5°	17.0°
Bis(β-ethyl-mercapto-ethyl) sulfone	$(EtSCH_2CH_2)_2SO_2$		64.0°
Bis(β-ethyl-sulfonyl-ethyl) sulfone	$(EtSO_2CH_2CH_2)_2SO_2$		223.0°
Bis(β-methyl-mercapto-ethyl) sulfone	$(MeSCH_2CH_2)_2SO_2$		77.0°
Bis(β-propyl-mercapto-ethyl) sulfide	$(PrSCH_2CH_2)_2S$	b. p. 193–5°	27.5°
Bis(β-propyl-mercapto-ethyl) sulfone	$(PrSCH_2CH_2)_2SO_2$		75.5°
Bis(β-propyl-sulfonyl-ethyl) sulfone	$(PrSO_2CH_2CH_2)_2SO_2$		254°.0
Bis(β-*iso*butyl-mercapto-ethyl) sulfone	$(i\text{-}BuSCH_2CH_2)_2SO_2$		94.2°
Bis(β-*sec.*-butyl-mercapto-ethyl) sulfone	$((sec.)BuSCH_2CH_2)_2SO_2$		15.0°
Bis(β-amyl-mercapto-ethyl) sulfide	$(AmSCH_2CH_2)_2S$		20.0°
Bis(β-amyl-mercapto-ethyl) sulfone	$(AmSCH_2CH_2)_2SO_2$		91.0°
4-Phenyl-1,4-thiazan	$Ph.N<(CH_2CH_2)_2>S$		108–111°
4-Phenyl-1,4-sulfanazan	$Ph.N<(CH_2CH_2)_2<SO$		123.5°
4-*p*-Cresyl-1,4-sulfonazan	$p\text{-}CH_3.C_6H_4N<(CH_2CH_2)_2>SO_2$		136.5°
4-*o*-Cresyl-1,4-sulfonazan	$o\text{-}CH_3.C_6H_4.N<(CH_2CH_2)_2>SO_2$		135.0°
Bis(β-thio-ethyl acetate)	$(CH_3COOCH_2CH_2)_2S$	b. p. 155–6°	(20 mm.)

BALTIMORE, MD.

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, HARVARD UNIVERSITY.]

ON THE NONEXISTENCE OF VALENCE AND ELECTRONIC ISOMERISM IN HYDROXYLAMMONIUM DERIVATIVES.

BY ARTHUR MICHAEL.

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In 1894, Dunstan and Goulding[1] showed that trimethyl-hydroxylammonium iodide is the sole substitution product formed in the action of methyl iodide on an excess of hydroxylamine; later,[2] that the base set free from that salt represents a hydrated trimethylamine oxide. Further, that methyl iodide unites at ordinary temperature with the product to give the iodide of an ammonium base, to which they assigned the structure

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[1] *Proc. Chem. Soc.*, **10**, 138 (1894); *Chem. News*, **69**, 308 (1894).

[2] *J. Chem. Soc.*, **69**, 839 (1896); **75**, 792, 1005 (1899).