as is observed when oxygen or air is used) would militate against Formula C.[13]

Summary

The following reaction takes place between peroxides and the Grignard reagent: ROOR + R'MgX ⟶ ROR' + ROMgX. The unusual quantities of diphenyl formed in the reaction between diethyl peroxide and phenylmagnesium bromide suggest a correspondence in structure between this peroxide and azo compounds.

AMES, IOWA

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF EDGEWOOD ARSENAL, UNITED STATES CHEMICAL WARFARE SERVICE,[1] AND JOHNS HOPKINS UNIVERSITY]

REACTIONS OF β,β'-DICHLORO-ETHYL SULFIDE WITH AMINO COMPOUNDS

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Four theories have been advanced to explain the remarkable vesicant action of β,β'-dichloro-ethyl sulfide. Each of these fits certain facts but none is entirely satisfactory. The present investigation was undertaken to obtain more information about the reactions of this compound with substances containing the amino group, since amino compounds are important constituents of living tissue. It was hoped to prepare derivatives from the more complicated amino acids but it seemed best to begin with a more thorough study of reactions with simpler amino compounds.

The present investigation comprises the following. (1) A further study of the thiazanes, $S<(CH_2CH_2)_2>NR$, from primary amines. (2) Investigation of the new thiazane-1-oxides, $OS<(CH_2CH_2)_2>NR$. (3) Extension of the preparation of thiazane-1-dioxides, $O_2S<(CH_2CH_2)_2>NR$, to aliphatic amines. (4) A study of the reactions of β,β'-dichloro-ethyl sulfide, sulfoxide and sulfone with secondary aliphatic amines to form $S(CH_2CH_2NR_2)_2$, $OS(CH_2CH_2NR_2)_2$ and $O_2S(CH_2CH_2NR_2)_2$. Among these, the sulfide derivative from dimethylamine lost one amine grouping in a surprising way to form the unsaturated compound $(CH_3)_2NCH_2CH_2SCH:CH_2$. (5) The preparation of salts of quaternary bases, $S(CH_2CH_2NR_3Cl)_2$, $OS(CH_2CH_2NR_3Cl)_2$ and $O_2S(CH_2CH_2NR_3Cl)_2$. (6) A study of the reactions of β,β'-dichloro-ethyl sulfone with free amino acids instead of their esters, to form such compounds as $O_2S<(CH_2CH_2)_2>NCH(COOH)CH_2C_6H_5$.

[13] It is probable that an aid to the solution of this problem will be found in some studies now in progress on the reaction between sulfenic esters (R—S—O—R) and the Grignard reagent.

[1] Published by permission of the Chief of the Chemical Warfare Service.

[2] From the dissertation of W. E. Lawson, Johns Hopkins University, 1925.

Hydrochlorides of the majority of the derivatives were prepared. Platinum salts were made of all the quaternary bases. The sodium salt was made of the condensation product from β,β'-dichloro-ethyl sulfone and phenylalanine.

Historical Part

Probably the most generally accepted theory is that the vesicant action of β,β'-dichloro-ethyl sulfide is due to the formation of free hydrochloric acid within the cell. This was suggested by E. K. Marshall[3] and others[4] but has been opposed by a number of investigators. Warthin and Weller[5] took exception to it from a pathological standpoint, Peters and Walker[6] showed that the rate of hydrolysis of lipoid-soluble substituted diethyl sulfides is not a critical factor and Lawson and Dawson[7] found no relation between the distribution ratio of a number of chlorine derivatives and their vesicant action. Their results on a number of homologous compounds arranged according to increasing distribution coefficients are given in Table I.

TABLE I

RELATION BETWEEN DISTRIBUTION COEFFICIENT AND VESICANT ACTION

Compound	Vesicant action	Distribution coefficient	Rate of hydrolysis in water, 20°	Rate of hydrolysis in alkali
Dichloro-ethyl sulfoxide	None	0.3	Little, if any	30 min., complete
Dichloro-ethyl sulfone	Severe	6	Little, if any	30 min., complete
Dichloro-ethyl sulfide	Severe	86	50 min., 90%	30 min., complete
Tetrachlorodiethyl sulfide	None	146	50 min., 10% of β-chlorine	40 min., all of β-chlorine

On the basis of these data, definite limits must be set for lipoid and water solubilities as well as rates of hydrolysis in order to explain the action of the two vesicant compounds by the liberation of hydrochloric acid within the cell. The existence of such limits appears doubtful. It must not be forgotten, however, that Lillie, Clowes and Chambers[8] obtained some important results by injecting starfish eggs with hydrochloric acid in concentrations equivalent to those freed by the hydrolysis of different amounts of dichloro-ethyl sulfide injected into other eggs. The results obtained with the hydrochloric acid were similar to those with dichloro-ethyl sulfide, but the onset of the symptoms was immediate. It may be that the absence of appreciable amounts of buffer salts in marine animals renders them more susceptible to damage by acid. However, until their

[3] Marshall, *J. Am. Med. Assoc.*, **13**, 684 (1919).

[4] *J. Pharmacol.*, **12**, 265 (1918).

[5] Warthin and Weller, "The Medical Aspects of Mustard Gas Poisoning," C. V. Mosby Co., St. Louis, **1919.**

[6] Peters and Walker, *Biochem. J.*, **17**, 260 (1923).

[7] Lawson and Dawson, Chemical Warfare Report, **1924.**

[8] Lillie, Clowes and Chambers, *J. Pharmacol.*, **14**, 75 (1819).

results are satisfactorily explained, the hydrochloric acid theory cannot be disregarded even though it does not seem to fit all the facts.

The theory advanced by Flury[9] involving the reactivity of the sulfur atom lost much of its probability when it was found that the sulfoxide containing quadrivalent sulfur is non-vesicant. The idea that the unlooked-for reaction of β,β'-dichloro-ethyl sulfide with sodium alcoholate to give the highly toxic divinyl sulfide[10,11a] might have a bearing on the vesicant action was discounted by the later investigations of Bales and Nickelson[11b] who found that the yield of divinyl sulfide decreases markedly when the percentage of alcohol drops below 80, and of Lawson and Dawson[7] who obtained no trace of divinyl sulfide from dichloro-ethyl sulfide when using secondary sodium phosphate and sodium carbonate in 50% alcohol, which substances give hydrogen-ion concentrations approaching those in body tissues.

The discovery of the reaction of β,β'-dichloro-ethyl sulfide with primary amines to form compounds of the thiazane type was made by Clarke,[12] who prepared four substituted thiazanes, using methyl-, ethyl-, *iso*-amyl- and benzylamines. Davies[13] made the parent substance, 1,4-thiazane, by heating β,β'-dichloro-ethyl sulfide with an excess of alcoholic ammonia in a sealed tube. Helfrich and Reid[10] extended the reaction to include primary aromatic amines and found that β,β'-dichloro-ethyl sulfone reacts more readily than the sulfide with these amines to form the similar sulfonazane ring.

That ring formation is not limited to closure with the nitrogen atom was first shown by Clarke[14] who prepared 1,4-thioxane from β,β'-di-iodo-ethyl ether. Later, Cashmore[15] found that β,β'-dichloro-ethyl sulfoxide and sulfone give thioxane derivatives on hydrolysis, thereby exhibiting a much greater ease of ring formation than is shown by the sulfide, which forms the open-chain thiodiglycol. The actual isolation of the sulfoxide reaction product, 1,4-thioxane-1-oxide was recently accomplished by From and Ungar.[16]

Cashmore and McCombie[17] suggested that the vesicant action of β,β'-dichloro-ethyl sulfide might be due to the product formed by its reaction with the amino acids present in the skin, and prepared the condensation products of β,β'-dichloro-ethyl sulfide and sulfone with glycine ester.

[9] Flury, *Zentr. Expt. Med.*, **13**, 367 (1921).
[10] Helfrich and Reid, THIS JOURNAL, **42**, 1208 (1920).
[11] Bales and Nickelson, (a) *J. Chem. Soc.*, **121**, 2137 (1922); (b) **123**, 2486 (1923).
[12] Clarke, *ibid.*, **101**, 1583 (1912).
[13] Davies, *ibid.*, **117**, 297 (1920).
[14] Ref. 12, p. 1806.
[15] Cashmore, *J. Chem. Soc.*, **123**, 1738 (1923).
[16] From and Ungar, *Ber.*, **56**, 2286 (1923).
[17] Cashmore and McCombie, *J. Chem. Soc.*, **123**, 2884 (1923).

They secured an open-chain compound with the sulfide and a closed thiazane ring with the sulfone, $S(CH_2.CH_2.NHCH_2COOC_2H_5)_2$ and $O_2S<(CH_2.CH_2)_2>N.CH_2.COOC_2H_5$, and concluded that the bulky residue attached to the amino group hinders the formation of the ring compound, the tendency towards ring formation being considerably less with the sulfide than with the sulfone.

The fact that β,β'-dichloro-ethyl sulfide does not form a thiazane compound with glycine ester under the conditions employed by Cashmore and McCombie would seem to invalidate the theory that thiazane formation is a basis for the vesicant action of the compound. However, proof that reactions with amino acids do not take place *in vitro* is no positive assurance that these same reactions will not take place in the highly reactive and unstable equilibria within the living cell.

Discussion of Results

Reactions.—The relative ease of reaction of β,β'-dichloro-ethyl sulfide and sulfone, which has already been noted by Cashmore and McCombie, was confirmed by us. Addition of an alcoholic solution of any primary amine to a mixture of β,β'-dichloro-ethyl sulfone, sodium carbonate and absolute ethyl alcohol always produced sufficient heat of reaction to bring the alcohol to boiling within one or two minutes. The analogous reaction with the sulfoxide led to a slight rise in temperature, while none was detectable with the sulfide. The rates of reaction with secondary and tertiary amines were in the same order, as were also the yields secured. In regard to the stability of the derivatives, the positions of the sulfoxide and sulfide were reversed.

The formation of the thiazane-1-oxides was not expected in view of the failure of the sulfoxide to condense with glycine ester as shown by Cashmore and McCombie. Three compounds of this series were readily prepared, the methyl, ethyl and benzyl derivatives. An apparent upper limit to which compounds containing the :S:O radical may be heated is indicated by the grouping of four melting or decomposition points very close to 240°. The melting of compounds at this temperature is accompanied by the escape of gas in comparatively large amounts. No tests were made to determine whether or not this gas was oxygen, but its evolution is of especial interest when considered with the findings of Helfrich and Reid[10] that distillation of the sulfoxide gave the sulfide, but no sulfone.

The only mention in the literature of a reaction between β,β'-dichloro-ethyl sulfide and a secondary amine is that by Cashmore and McCombie[17] who secured condensation with potassium phthalimide and the sulfide but none when using the sulfoxide or sulfone. We have isolated 12 derivatives of the sulfide, sulfoxide and sulfone with secondary aliphatic amines including piperidine. A most unusual reaction was encountered

when the condensation of β,β'-dichloro-ethyl sulfide with dimethylamine was tried. An unsaturated compound was secured whose formula corresponds to the structure $CH_2{=}CHSCH_2CH_2N(CH_3)_2$. The reaction was carried out in a sealed tube and repeated a number of times, always with the same result. Yields were very low, the maximum being 7%, the main reaction going to form the completely unsaturated divinyl sulfide, which was identified by its boiling point and odor. Large amounts of dimethylamine were given off in the process of purification, either during the treatment with sodium hydroxide to free from water or, when this was omitted and the reaction mixture distilled directly, during the distillation Chloroform solutions of bromine were promptly decolorized without evolution of hydrogen bromide but secondary reactions accompanied with escape of hydrogen bromide took place when an attempt was made to isolate the bromine addition product. The isolation of the tetramethyl-β,β'-diamino derivative was not effected, but the escape of dimethylamine and the formation of divinyl sulfide point to its formation and subsequent decomposition. All the remaining reactions between the sulfide, sulfoxide and sulfone, and secondary aliphatic amines proceeded smoothly and gave good yields of the expected type. Piperidine reacted as readily as did the diethyl- and dipropylamines. The crystallization of the hydrochlorides of these compounds was rendered difficult by reason of their great solubility in absolute alcohol, ranging as high as 1 g. per cc.

The reactions with trimethylamine proceeded readily and gave good yields. With the sulfide and sulfoxide the reactions were carried out in sealed tubes, but the condensation product with the sulfone was precipitated almost quantitatively when an alcoholic solution of the two reactants was warmed in an open beaker for a few minutes.

Reactions with pyridine and quinoline took place with more difficulty and were complicated by excessive side reactions with formation of tar. No condensation product from quinoline and the sulfide could be isolated, tarry products only being formed. Complete crystallization required as long as two weeks. These compounds were deliquescent, very soluble in water, insoluble in ether, and were decomposed by alcohol or dil. sodium hydroxide solution into their original constituents. The chlorine could be precipitated quantitatively by silver nitrate solution. All the crude compounds were purple. The condensation of the sulfone with quinoline led us to attempt the same with quinaldine, but neither an addition product nor a ring closure through the hydrogen of the methyl group was secured.

The reaction of β,β'-dichloro-ethyl sulfide and sulfone with the ethyl ester of an amino acid (glycine ester) has been carried out by Cashmore and McCombie,[17] but as ester formation is not believed to be a feature of amino acids in protein molecules, direct condensation between the amino acid and the sulfone was attempted. The free acid, $O_2S<(CH_2CH_2)_2>$-

NCH_2COOH, described by Cashmore and McCombie was secured in small amount from the reaction between glycine and the sulfone, as rectangular needles with wedge-shaped ends, m. p. 177° (corr.), analysis showing 16.31 and 16.16% of sulfur; calcd., 16.58%. With phenylalanine reaction proceeded readily. The yield was large and the purity high. No condensation product was secured involving the free amino acids and the sulfide instead of the sulfone.

A variety of reactions was tried where apparently no condensation took place or where no product of the reaction could be isolated. No condensation could be brought about with amides; acetamide, oxamide, benzamide, urea, thio-urea and asparagine all failed to react with either the sulfide or the sulfone. No new derivatives were secured with hydrazine sulfate, hydroxylamine, semicarbazide hydrochloride, guanidine carbonate and phenylhydrazine, although evidence was secured that all but the first react to give more or less unstable condensation products. The completion of the reaction with phenylhydrazine and the sulfone leaves only a smoking, carbonaceous mass, while purification of the reaction product with the sulfide leads to formation of tar. Failure was also recorded in attempts to form a ring structure involving lead which it was hoped would take place, giving $S<(CH_2CH_2)_2>Pb<(CH_2CH_2)_2>S$. The Wurtz reaction with the sulfide and *iso*propyl iodide failed completely, only 2,3-dimethylbutane being formed.

Reaction of the sulfide and sulfone with aromatic compounds, such as *m*- and *p*-phenylenediamine and benzidine, gave amorphous compounds with purities ranging around 90%. These compounds were of extreme insolubility, only concd. sulfuric acid acting as a solvent and all were colored. It may be that condensations valuable as dyes could be obtained by proper sulfonation, but as our interest lay toward the physiological side no further work was done on them. Diphenylamine and α-naphthylamine failed to combine with the sulfide or sulfone and were recovered unchanged.

No sulfonium compound of the formula $(ClCH_2CH_2)_2SCH_3I$ could be isolated, although Helfrich and Reid[10] secured evidence of its formation based on conductivity measurements, and From and Ungar[16] have made di-iodides of the type $I_2S<(CH_2CH_2)_2>O$ from thioxane.

Luminescence under Ultraviolet Light

About 50 of the new bases and hydrochlorides were submitted to Professor H. G. Byers, Cooper Union, New York City, who very kindly tested them for luminescence and phosphorescence under the influence of ultraviolet light screened from visible light by a filter of nickel glass (Wood screen). His report is as follows.

(1) None of the samples is phosphorescent; (2) β,β'-dichloro-ethyl sulfide, sulfone and sulfoxide are not luminescent; (3) of the samples submitted, 16 show effect of

the ultraviolet light as shown in Table II; (4) none of the other samples shows more than a trace of luminescence and in most cases not even a trace; (5) it would seem that all the free bases of the SO and SO_2 types are luminescent in the ultraviolet. Few of the sulfide compounds are luminescent and only two of the hydrochlorides. In both cases the luminescence may be due to free base or other impurity.

TABLE II

LUMINESCENCE UNDER ULTRAVIOLET LIGHT

Sample	Luminescence	Sample	Luminescence
$Me\text{-}N<(CH_2CH_2)_2>SO_2$	White	$(Q\text{-}(Cl)CH_2CH_2)_2>SO_2$	Deep purple on one side; dark red on dense portion shading to orange red on thin portion of deposit on other side
$n\text{-}Pr\text{-}N<(CH_2CH_2)_2>SO_2$	White, distinct blue fluorescence		
$iso\text{-}Bu\text{-}N<(CH_2CH_2)_2>SO_2$	Brilliant white		
$n\text{-}Bu\text{-}N<(CH_2CH_2)_2>SO_2.HCl$[a]	Lilac blue		
$C_6H_5CH_2N<(CH_2CH_2)_2>SO_2$	Brilliant white		
$n\text{-}Pr_2\text{-}N(CH_2CH_2)_2>SO_2$	White	$Me\text{-}N<(CH_2CH_2)_2>SO$	Brilliant white
$n\text{-}Bu_2\text{-}N(CH_2CH_2)_2>SO_2$	Brilliant white, bluish tinge	$Et\text{-}N<(CH_2CH_2)_2>SO$	White
$(C_5H_{10}NCH_2CH_2)_2>SO_2$	White	$(Et_2\text{-}NCH_2CH_2)_2>SO$	Yellow white, greenish fluorescence
$(Py\text{-}(Cl)CH_2CH_2)_2>SO_2$	Faint yellow		
$(C_5H_{10}NCH_2CH_2)_2>S$[a]	Brilliant dark yellow	$(n\text{-}Pr_2\text{-}NCH_2CH_2)_2>SO$	Yellow, greenish fluorescence
		$n\text{-}Pr\text{-}N<(CH_2CH_2)_2>S.HCl$[a]	

Me = methyl; Pr = propyl; Bu = butyl; Py = pyridyl; Q = quinolyl.

[a] May be due to impurities, as the compounds in question may have been partly decomposed.

Toxicities of Representative Compounds

None of the compounds prepared appears to be vesicant. This is in accord with the results of Marshall and Williams[18] on thiazanes. Tests were conducted with the undiluted bases, first on the bellies of guinea pigs, then on the forearms of men, all without result. The only compound at all vesicant was *bis*(β-thio-ethyl acetate), described by Helfrich and Reid, which was secured as a by-product from one of the experiments. This compound, applied to the skin undiluted, caused marked redness and swelling which passed away in about 24 hours. It was vesicant on but one individual, and he is particularly sensitive to dichloro-ethyl sulfide.

Toxicity tests were carried out by Miss Marjorie Allen, assistant pathologist at Edgewood Arsenal, using representative compounds from each group. Her results are based on the lethal dose by subcutaneous injection in white mice of a solution of the hydrochloride in physiological salt solution. For benzyl derivatives of thiazane, its oxide and dioxide, and the phenylalanine derivative of thiazane dioxide, together with *bis*(β-diethyl-amino-ethyl)sulfide, -sulfone and -sulfoxide, the lethal dose is above 200 mg. per kg. of body weight. The trimethylammonium salts of the sulfide, sulfoxide and sulfone show more toxicity, the doses being as follows.

Compound	$[(CH_3)_3N(Cl)CH_2CH_2]_2S$	$[(CH_3)_3N(Cl)CH_2CH_2]_2SO$	$[(CH_3)_3N(Cl)CH_2CH_2]_2SO$
Lethal dose, mg./kg. body weight	160	240	50

[18] Marshall and Williams, *J. Pharmacol.*, **16**, 259 (1920).

These are the first compounds to be prepared from β,β'-dichloro-ethyl sulfide by reactions involving the chlorine atoms in which these are not removed. They can give a chloride ion but not hydrochloric acid.

According to Marshall and Williams,[18] the toxicities of the parent substances are

Compound	$(ClCH_2CH_2)_2S$	$(ClCH_2CH_2)_2SO$	$(ClCH_2CH_2)_2SO_2$
Lethal dose, mg./kg.	125	125	105

It will be noted that in both our results and those of Marshall and Williams the toxicity of the more reactive sulfone is greatest, and that the sulfide and sulfoxide have the same order of toxicity. There is apparently a parallel between reactivity and toxicity with these compounds which extends to their derivatives. The high toxicity of the trimethylamine addition product of the sulfone is remarkable considering that it is a water-soluble chloride.

The amino acid condensation product with β,β'-dichloro-ethyl sulfone has low toxicity, in keeping with the other sulfone-azanes. However, it may be well to point out that the formation of toxic condensation products with the amino acids within the cell is by no means a vital part of the theory; the important part is the ability of the poison to react with compounds within the cell and thereby disturb its balance of metabolism. In this connection it was of interest to discover that no thiazane compound or other condensation product could be isolated when the $\alpha,\alpha',\beta,\beta'$-tetrachloro-ethyl sulfide was used instead of the β,β'-dichloro compound. Nor did the α,α'-dichloro-ethyl sulfide react with two molecules of benzylamine to form the α,α'-diamino compound. Both of these compounds are non-vesicant. The objection to the lack of vesicant action of β,β'-dichloro-ethyl sulfoxide, which is apparently about as reactive as the vesicant sulfide, can be explained on the basis of its low distribution ratio, which for ether: water is but 0.3. The low lipoid solubility of the sulfoxide would prevent its absorption through the skin; if it were injected subcutaneously, its greater solubility in the aqueous solutions of the body would cause a prompt removal from the site of the injection.

Experimental Part

Preparation of Thiazanes, Thiazane Oxides and Dioxides

All of the thiazanes, thiazane oxide and thiazane dioxide compounds were prepared by the same general method, using only such individual variations as were necessary for the compound in question. The general procedure was as follows.

A solution of 0.25 mole of β,β'-dichloro-ethyl sulfide and 0.25 mole of the amine in 100 cc. of absolute ethyl alcohol was heated with 0.25 mole of anhydrous sodium carbonate in a 500cc., short-neck, Pyrex boiling flask having a reflux condenser attached. The flask was kept immersed in a bath of boiling water for four hours. The contents

were filtered hot, the insoluble residue was boiled twice with fresh absolute alcohol and the three filtrates were combined. Analyses of the residue showed the presence of from 95 to 98% of sodium chloride. The bulk of the alcohol in the filtrate was evaporated on the hot-plate, water and hydrochloric acid were added and the solution, after it had cooled, was extracted two or three times with ether in order to remove any unchanged sulfide. The acid solution was made strongly alkaline with stick potassium hydroxide and the thiazane compound which separated was extracted with ether. The ether solution was dried (usually overnight, using stick potassium hydroxide to remove the water), decanted and distilled. After removal of the ether and the remainder of the alcohol, the residue in the distilling flask was fractionated three or four times under a pressure of 10-20 mm., or until a constant boiling point was secured. When the boiling point of the amine was low, as with the *normal* and *iso*propylamines, sealed tubes of about 150cc. capacity were used, fused sodium acetate took the place of the sodium carbonate, and the volume of alcohol was reduced from 100 cc. to 30 cc. The tubes were heated in a bomb furnace at 110° for six hours. After they had been opened and their contents washed out with absolute alcohol, the procedure as already outlined was carried out. Hydrochlorides were made by dissolving the pure bases in dry toluene and passing in dry hydrogen chloride, filtering off the precipitated hydrochloride and recrystallizing from dil. alcohol.

In place of absolute alcohol, 80–95% alcohol was used as a solvent in the preparation of the thiazane-1-oxides. The mixtures were heated for three hours on the water-bath. In the purification of the products the treatment with dilute acid was omitted and recrystallization of the hydrochlorides was relied upon. Otherwise, the method was that already described.

The preparation of the thiazane dioxides was carried out in a similar manner, but the time of heating was much reduced. Even the volatile amines could be handled without sealed tubes. For the methyl derivative an alcoholic solution of methylamine was added slowly through the condenser to a mixture of the solution of the sulfone in alcohol and sodium carbonate, the flask being immersed in ice water. After the complete addition of the amine, the flask was removed from the ice water and, when reaction had apparently ceased, heated for one hour on the water-bath. The isolation and purification of the lower members of the thiazane dioxide series followed the method already given for the thiazanes. With the higher members, purification was accomplished by forming the hydrochloride in dry toluene and recrystallizing three to five times, then setting free the base.

The corrections of the boiling points and melting points were obtained by comparison with a set of Anschütz thermometers, calibrated by the United States Bureau of Standards.

Thiazanes, $S<(CH_2CH_2)_2>NR$.—All of the thiazanes are colorless, mobile oils with densities less than 1.0; *n*-amyl thiazane; d_4^4, 0.9485; d_4^{25}, 0.9332. The propylthiazanes are water soluble, the butyl only very slightly so, and the *n*-amyl derivative is apparently insoluble. The low purity of the *n*-propyl compound was due to the small amount of *n*-propylamine on hand, the small yield of thiazane preventing a more careful purification. A nitrogen analysis on this compound gave percentages of 9.11 and 9.34; calcd., 9.65.

Thiazane Oxides, $OS<(CH_2CH_2)_2>NR$.—The thiazane-1-oxides are colorless, sirupy oils, miscible with water and alcohol and slightly soluble in ether. Only the methyl derivative crystallized, and this compound

TABLE III

ALKYL THIAZANES, $S<(CH_2CH_2)_2>NR$, AND THEIR HYDROCHLORIDES, B.HCl; ANALYSES AND PROPERTIES

Alkyl, R	Sulfur, % Calcd.	Sulfur, % Found	M. p. (corr.) °C.	B. p. (corr.) °C. (Pressure, mm.)	Form
n-Propyl	22.08	21.26, 21.12		82.5–83.5(12)	
hydrochloride			202		Rectangular plates
*iso*Propyl	22.08	22.02, 21.91		74.5–75(9)	
hydrochloride			184–184.5		Hexagonal plates
n-Butyl	20.13	19.97, 19.91		118(33)	
				101–102(19)	
*iso*Butyl	20.13	19.68, 19.59		93(17)	
n-Amyl	18.50	18.08, 18.08		119(15)	
				104(7)	
Benzyl[a]	16.59	16.58, 16.45		152.5(10)	
hydrochloride	13.91	13.62, 13.61	218		Rhombic plates

[a] First prepared by Clarke[12] who gave the boiling point as 154° (13 mm.).

required several days for crystallization. No crystals of the other derivatives had formed even after several weeks in a vacuum desiccator. The density of the benzyl derivatives was found to be slightly above 1.11. All the hydrochlorides decompose at their melting points, the methyl derivative with evolution of gas. When the heating of benzyl sulfoxazane hydrochloride is continued beyond the melting point it decomposes further at 236° and gives off a considerable quantity of gas.

TABLE IV

ALKYL THIAZANE-1-OXIDES, $OS<(CH_2CH_2)_2>NR$ AND THEIR HYDROCHLORIDES, B.HCl; ANALYSES AND PROPERTIES[a]

Alkyl, R	Sulfur, % Calcd.	Sulfur, % Found	M. p. (corr.) °C.	Form
Methyl			52	Long, colorless needles
hydrochloride	18.89	18.61, 18.60	241	
Ethyl				
hydrochloride	17.45	17.40, 17.61	177.5	Needles
Benzyl				
hydrochloride	13.10	13.11, 13.18	224	Thin, rectangular plates

[a] All three compounds decomposed without boiling.

Thiazane Dioxides, $O_2S<(CH_2CH_2)_2>NR$.—The thiazane-1-dioxides somewhat resemble the corresponding 1-oxides in their difficulty of crystallization. The liquids before crystallization are colorless oils. All of the compounds are soluble in alcohol and ether, but only the methyl and ethyl derivatives are water-soluble. The butyl-, amyl- and benzyl-thiazane-dioxides cannot be distilled without decomposition at 10 mm.-pressure. The low purity of the *iso*propyl derivative was due to the

small amount of sample prepared, only a small quantity of *iso*propylamine being available. Analyses of this compound for nitrogen gave 7.69%; calcd., 7.90%; of *n*-propyl-thiazane-1-dioxide, 7.73 and 7.69%; calcd., 7.90%. The benzyl derivative gave 6.09 and 6.15%; calcd., 6.22%.

TABLE V

ALKYL THIAZANE-1-DIOXIDES, $O_2S<(CH_2CH_2)_2>NR$ AND THEIR HYDROCHLORIDES, B.HCl; ANALYSES AND PROPERTIES

Alkyl, R, hydrochloride	Sulfur, % Calcd.	Sulfur, % Found	M. p. (corr.) °C.	B. p. (corr.) °C. (Pressure, mm.)	Form
Methyl			82	174.5–175(19)	Needles
	17.27	17.33, 17.16	>280		Hexagonal needles
Ethyl				175.5–176(19)	Needles
	16.06	15.90, 15.64	248–9		Needles
n-Propyl	18.09	18.36, 18.39		177.5–178.0(16)	Oil
			>225		Rect. needles
*iso*Propyl	18.09	17.45, 17.20		173.5(13)	Oil
			>225		Triang. needles
n-Butyl				Decomp.	Oil
	14.08	13.94, 13.90	195		Needles
*iso*Butyl	16.76	16.33, 16.13	45	Decomp.	Needles
			200.5		Hexagonal plates
n-Amyl			41.5		Thin plates
	13.26	13.11, 12.93	152		Needles
Benzyl	14.23	14.15, 14.01	76.5	Decomp.	
	12.25	11.92, 11.84	237–9		Prisms

Reactions with Secondary Amines

The preparation of the condensation products with secondary aliphatic amines was carried out in the same manner as with the corresponding primary amines, except that two molecular equivalents of secondary amine were used for each equivalent of sulfide, sulfoxide or sulfone. The purification of the condensation products was considerably more difficult because, with practically all, it necessitated conversion to the hydrochlorides and recrystallization of these. The hydrochlorides of the higher members were very soluble in absolute alcohol as well as water and usually came out of solution as oils unless considerable care was used in blending the solvents. They were insoluble in ether but usually slightly soluble in benzene.

The isolation of the lowest member of the sulfide series, *bis*(β-dimethylamino-ethyl) sulfide, was not effected, one amino group splitting out to give the unsaturated dimethyl-β-amino-ethylvinyl sulfide. In an effort to isolate the parent substance, the saturated derivative, the treatment of the crude product with acid and alkali was omitted, since the escape of dimethylamine and the development of the odor of divinyl sulfide were brought about by treatment with alkali, and instead the alcoholic solution was distilled directly. As the temperature rose, great quantities of dimethylamine were given off, and the usual products, divinyl sulfide and

dimethyl-β-amino-ethylvinyl sulfide, distilled. The fact that the odor of divinyl sulfide was not developed until treatment of the original solution with either alkali or heat indicates that the tetramethyl derivative is formed and that this compound is unstable, decomposing to give either the partially unsaturated dimethyl-β-amino-ethylvinyl sulfide or the completely unsaturated divinyl sulfide.

Dichloro-ethyl sulfoxide and sulfone reacted with all the secondary aliphatic amines to give the expected *bis*(β-dialkylamino-ethyl) derivatives, and the sulfide did the same for all of the secondary amines above dimethylamine.

All of the condensation products with dichloro-ethyl sulfide were colorless oils, soluble in organic solvents but almost insoluble in water except for the diethyl derivative, which had a solubility of about 0.1%. The density of the dipropyl compound was determined; d_4^4, 0.9007; d_4^{25}, 0.8855. The percentage of nitrogen was determined in dimethyl-β-amino-ethylvinyl sulfide and found to be 10.39 and 10.45; calcd., 10.68. No chlorine was found. This compound is included in Table VI with the other secondary amine derivatives of the sulfide. B^{II} represents the diacid base.

TABLE VI

bis(β-DIALKYLAMINO-ETHYL) SULFIDES, $(R_2NCH_2CH_2)_2S$ AND THEIR HYDROCHLORIDES, $B^{II}2HCl$; ANALYSES AND PROPERTIES

Alkyl, R	Sulfur, % Calcd.	Sulfur, % Found	M. p. (corr.) °C.	B. p. (corr.) °C. (Pressure, mm.)	Form
Methyl[a]	24.45	24.45, 24.52		168.5(763)	Unsaturated
Ethyl hydrochloride	10.50	10.69, 10.86	247	139–140(9)	Tiny plates
n-Propyl hydrochloride	11.11	11.39, 11.51	164.5	194(19)	Needles
n-Butyl hydrochloride	7.68	7.71, 7.81	130.5	205–206(10)	Silky needles
Piperidyl	12.51	12.91, 13.04		174.5–176(15)	

[a] Dimethylamino-ethylvinyl sulfide.

The sulfoxide derivatives were all oils which darkened considerably when heated even to 80°. The methyl and ethyl derivatives were slightly soluble in water, while the propyl was apparently insoluble. All were soluble in 95% alcohol, but only slightly so in ether. The hydrochloride of the dimethyl derivative was insoluble in absolute alcohol and only to the extent of about 8% in 80% alcohol. The hydrochloride of the corresponding ethyl derivative was very soluble in hot, but only slightly soluble in cold absolute alcohol. The hydrochloride of the *n*-propyl compound was very soluble in cold absolute alcohol and slightly soluble in benzene. Chlorine was determined in the hydrochlorides of the methyl and propyl derivatives by titration of their aqueous solutions.

Anal. *bis*(β-Dimethylamino-ethyl) sulfoxide. Calcd.: Cl, 22.07. Found: 22.07, 22.26.

bis(β-Dipropylamino-ethyl) sulfoxide. Calcd.: Cl, 18.79. Found: 18.89, 19.01.

TABLE VII

bis(β-DIALKYLAMINO-ETHYL) SULFOXIDES $(R_2NCH_2CH_2)_2SO$ AND THEIR HYDROCHLORIDES, $B^{II}2HCl$; ANALYSES AND PROPERTIES[a]

Alkyl, R	Sulfur, % Calcd.	Found	M. p. (corr.) °C.	Form
Methyl				Oil
hydrochloride	12.09	11.87, 11.81	234	Triang. or lozenge-shaped plates
Ethyl				
hydrochloride	9.98	10.02, 10.07	222	Needles
n-Propyl				
hydrochloride	8.40	8.40, 8.37	164	Needles

[a] All three compounds decomposed without boiling.

The aliphatic sulfone derivatives are viscous, colorless oils, only the lowest member of which has a constant boiling point. They are insoluble in water, but soluble in alcohol and ether. *bis*(β-Dimethylamino-ethyl) sulfone somewhat resembles the analogous sulfide derivative in that it is decomposed by strong alkali. No decomposition product, however, could be isolated; d_4^4, 1.0916; d_4^{25}, 1.0755. The same increasing solubility in absolute alcohol as exhibited by the hydrochlorides of the sulfoxide derivatives is also noted with the sulfone compounds. Chlorine was determined in two hydrochlorides.

Anal. *bis*(β-Dimethylamino-ethyl) sulfone. Calcd.: Cl, 25.25. Found: 25.12, 24.84.

bis(β-Dipropylamino-ethyl) sulfone. Calcd.: Cl, 18.03. Found: 18.08, 17.90.

TABLE VIII

bis(β-DIALKYLAMINO-ETHYL)SULFONES, $(R_2NCH_2CH_2)_2SO_2$ AND THEIR HYDROCHLORIDES, $B^{II}2HCl$; ANALYSES AND PROPERTIES

Alkyl, R	Sulfur, % Calcd.	Found	M. p. (corr.) °C.	B. p. (corr.) °C. (Pressure, mm.)	Form
Methyl				174–5(15)	
hydrochloride	11.40	11.48, 11.22	249		Rect. needles
Ethyl					Oil
hydrochloride	9.50	9.46, 9.40	202–2.5		Fine needles
n-Propyl				202–7(10)	
hydrochloride	8.15	7.95, 7.94	173		Pointed needles
n-Butyl				215–20(8)[a]	
hydrochloride	7.07	7.07, 6.95	162.5		Sheaves of needles
Piperidyl	11.12	11.28, 11.29	51.0	247(18)	

[a] Some decomposition at boiling point.

Reactions with Tertiary Amines

Condensation with tertiary amines was by addition, unaccompanied by the elimination of any by-product. Consequently only the two re-

acting compounds were used, except with trimethylamine, when an alcoholic solution was necessary.

With trimethylamine, 0.2 mole of a 33% solution in absolute alcohol was added to 0.1 mole of β,β'-dichloro-ethyl sulfide or sulfoxide in a tube of 150cc. capacity, sealed, and heated at 100° for six hours. The crystals were filtered off, washed with ether and recrystallized, the sulfide product from absolute alcohol and the sulfoxide from 95% alcohol as it was practically insoluble in absolute. The reaction with sulfone was carried out in a beaker with practically no loss of trimethylamine, as the yield was about 95%. A warm solution of the sulfone in absolute alcohol was added to an alcoholic solution of trimethylamine and the mixture allowed to stand for an hour. The precipitate, which did not appear for about 15 minutes after the solutions had been mixed, was filtered off, washed with absolute alcohol and dried. The sulfide and sulfone products crystallized in needles, the sulfoxide product in small, hexagonal plates. Titration of the chlorine in the sulfone condensation product gave 22.58 and 22.59% of chlorine; calcd., 22.93%.

A reaction between pyridine and dichloro-ethyl sulfide took place when the mixture was heated on the water-bath for six hours, giving a heavy, dark purple mass which was purified by solution in a small amount of water, repeated extraction with ether, and evaporation of the water in a vacuum desiccator over sulfuric acid. Crystallization in rosets of needles required several weeks. The reaction of pyridine with the sulfone took place when the mixture was warmed for a few minutes only, whereupon it became thick and turned red. Purified in the manner just described, it gave rosets of needles which were only slightly less hygroscopic than those from the sulfide condensation product. Quinoline and the sulfide reacted at 175° to give a black, viscous mass that could not be purified. No visible reaction took place below that temperature. Platinum salts from the purest aqueous solutions gave amorphous precipitates of varying composition. The

TABLE IX

TRIMETHYLAMMONIUM CHLORIDES FROM DICHLORO-ETHYL SULFIDE, SULFOXIDE AND SULFONE $[(CH_3)_3N(Cl)CH_2CH_2]_2S$, $[(CH_3)_3N(Cl)CH_2CH_2]_2SO$, $[(CH_3)_3N(Cl)CH_2CH_2]_2SO_2$, WITH THEIR PLATINUM SALTS, $[(CH_3)_3NCH_2CH_2]_2S$, $PtCl_6$; ANALYSES AND MELTING POINTS

Sulfur condensation	Sulfur, % Calcd.	Sulfur, % Found	Platinum, % Calcd.	Platinum, % Found	M. p. (corr.) °C.
Sulfide	11.56	11.41, 11.29			135.5
platinum salt			31.78	31.42, 31.08	253
Sulfoxide	10.93	10.59			239
platinum salt			30.97	30.21	240
Sulfone	10.37	10.34, 10.28			211.5
platinum salt			30.23	29.34, 29.26	257

TABLE X

QUATERNARY SALTS CONTAINING PYRIDINE AND QUINOLINE, $[Py(Cl)CH_2CH_2]_2S$, $[Q(Cl)CH_2CH_2]_2SO_2$; ANALYSES AND MELTING POINTS

Aryl group and state of sulfur	Sulfur, % Calcd.	Sulfur, % Found	Platinum, % Calcd.	Platinum, % Found	M. p. (corr.) °C.
Pyridine-sulfide	10.10	10.05, 10.20			
platinum salt			29.83	30.72, 30.82	190
Pyridine-sulfone	9.18	9.47, 9.49			
platinum salt			28.44	27.71	191.5
Quinoline-sulfone	7.13	6.97, 6.91			
platinum salt			24.82	25.94, 25.98	243

sulfone reacted suddenly with quinoline at the same temperature to give a deep ruby-red, viscous mass. Purification was carried out as with the pyridine condensation, giving long needles and rosets that were very hygroscopic. No condensation product of the sulfoxide with pyridine could be isolated. Platinum salts of the above-mentioned compounds were made by adding a solution of chloroplatinic acid to an aqueous solution of the compound. They were insoluble in both water and alcohol and could not be crystallized; hence their purities are low. All are yellow and amorphous.

Reactions with Amino Acids

An aqueous solution was used for the reaction between β,β'-dichloro-ethyl sulfone and both glycine and phenylalanine because of the insolubility of the amino acids in alcohol. Equivalent molecular amounts (0.1 mole) of the sulfone, phenylalanine and sodium carbonate were added to 150 cc. of water in a 500cc. flask with reflux condenser attached and the whole was heated on an asbestos gauze with a free flame for five hours. The product, which was deposited as the mixture cooled, was readily recrystallized from hot water. Part of it was further purified by the addition of copper sulfate solution, suspension of the light blue copper salt in water and its decomposition with hydrogen sulfide, filtration while hot to remove the precipitated copper sulfide and concentration of the filtrate. The compound purified in this way had a purity of about 99% as against 96% when it was simply recrystallized. The condensation product with glycine has been made by Cashmore and McCombie,[17] using the ester, followed by hydrolysis.

The product formed with phenylalanine was α-benzyl-4-thiazanacetic acid-1-dioxide, $O_2S<(CH_2CH_2)_2>NCH(COOH)CH_2C_6H_5$, separating in fine needles; m. p., 176° (corr.).

Anal. Calcd. for $C_{13}H_{17}O_4NS$: S, 11.32. Found: 11.50, 11.57.

Acidity (titration with phenolphthalein). Calcd.: 32.56 cc. Found: 31.53. Chlorine, trace; sodium, none.

It is soluble in both hot absolute alcohol and hot water, but only slightly so in the cold solvents. The sodium salt, made by adding alcoholic sodium hydroxide with phenolphthalein as an indicator, crystallizes in fine silky needles that are soluble in alcohol but insoluble in ether and do not melt at 280°.

The condensation product with glycine, $O_2S<(CH_2CH_2)_2>NCH_2COOH$, was purified in the same manner, giving rectangular needles with wedge-shaped ends; m. p., 177° (corr.). Cashmore and McCombie also report 177° as the melting point.

Anal. Calcd. for $C_6H_{11}O_4NS$: S, 16.59. Found: 16.16, 16.31.

The yield of this substance was very low, only about 8%. The yield of the purified phenylalanine product was 40%.

Summary

The reactions of β,β'-dichloro-ethyl sulfide, sulfoxide and sulfone with primary, secondary and tertiary amines and with amino acids have been studied. Thiazanes, $S<(CH_2CH_2)_2>NR$, have been prepared in which R is an aliphatic radical, likewise thiazane oxides, $OS<(CH_2CH_2)_2>NR$, and dioxides, $O_2S<(CH_2CH_2)_2>NR$. Derivatives have been made from several amino acids.

From secondary amines, compounds of the types $S(CH_2CH_2NR_2)_2$, $OS(CH_2CH_2NR_2)_2$ and $O_2S(CH_2CH_2NR_2)_2$ have been obtained. The dimethylamine derivative from the sulfide lost one amino group to form the unsaturated $CH_2{:}CHSCH_2CH_2N(CH_3)_2$.

Tertiary bases add directly to give salts of quaternary bases, $S(CH_2CH_2NR_3Cl)_2$, $OS(CH_2CH_2NR_3Cl)_2$ and $O_2S(CH_2CH_2NR_3Cl)_2$.

The results obtained are consistent with the theory that the vesicant action of β,β'-dichloro-ethyl sulfide is due to its reactions with constituents of the living cell.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

BORNEOL IN SPRUCE TURPENTINE

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In an investigation of the sulfite liquor obtained from the paper mills of northern Europe, Klason and Segerfelt[1] isolated a solid white, optically inactive substance of camphor-like odor and composition $C_{10}H_{18}O$; m. p., 207°. They regarded it as inactive borneol. Later Bergstrom[2] obtained a white solid which distilled at 205–210° and had the composition given above. In 1913 Klason and Segerfelt[3] isolated the same compound apparently, and called it a terpene alcohol. In 1915 Bergstrom[4] reported this product as inactive borneol. More recently Homberg and Sunesson[5] re-examined the product and showed that it was optically active, containing 14–22% of *l*-borneol. Since the composition of the spruce turpentine of northern Europe may easily be different from that of other localities, we examined the spruce turpentine from the paper mills of Erie, Pennsylvania, some of our material being very kindly furnished by the Eastman Kodak Company.

That portion of the spruce turpentine left after distilling the *p*-cymene fraction, b. p. 175–178°, was used for this work. Five hundred g. of this residue was distilled under a vacuum of 3 mm., using a 30cm. Glinsky fractionating column. After three fractionations, the portion coming over from 70° to 80° was cooled to —10° with a freezing mixture. Crystallization took place and 9 g. of a white solid was filtered off. This represents 1.8% of the original cymene residue, but doubtless a considerable portion remained in solution, for the solid is very soluble in the oil. On recrystallizing the product from dil. alcohol, it was obtained in large, hexagonal plates; m. p., 206°.

Anal. Subs., 0.2096: CO_2, 0.5996; H, 0.2193. Calcd. for $C_{10}H_{18}O$: C, 77.85; H, 11.76. Found: C, 77.99; H, 11.72.

A molecular-weight determination was made by the lowering of the freezing point of its benzene solution.

Calcd. for $C_{10}H_{18}O$: mol. wt., 154.2. Found: 153.

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[1] Klason and Segerfelt, *Svensk Kem. Tid.*, **23**, 149 (1911).

[2] Bergstrom, *Papier-Fabr.*, **13**, 229 (1915).

[3] Klason and Segerfelt, *Arkiv. Kemi. Min. Geol.*, **4**, No. 20, 3 pp. (1913).

[4] Bergstrom, Ref. 2, p. 229; *Svensk Pappers-Tid.*, **18**, 62 (1915).

[5] Homberg and Sunesson, *Svensk Kem. Tid.*, **35**, 215 (1923).