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PROTECTIVE AND THERAPEUTIC AGENTS FOR WAR GASES -  
BAL DERIVATIVES AND ANALOGS

to  
July 1, 1944

by

P. L. Salzberg, W. A. Lazier, F. K. Signaigo and A. N. Pavlic,  
Chemical Department  
E. I. duPont de Nemours and Company

Report OSRD No. 4604

Copy No. 60

Date: January 22, 1945

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OFFICE OF SCIENTIFIC RESEARCH AND DEVELOPMENT

PROTECTIVE AND THERAPEUTIC AGENTS FOR VEAR GASES -  
BAL DERIVATIVES AND ANALOGS

Service Directive: CWS-4

Endorsement (1) Homer Adkins, Member, Division 9 to  
Dr. Walter R. Kirner, Chief, Division 9.

Forwarding report and noting:

"This report describes the preparation of about 60 analogs and derivatives of BAL. The synthetic program was closely aligned to the studies of therapeutic action and toxicity carried out by other agencies, chiefly the CMR and CWS. The objective of the program was the preparation of a therapeutic agent superior to BAL from the standpoints of chemical stability, therapeutic action and toxicity."

(2) From Walter R. Kirner, Chief, Division 9 to  
Dr. Irvin Stewart, Executive Secretary of the National Defense Research Committee.

Forwarding report and approving.

This is a progress report under Contract 9-274, CEMsr-377 with  
E. I. duPont de Nemours and Company.

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INTRODUCTION

Following the discovery by British investigators that 1,2-dithioglycerol (DTH, BAL) is effective in the early treatment of arsenical burns, the NDRC asked the cooperation of the Chemical Department of the Du Pont Company in preparing a variety of thiols for evaluation as therapeutic agents for Lewisite (L). It was hoped that compounds might be found which would have equal or greater therapeutic effectiveness without some of the undesirable properties of BAL, such as its relatively high toxicity and chemical instability. The synthetic work covered by this report was preceded by a closely related program carried out in this laboratory on the synthesis of thiols, which was suggested by NDRC but not supported by an OSRD contract.

This report deals with that part of the synthesis program which was aimed specifically at the production of dithiol therapeutic agents other than BAL, and was supported by OSRD. Pharmacological and physiological evaluation tests were carried out on samples submitted to several other laboratories working on programs sponsored by NDRC and the Committee on the Treatment of Gas Casualties. Experimental work under this project was carried out by F. K. Signaigo and A. A. Pavlic under the direction of W. A. Lazier.

OBJECTIVES

The primary objective of this program has been the synthesis of compounds containing the vicinal dithiol structure in a wide variety of structural arrangements. In the event that a particular candidate showed promise in the testing program, a secondary objective was the preparation of homologs of that candidate so that structure and efficacy might be further correlated. An additional aim of the work was to supply the more promising compounds or their intermediates for other testing programs. Included in the broad objective was provision for preliminary process development for any of the analogs, which, because of demonstrated value, might be required in large quantities.

SUMMARY

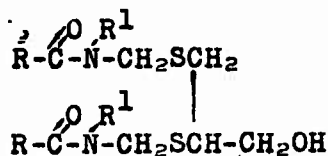
About sixty analogs and derivatives of BAL were prepared and submitted to the various medical investigators designated by the NDRC and CMR for therapeutic and toxicity studies (Table X). The scope and success of the synthesis program is illustrated in Table I where the compounds are arranged as classes related to a simple dithiol.

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Broadening of the testing program as the work progressed resulted in the inclusion of many of these compositions in tests as antidotes for chemical warfare agents other than Lewisite. For example, representative members of the dithiol series were submitted as possible antidotes for mustard, cadmium, and arsine therapy.

2,3-Dimercaptopropyl ethyl ether was found to be the most effective agent for arsine therapy, surpassing all other compounds submitted for this purpose. The CWS accordingly requested that consideration be given to the possibility of large-scale preparation of this analog and suggested that preliminary process work be initiated. Alternative routes for the preparation of the intermediate allyl ether were devised, and the existing synthesis based on hydrogenation of the trisulfide polymer was replaced by the more commercially feasible sodium hydrosulfide thionation.

A novel approach to the problems of dithiol synthesis has involved the preparation of derivatives of BAL or its analogs in which existing thiol groups were converted to new, labile structures. Outstanding examples of this class were the bis-S-amidomethyl thioethers of BAL prepared simply by mixing the dithiol with formalin and an amide to give compounds of the following structure:



Under the influence of Lewisite or similar hydrolytic material, the thioether link is cleaved with liberation of the dithiol in situ. Covering of the dithiol structure resulted in increased stability, lower toxicity and complete removal of objectionable odor from the parent compound. In addition, the water solubility of the resultant composition has given promise of greatly simplified formulations in ointments or other vehicles.

A new synthetic technique, developed in the course of this work, was applied to the preparation of dimercaptotetrahydrothiophene-1-dioxide and 2,3-dimercaptopropionic acid. The method involves the reaction of the appropriate halide with thioacetic acid in pyridine to form the thiolacetate which, by alcoholysis, is converted in good yield to the thiol. Sensitivity of the precursors of these dithiols to the usual thionating reagents, precluded their preparation by other routes.

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Dithioglycidol was condensed with aniline and methylaniline, by opening of the ethylene sulfide ring, to yield monomeric dithiols. Polymerization of dithioglycidol at the temperatures required for reaction complicated its condensation with other compounds (Table III).

Following the lead of earlier British investigators, who obtained excellent biological results with the glucoside of BAL, this compound was prepared from 2,3,4,6-tetraacetyl dibromopropylglucoside and isolated as the barium salt. This derivative is at present undergoing therapeutic tests.

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PROGRAM

Experimental work is being continued on the synthesis of BAL glucoside (Balintrav), thioxylitol, and related compounds for use as candidate antidotes for cadmium and arsenic therapy. It is also planned to investigate the applicability of selected BAL derivatives to the problem of preparing compound therapeutic ointments suitable for treating mixed agent splash contamination of the eyes.

DISCUSSION OF THE CHEMISTRY OF  
DITHIOL SYNTHESIS

The classical methods for obtaining thiols have failed in many cases to give the desired polyfunctional dithiols, and new modifications and methods had to be developed for most of the compounds obtained. Contributing to the difficulties encountered is the instability of 1,2-dithiols, particularly those containing other functional groups. In some cases this has hampered separation of the dithiol from the by-products usually present,

Many of the dithiols were obtained by selecting an appropriate unsaturated compound, converting this to the bromide and replacing the halogen atoms with mercapto groups. No one thionation technique worked in all cases, and usually several were tried before the desired dithiol was obtained. The side reactions encountered were chiefly those involving the elimination of halogen acid or reduction of the dihalide by the alkaline thionating agent. The experimental procedure used for obtaining each compound is given in the pages which follow. A summary of the various reaction systems investigated which did not yield the desired compounds is given in Table II.

Thionations using sodium hydrosulfide were successful in the preparation of 2,3-dimercaptopropyl urethane; 2,3-dimercaptopropylurea; 3,4-dimercaptobutanol; and 2,3-dimercaptopropyl diethyl acetal from the corresponding dibromides but failed in most other cases. When applied to the synthesis of dimercaptopropionic acid; dimercaptosuccinic ester; 2,3-dimercaptobutanol; etc., no dithiols were obtained but only mixtures which analyzed low in sulfur content. With dibromopropylacetamide, sodium hydrosulfide in methanol at room temperature apparently resulted in good conversion to dimercaptopropyl acetamide. The crude colorless oil, however, on distillation underwent dehydration to a cyclic thioamide, believed to be 2-methyl-5-mercapto-4,5-dihydrothiazine. Cyclo-dehydration also complicated the work-up of 3,4-dimercaptobutanol with formation of 3-mercaptotetrahydrothiophene.

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Although dimercaptpropionaldehyde could not be expected to have a real existence because of reactivity of the aldehyde toward the dithiol group, its diethyl acetal was prepared in 90% yield and 92% purity using the sodium hydrosulfide technique. Upon standing at room temperature the acetal group reacted with the dithiol function, to form a polymercaptal, liberating ethyl alcohol; for this reason it was not considered advisable to submit this compound for testing. The sulfur analog of this acetal (2,3-dimercaptpropyl diethyl mercaptal) could not be prepared by the usual methods because of the instability of the intermediate dibromide; however, reaction of the crude dimercaptoacetal with ethyl mercaptan in the presence of catalyst yielded, through mercaptan-acetal interchange, the desired compound. Its instability precluded its biologic evaluation.

A method developed earlier involved the conversion of the dihalide to a polymeric trisulfide by reaction with sodium trisulfide, followed by catalytic hydrogenation of the polymer to the dithiol. This was successful in yielding dimercaptpropyl ethyl ether and 10,11-dimercaptoundecanoic acid. On the other hand, dithiols were not obtained by applying this method to dichloropropionic acid, methyl dibromopropionate, methyl 2-chloro-3-acetylmercaptopropionate and dibromosulfolane.

In only one case has it been possible to use BAL as an intermediate in the synthesis of a dithiol with a new functional group. It was found that the hydroxyl group could be selectively acylated with certain acid anhydrides to yield 2,3-dimercaptpropyl acetate, propionate and butyrate (see Table IX). Phthalic and succinic anhydrides, on the other hand, only dehydrated BAL to a polymer.

The monododecyl ether of trithioglycerol had been prepared earlier by alkylating the trithiol with the alkyl halide in the presence of alkali. In attempting to extend this type of synthesis to include alkylation with ethylene chlorohydrin and chloroacetic acid, the sensitivity of the trithiol as well as the products towards alkali resulted in low conversions, and the products were not isolated in pure form.

A new thionation technique which was in certain cases applied successfully where other methods failed, was the use of thioacetic acid with pyridine as the alkaline agent. Dimercaptpropionic acid was obtained from methyl 2-chloroacrylate by adding thioacetic acid to the double

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bond and replacing the chlorine atom with thioacetic acid in pyridine. The resulting triester was hydrolyzed in stages to methyl dimercaptopropionate and the free acid. This thionating agent was also used to obtain 3,4-dimercaptotetrahydrothiophene-1-dioxide from the dibromide obtained from butadiene cyclic sulfone.

Other syntheses were tried in which the unsaturated compound was subjected to thionation directly. For example, ethanedithiol was obtained previously by sulfurizing ethylene and hydrogenating the resulting product. This method starting with undecylenic acid, gave, however, only a monomercapto compound. Sulfurization and subsequent hydrogenation of oleic acid yielded a product that analyzed for 74% dimercaptostearic acid but further purification by means of molecular distillation did not seem warranted because of extensive decomposition.

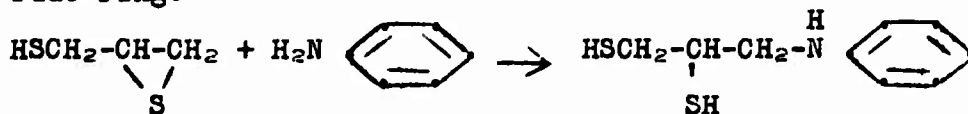
Thiocyanogen did not add to methyl acrylate nor could thioacetic acid be added to butenediol. A scheme for obtaining aromatic ortho-dithiols was explored briefly. Diphenyl disulfide was sulfurized with sulfur monochloride and the resulting product catalytically hydrogenated. The dithiol obtained proved to be the para-benzene-dithiol. Starting with di-p-tolyl disulfide, no dithiol was obtained. A sample of crude d-glucosone supplied by Dr. Wolfram of Ohio State University was hydrogenated in the presence of hydrogen sulfide in the hope of obtaining 1,2-dithiohexanehexol. This new technique has been generally successful as a means of obtaining thiols from aldehydes and ketones. The syrupy product rich in mercapto sulfur was submitted for evaluation, but there was no assurance that the desired dithiol was present.

Interesting compounds were obtained by modification of BAL and a number of its analogs through formation of derivatives by reaction of the mercapto groups with various reagents. These derivatives were of two types. The first were stable mercaptals and mercaptols prepared from aldehydes and ketones and the dithiol. Therapeutic results indicated that the active function, thus covered, was not available for reaction with the L-complex in the contaminated tissue. Use of the reaction was therefore limited to stabilizing the labile dithiol structure while other synthetic operations, ordinarily too drastic, were performed as an attempted route to new dithiols. These reactions and attempted liberation of the new dithiol are described below. The glucose mercaptal of BAL was of interest in connection with the separation of BAL into its optical isomers, a problem investigated elsewhere. A second, easily reversible, modification of BAL was pre-

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pared, after the method first proposed by Dr. Kharasch of the University of Chicago, from the dithiol and one or two equivalents of formaldehyde and amine. These compositions were water soluble and the dithiol structure was available for reaction; however, the aminomethyl compounds were not stable. A more satisfactory derivative was obtained from BAL (or analogs) if an amide was substituted for the amine; thus, the bis-s-amidomethyl thioethers of BAL were water soluble liquids stable in dilute aqueous solution. When dissolved in non-aqueous solvents, they exhibited no properties of thiols, but when diluted with water the thiol sulfur was available as indicated by complete titration with iodine. Samples of diethanolamine and methylglucamine salts of BAL were also submitted when it was found that these compounds were sufficiently stable to bring BAL into aqueous solution.

As reported previously, an interesting by-product encountered in BAL synthesis is dithioglycidol. This compound offered the possibility of preparing various dithiols by addition reactions involving opening of the cyclic sulfide rings:



The chief difficulty with this scheme is the rapidity with which dithioglycidol polymerizes especially under alkaline conditions. In view of the known behavior of ethylene sulfide and some preliminary experiments with dithioglycidol the reactants were heated at 100-130°C. in sealed tubes. These experiments are summarized in Table III.

Of the various compounds tried, only aniline gave a monomeric dithiol, the main reaction with most candidates being polymerization of the dithioglycidol or interpolymerization with the other reactant. The N-phenylaminopropanedithiol obtained in good yield from aniline was isolated as the crystalline hydrochloride. This product should have the vicinal dithiol structure illustrated above by analogy with the reactions of unsymmetrical ethylene oxides, but no proof of this assumption is at hand.

Aliphatic amines reacted like alkalies toward dithioglycidol, causing immediate and violent polymerization at room temperature. Though attempts were made to temper the reaction by dilution in an inert solvent at sub-zero temperatures, the course of the reaction was not changed.

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Amino-benzoic and sulfonic acids did not condense, and sludges of polymer containing unchanged acid were obtained. Aliphatic amino-acids and their sodium salts either did not react, or produced rubbery polymers (see glycine, Table III). The aminophenols gave insoluble gums from which no mercapto-containing compound could be extracted with acid. The substituted ureas were interesting in that they produced interpolymers ranging from a soft rubber (dimethyl-urea) to a hard, glassy material (dimethylolurea, Table III). Sodium bisulfite reacted with dithioglycidol and gave a solid interpolymer. This brittle, chalky product was not softened by organic solvents and after standing a week under concentrated hydrochloric acid was unchanged, though a faint odor of sulfur dioxide could be detected.

Anticipating that the amide function would impart desirable solubility characteristics to the dithiol structure, considerable attention was given to the synthesis of the lowest member of the series, 2,3-dimercaptopropionamide. None of the attempts were successful (Table IV). A number of experiments which involved the ammonolysis of the available methyl ester with both aqueous and alcoholic ammonia yielded polymeric materials from which it was possible to isolate a crystalline composition, probably a trimer, containing one sulfur (nontitratable) for each acrylamide unit. This would seem to indicate that either dehydrohalogenation or dehydrosulfurization followed by addition had occurred. Reaction of methyl 2,3-dimercaptopropionate with liquid ammonia in a steel vessel gave only tarry products. Protection of the mercapto groups by formation of the acetone mercaptol of the methyl ester, namely, 2,3-dimethyl-3-carbomethoxydithiolane, permitted the smooth conversion to the corresponding amide with alcoholic ammonia. In addition, the same carbonamidodithiolane was formed from the acetone derivative of 2,3-dimercaptopropionic acid by heating with urea; however, attempts to liberate the desired amide from the dithiolane by a variety of methods which are described elsewhere in this report, failed, and this route had to be abandoned.

Attempts to affix the mercapto groups as the last step in the synthesis, as in the thionation of dibromopropionamide with thioacetic acid in pyridine resulted in dehydrohalogenation that yielded only oils hydrolyzable to a fraction of the theoretical thiol value. In order to avoid the alkaline reagent which was assumed to be causing the dehydrohalogenation, a mixture of potassium thiolacetate and thioacetic acid was used, but reductive cleavage occurred with isolation of 3-acetylthiopropionamide. Details of the

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reaction and analysis of the product are described in Table IV. Another line of attack involved the selective dehydrobromination of dibromopropionamide to yield 2-bromoacrylamide to which it was intended to add thioacetic acid; the resulting 2-bromo-3-thioacetoxycyanide would then be converted to the dithiolacetoxo derivative by the reaction of the halogen with thioacetic acid in pyridine in the usual manner. The route to the first <sup>of the</sup> step synthesis, the selective dehydrohalogenation, could not be effected with pyridine, dimethylaniline and heat. Removal of the hydrobromic acid with sodium acetate in methyl alcohol gave a product different from starting materials in one small scale run, but repetition on a usable scale gave only polymeric materials, indicating at any rate, that the double bond had been produced. A similar attack involved the addition of thioacetic acid to bromoacrylonitrile, prepared by the dehydrohalogenation of dibromopropionitrile; to which it was intended to apply the thioacetic-pyridine thionation followed by hydrolysis to the desired amide. However, the addition of thioacetic acid could not be controlled and tarry, polymeric products were obtained.

Dimercaptopropionic acid was used as a starting material in a number of experiments, the first of which involved heating the acid with urea. Evolution of hydrogen sulfide, ammonia and water vapor was detected and a hard, water-soluble mass remained which contained no thiol sulfur. An alternate method using the acid as starting material involved, as the first step, oxidation of the sodium salt of dimercaptopropionic acid to a polymeric disulfide. Conversion of this polyacid to the acid chloride was effected by means of thionyl chloride and then ammonia was added to form what was presumed to be the polymeric amide. Chemical reduction to a dimercapto compound was attempted on this material but only acidic mercapto materials could be found in the reaction mixture, which indicated that hydrolysis occurred in the reduction step. The fact that any thiol sulfur could be regenerated from this oxidized form turned attention to the variation of the reaction. Oxidation of methyl dimercaptopropionate to the corresponding disulfide polymer was effected with hydrogen peroxide using potassium iodide as the catalyst. Ammonolysis of the ester group gave a product analyzing for a polymeric amide. However, hydrogenation of this polymer over cobalt sulfide catalyst was unsuccessful and the experiment was not repeated. A thioantimonite polymer was formed by trituration of antimony oxide with methyl 2,3-dimercaptopropionate. However, when this metallo-organic polymer was dissolved in alcohol and treated with ammonia, antimony sulfide separated and the next

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step, removal of antimony with hydrogen sulfide, was not carried out.

An attempt was made to effect the controlled dehydration of ammonium dimercaptopropionate with sulfuric acid to the corresponding amide, but only polymeric materials resulted.

A limiting factor in many of the projected syntheses was the lability of functional groups and activated mercapto groups under the conditions of thionation. Thus, the basic group of dithionopropylamine was apparently hydrosulfurized during thionation to the mercaptan and the trithiol was the main product obtained; again, in preparations designed to produce dimercaptopropionamide the mercapto group or its precursor was removed and only a monothiol was obtained. If, however, a readily available dithiol could be reversibly protected during subsequent reactions designed to affix a desirable functional group, a great number of otherwise unobtainable analogs would be made available.

Since the mercaptals and mercaptols of BAL and its analogs were most easily made and met the requirements of stability in ordinary chemical reactions, considerable attention was given to the interconversion and eventual liberation of the converted dithiols. In this series 2-phenyl-3-hydroxy methyl-1,3-dithiolane, prepared from benzaldehyde and BAL, was used as a test compound in a number of regenerations. Removal of the benzal function was never realized however; hydrogenation of this mercaptal yielded 25% of benzyl mercaptan as the only thiol that could be isolated, indicating that cleavage had occurred at the wrong C-S bond. In an attempt to influence the point of cleavage, the ortho-sulfobenzaldehyde derivative was used, but very little hydrogen was absorbed and no dithiol was isolated. Attempted preparation of the acetophenone and benzophenone mercaptals of BAL which might be expected to cleave at the desired point, failed; standard synthesis of the latter was supplemented by a preparation through benzophenone dichloride and BAL in pyridine or alcoholic potassium hydroxide, but only a complex, uncrystallizable mixture was obtained in which thiobenzophenone was recognized, indicating decomposition. Because of the ease of preparation and some early success in removal of the covering group, the acetone mercaptols (2,2-dimethyldithiolanes) of various dithiols were prepared. Their preparation and reactions are outlined in Table V. Cleavage of the C-S bond in these dithiolanes was effected using mercuric chloride in acetone or alcohol. Upon treatment with hydrogen sulfide, mercuric sulfide and the dithiol

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was formed. In the best experiment using BAL as the dithiol component of the dithiolane, 65% of BAL (identified by titration) was recovered. However, when the method was applied to other compounds, for example, the acetone-dimercaptopropionamide and acetone-dimercaptopropyl-diethylamine only a fraction of the theoretical thiol sulfur was liberated and no pure product was ever isolated. In other experiments, attempts were made to disturb the acetone-dithiol equilibrium to such an extent that the latter could be isolated. Thus, an excess of 2,4-dinitrophenylhydrazine was reacted with the acetone-mercaptol of BAL in the presence of a catalyst with slight formation of thiol sulfur; however, a dithiol could not be isolated. In this same category was a mercaptol-ketal interchange which involved heating acetone-BAL in an excess of ethylene glycol in the presence of a catalyst. In the event of interchange, dimethyl dioxalane and BAL would be the products, the dioxalane boiling lower than any other constituent in the mixture and by its removal the equilibrium in the direction of the dithiol would be favored. When the acetone derivative of BAL was used in this system an oil was obtained which contained but 7% mercapto sulfur; the acetone derivative of dimercaptopropionamide was recovered unchanged after 7 hours reflux.

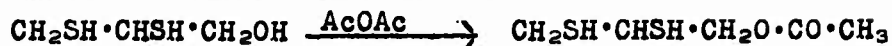
As with the benzal derivative, no hydrogenation could be demonstrated with the acetone derivative of BAL using palladium on charcoal as a catalyst; when the hydrogenation was carried out in the presence of water and a trace of acid in the hope of inducing dissociation to BAL and acetone there was no hydrogen up-take and the starting material was recovered unchanged. Other covered derivatives of dithiol included the S-amidomethyl thioethers prepared by reacting methylolacetamide or methylol benzamide with BAL. In general, these derivatives were too unstable for interconversion to other functional compounds. O,O-diethyl chloromethyl ethylene-S-bis-thiocarbonate, prepared in good yield from two moles of ethyl chloroformate and one of dimercaptopropyl chloride, was found to be very stable in acid solution but rapidly hydrolyzed in basic medium, thereby making it unsuitable for many of the conversions to other functional groups which required alkali as the driving force. Other covering attempts including the disulfide polymer and polythioantimonite formation are described in the section on dimercaptopropionamide.

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EXPERIMENTAL PART

2,3-Dimercaptopropyl Acetate



Two drops of concentrated  $\text{H}_2\text{SO}_4$  were added to 100 g. of BAL which was stirred and maintained at  $20-30^\circ$  by cooling while 87 g. of acetic anhydride was added drop-wise. The mixture was then heated to  $60^\circ$  and cooled. The crude product was washed with 3 portions of 250 cc. of water each, ether being used to break the emulsion. The ether solution was dried over sodium bicarbonate and calcium sulfate and distilled at 0.2 - 0.3 mm. (bath  $125-137^\circ$ ), 94 g. of colorless oil containing 40 percent mercapto. sulfur was obtained. This appeared to be principally the acetate mixed with some unchanged BAL. The product was then fractionated through a 20 inch, packed column at 1.0 - 1.5 mm. (bath  $155-160^\circ$ ) and the distillate, boiling range  $80-90^\circ$ , was collected in 5 equal fractions. The mercapto sulfur content of these fractions indicated the purity of each to be respectively 83, 91, 94, 96 and 97 percent, assuming the contaminant to be BAL.

This acetate is a colorless mobile liquid with a sharp penetrating odor. It is soluble to the extent of about 1 g. in 100 g. water and hydrolyzes rapidly in water as the following pH measurements on a 0.5% solution indicate:

pH	4.5	4.0	3.0	2.0	1.5	1.3	1.2	1.1
Time (hrs.)	0	1.0	1.25	1.75	2.25	2.75	3.25	3.75

The properties and analyses are given in Table IX.

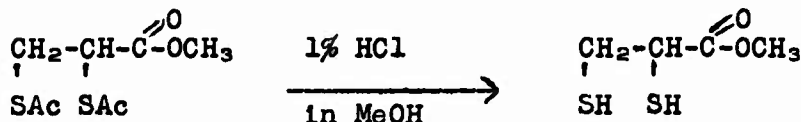
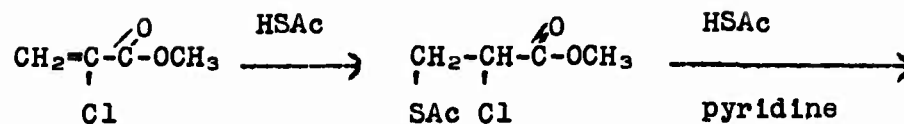
In precisely the same manner, using the appropriate acid anhydrides, 2,3-dimercaptopropyl propionate and butyrate were synthesized. The properties and analyses of these homologs are summarized in Table IX.

2,3-Dimercaptopropionic Acid

This acid was prepared by the following series of reactions:

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Methyl 3-Thiolacetoxy-2-chloropropionate

This compound was prepared by the addition of thioacetic acid (5% excess) to methyl 2-chloroacrylate. The reactants were mixed and the moderately exothermic reaction was controlled by external cooling. After 2 to 3 hrs., the reaction had subsided and the mixture was maintained at 60° for 24 hours and then distilled at reduced pressure. The product boiled at 89-90/2.5 mm.;  $n_D^{25} = 1.4898$ . The yield was 84%.

Methyl 2,3-Dimercaptopropionate

To a rapidly stirred solution of 300 g. methyl 3-thiolacetoxy-2-chloropropionate in 300 g. of pyridine was added, over a period of 6 hours, 140 g. (10% excess) of thioacetic acid. The temperature of the mixture rose to a maximum of 40° during the addition and pyridine hydrobromide precipitated after about one-fifth of the acid had been run in. After stirring overnight, the slurry was heated to 50° for 1 hour. Removal of excess pyridine was accomplished by the dropwise addition of 150 cc of concentrated hydrochloric acid to the solution cooled to -15° to -5°. Stirring, if hindered by the salt deposited, could be facilitated by the addition of 50 to 100 cc. of water. The oil was removed by three extractions with 200 cc. portions of ether and the combined ether extracts washed once with 10% HCl and twice with water. After drying over Na<sub>2</sub>SO<sub>4</sub>, the ether was removed by distillation leaving 354 g. (theory, 344 g.) of brownish-red oil. This intermediate methyl 2,3-dithiolacetoxypropionate could be isolated or subjected to methanolysis directly to yield the dimercapto ester.

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In the latter case, the crude triester was dissolved in 1500 cc. of 1% methanolic HCl and refluxed for 4 hours. At the end of this time the thiol content had risen to 90% of theory and additional heating did not materially increase this value.

The product was separated from the methanol and polymeric material by a primary distillation. The crude distillate was then fractionated through a ring-packed column to yield 116 g. (50%) of methyl dimercaptopropionate, boiling point 52-54°/0.5 mm.

Analysis: S(H) = 42.0%, Total S = 42.05, 41.79%,  
Cl = Trace, C = 32.44%, H = 5.43%,  $N_{25}^D = 1.5251$ ,  $d_{45}^{25} = 1.2309$ .  
Calc. for  $C_4H_8O_2S_2$ : S(H) and Total S = 42.10%, C = 31.6%,  
H = 5.36%.

Methyl 2,3-Dithiolacetoxypionate

In a run similar to that described above, about one-half of the crude oil was removed and distilled through a small vigreux column. One hundred and thirty two grams of product, distilling at 112-114°/0.5 mm., was collected.

Calc. for  $C_8H_{12}O_4S_2$ : C, 40.65%; H, 5.12%; S, 27.11%

Found: C, 40.97, 41.09%; H, 5.25, 5.26%; S, 27.88,  
27.63%.

2,3-Dimercaptopropionic Acid

The acid was prepared by hydrolysis of 59 g. of the methyl ester in 650 cc. of 1% aqueous HCl. The mixture was refluxed for 8 hours or 4 hours after the disappearance of the oily layer. Isolation was best accomplished by extraction of the aqueous solution with ether until the thiol content of the former was decreased to less than 1% of its original value.

The ether extract, after drying over  $CaSO_4$ , was distilled under reduced pressure and the residual solid dissolved in 60 cc. of hot chloroform. From this solvent the dimercaptopropionic acid crystallized in large, brittle, transparent crystals, melting point 73.5-74.5°C. Yield 44 g. (83%). The melting point could be raised slightly by recrystallization from water.

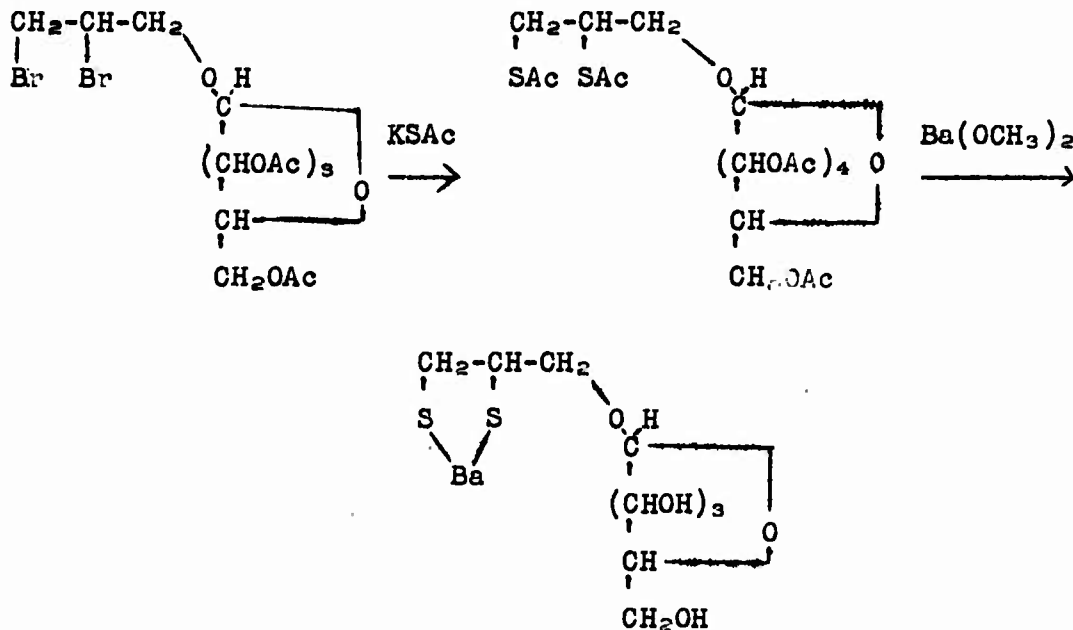
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Calc. for  $C_3H_6O_2S_2$ : C, 26.07%; H, 4.38%; S, 46.40%;  
S(H), 46.40%; N.E., 138.2.

Found: C, 25.95%; H, 4.73%; S, 45.73%; S(H), 46.0%;  
N.E., 139.1.

2,3-Dimercaptopropyl Glucoside



The preparation of the intermediates for this synthesis has been described by Fischer, Z. Physiol. Chemie, 108, 3 (1919). 2,3,4,6-Tetraacetyl allyl-~~g~~glucoside was prepared from bromoacetylglucose and allyl alcohol in the presence of silver carbonate. White needles from dilute alcohol, melting at 89-90° were obtained in 55-65 percent yield. The dibromide, prepared by directions given by the same author, was obtained in 80-90 percent yield, m.p. 91-92°.

Seventy five grams (0.14 mole) of tetraacetyl dimercaptopropyl glucoside, 38 g. (0.33 mole) of potassium thioacetate and 325 cc. of absolute alcohol were refluxed for 5-6 hours on a steam bath. During the early stages of the reaction the solution turned yellow and salt was precipitated; hydrogen sulfide was detected in the off-gases. After cooling, the solution was poured into 1000 cc. of water and the oil extracted three times with ether, the ether

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extracts being combined, washed once with water and dried over  $\text{CaSO}_4$  and  $\text{Na}_2\text{SO}_4$ . The ether was distilled and last traces of solvent removed by warming the flask to  $50^\circ\text{C}$ . in vacuo. Eighty eight grams of a yellow oil, presumably the hexacetate of BAL glucoside, remained.

This oil was taken up in 80 cc. of methanol and cooled to  $-10^\circ$ . While stirred in a atmosphere of nitrogen, 0.17 mole of barium methoxide in 300 cc. of methanol was added dropwise over a period of 30 minutes and the slurry allowed to stand 15 minutes more. Barium methoxide was prepared by solution of either  $\text{BaO}$  or barium metal in methanol; it was usually necessary to filter the solution before use. The barium salt was filtered, washed with methanol and dried in a nitrogen-filled vacuum desiccator. The yield was 64 g., slightly above theory.

Anal. Calcd. for  $\text{C}_9\text{H}_{16}\text{O}_6\text{S}_2\text{Ba}$ : Ba, 32.58 %, S, 15.21%

Found: Ba, 30.64, 30.65%; S, 12.09, 11.90%;  
S(H), 11.5%; Br, trace.

Repetition of this synthesis a number of times gave essentially the same product and the results of the British, who obtained a salt with high sulfur and metal content (16.8% and 33.4% respectively) were never duplicated. Carbon, hydrogen analyses were difficult to check, although the former were consistently 2-3% low.

If a sample of the barium salt was titrated immediately after preparation first with standard acid and then with iodine, values could be obtained which very nearly approximated the regular barium and sulfur analyses. However, upon standing for several weeks at room temperatures, the dry salt apparently underwent some change for only about 60% of the original titration was obtained with acid, indicating that a part of the mercaptide linkage had been changed to a more stable structure. The thiol analysis with standard iodine was also reduced a similar amount, although the end point would fade after the initial rapid titration and eventually a thiol sulfur value higher than originally obtained would result. A plausible explanation of this phenomenon would be that a reaction had taken place in the dry state with partial formation of  $\text{BaS}$  and, presumably, a mono- or disulfide involving the glucoside units. In this form, the barium does not titrate, at least immediately, with dilute acid, but upon standing the  $\text{BaS}$  is converted to the halide with liberation of hydrogen sulfide. The sulfide ion, requiring two equivalents of iodine as

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compared with one for the mercapto group, would account for the high, though tardy, "thiol" value.

Although the potassium thioacetate could be prepared in solution and used as such, best results attended its isolation and purification prior to use. This was done as follows: 76 g. (1.0 mole) of thioacetic acid was dissolved in 100 cc. of methanol and cooled to  $-10^{\circ}$ . To this rapidly stirred solution was added slowly 0.95 mole of KOH as a concentrated (30-40%) methanolic solution, the temperature being kept below  $0^{\circ}$  with proper cooling. While stirring was maintained, 500 cc. of ice-cold ether was added, the salt separating as fine needles which were filtered and washed with ether. Reprecipitation from methanol solution with ether served to purify the salt; the yield of potassium thioacetate prepared in this manner was usually 50-60%.

Dimercaptopropyl Ethyl Ether

Sodium trisulfide was prepared by warming 252 g. (1.05 moles) of  $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$ , 69 g. (2.1 atoms) of sulfur and 100 cc. of  $\text{H}_2\text{O}$  at  $50^{\circ}$  until all the sulfur had gone into solution. Magnesium hydroxide, to be used as a dispersing agent, was prepared in situ by adding 12 g. of NaOH and a solution of 30.6 g. of  $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$  in 30 cc.  $\text{H}_2\text{O}$  to the rapidly stirred mixture. Two hundred and forty six grams (1 mole) of dibromopropyl ether was added dropwise to the stirred solution maintained at  $50^{\circ}$ , the addition requiring about 4 hours. After all the dibromide had been added, the brown gummy suspension was digested with stirring at  $65-75^{\circ}$  for 7 hours. The paste was then filtered off and washed on a Buchner funnel until the washings were clear; the polymer was then superficially dried in a vacuum desiccator overnight.

The 230 g. of sticky polymer was divided into 2 portions and hydrogenated at  $125^{\circ}$  in 130 cc. of dioxane over 10 g. of cobalt trisulfide catalyst. The suspended catalyst was filtered off and the hydrogen sulfide blown out of the solution in a stream of nitrogen. The solution analyzed for 79% of theoretical mercapto sulfur content assuming only dimercaptopropyl ethyl ether to be present. The dioxane was removed by distillation at 80 mm. pressure; a low boiling thiol which co-distilled with the solvent was not identified. The dimercapto-ether, distilled at  $51.5-52.5^{\circ}$  at 1 mm. The analysis is given in Table VIII.

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2,3-Dimercaptopropyl Methyl Ether

Allyl methyl ether, prepared from sodium methoxide and allyl bromide, was brominated in 83.5% yield to give a product distilling at 71°/11 mm. One hundred and ninety three grams of polymer was prepared from 232 g. of this dibromide using the directions for the ethyl homolog as described above. Hydrogenation of the polymer yielded 56 g. of product distilling at 63°/5.5 mm. The analysis and properties of dimercaptopropyl methyl ether are outlined in Table VIII.

2,3-Dimercaptopropyl Isopropyl Ether

A trisulfide polymer was prepared from 210 g. of  $\text{Na}_2\text{S}\cdot 9\text{H}_2\text{O}$ , 55 g. of sulfur, 60 cc. of  $\text{H}_2\text{O}$  and 200 g. of dibromopropyl isopropyl ether (b.p. 63°/ 2.8 mm.). By the usual work-up there was obtained 67 g. of product analyzing for 34.2% mercapto sulfur (theory, 38.56%). Distillation through a precision still was not sufficient to purify this product, presumably because of the presence of unreacted dibromide which would be expected to codistill with the dithiol. Consequently, the crude product was taken up in 150 cc. of 40% NaOH and the neutral impurities extracted from the sodium mercaptide thus formed, with ether. Liberation of the dithiol was accomplished by acidification followed by extraction; all operations were conducted under nitrogen to prevent loss due to oxidation. Distillation of purified product yielded 37 g. of dithiol distilling at 75-76°/5.5 mm. The analyses and other properties are recorded in Table VIII.

2,3-Dimercaptopropyl Butyl Ether

The previous directions were modified slightly in this preparation because of the lower reactivity of the dibromopropyl butyl ether. Two hundred and sixty grams (1.1 moles) of  $\text{Na}_2\text{S}\cdot 9\text{H}_2\text{O}$  and 68 g. (2.1 atoms) of sulfur were melted together by stirring at 50°. To this stirred solution was added 275 g. (1 mole) of dibromopropyl butyl ether (b.p. 66°/5 mm.) in 250 cc. of methanol over a period of 5 hours, the temperature being maintained at 50°. The digestion was prolonged for 18 hours at 70-75°. The tacky polymer was washed by trituration with water and then with methanol.

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One half of the superficially dried polymer was hydrogenated in 100 cc. of dioxane at 125° over 10 g. of cobalt trisulfide catalyst. The dioxane was removed, after filtration of the catalyst, at 60 mm. pressure and the product was distilled at 61.5°/0.35 mm. Purification of the product was complicated by the presence of a co-distilling thiol recognized by a high mercapto sulfur analysis. The properties of the best fraction are described in Table VIII.

Sulfurization of Diphenyl Disulfide

55 g. of diphenyl disulfide was melted on a steam bath and stirred at 80° while 34 g. of S<sub>2</sub>Cl<sub>2</sub> was added. After the addition of the first part of the S<sub>2</sub>Cl<sub>2</sub>, no HCl was evolved, so a fraction of a gram of ferric chloride was added as a catalyst. This brought about rapid evolution of HCl. When the mixture thickened, benzene was added. After 2 hours the evolution of HCl ceased, the total amount evolved being 80 percent of the theoretical. The mixture was hydrogenated at 125° using a cobalt sulfide catalyst. On working up the hydrogenated mixture, there was obtained, in addition to thiophenol and non-volatile resin, approximately 15 g. of impure p-dimercaptobenzene, melting point 80-90°, containing 40% S(H). (Calculated for C<sub>6</sub>H<sub>6</sub>S<sub>2</sub>: S(H) = 45.0%). Reported melting point = 98°C.

The same procedure starting with di-p-tolyl disulfide yielded no dithiol.

N-Dibromopropylacetamide

For preparing this compound the work of Bergmann (Ber. 54, 2139 (1921)) was followed in brominating allyl-acetamide. Working on a much larger scale a yield of only 11% of theoretical was obtained as compared with the 47 percent yield reported. The principal by-product was a crystalline amine hydrobromide melting at 115-6°, apparently 3-bromo-2-hydroxypropylamine hydrobromide, the hydrolysis product of the 3-bromo-2-acetoxypropylamine hydrobromide obtained by Bergmann.

Anal. Found: N, 6.14, 6.05%; Br, 67.66, 67.86%.

Calcd. for C<sub>3</sub>H<sub>9</sub>ONBr<sub>2</sub>: N, 5.96%; Br, 68.1%.

Reaction of Dibromopropylacetamide with Sodium Hydrosulfide.

Seven grams of sodium was dissolved in 75 cc. of methanol, the solution cooled to 0° and saturated with H<sub>2</sub>S. 26 g. of dibromopropylacetamide was added to the cooled so-

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lution, the pressure bottle stoppered and allowed to warm slowly. When the temperature rose to 12° salt began to separate out. After standing for 2 days, titration of a aliquot for alkali and thiol indicated that reaction was substantially complete. The mixture was cooled in ice, acidified with concentrated hydrochloric acid, and the methanol removed by distillation at reduced pressure. The residue of oil and salt was extracted with chloroform and after drying the chloroform was removed from the product by distillation at reduced pressure. The colorless oily residue was water soluble and rich in mercapto groups. It was distilled at 0.3-0.5 mm. The distillate, 6 g., was relatively insoluble in water, but soluble in alkali and dilute acid.

Anal. Found: S, 41.05, 40.82%; S(H), 20.4%;  
N, 9.59, 9.73%.

Calc. for C<sub>5</sub>H<sub>9</sub>NS: S, 43.5%; S(H), 21.7; N, 9.53%.

Apparently on distillation the desired product, dimercaptopropylacetamide, underwent cyclodehydration to form either 2-methyl-5-mercaptomethylthiazoline, or 2-methyl-5-mercaptodihydrothiazine. The stability of this product toward mineral acids favors the latter structure.

10,11-Dimercaptoundecanoic acid

To a prepared sodium trisulfide solution (90 g. Na<sub>2</sub>S·9H<sub>2</sub>O, 23 g. S in 150 cc. H<sub>2</sub>O) at 50° was added a solution of sodium 10,11-dibromoundecanoate prepared from 120 g. of 10,11-dibromoundecanoic acid and 14 g. of sodium hydroxide in 100 cc. water. The reaction was maintained at 50° during the two hours required for addition of sodium salt and was then raised to 60° for 6 hours. After cooling concentrated HCl was added dropwise until the solution was distinctly acid and the soft polymer was washed by decantation.

Eighty grams of air-dried polymer was hydrogenated at 125° in 125 cc. dry dioxan, over 15 g. of CoS<sub>3</sub> catalyst. After removal of the suspended catalyst by filtration, dissolved H<sub>2</sub>S was blown out in a stream of nitrogen. The dark brown solution was placed in a separatory funnel and 600 cc. of water added which precipitated 82 g. of dark oil containing all of the mercapto-acid. Attempts to distill this crude mixture were unsuccessful because the high proportion of high boiling material present necessitated excessive pot temperatures. It was found that fractional precipitation with petroleum ether from ethyl ether solutions of the crude would remove polymeric material. The proportion

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of solvents varied with each purification, but, in general, for this size experiment 100 cc. of petroleum ether would precipitate 16 grams of heavy dark paste from a solution of 82 g. of crude in 100 cc. ethyl ether. The mixed ethereal solution was then evaporated in a stream of nitrogen and this partially purified product was distilled through a short still-head under reduced pressure. Forty six g. of distillate boiling at 135-188°/0.2-0.4 mm. and 16 g. of residue were obtained. An attempt to fractionate a portion of the distillate through a 20" ring-packed column failed owing to excessive decomposition, but the small amount of foreshot collected at 150-170°/0.3 mm. contained monomercaptoundecanoic acid, melting-point 42°C. with previous softening; S(H), Found 14.3%. Calculated 14.8%.

Final purification of the dimercapto acid was effected by careful distillation through a short unpacked still-head, the fraction boiling between 166-167°/0.2 mm. being retained. The yield was 23 grams or 26% of the theoretical.

Analysis Calcd. for  $C_{11}H_{22}O_2S_2$ : S, 25.6%;  
N.E., 250.4.

Found: S, 27.46%; S(H), 25.2%; Br, Trace; N.E., 249.

N-Phenylaminopropanedithiol Hydrochloride

Eighteen and six tenths grams (0.2 mol) of aniline and 22.6 g. (0.2 mol + 7%) of dithioglycidol were heated in a Carius tube for 8 hours at 130°C. At the end of this time the contents of the tube were dissolved in ether and the unreacted aniline and aminodithiol extracted with 10% HCl. The solvent was removed by distillation at reduced pressure and the residual cake crystallized from alcohol-ether mixtures. Yield 27 g. (57%); melting point 137-139°C.

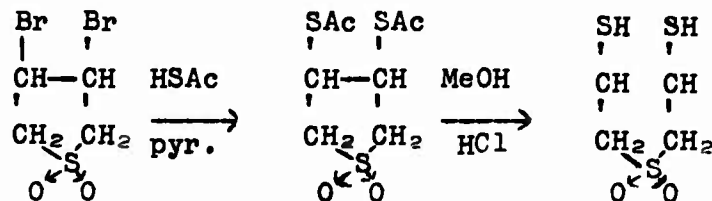
Analysis: S(H), 27.3%; Total S, 26.6%; Cl, 15.3%;  
N, 5.74%.

Calculated for  $C_9H_{14}NCl:S(H)$ , 27.18%; Cl, 15.08%;  
N, 5.94%.

As the hydrochloride, the dithiol was soluble to the extent of 15% in water at 25°C. but the free base was practically insoluble.

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3,4-Dimercaptotetrahydrothiophene-1-dioxide



Two hundred seventy eight grams (1.0 mol) of 3,4-dibromotetrahydrothiophene-1-dioxide (from the bromination of butadiene cyclic sulfone in  $\text{CCl}_4$ ) was dissolved in 400 g. of pyridine and cooled to  $-25^\circ$ . To the rapidly stirred solution was added 265 g. (3.5 mols) of thioacetic acid as rapidly as compatible with maintenance the temperature below  $-15^\circ$ . After all the acid had been added, the mixture was stirred at  $-10^\circ\text{C}$ . for 5 hrs. and then at  $+5^\circ$  for an additional 14 hrs.

At the end of this time the yellow-orange solution, containing suspended pyridine hydrobromide, was poured in a thin stream into 350 cc. of conc. HCl which had been pre-cooled to  $-30^\circ$ , a heavy tan-colored paste precipitating. The paste was washed 5 times with water by decantation then dried in a vacuum desiccator overnight; it weighed 165 g. after drying.

The solid was dissolved in 1500 cc. of hot methanol, filtered and cooled, 66 g. of brown needles depositing. Recrystallization from 1200 cc. methanol and clarification with charcoal produced 48.5 g. (21.5%) of 3,4-dithiolacetoxy-tetrahydrothiophene-1-dioxide, m.p.  $156.5-157.5^\circ\text{C}$ .

Analysis: S, 35.18%; Br, Trace; C, 35.58%; H, 4.44%

Calcd. for  $\text{C}_8\text{H}_{12}\text{S}_3\text{O}_4$ : S, 35.84%; C, 35.80%; H, 4.51%

The dimercapto sulfone was obtained from the dithiolacetoxy derivative by alcoholysis with 1% methanolic HCl for 3 hrs. at  $50^\circ\text{C}$ .; 18 ml. of solvent per gram of compound was the arbitrary dilution used. 3,4-Dimercapto-tetrahydrothiophene-1-dioxide crystallized from the methanol upon cooling and was recrystallized from chloroform, water, methanol or ethanol to yield 31 g. of small, flat plates, m.p.  $126-28^\circ$ .

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Calcd. for  $C_4H_8O_2S_3$ : S, 52.19%; S(H), 34.79%;  
C, 26.07%; H, 4.38%.

Found: S, 49.41, 50.06%; S(H), 33.1%; C, 26.36,  
26.46%; H, 4.61, 4.71%, halogen, trace.

If the reaction was run at room temperature rather than  $-10^\circ$ , dehydrohalogenation accompanied replacement of bromine and the only product isolated was 3-thiolacetoxy-2,3-dihydrothiophene-1-dioxide which could be hydrolyzed to the corresponding thiol in the usual manner. The mono-thiolacetoxy derivative was obtained in 30-35% yield by crystallization of the HCl-precipitated crude from alcohol-ether mixtures, m.p.  $71-73^\circ$ .

Analysis: S, 33.19%; C, 37.6%; H, 4.97%.

Calcd. for  $C_6H_8O_3S_2$ : S, 33.3%; C, 37.5%; H, 4.19%.

The position of the double bond at 2,3 is assumed from analogy to known dehydrohalogenation reactions of the dibromide. Further proof of the monothiolacetoxy structure was obtained by following the formation of mercapto sulfur by iodine titration during alcoholysis; one S(H) was produced per molecule assuming the above formula.

4-Mercapto-2,3-dihydrothiophene-1-dioxide was obtained as a pale yellow oil upon evaporation of the methanol after alcoholysis; it analyzed for 21.9% S(H) as compared with 21.3% theoretical.

Thionation of Methyl Dibromopropionate and Methyl 2-Chloro-3-thiolacetoxypropionate with  $Na_2S_3$ .

These reactions were carried out in an attempt to prepare dimercaptopropionic acid. One hundred twenty three grams of the dibromoester in 200 cc. methanol was added at room temperature to a solution of 123 g.  $Na_2S \cdot 9H_2O$  and 33 g. S in 50 cc.  $H_2O$  containing  $Mg(OH)_2$  as the dispersing agent. The resulting polymer was hydrogenated at  $125^\circ$  over  $CoS_3$  catalyst in dioxane. On distillation of the reaction mixture 12 g. of product was obtained which boiled at  $25-6^\circ/1$  mm.,  $49^\circ/8$  mm.  $N_D^{19} = 1.4626$ ,  $N_D^{25} = 1.4605$ . This appears to be methyl 3-mercaptopropionate reported by Drummond & Gibson, J.C.S. 1926, 3073 to boil at  $54-55^\circ/14$  mm.,  $N_D^{19} = 1.4628$ .

Anal. Found: S(H), 26.3%; S, 26.46%.

Calcd. for  $C_4H_8O_2S$ : S(H), 26.67%; S, 26.67%

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Hydrogenation of the trisulfide dimer obtained from methyl 2-chloro-3-thiolacetoxypionate and sodium trisulfide also gave methyl 3-mercaptopropionate in 28% yield. No other thiol could be isolated.

In these reactions it appears that the alpha halogen or sulfide group is reduced off by the thionating agent. It is possible however that the alpha mercapto group is lost during hydrogenation.

Dibromopropionaldehyde

Dibromopropionaldehyde was prepared in 89 percent yield by the addition of 350 g. (2.19 mols) of bromine to 124 g. (2.21 mols) of freshly distilled (b.p., 52-53°C.) acrolein in 300 cc. of carbon tetrachloride at temperatures below 0°. The product, which was distilled directly from the reaction mixture (b.p. 45-47°/1.5 mm.), was unstable and was used directly for the following preparation.

Dibromopropionaldehyde Diethyl Acetal

Dibromopropionaldehyde diethyl acetal, following the directions of Grard, Ann. Chem. 107 13, 37, was obtained in 93 percent yield from the aldehyde and orthoformic ester; b.p. 60-63° at 0.4 mm.

2,3-Dimercaptopropionaldehyde Diethyl Acetal

Into a 1-l. stainless steel autoclave was charged 150 g. of dibromopropionaldehyde diethyl acetal and sodium hydrosulfide prepared by dissolving 37 g. of sodium in 500 cc. of methanol and saturating the resulting solution with hydrogen sulfide at 0°. After closure, the vessel was shaken under 100 lbs. hydrogen sulfide pressure for 48 hours at room temperature. The pale green solution was transferred to a 2-l. separatory funnel and saturated with carbon dioxide; flakes of what is presumed to be sodium bicarbonate separated and eventually the solution set to a pink gel. Addition of 1000 cc. of water caused the separation of an oil and this was extracted with ether in a carbon dioxide atmosphere. The combined ether extracts were washed twice with water containing 1/2 cc. of acetic acid to neutralize last traces of alkali. After drying over sodium sulfate-calcium sulfate under carbon dioxide, the ether was stripped off leaving 98 g. of a tan colored oil analyzing for 29.9% thiol sulfur or a purity of 91.5% assuming only the desired dithiol to be present.

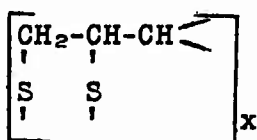
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Twenty five grams of this residue was distilled through a short path still-head at 0.25 mm. from a pot held at 110-120°. Seventeen grams of distillate was collected which analyzed for 31.2% thiol sulfur or a purity of 95.4%. The viscous residue, 7 g., contained 19.3% thiol sulfur. Attempts to redistill the purified acetal in a precision ring-packed still resulted in polymerization with loss of all the product.

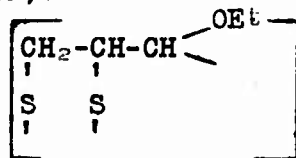
Anal. Calc. for  $C_7H_{16}O_2S_2$ : C, 43.09%; H, 8.15%; S, 32.68%.

Found: C, 43.19, 43.12%; H, 7.94, 8.07%; S, 30.74, 31.26%; S(H), 31.2%.

Upon standing at room temperature for about one week, distilled and crude samples of this derivative were observed to separate into two layers, the lower viscous layer eventually (2 months) became opaque and solid. No odor of hydrogen sulfide was detected. Distillation of 4 cc. of the upper layer, which after two weeks contained but 8% mercapto sulfur, indicated that it was largely ethanol (b.p. 75-79°C, miscible with water, iodoform test, etc.). The mechanism compatible with these facts would involve reaction of ethoxyl of the acetal function with neighboring thiol groups to yield a polymeracetal. A completely polymerized product would be represented by (I), although analysis of a distillation residue indicated a structure more nearly represented by (II).



(I.)



(II.)

Attempt to Prepare Dibromopropionaldehyde Diethyl Mercaptal

Two hundred thirty seven grams of dibromopropionaldehyde was cooled to 5° in a 500 cc. 3-necked flask equipped with thermometer, stirrer and dropping funnel and 3 drops of 48% hydrobromic acid was added. While stirred, 140 g. of ethyl mercaptan was added dropwise over a period of 3 hours, the temperature being maintained below 15° by cooling the flask with an ice bath. After the addition was complete the contents were stirred at room temperature an additional 3 hours. The mixture was then transferred to a separatory funnel, the water layer removed and the product dried over sodium sulfate.

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By the next day the drying product had turned jet black and fumes of hydrogen bromide were observed when the stopper was removed. An attempt was made to distill 50 g. of this residue but the pressure could not be maintained when the pot reached 100° and the oil bath was removed. After 1 or 2 minutes the contents of the pot began to fume and the still-head was blown off before the pressure could be relieved.

Attempt to Thionate Crude Dibromopropionaldehyde Diethyl Mercaptal

Twenty one grams of dibromopropionaldehyde and 12 g. of ethyl mercaptan were reacted as described above. Meanwhile a solution of sodium hydrosulfide was prepared in a pressure bottle (7 g. of sodium, 200 cc. of methanol saturated with H<sub>2</sub>S). To this cooled solution was added the superficially dried reaction mixture (above) and after saturation with H<sub>2</sub>S the bottle was capped and placed in the cold room for two days. At the end of this time the reaction mixture was transferred to a separatory funnel and carbon dioxide run in until the usual paste had formed. Five hundred cc. of water was added and the clear yellow oil which separated extracted with ether. The ethereal solution was dried and then distilled, leaving 6 g. of an opaque paste which was only partially soluble in alcohol. Analysis indicated but 8 percent thiol sulfur.

Preparation of Dimercaptopropionaldehyde Diethyl Mercaptal

Thirty two grams of crude dimercapto propionaldehyde diethyl acetal which analyzed for 92 percent of theoretical thiol sulfur was mixed with 100 g. of ethyl mercaptan and cooled to 30°. Two drops of hydrochloric acid was added and after standing at this low temperature for 1/2 hour the reaction was allowed to warm up to 25°. After standing overnight the excess ethyl mercaptan was removed by heating the mixture in a stream of nitrogen. The residue was washed with water twice and then dried over sodium sulfate. The mercaptal was transferred to a small Claisen flask and distilled at 0.5 mm. Thirteen grams of viscous pink liquid containing suspended water was collected at 70-100°. By shaking with a few grains of sodium sulfate the water was removed.

Anal. Calcd. for C<sub>7</sub>H<sub>16</sub>S<sub>4</sub>; S, 56.16%; S(H), 28.08%

Found: S, 50.14, 49.73%; S(H), 28.08%.

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All other attempts to purify this product further by distillation failed. Only polymerized products were obtained.

Allyl Carbinol

Into a dry 2-l. nitrogen-filled 3-necked flask was placed 73 grams of magnesium, 50 cc. of sodium-dried ether and a few drops of allyl bromide. Once the reaction had commenced an additional 120 g. (1 mole) of allyl bromide in 800 cc. of ether was added dropwise while the magnesium suspension was vigorously stirred. This addition of allyl bromide required 2 days and at the end of this time titration indicated the presence of 0.93 moles of Grignard reagent.

The supernatant solution was transferred by means of a filter stick to a dry, nitrogen-filled 3-necked flask. Gaseous formaldehyde, prepared by heating paraformaldehyde to 180-190°, was now run into the cooled solution (0°) and stirred until no further test was obtained with Michler's ketone. The two layers were vigorously stirred while 150 cc. of saturated ammonium chloride solution was added. The ethereal solution of the allyl carbinol was removed and the remaining solid washed 3 times with ether. After drying, the ether was removed and the product distilled in a small short path still. The fraction collected at 103-113°, 42 g., was refractionated in a precision still; 32 g. of allyl carbinol (45 percent yield) distilling at 113° was obtained.

3,4-Dibromobutanol

Fifty seven grams of allyl carbinol was brominated in 150 cc. of chloroform; 125 g. of bromine was absorbed. The solvent was removed directly from the reaction mixture and the product distilled at 72-74°/4 mm. The yield was 141 g. or 77 percent of theory.

3,4-Dimercaptobutanol

Into a 1-l. stainless steel autoclave was charged 120 g. of 3,4-dibromobutanol and 500 cc. of sodium hydro-sulfide (35 g. of sodium in methanol saturated with H<sub>2</sub>S). The mixture was heated at 40° for 40 hours under 135 lb. hydrogen sulfide pressure while intermittently shaken. After discharging, the solution was acidified with 60 cc. of concentrated hydrochloric acid and the precipitated salt filtered. The clear filtrate was transferred to a short-path still and solvent removed under reduced pressure. The residue, consisting of an oil and white solid, was shaken

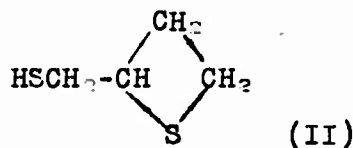
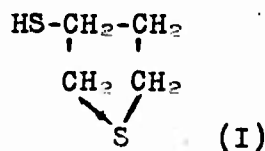
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with 100 cc. of water and the organic layer removed. The aqueous layer was extracted twice with ether, these extracts being combined with the previous extraction. Analysis indicated the presence of 49 g. (58 percent of theory) of dithiol. After removal of the ether, the residue was distilled through a short head at 2.5 mm., 40-50°, a material co-distilled with water and some of this cut was carried into the cold trap. Another fraction was collected at 80-100° at 1.5 mm. (30 g.) which, upon redistillation in a precision still, b.p. 96-97°/1 mm. (18 g.), analyzed for 45.9 percent thiol sulfur or 98.8 percent of theory for dimercaptobutanol.

Anal. Calcd. for  $C_4H_{10}OS_2$ : S, 46.35%; C, 34.73%; H, 7.29%.

Found: S, 46.10, 45.86%; S(H) 45.9%; C, 35.15, 35.35%; H, 7.39, 7.67%.  $N_{25}^{25} = 1.5583$ .  $d_4^{25} = 1.1842$ .  
Solubility, 4% in water D at 25°.

The foreshot and the material collected in the dry ice trap during the primary distillation was washed with water, dried, and redistilled in a precision still. The 12 g. main fraction boiling at 68°/5 mm. analyzed for 26.2 percent thiol sulfur, as compared with 26.7 percent for the dehydration product of dimercaptobutanol. Although no attempt was made to distinguish between the two possible structures, 3-mercaptotetrahydrothiophene (I) would be expected to be formed rather than 2-(mercaptomethyl) propylene sulfide (II).



Anal. Calcd. for  $C_4H_8S_2$ : S, 53.35%; S(H), 26.68%; C, 39.95%; H, 6.66%.

Found: S, 51.27%; S(H), 26.2%; C, 39.92, 40.15%; H, 6.76, 6.73%.  $d_4^{25} = 1.1862$ .

2,3-Dimercaptopropyl Urethane (Ethyl N-(2,3-dimercaptopropyl))  
carbamate

Allyl urethane was prepared from allyl amine and chloroformic ester in aqueous alkali, b.p. 77-78°/9 mm. The dibromide, described by Bergmann, et. al, Ber. 54 2147, was obtained in 87 percent yield as a low melting white solid.

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A 1-1. Parr bomb was charged with 188 g. (0.65 mole) and a sodium hydrosulfide solution prepared by dissolving 46 g. (2 atoms) of sodium in 450 cc. of methanol and saturating the resulting alkoxide with  $H_2S$  at  $0^\circ C$ . After pressuring to 100 lbs. with  $H_2S$ , the vessel was shaken for 16 hours at  $25^\circ C$ . and then at  $50^\circ C$ . for two hours. The cooled solution was acidified to congo red paper with conc.  $HCl$  and after filtration of the precipitated salt the solvent was distilled in vacuo. The residue of salt and oil was taken up in 200 cc. of water and extracted three times with ether. After drying, the ether was removed and the product distilled through a 4 inch vigreux column. Following a 13 g. foreshot, 84 g. (65%) of product (S(H) = 32.1% as compared with 32.8% theory) distilled at  $129-131^\circ/1.1$  mm.; the white, opaque residue weighed 26 g. In one instance a cloudy product was obtained and it was washed once with water prior to final distillation.

Distillation of the crude in a precision still gave a product with the following properties.

Anal. Calcd. for  $C_6H_{13}O_2NS_2$ : C, 36.91%; H, 6.72%; S, 32.82%; N, 7.17%.  
Found: C, 36.98, 36.89%; H, 7.00, 6.97%; S, 32.16, 31.83%; S(H), 32.8%; N, 7.58%.  $d_4^{20} = 1.1976$ ,  $d_4^{25} = 1.1924$ ;  
 $N_D^{20} = 1.5290$ ,  $N_D^{25} = 1.5277$ .

2,3-Dimercaptopropyl Urea

A sodium hydrosulfide solution, prepared by dissolving 41 g. of sodium in 500 cc. of methanol and saturating with  $H_2S$  at  $0^\circ$ , was charged into a one liter Parr bomb with 150 g. of dibromopropyl urea, prepared according to the method of Taal and Heupel, Ber. 24, 303. The bomb was agitated under a hydrogen sulfide atmosphere at 50-75 lb. pressure at room temperature for 50 hours then at  $50-60^\circ$  for an additional two hours. The reaction mixture was acidified with 50 cc. of concentrated  $HCl$  and the precipitated salt filtered off. After removing the solvent under reduced pressure at a bath temperature of less than  $60^\circ$  the residue of salt and moist product was taken up in 500 cc. of Starr solvent and 300 cc. of water. The organic solvent layer titrated for 55 g. of dithiol, and the water layer for 17 g. The latter was extracted four times with a total of 500 cc. of Starr solvent which reduced the thiol content to an equivalent of 2.5 g. of the dithiol in the aqueous layer. The combined extracts were dried over anhydrous calcium sulfate overnight and the solvent was then removed at reduced pressure. The residue consisted of a colorless to pale pink viscous syrup and weighed 85 g. It analyzed for 83.5% pure dimercaptopropyl urea.

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The impure oil was shaken under nitrogen with 800-850 cc. of warm distilled water, cooled to room temperature and allowed to settle. The cloudy solution was decanted from undissolved oil (18 g.) and shaken with 20 g. of acid-extracted kieselguhr and filtered by suction. The clear filtrate was rapidly stirred while cooled in a freezing mixture of dry ice and methanol until the solution solidified. The solid ice cake, in which fine crystals of product were dispersed, was allowed to warm up to the melting point and the crystals were then filtered by suction, dried in a desiccator, yielding 36 g. of tiny white flakes analyzing for 36.2% mercaptosulfur or 94% purity.

The product was usually submitted in this form since further purification of dimercaptpropyl urea was not generally possible although crystallization of small amounts was effected in isolated cases. A sample which analyzed for 99% of the theoretical thiol sulfur (mp. 79-81°) was obtained from ethanol-ether mixtures but when applied to the purification of larger or less pure samples, only oils were obtained. Evaporation of a methyl acetate solution of 82% crude, after removal of the insoluble oil, raised the purity to 89%, but reprocessing beyond this value was not possible. The total analysis of this product is as follows.

Calcd. for  $C_4H_{10}ON_2S_2$ : C, 28.90%; H, 6.03%; S, 38.57%; N, 16.85%.

Found: C, 28.75, 28.78%; H, 6.20, 6.19%; N, 16.23%; S, 36.93, 36.49%; S(H), 34.4%; Br, 0.22, 0.20%.

Ammonium 2,3-Dimercaptpropionate

Thirty five grams of dimercaptpropionic acid was dissolved in 200 cc. of ether and cooled to 0°. Ammonia gas was bubbled into the solution until no further precipitation occurred. One-half of the ether was removed by evaporation on a steam bath and enough absolute alcohol was added (about 120 cc.) to just dissolve all the solid. Upon cooling, the product crystallized as white flakes; these were filtered off and dried in vacuo, yielding 36 g. (93% of theory) of slightly hygroscopic crystals which melted between 80 and 85° with decomposition.

Anal. calcd. for  $C_3H_9O_2NS_2$ : C, 23.21%; H, 5.84%; S, 41.31%; N, 9.02%.

Found: C, 23.70%; H, 5.99%; Total S, 40.5%; S(H), 41.3%; N, 8.89%.

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Monoglyceride of 2,3-Dimercaptopropionic Acid

Thirteen and eight tenths grams (0.1 mole) of dimercaptopropionic acid and 11 g. (0.12 mole) of clear glycerol were placed in a 100 cc. flask provided with stirrer and inlet for purified nitrogen. The flask was heated to 115-118° while nitrogen was slowly bubbled through the solution. Analyses were taken periodically to determine the degree of esterification and also the extent of decomposition as shown by the drop in thiol value. These figures are listed in the table below.

Time (hrs.)	0	4	7	10	12
% Residual Acid	55.6	25.6	18.3	12.9	12.0
% Acid by Thiol Titration	55.6	59.0	57.0	55.5	55.5

When corrected for volatilization of water produced, the last figure in line 3 represents 5.5% decomposition. The analysis indicated roughly 65% esterification. Attempts to purify the product by distillation or extraction resulted in decomposition.

2,2-Dimethyl-4-Hydroxymethyl-1,3-Dithiolane

Fifty grams of BAL was dissolved in 200 cc. of acetone and dry HCl was bubbled into the solution for a few minutes. By the time the mildly exothermic reaction had subsided, no thiol sulfur remained. The solution was poured into water, extracted with ether and the ether extracts dried over Na<sub>2</sub>SO<sub>4</sub>. Upon evaporation of the ether, the residue crystallized; recrystallization from petroleum ether (b.p. 30-75°) yielded 63 g. (93%) of white needles, m.p. 54-55°.

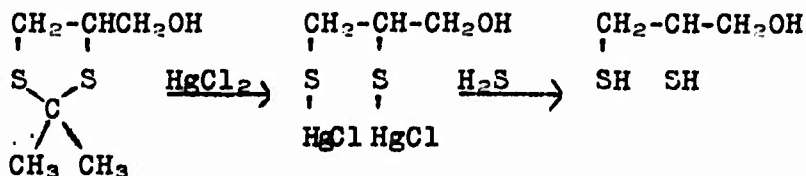
Anal. calcd. for C<sub>6</sub>H<sub>12</sub>OS<sub>2</sub>: C, 43.86%; H, 7.36%; S, 39.03%.

Found: C, 43.68%; H, 7.79%; S, 39.13%.

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Regeneration of BAL from the Acetone Derivative



Twelve grams of 2,2-dimethyl-4-hydroxymethyl-1,3-dithiolane was dissolved in 100 cc. of methanol and a solution of 80 g. of  $\text{HgCl}_2$  in methanol was added with immediate precipitation of a white solid. After standing overnight, the now tan-colored solid was filtered off and washed with methanol. A sample dried in vacuo had the following analysis:

Found: Hg, 64.8%; S, 8.62%; Cl, 15.82%.

Calcd. for  $\text{C}_3\text{H}_6\text{OS}_2\text{Hg}_2\text{Cl}_2$ : Hg, 67.4%; S, 10.8%; Cl, 11.95%.

Thirty seven grams of the mercury mercaptide was suspended in methanol in a pressure (citrate) bottle and the suspension saturated with  $\text{H}_2\text{S}$  at  $0^\circ\text{C}$ . The bottle was capped and allowed to stand overnight at room temperature. After filtering off the mercuric sulfide, the solvent was removed under reduced pressure leaving 6 g. of brown oil analyzing for 50.3% thiol sulfur as compared with 51.6% theory for BAL. The compound was not characterized further.

2,5-Dimercaptothiadiazoole

The directions of Dubsy and Okac, Zeit. Anal. Chem., 96 268 (1934), were modified slightly to permit the substitution of hydrazine hydrate for the sulfate in this preparation. Thirty five grams of 85% hydrazine hydrate, 60 g. of carbon disulfide, 300 cc. of water and 100 cc. of alcohol were mixed in a 1-l. round-bottomed flask. A solution of 20 g. of sodium hydroxide in 80 cc. of water was added carefully to the stirred solution, some heat being generated during this addition. The contents of the flask, which consisted of 2 layers, were refluxed carefully for about 3 hours after the lower, carbon disulfide, layer had disappeared. At the end of this time, the solution was cooled and acidified with a large excess of conc.  $\text{HCl}$ , a white voluminous precipitate forming. The dried solid, 30 g., which had turned slightly yellow was recrystallized from

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either ethyl acetate or benzene-alcohol mixtures to yield 11 g. of large, yellow crystals. Analysis for mercapto sulfur was best accomplished in water, one hour being required for each titration. Two melting-points have been reported for this derivative, 163 and 173°; this preparation corresponded to the lower figure.

Anal. calcd. for  $C_2H_2N_2S_2$ : S, 64.02%; S(H), 42.7%; C, 15.99%; H, 1.34%; N, 18.65%.

Found: S, 64.73%; S(H), 43.0%; C, 16.14, 16.06%; H, 1.18, 1.59%; N, 18.35%.

BAL-bis-Phenyl Urethane

1.1 cc. of phenyl isocyanate was mixed with 1 cc. of BAL, a small drop of triethylamine was added and the mixture became warm. A second and then a third addition of 1.1 cc. of the isocyanate was made. The solidified reaction mixture was cooled, broken up, stirred with petroleum ether, filtered, and washed with benzene. After recrystallization from 95% ethanol, the white solid melted at 136-137°.

Anal: Found, S(H), 0%; S, 17.53, 17.4%; N, 7.88, 8.01%.

Calcd. for  $C_{17}H_{18}O_3N_2S_2$ : S, 17.7%; N, 7.75%.

BAL-Glucose Mercaptal

24.8 g. of BAL and 36.0 g. of glucose were mixed. Forty cc. of concentrated hydrochloric acid was added during 15 minutes with shaking and cooling. The viscous mixture was then allowed to stand at room temperature for 1.5 hours. Titration of an aliquot of the solution indicated the disappearance of substantially all of the mercapto groups. The mixture was then poured into 300 cc. of stirred anhydrous ethanol. A gummy solid separated which on recrystallization from dilute methanol yielded 11 g. of hard white solid. On cooling the original filtrate 26 g. of white crystals were obtained. Recrystallization of the latter from aqueous methanol yielded 14 g. of the BAL-glucose mercaptal.

This mercaptal does not melt well and the yield of crystalline product is low presumably because it is a mixture of diastereomers. The main solid fraction shrunk at 110-120°, darkened and melted with decomposition at 123-128°. Other crops and batches similarly melting variously from 100 to 150°C. The mercaptal is but sparingly soluble in cold water.

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Anal. Found: C, 37.34%; H, 6.35, 6.68%; S, 23.3, 23.1%; Cl, 0.36%. M.W. = 256.

Calcd. for  $C_9H_{18}O_6S_2$ : C, 37.78%, H, 6.35%; S, 22.4%.  
M.W. = 286.

BAL-ortho-Sulfobenzaldehyde Mercaptal

Forty grams of the sodium salt of benzaldehyde orthosulfonic acid and 23.8 g. of BAL were dissolved in 150 cc. of anhydrous ethanol and warmed on a steam bath for 1 hour. On cooling 40 g. of green crystals separated. These were recrystallized from aqueous ethanol, yielding 20 g. nearly white solid. The compound did not melt up to 220°. This mercaptal is very soluble in water.

Anal. Found: C, 37.78, 38.13%; H, 4.93, 4.80%;  
S, 28.77, 28.62%;

Calc. for  $C_{10}H_{11}O_4S_3Na$ : C, 38.2%; H, 3.52%;  
S, 30.6%.

The hydrogen and sulfur analyses are not in good agreement possibly indicating that the salt may form a hydrate or alcoholate.

BAL-Formaldehyde-Diethanolamine

Twenty six and five tenths grams of 37% formaldehyde solution was added with cooling to 33.6 g. of redistilled diethanolamine. To the resulting mixture 40 g. of BAL was added in portions and with cooling. The product was a viscous colorless syrup freely soluble in water. Titration of a sample with iodine solution indicated that practically all the mercapto groups in the BAL were still reactive toward the reagent.

BAL-Formaldehyde-Ethylacetamide

This derivative could be prepared by mixing 124 g. (1 mole) of BAL, 174 g. (2 moles) of N-ethyl acetamide and 162 g. (2 moles) of 40% formalin in that order. The reaction was exothermic but cooling was not required since it seldom exceeded 50°. After cooling the derivative was characterized by titration of a weighed sample with standard iodine first in absolute and then in dilute alcohol or water. The first figure represented free thiol and was used to define "percent coverage"; in general, 93-95% of the BAL was "covered" in this derivative and was therefore not available for titration

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in non-aqueous systems. Upon dilution with water, cleavage of the unstable thioether link of the compound occurred, and all the BAL present would titrate with dilute iodine.

If paraformaldehyde was used in the preparation, a high proportion of stable mercaptal linkages would form as shown by low values for titration in dilute alcohol (70-80% of theory) and formation of water insoluble products.

BAL-Methylglucamine

Forty and three tenths grams of recrystallized methylglucamine was partially dissolved in 34.7 g. of water. Twenty five grams of BAL was then added and the mixture shaken until solution was complete. This product also developed a pink color and was fully water-soluble.

Sulfurization of Undecylenic Acid

Sixty one grams of undecylenic acid, 32 g. of sulfur, and 0.6 g. of diphenylguanidine were stirred and heated at 135° for 8 hours. The resulting product was a black viscous oil which contained no undissolved sulfur. This material was heated in a shaker tube for 4 hours at 150° with 15 g. of hydrogen sulfide and 10 g. of cobalt trisulfide catalyst. Hydrogen was then added to 2000 lbs. per sq. in. pressure, and hydrogenation continued 4 hours. After removal of the catalyst, excess hydrogen sulfide, and solvent, the residue consisted of 76 g. of a slightly brown viscous oil containing 11.2% S(H). It was distilled at 0.3 to 0.7 mm. (bath 160-200°). The distillate came over at a head temperature principally of 150-165°. On cooling, 19 g. of white solid separated from the distillate. It contained 13.7% S(H) and melted at 40.5-41.0°. The calculated value for monomercaptoundecanoic acid is 14.7% S(H).

Allyl 2,3-Dihydroxypropyl Ether

This intermediate was first prepared by the reaction of sodium monoglycerate with allyl bromide, but mechanical difficulties involved in separating the product from the viscous mixture resulted in low yields. For this reason, the Williamson synthesis was reversed as described below, with better results.

Seventy nine grams (3.3 atoms) of sodium was dissolved in 750 cc. of allyl alcohol and to the still warm (50-60°) solution was added 330 g. (3.0 mole) of glycerol-alpha-monochlorohydrin, the addition requiring about 3 hours.

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The contents of the flask were then heated to 50° for 1 hour after which titration of an aliquot indicated the correct amount of residual alkali.

The excess allylate was neutralized with conc. HCl (17 cc.) and after cooling the salt was filtered off and washed with ether. The ether and excess allyl alcohol were removed by distillation under reduced pressure. The product was distilled through a 2' precision still, boiling range 90-93°/1.9 mm. The yield was 220 g. or 55% of theory.

2,3-Dibromopropyl-2',3'-Dihydroxypropyl Ether

One hundred and thirty two grams of allyl dihydroxy-propyl ether was dissolved in 200 cc. of chloroform and brominated with 160 g. of bromine, the temperature being kept below 15°. The solution was then placed over sodium sulfate containing 1 g. of sodium bicarbonate and 1 g. of sodium bisulfite. After filtering, the solvent was removed under reduced pressure leaving a thick brownish syrup weighing 252 g. The material was used as such after some preliminary work indicated that purification by distillation or crystallization was not feasible.

Anal. calcd. for  $C_6H_{12}O_3Br_2$ : C, 24.69%; H, 4.14%; Br, 54.73%.

Found: C, 24.64%; H, 4.43%; Br, 54.91, 55.27%.

2,3-Dimercaptopropyl-2',3'-Dihydroxypropyl Ether

Into a precooled 1-1. Parr bomb was charged 165 g. of crude dibromopropyl dihydroxypropyl ether and 500 cc. of a sodium hydrosulfide solution prepared from 35 g. of sodium in methanol saturated with hydrogen sulfide. After pressuring to 100 lb. with hydrogen sulfide, the bomb was shaken for 20 hours at room temperature and then 1 hour at 50°.

The reaction mixture was acidified with 43 cc. of conc. HCl and filtered from the precipitated salt. The solvent was removed under reduced pressure leaving a pasty mixture of salt and thick oil. One hundred cc. of water was added and the lower organic layer was withdrawn, weight 118 g., thiol sulfur 11.8% as compared with 32.6% calculated for the dithiol. This crude product was suspended in 200 cc. of water and cooled, with stirring, to -10°. While a stream of nitrogen was flowing over the surface of the solution, 150 cc. of 40% NaOH was added in a thin stream. The neutral impurities were extracted, under  $N_2$ , with 200 cc. of ethyl

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acetate, and the aqueous solution of sodium mercaptide returned to reaction flask. Conc. HCl was added to the solution kept below 10° by appropriate cooling until acid to congo red paper. The oil was extracted with ethyl acetate, dried and the solvent removed under reduced pressure. There remained 52 g. of oil analyzing for 23% S(H). or 71 percent purity.

Distillation of this product resulted in decomposition and further purification by extraction of the mercaptide did not increase the thiol value.

Attempted Preparation by Hydrogenation of the Trisulfide Polymer

Sixty grams of dibromopropyl dihydroxypropyl ether was added dropwise to a solution of Na<sub>2</sub>S<sub>3</sub> prepared from 51 g. of Na<sub>2</sub>S·9H<sub>2</sub>O, 14 g. of sulfur and 50 cc. of water. Magnesium hydroxide was used as the dispersing agent. The addition of dibromide was conducted at 50° and the stirred mixture was digested for 4 hours at 65-70°.

The brown granular precipitate was filtered and washed several times with alcohol to remove a dark gummy coating to yield 40 g. of air-dried polymer. Hydrogenation of this material in dioxane at 125°C. over 7 g. of cobalt sulfide catalyst was apparently unsuccessful since the hydrogen absorption was very small. Upon removal of the catalyst it was observed that fine granules of the original polymer which apparently did not dissolve were retained on the filter paper. A clear yellow filtrate was blown with nitrogen to remove hydrogen sulfide by titration of an aliquot with normal iodine. Only 3 g. of the desired dithiol was indicated

Process Development Work on Dimercaptpropyl Ethyl Ether

In the exploratory stages of the program on dithiols this analogue of BAL had been prepared by hydrogenation of the corresponding trisulfide polymer, a process which does not lend itself readily to synthesis on a plant scale. In addition, yields obtainable by this method were 40% for the hydrogenation step and precise fractionation was required to obtain samples of acceptable purity. These considerations suggested that other synthetic methods be investigated to fulfill a special request of the services, assuming that toxicity and therapy data could be duplicated with the new compositions. One of the considerations in the choice of an alternate procedure was practicability for large scale operation and availability of starting materials and equip-

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ment. This ruled out the more involved techniques such as thioacetic acid-pyridine thionation. Direct alkylation of BAL did not seem feasible in the light of previous chemical experience with this compound. Sulfurization and subsequent hydrogenation of allyl ethyl ether was known to give low yields of a product containing a considerable amount of high thiol sulfur impurities and in all probability would not be therapeutically acceptable. Early in the analog program a run had been made on the 2,3-dibromopropyl ethyl ether under the preferred BAL conditions without success, however. It seemed advisable to repeat this experiment since its transfer to production could utilize existing BAL equipment and experienced personnel. An additional factor in any case would be the production of allyl ethyl ether as a starting material because of its present limited commercial availability. Several leads were at our disposal and required investigation.

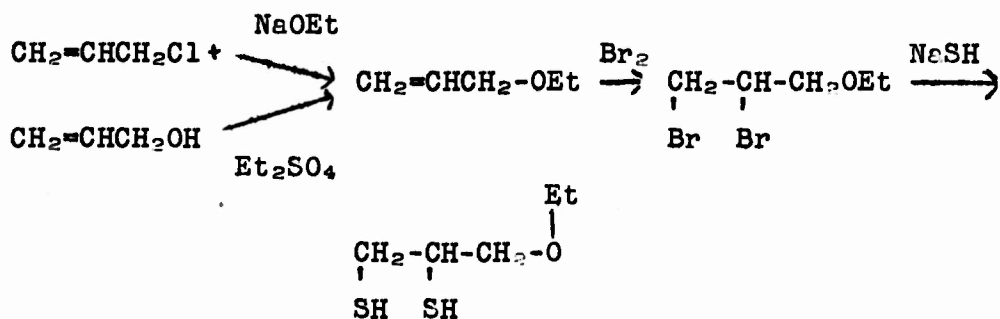
Some of the difficulties previously encountered with the BAL process are not to be anticipated with this analog and the stability of the ether as compared with the hydroxyl function is reflected in increased yields and greater stability of the product and its intermediates. Thionation with sodium hydrosulfide proceeded with unexpected smoothness and yields of 60 to 68% were consistently obtained. Dibromopropyl ethyl ether of excellent purity was prepared almost quantitatively from allyl ethyl ether. Lacking a commercial source for the latter intermediate two methods for its preparation were studied. The classical Williamson method, i.e. allyl chloride and sodium ethylate, gave a yield of 85% of the desired ether although the twice distilled product contained more than 15% ethyl alcohol. Bromination in the presence of this impurity did not affect the yield or quality of the dibromopropyl ethyl ether but it is conceivable that difficulty might arise if the reaction were not controlled. Alcohols in the presence of bromine are known to form perbromides which might possibly lead to secondary reactions. In addition these higher bromides are undoubtedly corrosive to steel equipment. Operation of a plant using absolute alcohol would be necessarily limited by government regulations.

Consequently, an alternative process, the alkylation of allyl alcohol with diethyl sulfate was studied. In this case water was the main impurity and some difficulty was encountered in its removal. Drying agents for ethers were not satisfactory and fractionation during which all the water collected in the foreshots resulted in considerable

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material losses. An undried sample was carried through the bromination and thionation procedures with no adverse effects on the final product. This process should therefore have important advantage over others because of its simplicity.

A formulation of the preferred synthesis is given below, together with experimental details on the several steps:



I. Preparation of Allyl Ethyl Ether

A. ex-Allyl chloride

Two hundred and forty-eight grams (10.8 atoms) of sodium was dissolved, with heating in the later stages, in 3250 cc. of absolute alcohol contained in a 5-l. 3-necked flask equipped with a sealed stirrer, dropping funnel and reflux condenser. To the still warm (50-60°) solution was added 765 g. (10 moles) of allyl chloride, the rate of addition being such as to maintain slow reflux, altogether requiring about 4 hours. At the end of this time 0.9 mole of alkali remained as compared with 0.8 mole calculated. This excess was neutralized with 80 cc. of conc. HCl and the reflux condenser was replaced with one designed for downward distillation. The solution was stirred, to prevent bumping because of the salt precipitate, while heated on a water bath. The following data characterizes this primary distillation:

B.p.	Wt.	I <sub>2</sub> No.	Allyl ethyl ether content
64-74°	1615 g.	141.3	47.9%
74-78	1290 g.	22.3	7.5%
Residue	755 g.		

The total weight of distillate and residue was 3660 g. compared with calculated 3679 g. which represents less than 0.6% material loss.

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Redistillation of the first cut of the primary distillation in a precision still gave the following fractions:

1	41-61°	(2 phases)	110 g.
2	61-63°	(66-67° = pure product)	775 g. (81% product, I <sub>2</sub> No.=238,2, d <sub>4</sub> <sup>25</sup> = .8853)
3	63-78°	(EtOH)	<u>620 g.</u> 1505 g.

Cut 1, upon removal of the water and drying, gave an additional 64 g. of product or a total yield, with allowance for purity, of 80%.

B. ex-Allyl alcohol

Into a 5-l. 3-necked flask equipped with swivel stirrer, dropping funnel and a total-reflux, partial take-off condenser was charged a solution of 368 g. (8.15 moles) of U.S.P. sodium hydroxide in 800 cc. of water and 465 g. (8.0 moles) of allyl alcohol. The flask was cooled in running water and 1355 g. (8.1 moles) of diethyl sulfate was added in a thin stream to the rapidly stirred solution. The reaction was only slightly exothermic and no difficulty was experienced in maintaining the temperature of the mixture below 30°. Following the addition, which required about 1.5 hours, stirring was continued at room temperature overnight. At the end of this, titration of an aliquot of the solution for excess alkali indicated that the reaction was 95% complete. Distillation was effected by heating the stirred contents of the flask to 80° by means of a water bath, 775 cc. (590 g. ) of distillate being collected. This wet product was dried, after removal of a 22 cc. water layer, with 45 g. of CaSO<sub>4</sub> and distilled. Prior to distillation 88 g. of the crude was withdrawn for a special use.

Charge: 461 g. of filtered crude.

1.	b.p. 48-64°	28 g.
2.	b.p. 64-67°	376 g. (88% pure)
3.	Residue	26 g.

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Cut 2 represents a 65% yield with suitable allowance for the 88 g. which was not further purified. The product has a density at 25° of 0.7653 and an iodine no. of 259.1, 261.9 (theory = 296).

A test piece of 18-8 stainless steel placed in the reactor was in no way affected by the reagents as shown by constant weight.

II. Preparation of 2,3-Dibromopropyl Ethyl Ether

A. From Allyl Ethyl Ether ex-Allyl Chloride

In a 5-l. 3-necked flask equipped with stirrer, dropping funnel and thermometer well was placed 765 g. of allyl ethyl ether (ex-allyl chloride, 81% pure, therefore 7.2 moles) and 2270 g. of chloroform. The solution was cooled in ice to 10° and 1185 g. (7.4 moles) of bromine was added at the rate of 400 g./hr., the temperature being maintained below 20° by appropriate cooling. A yellow color developed, probably due to perbromide formed as the result of the presence of ethanol as an impurity in the ether. At the end of the reaction, the orange solution was stripped of a large part (1935 g.) of the solvent by passage through a flash still and the residue was distilled through a short (4 inch) still-head. An additional 540 g. of  $\text{CHCl}_3$  was collected at 200 mm. followed by a 37 g. cut of indeterminate boiling point. The latter was highly colored and probably was the cause of color in the bromination. Product was collected at 61°/4 mm., 1739 g. or 96% of theory.  
 $n_D^{25} = 1.4979$ ,  $d_4^{25} = 1.6833$ .

A test piece of 18-8 stainless placed in the reactor lost 0.03 g./sq.cm. No corrosion tests were made during the distillation of product.

B. From Allyl Ethyl Ether ex-Allyl Alcohol

Two hundred forty-seven grams (88% pure, therefore, 2.53 moles) of allyl ethyl ether (ex-allyl alcohol) was brominated in 650 g. of chloroform with 460 g. of bromine as described above. The boiling point of the product was 67-69°/6 mm., weight 646 g. (92%). A stainless steel test piece suspended in the bromination lost 0.031 g./sq. cm.

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C. Bromination of Crude Allyl Ethyl Ether

To determine whether crude allyl ethyl ether could be brominated directly without the costly distillation step, a sample of the ether prepared in Section I-B, above, which had been distilled directly from the reaction mixture, was reacted as follows: Eighty-six grams (about 83% pure) of the superficially dried ether was dissolved in 200 cc. of  $\text{CHCl}_3$  and cooled ice. A cloudiness due to separating water developed. To the stirred solution was added, dropwise, 160 g. (1 mole, therefore an excess) of bromine. After all the bromine had been added, the chloroform was removed by distillation at 60 mm, and a highly colored foreshot (10 g.) of indeterminate boiling point was collected. Water-white product distilled at  $69-72^\circ/7$  mm. and weighed 205 g. or 83% based on the crude ether.

Anal. Calc. for  $\text{C}_5\text{H}_{10}\text{OBr}_2$ : Br, 65.0%

Found: Br, 65.31, 65.40%  $d_{25}^{25} = 1.7000$

The refractive index at  $18^\circ$  was 1.5020 as compared with 1.5011 for the dibromide prepared from redistilled ether.

III. Thionation of Dibromopropyl Ethyl Ether

A solution of sodium hydrosulfide was prepared by dissolving 66 g. (1.65 moles) of U.S.P. sodium hydroxide in 500 cc. of methanol and saturating the solution with  $\text{H}_2\text{S}$  at  $0^\circ$ . Into a 1-1. stainless steel (18-8) rocking autoclave was charged this solution and 123 g. (0.5 mole) of 2,3-dibromopropyl ethyl ether. The vessel was closed and hydrogen sulfide admitted with intermittent rocking until a constant pressure of 75-100 lbs. was obtained indicating complete saturation. About 50 minutes was required for the charging and pressuring operations. The autoclave was then heated with rocking according to a schedule designed to explore for optimum conditions; the results are given in Table I-A. When the heating schedule was completed, the bomb was cooled, discharged and rinsed twice with 50 cc. portions of methanol. About 1 lb. of  $\text{H}_2\text{S}$  was used for each run although no attempt was made to collect the gases during the bleeding-off. The green solution upon acidification with conc.  $\text{HCl}$  (50 cc.) turned yellow. Salt was removed by filtration and the methanol stripped off by passage through a flash still. The

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residue, which consisted of a wet suspension of salt in a yellow oil, was diluted with 500 cc. of water and the separating oil layer removed. For Run 3, Table I-A. The product at this point weighed 64 g. and analyzed for 39.6% S(H) as compared with 42.1% theory. After drying over 15 g.  $\text{CaSO}_4$ , the dithiol was distilled without fractionation through a 4 inch vigreux still head, in this way succeeding runs could be compared without the complication of duplicating a previous fractionation. Redistillation of any of the runs in Table I-A gave products which were identical in every way chemically and therapeutically with the dithiol prepared by the polymer-hydrogenation method.

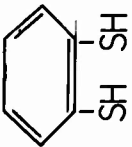
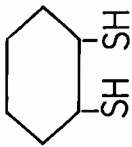
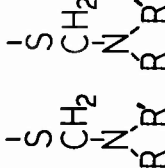
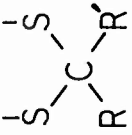
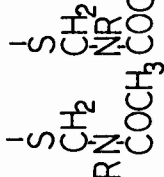
F. K. Signaigo

A. A. Pavlic

Approved by  
W. A. Lazier  
Group Leader

AAP:JHS  
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11/6/44

TABLE I.

$\begin{array}{c} \text{H}-\text{CH}-\text{CH}-\text{H} \\   \quad   \\ \text{SH} \quad \text{SH} \end{array}$	$\begin{array}{c} \text{CH}_2-\text{CH}-\text{CH}_2-\text{OH} \\   \quad   \\ \text{SH} \quad \text{SH} \end{array}$	$\begin{array}{c} \text{H}-\text{CH}-\text{CH}-\text{COOH} \\   \quad   \\ \text{SH} \quad \text{SH} \end{array}$
<ul style="list-style-type: none"> <li>-CH<sub>3</sub></li> <li>-C<sub>2</sub>H<sub>5</sub></li> <li>-C<sub>6</sub>H<sub>13</sub></li> <li>-C<sub>14</sub>H<sub>29</sub></li> <li>-CH<sub>3</sub></li> <li>-C<sub>6</sub>H<sub>5</sub></li> </ul>	<ul style="list-style-type: none"> <li>-CH<sub>2</sub>OH</li> <li>-OCOC<sub>2</sub>H<sub>5</sub></li> <li>-OCOC<sub>2</sub>H<sub>5</sub></li> <li>-OCOC<sub>3</sub>H<sub>7</sub></li> <li>-OCH<sub>3</sub></li> <li>-OC<sub>2</sub>H<sub>5</sub></li> <li>-OC<sub>3</sub>H<sub>7</sub> (iso)</li> <li>-OC<sub>4</sub>H<sub>9</sub></li> <li>-OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OH</li> <li>-GLUCOSIDE</li> </ul>	<ul style="list-style-type: none"> <li>-COOCH<sub>3</sub></li> <li>-COONH<sub>4</sub></li> <li>-(CH<sub>2</sub>)<sub>6</sub>COOH</li> <li>-(CH<sub>2</sub>)<sub>7</sub>COOH</li> </ul>
<ul style="list-style-type: none"> <li>CH<sub>3</sub></li> <li></li> <li></li> </ul>	<ul style="list-style-type: none"> <li></li> <li></li> <li></li> </ul>	$\begin{array}{c} \text{CH}_2-\text{CH}-\text{CH}_2-\text{NH}_2 \\   \quad   \\ \text{SH} \quad \text{SH} \end{array}$
$\begin{array}{c} \text{CH}_2-\text{CH}-\text{CHO} \\   \quad   \\ \text{SH} \quad \text{SH} \end{array}$	$\begin{array}{c} \text{CH}_2-\text{CH}-\text{CH}_2-\text{SH} \\   \quad   \\ \text{SH} \quad \text{SH} \end{array}$	$\begin{array}{c} \text{N}=\text{N} \\    \quad   \\ \text{HSC} \quad \text{S} \\   \quad   \\ \text{CSH} \end{array}$
<ul style="list-style-type: none"> <li>-OC<sub>2</sub>H<sub>5</sub></li> <li>-OC<sub>2</sub>H<sub>5</sub></li> <li>-SC<sub>2</sub>H<sub>5</sub></li> <li>-SC<sub>2</sub>H<sub>5</sub></li> </ul>	$-\text{SC}_{12}\text{H}_{25}$	$\text{H}_2\text{N}-\text{C}(\text{S})-\text{NH}-\text{C}(\text{S})-\text{NH}_2$

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TABLE I-A  
 THIONATIONS OF DIBROMOPROPYL ETHYL ETHER

Run	Source of Ether	Heating Schedule	B.P.	Weight of Distillate	Yield	%Purity by S(H)	$n_D^{25}$ *
1	ex-allyl chloride, prepn II, .	25°/24 hrs. then 50°/2 hrs.	47-49°/1mm	49 g.	64%	93.8%	1.5028
2	"	50°/6 hrs.	54-56°/2mm	48 g.	63%	98.8%	1.5030
3	"	65°/6 hrs.	51-53°/1.2mm	51 g.	67%	99%	1.5032
4	"	75°/6 hrs.	51-53°/1.5mm	52 g.	68%	99%	1.5030
5	ex-allyl alcohol, prepn II, B.	65°/6 hrs.	47-49°/1mm	47 g.	62%	99.5%	1.5042




\*Compare with  $n_D^{25} = 1.5047$  for pure sample of 2,3-dimercaptopropyl ethyl ether

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TABLE II

Summary of Experiments which did not lead to Dithiols

CASPER - COMMENT

A	Reactants and proportions		Molar B/A	Conditions	Remarks	Ref.
	1	2				
$\text{CH}_2=\text{CH}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{COOH}$	NASH	3		55°C., 4 hrs., MeOH under H <sub>2</sub> S pressure	Incomplete reaction - crude product contained no SH	4941-16
"	AS-CO <sub>2</sub> H <sub>2</sub>	2		5°C., 48 hrs., MeOH (KI catalyst)	After hydrolysis, product was low in SH	4941-81
$\text{CH}_2=\text{CH}-\text{CH}_2-\text{CH}_2-\text{COOH}$	ASH	2		75°C., 3 hrs., MeOH also at 25°C. for 18 hrs.	Incomplete reaction - crude products contained Br but only trace of SH	4941-14
$\text{CH}_2=\text{CH}-\text{COO}-\text{CH}_3$	NASH	3		-30°C. to 25°C., 30 hrs. in MeOH	Crude product contained but 6% SH	4941-109
"	As <sub>2</sub> S <sub>3</sub> (then H <sub>2</sub> )	1.05		25°C. in MeOH then hydrogenated at 100°C. (CS <sub>2</sub> cat.)	Only product isolated was methyl β-mercaptoacetate (36% yield)	4941-114
"	AS-CO <sub>2</sub> H <sub>2</sub> + 	2:2		15°C., 3 hrs. then hydrolyze (MeOH:H <sub>2</sub> O)	Crude product very low in SH	4941-120
$\text{CH}_2=\text{CH}-\text{COOEt}$	AS-CO <sub>2</sub> H <sub>2</sub>	2		25°C., 3 hrs. in MeOH then hydrolyze (HCl:MeOH)	Reaction - Some dithiol may have been produced but product low in SH	4941-75
$\text{CH}_2=\text{CH}-\text{COOEt}$	As <sub>2</sub> S <sub>3</sub> (then H <sub>2</sub> )	0.5:3		25°C. in MeOH then hydrogenated at 125°C. (CS <sub>2</sub> )	Only product isolated was methyl β-mercaptoacetate (23% yield) Chemical reduction also unsuccessful	4941-102
"	NASH	2:5		15°C., 30 hrs. in MeOH:SH also tried	3m produced - little thiol	4941-25
"	AS-CO <sub>2</sub> H <sub>2</sub>	2		25°C., 30 hrs. in EtOH	Product - an insoluble oil - did not hydrolyze to a thiol	4941-73
"	ASH	3		100°C., 1 hr. in H <sub>2</sub> O also in EtOH	No apparent reaction	4941-46, 58
"	As <sub>2</sub> S <sub>3</sub>	1.05		55°C. in H <sub>2</sub> O	Incomplete reaction but sulfone had partially hydrolyzed	5075-17
$\text{CH}_2=\text{CH}-\text{CH}_2-\text{CH}_2-\text{COOEt}$	S, then H <sub>2</sub>	3		125°C., 6 hrs. (diphenyl amine, cat.) then hydrogenate at 150°C., CS <sub>2</sub> cat.	Only monomercaptoacetic acid could be isolated	5075-18
	S <sub>2</sub> O <sub>12</sub> (then H <sub>2</sub> )	1		25°C., 26.15 cat. then hydrogenate, 125°C., CS <sub>2</sub> cat.	Thiophenol main product - low yield of β-benzenedithiol	5075-10
	S <sub>2</sub> O <sub>12</sub> (then H <sub>2</sub> )	1		"	p-Thiophenol main product - no dithiol obtained	5075-10
$\text{HOCH}_2-\text{CH}_2-\text{CH}_2-\text{OH}$	AS-CO <sub>2</sub> H <sub>2</sub>	3		25°C., 14 hrs. in U.V. radiation (ascorbic acid cat.)	No reaction	4941-91
$\text{CH}_2=\text{CH}-\text{COO}-\text{CH}_3$	ASCl <sub>2</sub>	1:1		5°C. - Several hrs. in CH <sub>2</sub> Cl <sub>2</sub> :CF <sub>2</sub>	No addition - (SCN) <sub>2</sub> polymerized	4941-76
$\text{CH}_2=\text{CH}-\text{COO}-\text{CH}_3$	AS-CO <sub>2</sub> H <sub>2</sub>	2		25°C. in MeOH	Immediate reaction but no thiol produced	4941-89
"	NASH	2:5		-30° to 5°C., in MeOH	Product contained but little SH (theory = 55.4% SH)	4941-24

CASPER - COMMENT

TABLE I (continued)

Reactants (and proportions)		Molar Ratio	Conditions	Remarks	Ref.
Phal	<chem>c1ccc(cc1)C(=O)O</chem>	1	100% in benzene, 12 hrs.	No reaction	4/25-2
"	<chem>c1ccc(cc1)C(=O)OC</chem>	1	25°C., 2 w/vs (12% est.) in dioxane	"	5/75-27
"	"	1	50°C., 4 hrs. (125% est.)	Malic acid produced	5/75-28
"	"	1	Same as 1 to dioxane soln. of reactants	Only itthalic acid produced	5/75-29
"	<chem>CC(=O)OC</chem>	1	50°C., 20 hrs. in dioxane	Succinic acid produced	5/75-25
"	<chem>CC(=O)OC</chem>	2	25°C., 101 est., 4 days	Very slow reaction	5/75-22
"	<chem>c1ccc(cc1)C(=O)OC</chem>	1	25°C., 101 est., 20 days	No reaction	5/75-23
"	<chem>c1ccc(cc1)C(=O)OC</chem>	1	50°C., 20 hrs. (103 est.)	Little reaction - 1/25 evolved	5/75-21
"	<chem>c1ccc(cc1)C(=O)OC</chem>	1	100% in dioxane, 50°C., 10 hrs.	No reaction, no loss of SO <sub>2</sub> or acid	5/75-24
"	<chem>c1ccc(cc1)C(=O)OC</chem>	1	100°C., 17 hrs.	Acid PVI recovered unchanged, 5% of SAH destroyed	5/75-26
<chem>c1ccc(cc1)C(=O)OC</chem>	<chem>c1ccc(cc1)C(=O)OC</chem>	4	25°C., 20 hrs. 1. est. under 1/25 pressure	Complete reaction as indicated by residual alkali and produced thiol. No crystalline product obtained and extracted residue contained fraction of theoretical thiol sulfur	5/75-12
"	"	4	25°C., 4. est. in benzene at 1/25 pressure	Small amount of what appeared to be monomercaptamine isolated	5/75-15
"	"	2	25°C., 49 days at 1/25 pressure	No reaction, no loss of SO <sub>2</sub> or acid	5/75-20
"	"	1:05	25°C. in 20 v/v benzene ester at 125% over / 100 g in dioxane	No reaction	5/75-130
"	"	3	25°C., 7 days	5% theoretical thiol sulfur produced	5/75-113
<chem>c1ccc(cc1)C(=O)OC</chem>	Station E2)	3	100°C., 0 hrs. di-tert-butylamine catal. at 1/25 pressure	All obtained reacting for fraction of theory	5/75-126
<chem>c1ccc(cc1)C(=O)OC</chem>	"	1:05	25°C., 10 hrs.	Order of ariene, incomplete reaction	5/75-137
<chem>c1ccc(cc1)C(=O)OC</chem>	<chem>c1ccc(cc1)C(=O)OC</chem>	1	50°C. mixture of reactants run into 100% dioxane	High molecular weight materials formed, 1 fraction seemed to be the di-(p-hydroxyethyl) thioether	4/41-17
<chem>c1ccc(cc1)C(=O)OC</chem>	<chem>c1ccc(cc1)C(=O)OC</chem>	1	25°C., 6 hrs.	Heterogeneous mixture. No pure product isolated	4/41-29
<chem>c1ccc(cc1)C(=O)OC</chem>	<chem>c1ccc(cc1)C(=O)OC</chem>	2	effluent in 100% dioxane	No esterification	4/41-125
<chem>c1ccc(cc1)C(=O)OC</chem>	Mannitol	1	Heated 100°C., 3 hrs.	Decomposition, no water soluble ester formed	4/41-165
<chem>c1ccc(cc1)C(=O)OC</chem>	1:5 (100%)	Large excess	4 days in 100% dioxane under 1/25	Rubbery polymer	4/41-152, 153
<chem>c1ccc(cc1)C(=O)OC</chem>	1:20 (100%)	1	Sealed tube, 100°C., 24 hrs.	Polymer formed, no water soluble thiol	4/41-153

CONTINUED - SUPPLEMENT



TABLE III

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## Reactions of Dithioglycidol

Compound	Time Hours	Temp. °C.	Remarks	N.S. 1961
Aniline	6	130	S(N) 17.6% before, 30.2% after heating.	33
"	12	130	" 17.6% " 29.2% "	35
"	12	150	" 16.9% " 23.4% "	36
"	8	130	0.3 Molar runs, yield 5% as hydrochloride.	42
Anthranilic acid	6,12,6,	130,130,	Polymeric sludges in all cases. Some evidence of reaction since no acid was	44
"	6	130,170	recovered but no monomeric dithiol isolated.	51
m-Aminobenzoic acid	6	130	" " "	107
p-Aminobenzoic acid	6	130	" " "	107
Et p-aminobenzoate	8	130	No reaction except partial polymerization of dithioglycidol. Ester recovered	117
"	6	130	as hydrochloride.	158
Aminosalicylic acid	6	130	Dark viscous polymer. Not worked up.	107
Sulfanilic acid	6	130	No reaction.	52
o-Aminophenol	6	130	Gum formation with residual phenol.	107
m-Aminophenol	6	130	No thiol extractable with acid.	107
p-Aminophenol	6,8	130,130	" " "	107,117
sym.-Dimethylurea	5	130	Contents of tube completely polymerized. Hard, glassy polymer; S = 30.76%,	52
"	6,6	110,130	N = 12.3%. Soft, insoluble gums; unreacted material removed with CHCl <sub>3</sub> leaving rubbery,	79
"	6	130	transparent polymer. S = 56.67%, N = .47%. Used 100% excess Me <sub>2</sub> urea to favor mono substitution but same results as previous	79
Thiourea	4,8,12,	120,120,	Rubbery polymer (S = 55.66, 55.23%, N = 3.79, 3.96%) and unreacted thiourea.	60,65,79
"	6	120,130	Analysis for polymer corresponds to 1 mol thiourea and 6 of DTG.	
Thioacetamide	4	130	No reaction except partial polymerization as shown by S(N) decrease during	52,77
Diethyl carbonate	2	-80	reaction. 30% excess BuSH stirred with dithioglycidol, one drop Et <sub>3</sub> N added. Partial	85
m-Dimethylurea	0,2	0	polymerization but BuSH recovered unchanged.	
"	24	25	Polymerization without incorporation of N. 0.05 N solution in CHCl <sub>3</sub> , deposited rosy polymer overnight. Polymer contained	53
"	Instantaneous	0	no N.	53
Isopropylamine	"	25	Clear, viscous polymer. No N.	53
Iperidone	6	130	Polymer.	53
Methyl glucamine	14	100	Unchanged Me glucamine and polymer. S = 53.96, N = 0.98%.	107
Ammonium chloride	"	"	No reaction.	54
Hydroxylamine hydrochloride	"	"	"	54
Sulfamic acid	4	150	"	66
Sodium sulfamate	6	130	Contents of tube solidified. Brittle polymer. S = 42.43%, Me = 15.79, 14.33%.	107,117
Sodium bisulfite	6	120	Partial reaction, but with carboxyl function.	54,60
o-Dimethyl glycine	4	130	Polymeric material only.	85
Sodium o-Aminethyl glycinate	6	120	Polymerization.	54
Leucine	12	130	Unreacted material washed away with CHCl <sub>3</sub> leaving rubbery polymer. S = 58.27%,	56
Oxycine	12	130	N = 0.86%. As above + 0.5 g. phenol as "catalyst" but same result.	56
Sodium phenylsulfonate	4	150	Reaction but no soluble thiol.	79
Cephalotin	1	25	Clear viscous polymer. S(N) = 20.1% at start, 6% in polymer.	82
Methyl xanthamide	3	"	Formed two layers: unchanged amide and clear polymer.	82
Nitroethane	3	"	Refluxed in methanol, no reaction.	82
"	6	120	" + 1 drop H <sub>2</sub> SO <sub>4</sub> . No reaction.	86
"	6	120	Heated on steam bath as 5% pyridine solution, formed polymer, N = Trace.	82
2-Nitroethanol-1	6	120	Partial polymerization; drop in original S(N). Two layers. Mercapto group probably reduced nitro group which then caused	82
Methoxyamine	8	130	polymerization. S(N) 16.8% before, 27.4% after reacting. Product would not distill or form a	140,166
Thioacetamide	6	130	crystalline hydrochloride, methoxide, etc. Reaction other than polymerization occurred but no dithiol isolated.	149

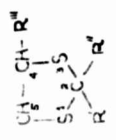
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TABLE V  
DIPICOLAYS DERIVED FROM VARIOUS DIIMIDES

COMPOUND	SOURCE	PREPARE	ANALYSIS	NOTEBOOK
2,2-Dimethyl-4-hydroxymethyl-1,3-dithiolane	HAL + HCl in excess acetone	needles from petroleum m.p. 54-55°C.	Calcd. for $C_6H_{12}O_2$ : C, 43.86%; H, 7.36%; S, 39.03% Found: C, 43.66%; H, 7.79%; S, 39.13%	5321-25
2,2-Dimethyl-4-chloromethyl-1,3-dithiolane	diacetoacetyl chloride + HCl in excess acetone	Not analyzed but converted to solid amine hydrochloride, m.p. 104-120°C.		5321-26, 31
2,2-Dimethyl-4-methylaminomethyl-1,3-dithiolane hydrochloride	corresponding chloride (above) and Et <sub>3</sub> NH in alcohol.		Calcd. for $C_8H_{22}NS_2Cl$ : C, 47.03%; H, 8.23%; S, 25.08%; Cl, 13.72% Found: C, 47.75%; H, 9.39%; S, 25.48%; Cl, 14.57%	5321-32
2,2-Dimethyl-4-carboxyl-1,3-dithiolane	diacetoacetyl acid + HCl in excess acetone	b.p. 121-220/1.5mm p.p. 51-53°C. from petroleum.	Acid no., called 170; Found, 182	5321-29
2,2-Dimethyl-4-carbamido-1,3-dithiolane	corresponding acid + urea or corresponding ester (below) + methanolic ammonia	m.p. 9-10°C.	Calcd. for $C_8H_{11}O_2N_2S_2$ : C, 40.68%; H, 6.23%; S, 36.17%; N, 17.90% Found: C, 40.44%; H, 6.75%; S, 36.75%; N, 17.87%	5321-33, 37, 60
2,2-Dimethyl-4-carbamatoxy-1,3-dithiolane	methyl diacetoacetyl ester + HCl in excess acetone	b.p. 73-74°C./0.5mm.	Not analyzed, converted to amide, above.	5321-37, 51
2,2-Dimethyl-4-bromomethyl-1,3-dithiolane	corresponding alcohol, above and HBr, H <sub>2</sub> SO <sub>4</sub>	b.p. 64-65°C./0.5 mm unstable at room temp. n <sub>D</sub> <sup>20</sup> 1.5757	Not analyzed, converted to solid amine hydrobromide, below	5321-38, 40, 58
2,2-Diethyl-4-piperidinium methyl-1,3-dithiolane hydrobromide	corresponding bromide and piperidine	measured m.p.	Calcd. for $C_{11}H_{22}NS_2Br$ : Br, 25.69%; S, 20.59%; N, 4.50% Found: Br, 26.23; S, 20.89; N, 4.65%	5321-56
2,2-Dimethyl-4-cyanomethyl-1,3-dithiolane	bromide + KCN	b.p. 73-73.5°C./0.25mm.	Calcd. for $C_7H_{11}S_2N$ : C, 48.51%; H, 6.35%; S, 37.04%; N, 8.08% Found: C, 53.05; S, 37.27; H, 7.50; N, 8.12; S, 37.04; N, 8.07%	5321-63
2-Thenyl-4-hydroxymethyl-1,3-dithiolane	HAL + $C_6H_5CHO$ + HCl in benzene 75% yield	m.p. 70-72°C.	Not analyzed, m.p. identical with earlier preparation	4941-180
2-Phenyl-4-chloromethyl-1,3-dithiolane	diacetoacetyl chloride + $C_6H_5CHO$ + HCl in benzene	m.p. 116-120°C.		4411-183
2-(2-sulfopropyl)-4-hydroxymethyl-1,3-dithiolane	0-sulfobenzaldehyde + HAL dissolved and heated in ethanol	m.p. 130-132°C.	Calcd. for $C_{10}H_{11}O_4S_2Na$ : C, 38.7%; H, 3.52%; S, 30.64%; Na, 7.3% Found: C, 38.13%; H, 4.93%; S, 28.77%; Na, 6.44%	5076-73
2-Propyl-4-hydroxymethyl-1,3-dithiolane	alucose + HAL in conc. aq. HCl	m.p. 123-125°C. with previous softening	Calcd. for $C_9H_{15}O_2S_2$ : C, 37.78%; H, 6.35%; S, 22.44%; Na, 28.6% Found: C, 37.34%; H, 6.35%; S, 23.3; Na, 23.1%	5075-46
2-(4-dimethylaminophenyl)-4-chloromethyl-1,3-dithiolane	HAL + p-dimethylaminobenzaldehyde + HCl (aq) hydroxyl replaced by Cl during condensation	obtained as a strip	Calcd. for $C_{12}H_{17}NS_2Cl$ : C, 20.04%; H, 4.52%; Cl, 22.6% Found: C, 18.44%; N, 4.55%; Cl, 23.06%	5075-52



ANALYSIS

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TABLE IV

ATTEMPTED MERCAPTANOLYSIS OF DITHIOLANES WITH "UNCOVERED" DERIVATIVES

REPROD AND WORK-UP

DERIVATIVE

2,2-Dimethyl-4-hydroxymethyl-1,3-dithiolane

0,0-Diethyl chloromethylthylene-S-  
of thiouracils (The bis-dithiocarbamate  
of dimercaptopropyl chloride)

2,2-Dimethyl-4-hydroxymethyl-1,3-dithiolane

REMARKS

NOTEBOOK

4941-134

Cleavage occurred but at wrong side of carbon-sulfur bond to yield benzyl mercaptan as the only thiol.

5321-15

Alkyl seems to be the correct reagent for the conversion but the lithium dimercaptopropyl chloride is not stable in its presence.

5321-27

HCl cleavage is not clear cut, high Cl may be indicative of replacement of hydrogen substituted HCl.

5321-28

Only successful regeneration

5321-42

5321-55

Attempted to induce dissociation to HAl and acetone the latter being hydrogenated to form the reaction to completion.

5321-44

Equilibrium lies too far on the mercaptols side. Might be forced. See next sample.

5321-46-59

5321-49-62

Generation of vinyl mercaptan derivatives seems indicated which rapidly condense to form sulfides.

5321-57

5321-54

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Hydrogenated 60% of mercaptol in 140 ml. dioxane for 2 hrs. over 1%  
20% Tack up 500-600 lbs. to yield a solid which was analyzed for 25%  
of liberated H<sub>2</sub>. Methylated, solids separated from main cut (40%) proved  
to be the starting material. Forcort contained benzyl mercaptan; 2,4-dinitro-  
phenylthioether, mixed est. with unknown amide 15%, reported 1940.

1. 1g. refluxed with 50 cc. 5% HCl for 2 hrs. No thiol S detected

2. 2g. refluxed 20 minutes with 5% NaOH. Polymer formed.

3. 2g. in 50 cc. 40% H<sub>2</sub>O - 2 jars. Deposited polymer

4. 2g. in 50 cc. methanolic HCl. Thiol S detected but somewhat less than  
theory after reflux overnight.

1. 0.1 mol of mercaptol and 0.5 mol of HCl, reacted in acetone to give 17 g.  
of mercaptolthioether deriv. of the dithiol. Calc. for C<sub>10</sub>H<sub>18</sub>S<sub>2</sub>: 46.4% S,  
77.4% C, 10.8% H, 11.9% S. Found, H<sub>2</sub> 44.8%, S 54.2%, C 15.5%, H  
7.4%. Solids suspended in methanol and after the necessary fil-  
tration, evaporation and distillation, 1g. of oil containing 96% S.H.  
(Theory for S.H. = 51.6%).

2. Repeated in presence of PbO<sub>2</sub> as HCl acceptor. Assa indicated no  
increase in thiol S over previous run.

3. 0.075 mol of mercaptol and 0.5 mol H<sub>2</sub>O<sub>2</sub> reacted in methanol. Mercaptol  
treated with H<sub>2</sub>S in methanol under pressure (citrates bottle). 6% (25%)  
of brown oil analyzing for 50.2% S.H. (S.H. = 51.6%)

4. 5% of dithiouracil hydrate and 3% of mercaptolthioether in NaOH to  
attempt exchange reaction. Thiol detected but by-products complicated  
work-up.

5. 0.1 mol mercaptol, 100 cc. NaOH and 20 cc. of standard Pd on C  
shaken in tube at 110°C. under 2000 lbs. H<sub>2</sub> pressure. No uptake of H<sub>2</sub>.

6. 0.1 mercaptol, in 50% dioxane, H<sub>2</sub>O containing 1 drop HCl. Pd-C catalyst  
no hydrogen adsorption

7. 0.2 g. para-toluene sulfonic acid. No appearance of thiol sulfur on  
reflux

8. 0.2 mol of the dithiolane, 70 cc. of ethylene glycol (C.P. Lytec) and  
para-toluenesulfonic acid reduced under 2000 lbs. H<sub>2</sub> pressure. No  
thiol S detected. Small amount of dioxane distilled and residual oil  
contained 1.5% of theoretical thiol sulfur.

1. 0.1 mol dithiolane, 70 cc. ethylene glycol and 0.1 g. para-toluenesulfonic  
acid (or HCl) as described previously, above, no H<sub>2</sub> or any thiol S  
or any thiol S liberated. 70% starting material recovered.

2. The mercaptolthioether derivative was formed from 17 g. of dithiolane and  
10 g. of H<sub>2</sub>O<sub>2</sub> in 50% dioxane. It was analyzed for thiol S and  
to no simple composition. It was suspended in acetone and  
presence of 10% of H<sub>2</sub>O<sub>2</sub>. H<sub>2</sub>S was run in to complete precipitation of H<sub>2</sub>S.  
Isolated although mercaptan was generated.

Found 8.1% chlorine. Amarat lizable oil containing 1% S.H. obtained.

Found 8.1% chlorine. S.P.P. containing 1% S.H. obtained.

APPENDIX  
9-25-44

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TABLE VII  
REACTIONS DIRECTED TOWARD COVERED-DIATYPES OF THE DITHIOLS

A		B		RATIO B/A	CONDITIONS	REMARKS	N.B.
REACTANTS	REACTANTS	REACTANTS	REACTANTS				
Dimercaptopropyl chloride	Ethyl chloroformate			2	Pyridine in ether added to cold mixture of A, B	5% yield of product distilling 160-162°C/7mm. Analysis: calc. for $C_{12}H_{18}O_4S_2$ : C, 52.7%; H, 5.2%; S, 22.7%. Found: C, 51.6%; H, 5.2%; S, 22.0%. Reaction indicated by complete disappearance of S(AE)	5321-17
Dimercaptopropyl chloride	Methylacetamide			2	Dry HCl run into mixture of B, A	No crystalline end. obtained. Reaction indicated by complete disappearance of S(AE)	5321-72
Dimercaptopropyl chloride	Methyl formate			1	HCl in benzene	No loss of thiol titer upon refluxing	5321-4
	Benzophenone			1	HCl in benzene	No loss of thiol titer upon refluxing	4941-179
	Benzophenone chloride (diphenylchloromethane)			1	2 Equiv. alc. KOH in benzene added. Mixture heated.	Blue coloration indicative of thiobenzophenone, observed. No crystalline material isolated.	5321-7
	Benzophenone chloride (diphenylchloromethane)			1	Pyridine solvent	Blue coloration indicative of thiobenzophenone, observed. No crystalline material isolated.	5321-18
	Acetic benzene			1	HCl in benzene	Slight loss of thiol titer but no product isolable.	5321-2
	Benzyl chloride			2	2 Equiv. of A:B in EtOH 60°C.	Incomplete reaction. Distillation yielded a fraction analyzing for thioether derivative (M.W. 200) compared with 14.2% theory.) but higher fractions decomposed.	5321-65
	Triethylamine			2	Pyridine in benzene at 25°C.	Partial reaction but product could not be crystallized.	5321-98
	N-Ethoxymethyl-methylacetamide			2	HCl in EtOH at 25°C.	Thiol sulfur largely "covered" but product could not be isolated.	5321-67
	N-Methylacetamide			1	HCl required to initiate reaction	One thiol group 50% covered.	5321-80
	N-Ethylacetamide			2	HCl in EtOH	Classy product obtained. Calc. for dibenzamidoethyl thioether of B:1: N, 7.2%; S, 16.4%. Found: N, 6.9%; S, 14.1%.	5321-74

ANAL. 3/26/44

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TABLE I

Yield of Purified Material

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Run	Dist.	Yield (%)	Yield (g)	Yield (Purified Material)
1-1102	1.1102	1.510	1.510	1.510
1-1102	1.5102	1.5102	1.5102	1.5102
1-1102	1.5102	1.5102	1.5102	1.5102
1-1102	1.5102	1.5102	1.5102	1.5102
1-1102	1.5102	1.5102	1.5102	1.5102

TABLE II

Yield of Purified Material

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Run	Dist.	Yield (%)	Yield (g)	Yield (Purified Material)
1-1102	1.5102	1.5102	1.5102	1.5102
1-1102	1.5102	1.5102	1.5102	1.5102
1-1102	1.5102	1.5102	1.5102	1.5102
1-1102	1.5102	1.5102	1.5102	1.5102
1-1102	1.5102	1.5102	1.5102	1.5102

1-1102

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TABLE X  
DISTRIBUTION OF BAL ANALOGS AND RELATED COMPOUNDS

NR	Compound	Submitted to	Acknowledgement
250	2,5-Dimercaptopropyl acetate	Dr. A. C. Cope, Dr. W. S. Durlacher, Dr. McKee Cattell, Dr. C. S. Marvel, Dr. K.S.G. Barron, Dr. H. G. Calvery, Dr. Wm. Bloom, Capt. A. L. Gilman, C. J. Kensler, Lt. TB. Talbot, Jr., Dr. P. H. Adler	
607	2,5-Dimercaptopropyl propionate	Calvery, Gilman	
608	2,5-Dimercaptopropyl butyrate	Calvery, Gilman	
391	2,5-Dimercaptopropyl methyl ether	Calvery, Gilman, Adler, Kensler, Durlacher, Talbot, Bloom	
293	2,5-Dimercaptopropyl ethyl ether	Dr. J. S. Friedenwald, Dr. Wm. Bloom, Dr. R. K. Harrison, Dr. L. H. Leopold, Dr. P. D. McMaster, Kensler, Durlacher, Barron, Calvery, Marvel, Cattell, Talbot, Gilman	
609	2,5-Dimercaptopropyl isopropyl ether	Calvery	
420	2,5-Dimercaptopropyl butyl ether	Kensler, Durlacher, Cattell, Gilman	
399	2,5-Dimercaptopropyl urea	Adler, Kensler, Cope, Bloom, Friedenwald, Durlacher, Talbot, Gilman	
400	2,5-Dimercaptopropyl urethane	Col. J. R. Wood, Cope, Kensler, Adler, Friedenwald, Bloom, Durlacher, Talbot, Barron, Calvery, Gilman	
709, 715	2,5-Dimercaptopropyl glucoside	Dr. Homer Smith, Harrison, Durlacher, Gilman	
153	2,5-Dimercaptopropyl dodecyl sulfide	Col. C. F. Rhoads, Marvel	
387	2,5-Dimercaptopropylamine	Bloom, Kensler	
420	Dimercaptopropyl chloride	Prof. Henry Runtig, Dr. F. C. McLean, Kensler, Calvery, Bloom, Gilman	Prepared by Dr. E. K. Ellingboe
417	2,4-Dimercaptopropionic acid	Dr. H. M. S. Thompson (Great Britain), Kensler, Bloom, Calvery, Friedenwald, Runtig, Cope, McLean, Wood, Adler, Durlacher, Talbot, Gilman	
518	Methyl 2,5-dimercaptopropionate	Kensler, Bloom, Durlacher, Calvery, Cope, Marvel, Talbot, Friedenwald, Gilman	
362	Ammonium 2,5-dimercaptopropionate	Dr. Karl Folkers, McMaster, Bloom, Adler, Kensler, Gilman, Durlacher	
386	3,4-Dimercaptotetrahydrothiophene-1-dioxide	McMaster, Kensler, Bloom, Durlacher, Friedenwald, Talbot, Gilman	
225	N-Phenylamino propanedithiol hydrochloride	Com. Marion B. Sulzberger, Dr. Maurice Sullivan, Dr. D. Wright Alton, Friedenwald, Cope, Bloom, Durlacher, Kensler	
202	10,11-Dimercaptoundecanoic acid	Friedenwald, Kensler, Bloom, Cope, Adler	
140	1,3,5-Trithioglycerol	Dr. W. R. Kirner, Dr. Homer Adkins, Dr. Harry Eagle, Talbot, Adler, Cattell, Durlacher, Calvery, Kensler, Barron	
154	1,2-Dimercaptopropene	Kirner, Adkins, Rhoads, Wilson, Kensler, Calvery, Gilman	Prepared by C. G. Wertz
152	1,4-Dimercaptopropene	Dr. L. L. Waters, Kirner, Rhoads, Kensler, Gilman, Bloom, Barron, Calvery	
121	Ethanedithiol-1,2	Dr. Vincent du Vigneaud, Dr. M. S. Kharasch, Lt. Col. W. E. Catlin, Adkins, Wilson, Gilman, Rhoads	
509	Dithiosorbitol	Runtig, Kensler	
428	Dithioacetohol	Bloom, Friedenwald, Kensler	Prepared by Dr. M. W. Farlow
164	Dithiopentacerythritol	Kirner, Rhoads	Prepared by C. G. Wertz with Dr. H.W. Parks
224	Dithiothuret	Dr. M. C. Minternitz, Kensler, Bloom, Friedenwald, Talbot, Sullivan, Sulzberger, Cope, Durlacher, Calvery, Gilman	
470	Phenylethanedithiol-1,2	Bloom, Durlacher, Gilman	Prepared by Dr. C. M. Langkammerer
447	Cyclohexanedithiol-1,2	Durlacher, Gilman	Prepared by Dr. C. M. Langkammerer
493	Octanedithiol-1,2	Durlacher, Gilman	Prepared by Dr. C. M. Langkammerer
494	Hexanedithiol-1,2	Durlacher, Gilman, Talbot	Prepared by Dr. C. M. Langkammerer
644	3,4-Dimercaptobutanol	Calvery, Adler, Talbot	
287	Diethanolaminoethyl dithioglycerol-1,2	Col. W. T. Fleming, Friedenwald, Kensler, Durlacher, Runtig, Bloom, Cope, Adler, Calvery, Gilman	KD-2 derivative of Dr. H. S. Kharasch
288	Methylglucaminomethyl dithioglycerol-1,2	Friedenwald, Kensler, Durlacher, Bunting, Bloom, Cope, Adler, Calvery	
289	Diethanolammonium dithioglycerol-1,2	Friedenwald, Kensler, Durlacher, Bunting, Bloom, Cope, Adler, Calvery	
290	Methylglucammonium dithioglycerol-1,2	Friedenwald, Kensler, Durlacher, Bunting, Bloom, Cope, Adler, Calvery	
372	Methylglucaminomethyl propanedithiol-1,3	Kensler, Cattell, Adler, Talbot, Durlacher, Eagle	
373	Methylglucaminomethyl trithioglycerol	Kensler, Talbot, Adler, Cattell, Durlacher, Eagle	
374	Methylglucaminomethyl dithioglycerol-1,3	Kensler, Adler, Durlacher, Cattell, Talbot, Eagle	
375	Methylglucaminomethyl dithioglycerol-1,3	Kensler	
376	Methylglucaminomethyl dimercaptopropyl ethyl ether	Kensler	
411	Diethanolaminoethyl propanedithiol-1,3	Calvery	
436	bis-S-(acetamidomethyl) dithioglycerol-1,2	Dr. R. E. Harrison, Durlacher, Talbot, Cattell, Adler, Calvery, Gilman, Rhoads, Eagle, Bloom, Kensler	
407	bis-S-(N-ethylacetamidomethyl) dithioglycerol-1,2	Dr. R. W. Gerard, Durlacher, Talbot, Cattell, Adler, Calvery, Rhoads, Eagle, Bloom, Barron, Gilman	
475	mono-S-(acetamidomethyl) dithioglycerol-1,2	Talbot, Cattell, Adler, Calvery, Rhoads, Eagle, Bloom, Durlacher, Gilman	CLASSIFIED - CONFIDENTIAL

TABLE X (Cont'd.)

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NR	Compound	Submitted to	Acknowledgement
110	2-Methylpentanedithiol-2,4	Dr. Roger Adams, Kensler, Gilman	Prepared by Dr. W. J. Poppel
111	2-Ethylhexanedithiol-1,5	Kensler, Gilman, Adams	Prepared by Dr. W. J. Poppel
112	Decanedithiol-1,10	Maj. P. W. Van Tuyle, Barron, Kirner, Rhoads, Kensler, Gilman	Prepared by Dr. W. J. Poppel
115	Butanedithiol-1,5	Gilman, Marvel	Prepared by Dr. C. M. Langkammerer
150	Butanedithiol-2,4	Kensler, Gilman	Prepared by C. G. Worts
229	Butanedithiol-1,4	Winternitz, Kensler, Barron, Gilman	Prepared by Dr. W. J. Poppel
149	Hexanedithiol-1,6	Kramer, Rhoads, Kensler, Water, Bloom, Barron, Gilman	Prepared by Dr. W. J. Poppel
166	Dithioglycidol	Dr. P. D. Bartlett, Bunting, McLean, Marvel	
170	1-Thioanethiol	Gilman, Harrison	
715	1-Thioxylthiol	Gilman	
174	Dodecanethiol-1	Dr. Samuel Garin, Dr. Albert Potts, Kensler	Prepared by Dr. W. J. Poppel
100	Pentadecanethiol-2	Potts, Marvel	
495	2-Methylpropenedithiol-1,2	Kensler	Prepared by Dr. C. M. Langkammerer
208	Methyl 4-oxopentanoate propionate	Friedenwald	
501	2-Methyl-5-mercapto-2,5-dihydro-1,5-thiazine	Friedenwald	
291	Glucose mercaptal of dithioglycerol-1,2	Friedenwald, Kensler, Bunting, Bloom, Adler	
282	2-Mercapto-2-methylpentanone-4	Friedenwald, Winternitz, Cope, Marvel	

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REEL - C

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A.T.I.A

30 284

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ABSTRACT:

A synthesis of compounds containing the vicinal dithiol structure in a wide variety of structural arrangements is given. Homologs were prepared so that structure and efficacy could be further correlated. About sixty analogs and derivatives of BAL were prepared and submitted for therapeutic and toxicity studies; 2, 3-dimercaptopropyl ethyl ether was found to be the most effective agent for arsine therapy, surpassing all other compounds tested. A novel approach to the problems of dithiol synthesis has involved the preparation of derivatives of BAL or its analogs in which existing thiol groups were converted to new, labile structures. A new synthetic technique was applied to the preparation of dimercaptotetrahydrothiophene-1-dioxide and 2,3-dimercaptopropionic acid. Dithioglycidol was condensed with aniline and methylaniline, by opening of the ethylene sulfide ring, to yield monomeric dithiols.

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