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THE CHEMISTRY OF ORGANIC DISULFIDES. DESULFURIZATIONS WITH AMINOPHOSPHINES.

ABSTRACT

Organic disulfides undergo facile desulfurization to the corresponding sulfides on treatment with aminophosphines. This reaction is applicable to alkyl, aralkyl and alicyclic disulfides and is compatible with a wide variety of common functional groups. The desulfurization process is stereospecific in that inversion of configuration occurs at one of the carbon atoms α to the disulfide group. The reaction proceeds by way of an intermediate phosphonium salt which is formed in the rate limiting step. This desulfurization reaction is applicable to a variety of sulfenyl derivatives and is of considerable synthetic value.

The mass spectra of a variety of disulfides and sulfides are discussed and new methods for the preparation of α-bromo acids and cyclic disulfides are presented.

THE CHEMISTRY OF ORGANIC DISULFIDES. J.G. GLEASON

THE CHEMISTRY OF ORGANIC DISULFIDES.
DESULFURIZATIONS WITH AMINOPHOSPHINES.

by

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J.G.G.

CHAPTER I

INTRODUCTION

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Since sulfur is directly below oxygen in the periodic table, it is not surprising to find that much of sulfur chemistry closely parallels the chemistry of the analogous oxygen compounds. For example, the chemistry of thiols (RSH) is very similar to that of alcohols (1); they are both weakly acidic, both readily form esters with acids, ethers with alkylating agents. In view of this similarity of chemical properties, the differences in the chemistry of disulfides and peroxides is somewhat surprising. This dissimilarity is noticeable in a comparison of the bond dissociation energies of selected organo-sulfur and organo-oxygen compounds (Table I).

TABLE I

BOND DISSOCIATION ENERGY (2)

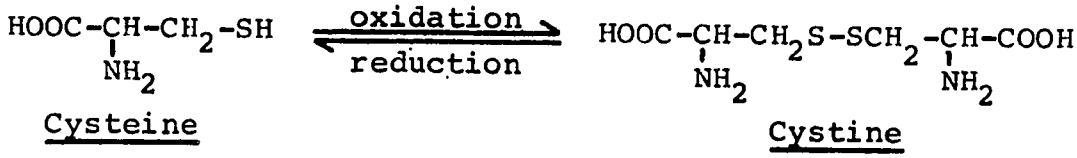
Bond	D, Kcal/mole	Bond	D, Kcal/mole
CH_3S-SCH_3	77	CH_3O-OCH_3	44
CH_3S-CH_3	73	CH_3O-CH_3	77
CH_3S-H	90	CH_3O-H	100

While the bond energies of both the thiols and thioethers are very similar to their oxygen analogues, the disulfide bond is approximately 35 Kcal/mole more stable than the peroxide bond. This difference in stability may, in part, be

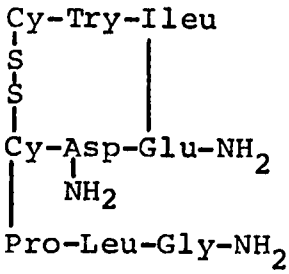
due to the lower electronegativity of sulfur coupled with its greater radius. The repulsion of two compact, highly electronegative oxygen atoms would be much greater than two diffuse, less electronegative sulfur atoms. Other differences exist between oxygen chemistry and sulfur chemistry; these will be discussed when pertinent.

Disulfides in Nature.

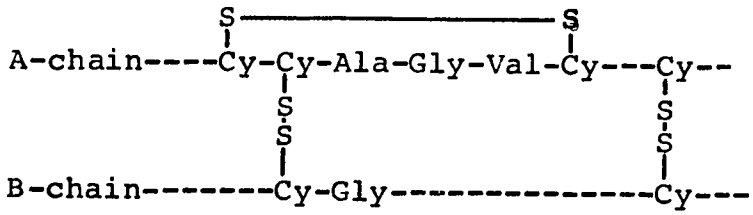
The interest in the chemistry of disulfides has been, in large part, a result of the importance attached to this group in biological systems. In 1810, Wollaston (3) isolated a sulfur-containing amino acid from the urinary calculus of a patient suffering from cystinuria. This amino acid was shown to be the disulfide of β-mercapto-alanine. This disulfide presumably results from the biological oxidation of β-mercapto-alanine (cysteine); this oxidation may be effected chemically by most mild oxidizing agents (I_2, O_2, $FeCl_3$ for example). This disulfide is widely distributed in natural peptides, best known of which are oxytocin and insulin. In



Cysteine Cystine



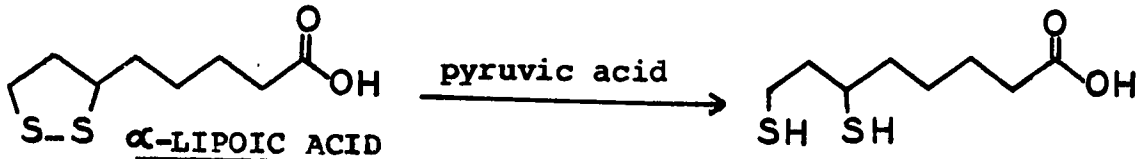
Oxytocin



Sheep Insulin

most peptides, the main function of the disulfide bridge is to fix the peptide in a suitable conformation for biological interaction. Cleavage of the disulfide bridge results in complete inactivation of the hormones oxytocin (4) and insulin (5). In some cases, replacement of a sulfur atom by a methylene group does not significantly alter the conformation of these peptides and,hence, their biological activity is not altered (6).

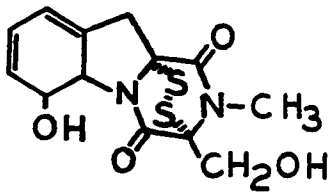
One disulfide which owes its biological activity to the disulfide bond is the growth promoting vitamin, α-lipoic acid (7). This disulfide acts as a co-enzyme in the oxidation of pyruvic acid by undergoing reduction to a bis-thiol. Lipoic acid



α-LIPOIC ACID

has been reported (8) to have a significant role in photosynthesis.

A third group of naturally occurring disulfides are the antibiotic disulfides of which gliotoxin is a representative member. The structure of this unusual antibiotic was deduced by



GLIOTOXIN

Johnson and Woodward (9) in 1958, climaxing a 15 year structural study. Several other antibiotics incorporating this tricyclic disulfide system have been reported (10,11).

Stereochemistry and Bonding of Disulfides.

Two structural isomers of disulfides are theoretically possible, a linear isomer and a "branch bonded" isomer.

A few branch-bonded sulfur compounds, thionosulfites, have recently been synthesized (12) and apparently require special circumstances for stability. However, X-ray (13), dipole moment (14), spectrochemical (15) and radiochemical ^{35}S studies (16) have shown that the branch-bonded isomer is not present in disulfides.

The nature of the bonding in disulfides has been discussed by Pauling (17). Both the σ bond joining the two sulfur atoms and the σ bond joining the sulfur and carbon atoms are thought to be nearly pure p in character with one non-bonded pair of electrons on each sulfur atom in the 3s orbital, spherically distributed about the nucleus. The remaining non-bonded pair of electrons on each sulfur atom occupy the remaining 3p orbitals; the repulsion of these p orbitals on adjacent sulfur atoms being minimized when the dihedral angle (CSS-SSC) is 90° (Fig. 1). This mutual repulsion of the non-bonded electron pairs gives rise to a rotational barrier of 10-14 Kcal/mole. In cyclic disulfides, where the dihedral angle of 90° is not possible (for example, the dihedral angle in five membered disulfides rings is 26° (18)), this mutual repulsion of electron pairs has a considerable effect on the stability of such molecules.

Reactions of Disulfides.

Two of the most important reactions of disulfides are

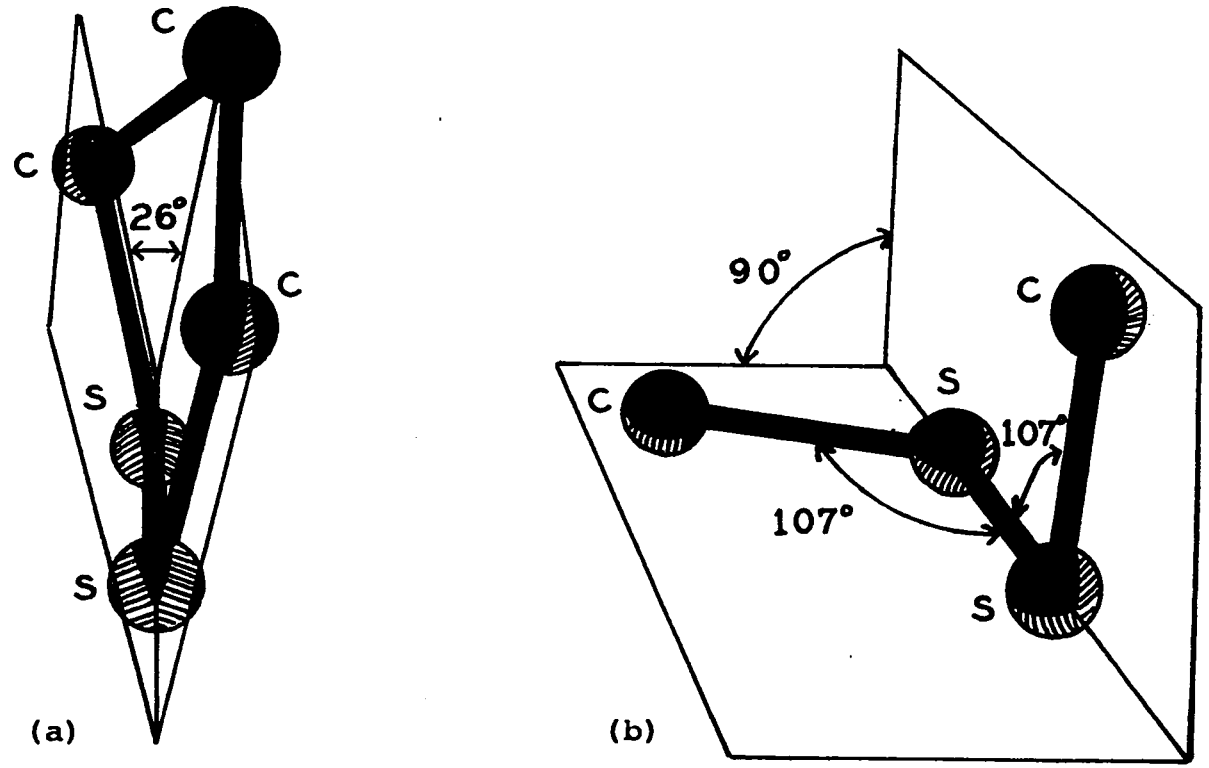


Figure 1. Dihedral angle of disulfides: (a) pentacyclic disulfides, (b) open chain disulfides.

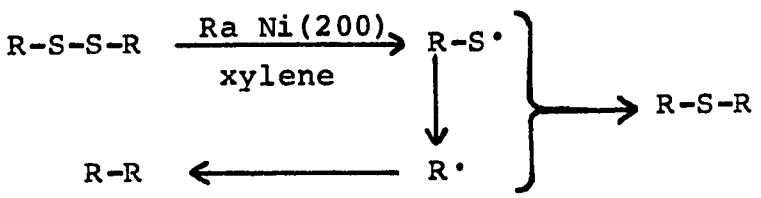
reduction and oxidation. The reduction of disulfides to thiols was mentioned earlier during a discussion of naturally occurring disulfides; the oxidation of disulfides has been reviewed by Kharasch(19). A third reaction of disulfides which has attracted considerable attention is that of desulfurization. Because of the ready availability of disulfides, a reaction in which one or both of the sulfur atoms is removed would be of considerable synthetic value. In addition, because of the prevalence of disulfides in biological systems, such a reaction could be of special interest.

The sulfur-sulfur bond of disulfides may suffer cleavage both homolytically and heterolytically. Homolytic cleavage of the disulfide bond may be effected either photolytically (20) or thermally at temperatures above 125°(21,22). For example,

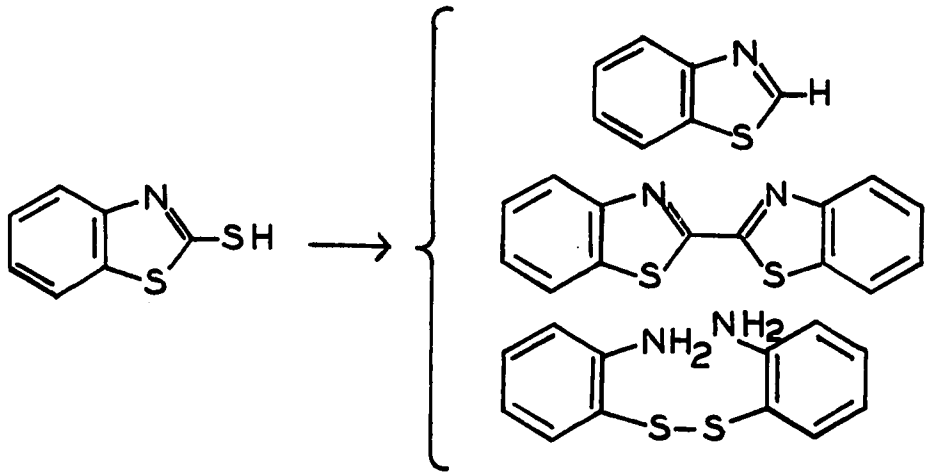
$$\text{R-S-S-R}' \xrightarrow[170^\circ]{} \text{R-S}\cdot + \text{R}'\text{-S}\cdot \longrightarrow \text{R-S-S-R} + \text{R}'\text{-S-S-R}'$$

$$2\ \text{R-S}\cdot \longrightarrow \text{R-S-S-R}$$

unsymmetrical disulfides dissociate at 170° to give symmetrical disulfides (22). This radical cleavage also plays an important role in the desulfurization of disulfides by active nickel catalysts (23). Raney nickel, a nickel-aluminum alloy which has been leached with hot alkali, will reduce disulfides to sulfides and hydrocarbons. It has been suggested by Hauptmann and Wladiskaw (24) that free aryl and arylthio radicals



are formed on the nickel surface. Sulfur compounds may react in several ways with Raney nickel; the pathway of the reaction is dependent upon temperature, solvent,and degree of activation of the catalyst. For example, 2-mercaptobenzothiazole



may be oxidized, desulfurized, or dimerized all dependent upon reaction conditions (25). The use of Raney nickel for the desulfurization of thioketals to hydrocarbons has become a

commonly used alternative to the Wolff-Kishner reduction of ketones (26). However, the multiplicity of reaction pathways has greatly limited the synthetic utility of this catalyst.

Heterolytic cleavage of the sulfur-sulfur bond of disulfides may be induced by both electrophilic and nucleophilic reagents. Each sulfur atom of a disulfide possesses non-bonded electrons and therefore may act as a Lewis base in the presence of electrophilic reagents. An example of electrophilic scission of a sulfur-sulfur bond is the chlorinolysis of a disulfide (27).

$$R\text{-}S\text{-}S\text{-}R + Cl_2 \longrightarrow R\text{-}\overset{+}{S}(Cl)\text{-}S\text{-}R\ {}^{-}Cl \longrightarrow 2\ R\text{-}S\text{-}Cl$$

This reaction has been shown to proceed via a chloro-sulfonium

intermediate (27b) which reacts further to form two molecules of the sulfenyl halide.

Nucleophilic Scission of the Sulfur-Sulfur Bond

Despite the high bond energy of the sulfur-sulfur bond, several factors make the disulfide bond particularly susceptible to cleavage by nucleophilic reagents. The large polarizable sulfur atom may readily accomodate the negative charge of a

$$R\text{-}S\text{-}S\text{-}R + Nu \longrightarrow Nu^{+}\text{-}S\text{-}R + {}^{-}S\text{-}R$$

mercaptide ion. In addition to this ability of the mercaptide ion to act as a good leaving group in nucleophilic substitution reactions, the long C-S bond length of 1.82 Å renders the sulfur atom much more sterically accessible than, for example, would be an oxygen atom (C-O bond; 1.43 Å) (Fig. 2).

Figure 2. Accessibility of sulfur and oxygen (28).

In addition, the stretching force constants for second-row elements bonded to other atoms are generally lower than for first-row elements. Consequently, less energy would be required to stretch a sulfur-sulfur bond than would be required for bonds between first row elements (28). Several reviews on nucleophilic cleavage of disulfides have been published (29,30,31), therefore only a few examples of this important

reaction will be presented.

The thiol-disulfide exchange reaction is an excellent example of nucleophilic scission of a disulfide. Fava (32) has demonstrated that the reaction is bimolecular, first

$$R'SH + {}^-OH \rightleftharpoons R'S^- + H_2O$$

$$R'S^- + RS\text{-}SR \rightleftharpoons R'S\text{-}SR + RS^-$$

order both with respect to disulfide and to mercaptide ion, and is base catalyzed. The above sequence of reactions have been forwarded to account for these observations. Another example of nucleophilic scission of the sulfur-sulfur bond is the reaction of disulfides with cyanide ion (33,34):

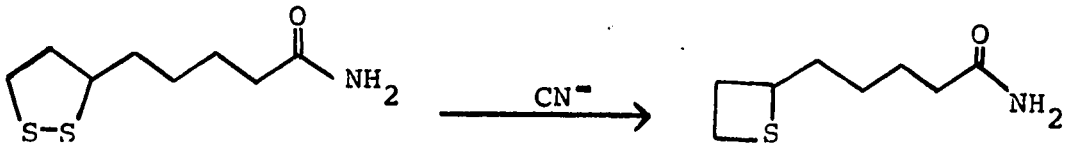
$$R\text{-}S\text{-}S\text{-}R + CN^- \rightleftharpoons R\text{-}S\text{-}CN + R\text{-}S^-$$

This cleavage reaction occurs with most disulfides and, as would be expected from an equilibrium process, if a possibility exists for the displacement of two different mercaptides, the reaction proceeds with displacement of the least basic mercaptide. When the reaction was performed in the presence of an efficient mercaptide scavenger, the displacement of the least acidic mercaptide, the kinetically more favorable process, was detected (34a). In some cases, the cyanide cleavage of disulfides may lead to desulfurization of the disulfide:

$$RS\text{-}SR + CN^- \longrightarrow RS^- + R\text{-}SCN \longrightarrow RSR + {}^-SCN$$

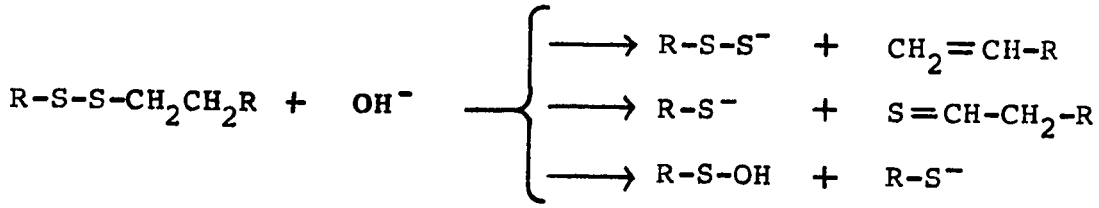
$$R = Ph\text{-}\overset{O}{\overset{\|}{C}}\text{-}$$

This reaction normally is important only if strongly electron withdrawing substituents are present (35), although it has



been reported (36) to occur as well for the cyclic disulfide, α-lipoic acid amide.

A distinction should be made between cleavage of disulfides by nucleophiles and by strong bases. While the former proceeds with ionic scission of the sulfur-sulfur bond, the reaction with strong bases may proceed as well via hydrogen



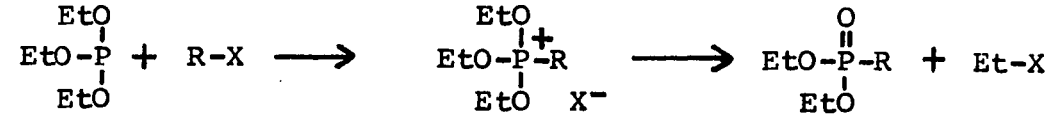
abstraction both α and β to the disulfide bond (37).

Desulfurization with Trivalent Phosphorus Compounds.

The reduction of disulfides to thiols may be accomplished by most reducing agents including metal hydrides (38) and dissolving metal reducing agents (39). Catalytic hydrogenation, however, does not reduce disulfides since these sulfur compounds poison the catalytic surface (40). As mentioned previously, Raney nickel will reduce disulfides, but normally affords a variety of products.

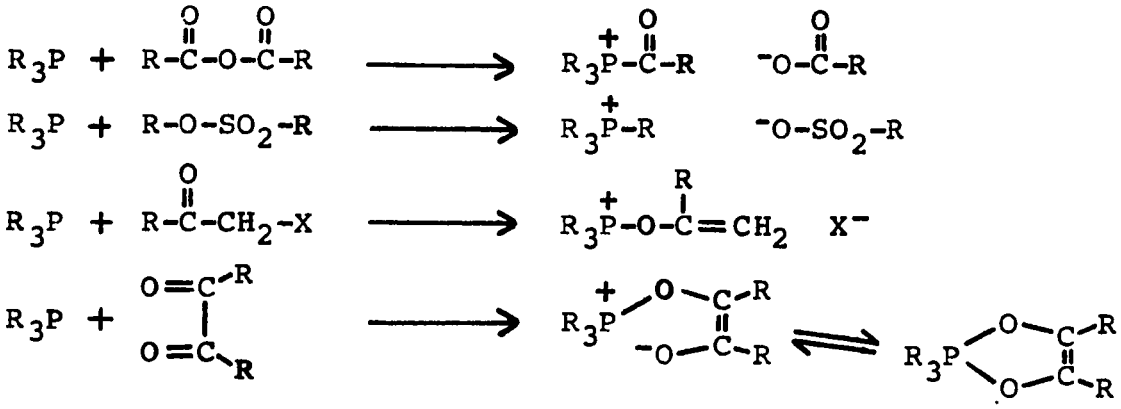
The ability of trivalent phosphorus compounds (phosphines and phosphites) to undergo valence expansion ($P^{III} \rightarrow P^{V}$) makes it a selective reducing agent. For example, phosphites are oxidized by alkyl halides in the Michaelis-Arbuzov reaction (41).

This oxidation proceeds via a nucleophilic displacement reaction

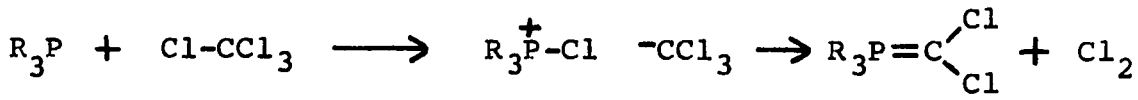


on the alkyl halide followed by rearrangement of the intermediate phosphonium salt.

Phosphites and phosphines, while very weak bases, are quite nucleophilic. They react with a wide variety of compounds which have easily polarizable linkages such as anhydrides (42),



sulfonates (43), α-haloketones (44), and α,β-diketones (45). The more reactive phosphines and phosphites will react with



carbon tetrachloride in a nucleophilic reaction (46).

Many of the reactions of phosphites and phosphines lead to the formation of phosphates or phosphine oxides. Here the high bond energy of the P=O bond (140 Kcal/mole (47)) provides a substantial driving force for its formation. The more reactive phosphorus compounds will therefore react with non-polarizable linkages such as peroxides to form phosphorus oxides (48). Although the bond energy of a P=S bond is not

$$R_3P + O_2 \longrightarrow R_3P{=}O$$
$$R_3P + R\text{-}O\text{-}O\text{-}R \longrightarrow R\text{-}O\text{-}R + R_3P{=}O$$
$$R_3P + R\text{-}S\text{-}S\text{-}R \longrightarrow R\text{-}S\text{-}R + R_3P{=}S$$

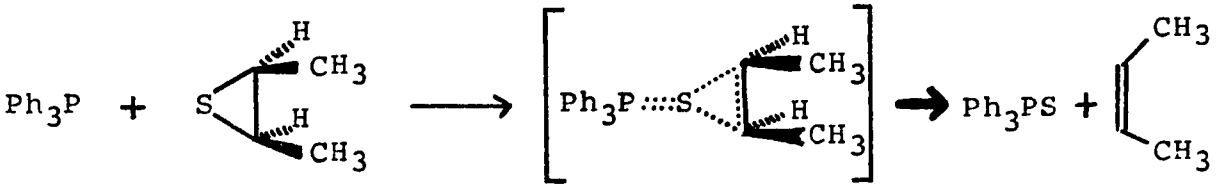
as high as a P=O bond, the more polarizable sulfur-sulfur bond could facilitate an analogous reduction of disulfides to thioethers.

The reaction of triphenylphosphine with sulfur has been investigated in detail by Bartlett and Meguerian (49)

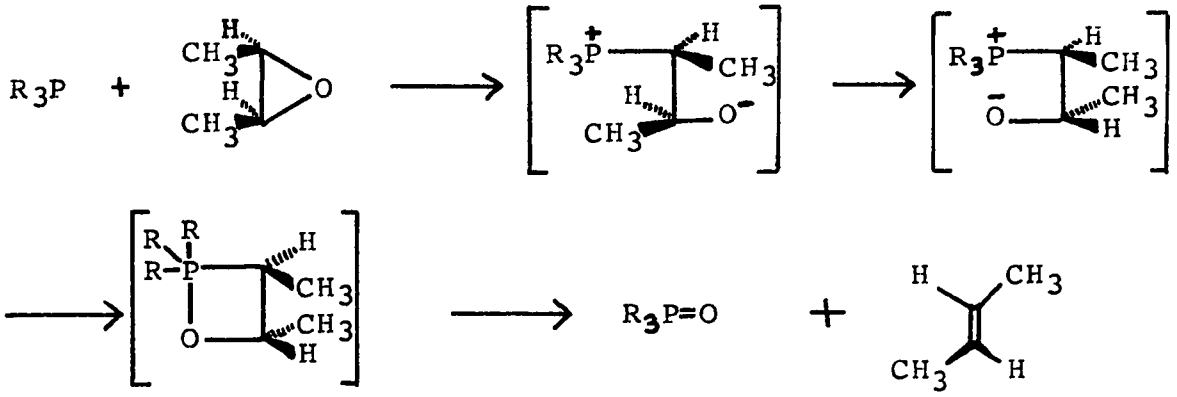
$$Ph_3P + S_8 \longrightarrow Ph_3\overset{+}{P}\text{-}S\text{-}S_6\text{-}S^- \xrightarrow{Ph_3P} Ph_3P{=}S + Ph_3\overset{+}{P}S\text{-}S_5\text{-}S^-$$

who postulated an ionic intermediate in this desulfurization on the basis of the large solvent effect observed for this reaction.

In contrast to this ionic reaction, the removal of sulfur from episulfides proceeds with retention of stereochemistry (50)



and exhibits little solvent dependence (51); this is suggestive of a non-polar transition state. In contrast, the reaction of epoxides with phosphines proceeds via an ionic intermediate



and inversion of stereochemistry predominates (52). In all of these reactions, the phosphine undergoes valence expansion from the P^{III} to the P^{V} state.

One of the earliest reports of a reaction of phosphines with organo-sulfur compounds was by Schönberg (53) who observed that triphenylphosphine removed one sulfur atom from

$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}S\text{-}S\text{-}\overset{O}{\overset{\|}{C}}\text{-}R + Ph_3P \longrightarrow R\text{-}\overset{O}{\overset{\|}{C}}\text{-}S\text{-}\overset{O}{\overset{\|}{C}}\text{-}R + Ph_3P{=}S$$

dithioanhydrides to afford the corresponding thioanhydrides. (While dithioanhydrides and thioanhydrides could be considered disulfides and sulfides respectively, they appear to be more similar in chemical properties to anhydrides and should therefore be considered as such.) With the possible exception of bis(p-dimethylaminophenyl)disulfide, which did undergo desulfurization (this reaction could not be repeated under identical conditions), the reaction was limited to the very reactive acyl disulfides (53,54).

Attempts to extend this novel reaction to non-activated disulfides have not been successful; either no reaction occurs or rearrangement accompanies desulfurization. Moore and Trego (55) demonstrated that no desulfurization takes place when triphenylphosphine is heated in dry benzene at 140° with dialkyl and diaryl disulfides[1]. Trisulfides, however, readily

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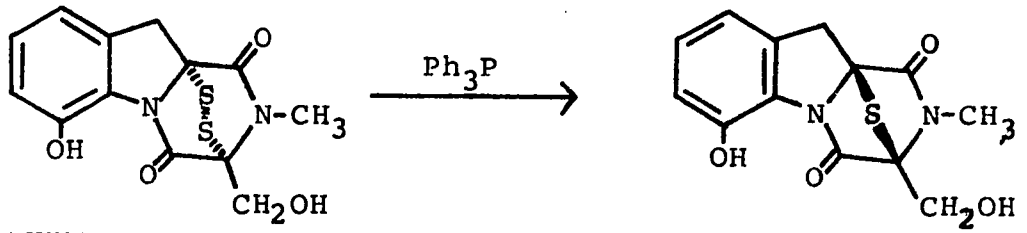
[1] S. Hayashi (58) reported that several disulfides including benzyl disulfide are smoothly desulfurized by Ph_3P. This work is in direct conflict with earlier work of Schönberg (53,54) and Moore and Trego (55) who found benzyl disulfide to be unreactive under the most forcing of conditions. Furthermore, attempts to repeat this work (both the desulfurization reaction and several deoxygenation reactions also reported) have been unsuccessful; this reported desulfurization should therefore be held suspect.

$$PhCH_2S\text{-}SCH_2Ph + Ph_3P \xrightarrow[140^\circ]{\text{benzene}} \text{NO REACTION}$$

$$RS\text{-}S\text{-}SR + Ph_3P \longrightarrow RS\text{-}SR + Ph_3P{=}S$$

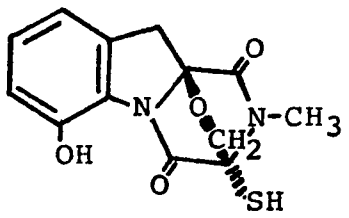
lose one sulfur atom on reaction with triphenylphosphine (56, 57,58,59).

It has recently been reported (60) that dehydrogliotoxin, a derivative of the natural product gliotoxin, is desulfurized



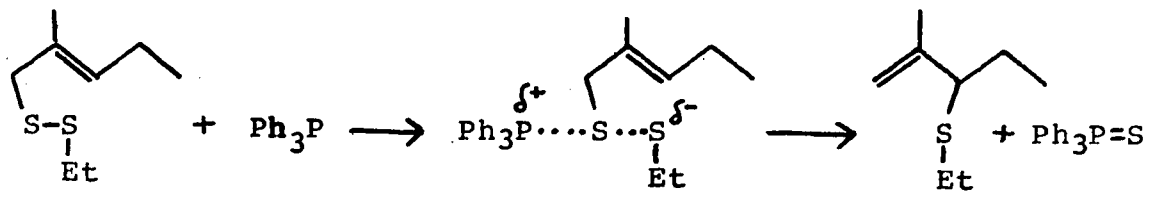
DEHYDROGLIOTOXIN

by triphenylphosphine. Although reported to be a bridged sulfide, the structure of this desulfurized product is uncertain. An alternate formulation which must also be considered is a bridged ether structure as depicted below:



This reaction is reported to proceed with inversion of configuration at both of the carbon atoms ∝ to the disulfides; this important observation will be discussed later.

Disulfides which are activated by an allylic bond are desulfurized by triphenylphosphine (55,56). However the products obtained from such a reaction are indicative of a



rearrangement, as depicted above, being operative. As in the reaction of triphenylphosphine with sulfur, the polarity of the medium has a considerable effect upon the rate of desulfurization of allylic disulfides (55). This observation is indicative of a charged intermediate being formed in the kinetic step of this reaction.

In contrast to the lack of reactivity of triphenylphosphine towards alkyl disulfides, trialkyl phosphites readily desulfurize most disulfides (61). However, the product sulfide has exchanged

$$EtS\text{-}SEt + (BuO)_3P \longrightarrow \begin{matrix} BuO \\ | \\ EtS\text{-}P^{+}\text{-}OBu \\ | \\ BuO \quad {}^{-}S\text{-}Et \end{matrix} \longrightarrow Bu\text{-}S\text{-}Et + EtS\text{-}\overset{O}{\overset{\|}{P}}(OBu)_2$$

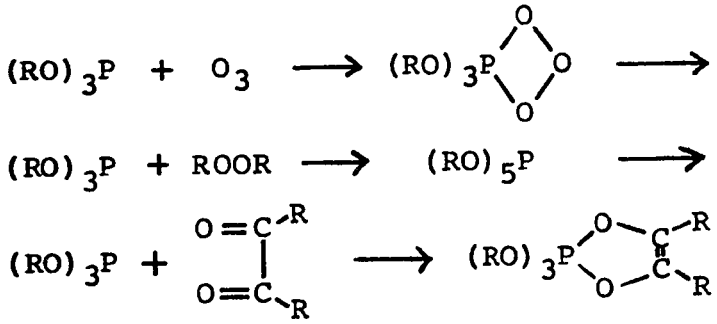
one alkyl group with the phosphite. For example, desulfurization of diethyl disulfide yields not diethyl sulfide, but ethyl butyl sulfide. This rearrangement, similar to the Michaelis-Arbuzov rearrangement, derives its driving force from the high bond energy (140 Kcal/mole) of the P=O bond. If an unsymmetrical disulfide is desulfurized, in all cases, it is the more stable mercaptide which is displaced, although this is kinetically the least favored process. The reactivity of the disulfide in this reaction is a function of both the stability of the mercaptide being formed and the degree of polarization of the sulfur-sulfur bond. Thus, the order of increasing reactivity is

$$EtS\text{-}SEt + (MeO)_3P \xrightarrow[\text{reflux}]{9\ hr} Et\text{-}S\text{-}Me + EtS\text{-}\overset{O}{\overset{\|}{P}}(OMe)_2$$

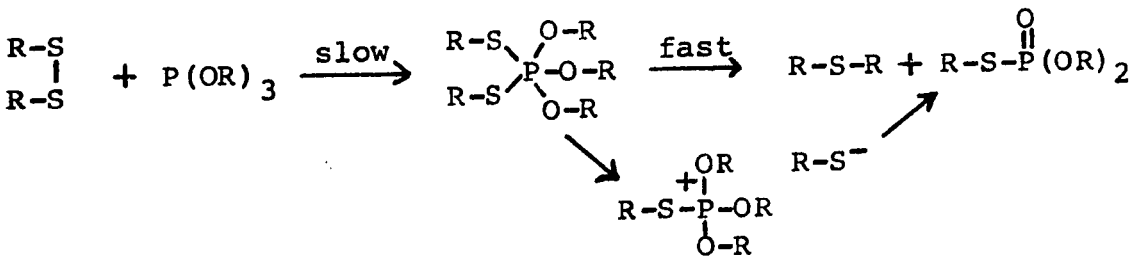
$$PhS\text{-}SPh + (MeO)_3P \xrightarrow[\text{reflux}]{2.5\ hr} Ph\text{-}S\text{-}Me + PhS\text{-}\overset{O}{\overset{\|}{P}}(OMe)_2$$

$$PhS\text{-}SMe + (MeO)_3P \xrightarrow[R.T.]{5\ min} Ph\text{-}S\text{-}Me + MeS\text{-}\overset{O}{\overset{\|}{P}}(OMe)_2$$

diethyl disulfide, diphenyl disulfide, with phenyl methyl disulfide being most reactive. In this latter case, attack of phosphite must occur on the more negatively charged sulfur atom, kinetically an unfavorable process. However, Harvey (61) suggested that the rate determining step is the initial attack of phosphite on disulfide and that unsymmetrical substitution facilitates this attack by effecting polarization of the disulfide linkage. Furthermore, he proposed that either nucleophiles attack the same sulfur atom as do electrophiles (thus explaining the formation of the more stable mercaptide) or the cleavage process involves the formation of a "transition intermediate" such that no matter which sulfur atom is initially attacked, the more stable mercaptide ion is ultimately ejected. One possibility for this transition intermediate is a penta-covalent phosphorus compound. Such intermediates have been observed in the reaction of phosphites with ozone(62,63), peroxides(64) and α,β-diketones (45), and have been suggested



as intermediates in several other reactions (54,64). Thus the mechanism for the desulfurization of disulfides by phosphites may be as depicted below:



No evidence, however, exists for this mechanism.

If the reaction of phosphites with disulfides is carried out in the presence of radical initiators or ultraviolet light the reaction may proceed without rearrangement (65). A radical

$$RS\text{-}SR + h\nu \longrightarrow 2RS^{\bullet}$$

$$RS^{\bullet} + :P(OEt)_3 \longrightarrow RS\text{-}\dot{P}(OEt)_3$$

$$RS\text{-}\dot{P}(OEt)_3 \longrightarrow R^{\bullet} + S{=}P(OEt)_3$$

$$R^{\bullet} + RS\text{-}SR \longrightarrow R\text{-}S\text{-}R + {}^{\bullet}SR$$

$$2R^{\bullet} \longrightarrow R\text{-}R$$

$$R^{\bullet} + {}^{\bullet}SR \longrightarrow R\text{-}S\text{-}R$$

mechanism has been proposed for this reaction. Because of the radical nature of this process, its scope is greatly limited. For example, benzyl disulfide reacts with triethyl phosphite to yield toluene (19%) and bibenzyl (26%) as major products

$$PhCH_2S\text{-}SCH_2Ph + P(OEt)_3 \longrightarrow \underset{19\%}{PhCH_3} + \underset{26\%}{PhCH_2CH_2Ph} + \underset{5\%}{(PhCH_2)_2S}$$

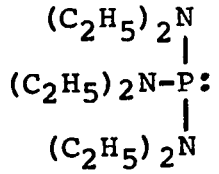
while benzyl sulfide was formed in less than 5% yield.

Aminophosphines.

Attempts to effect controlled desulfurization of disulfides have been unsuccessful; either the phosphine is unreactive, or if reactive, rearrangement occurs during desulfurization. For this approach to selective desulfurization to be successful, a trivalent phosphorus compound is required which combines the reactivity of phosphites with the lack of rearrangement of phosphines. The placing of an electronegative atom, oxygen, adjacent to the phosphorus atom appreciably decreases its nucleophilicity. In general, phosphites are less reactive than

triphenylphosphine in nucleophilic processes (56,66). However, the possibility of electromeric release in the intermediate phosphonium salt and the eventual formation of a strong P=O bond may have a beneficial effect in desulfurization reactions. This latter effect, however, is an important factor in the Arbuzov rearrangement which is observed for most phosphites.

One class of trivalent phosphorus compounds which appears to fill these requirements of reactivity without rearrangemant would be the aminophosphines. Trialkylaminophosphines, tris(diethylamino)phosphine (1) for example, are extremely



1

reactive nucleophiles (67,68). The lower electronegativity of nitrogen as compared to oxygen would be expected to render the aminophosphines more nucleophilic by making the phosphorus lone pair more available for reaction, while electromeric release by nitrogen would considerably enhance the stability of a tetravalent intermediate or transition complex. Moreover, since aminophosphines are unlikely to enter into an Arbuzov-like rearrangement(69), they should be suitable reagents for the selective desulfurization of disulfides.

CHAPTER II

DISCUSSION

(Throughout the text, compounds have been numbered in underlined Arabic numerals.)

CHAPTER II

DISCUSSION

Synthesis of Aminophosphines.

Substituted aminophosphines may be prepared by the reaction of phosphorus trichloride with dialkylamines (70,71, 72). Because of the high reactivity of these aminophosphines,

$$6\ R_2NH + PCl_3 \longrightarrow 3\ (R_2N)_3P + 3\ R_2NH_2\ Cl$$

caution must be observed in the choice of solvents for both the preparation and reactions of these compounds. Aminophosphines react violently with alcohols (71) and carbon tetrachloride (46, 72); ketones and 1,3-diketones may also react with the phosphine (71,73). Solvents which may be used are benzene, ether, hexane and ethyl acetate.

Several workers have experienced difficulty in preparing tris(dimethylamino)phosphine (72,74); the reaction of dimethylamine with phosphorus trichloride is difficult to control and the presence of significant amounts of bis(dimethylamino)chlorophosphine greatly complicates the isolation and purification of the phosphine (74). (This phosphine has since become commercially available from Aldrich Chemical Corp.) The next higher member of this series, tris(diethylamino)phosphine (1) could be prepared in large quantities (100-150 gm.) and in good yield (50-70%) by a slight modification of reported proceedures (70,72), and was therefore used in most of the desulfurization experiments. As will be shown later, the difference in reactivity between the methyl and ethyl derivatives is negligible.

Synthesis of Disulfides.

The synthesis of disulfides may be accomplished by a variety of methods. The action of sodium disulfide on alkyl halides provides a direct approach; however, this

$$R\text{-}Br + Na_2S_2 \longrightarrow RS\text{-}SR + 2\ NaBr$$

$$Na_2S_2 \rightleftharpoons Na_2S + Na_2S_3$$

$$R\text{-}Br + Na_2S \longrightarrow R\text{-}S\text{-}R + 2\ NaBr$$

reaction is complicated by the formation of sulfides (75).

A better approach is the controlled oxidation of the corresponding thiol which may be prepared by classical techniques. Many oxidizing agents have been utilized in this reaction including iodine (76), ferric chloride (77), dimethylsulfoxide (78), hydrogen peroxide (79), bromine (80), thiocyanogen (81), oxygen (82), ethyl azodicarboxylate (83) and toluenesulfonyl chloride (84). In all of these oxidations, a derivative of a sulfenic acid (R-S-OH) is initially formed which subsequently reacts with a second molecule of thiol to

$$R\text{-}SH + M_2 \xrightarrow{-HM} R\text{-}S\text{-}M \xrightarrow{R\text{-}SH} R\text{-}S\text{-}S\text{-}R + HM$$

$$M = OH,\ Br,\ Cl,\ I,\ SCN$$

form a thiolsulfenate ester, or disulfide. The use of hydrogen peroxide in this reaction is often complicated by the further oxidation of the disulfide to thiolsulfinates (RS-SO-R),

$$RS\text{-}SR \xrightarrow{H_2O_2} RS\text{-}\overset{O}{\overset{\|}{S}}R \xrightarrow{H_2O_2} RS\text{-}\underset{O}{\overset{O}{\overset{\|}{\underset{\|}{S}}}}R \xrightarrow{3\ H_2O_2} 2\ RSO_3H$$

thiolsulfonates ($RS\text{-}SO_2R$) and sulfonic acids (RSO_3H). Under appropriate conditions, good yields of the various oxidation intermediates may be realized. This reaction has been discussed by Kharasch (18).

The preparation of unsymmetrical disulfides presents a special problem since oxidation of the requisite thiols will

$$R\text{-}SH + R'\text{-}SH \xrightarrow{I_2} R\text{-}S\text{-}S\text{-}R + R'\text{-}S\text{-}S\text{-}R + R'\text{-}S\text{-}S\text{-}R'$$

result in the formation of a statistical mixture of the three possible disulfides. To reduce the amount of symmetrical disulfide being formed, it is necessary to activate one of the thiols. For example, careful chlorinolysis of a thiol will afford the

$$2\ R\text{-}SH + Cl_2 \longrightarrow 2\ R\text{-}S\text{-}Cl$$

$$R\text{-}S\text{-}Cl + R'\text{-}SH \longrightarrow R\text{-}S\text{-}S\text{-}R'$$

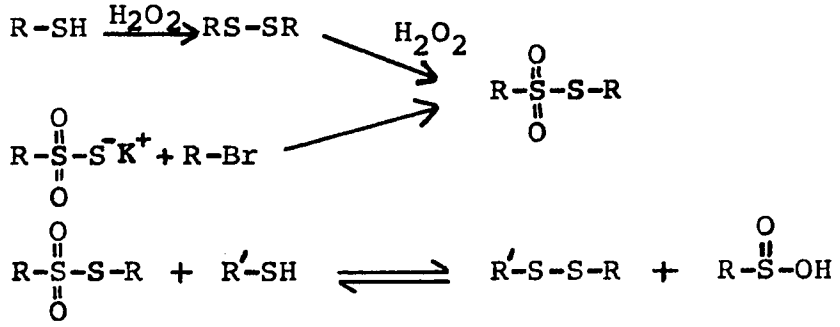
very reactive sulfenyl chloride which may be used in a subsequent reaction to prepare unsymmetrical disulfides (85). A more convenient sulfenyl derivative is the sulfenyl thiocyanate (86). This derivative may be generated by the reaction of a

$$C_6H_5CH_2\text{-}SH + (SCN)_2 \longrightarrow C_6H_5CH_2\text{-}S\text{-}SCN + HSCN$$

$$C_6H_5CH_2\text{-}S\text{-}SCN + C_2H_5\text{-}SH \longrightarrow C_6H_5CH_2\text{-}S\text{-}S\text{-}C_2H_5 + HSCN$$

thiol with thiocyanogen. Reaction of this intermediate with a second thiol will afford the unsymmetrical disulfide. Using this technique, benzyl ethyl disulfide and benzyl tolyl disulfide were prepared in 50% and 28% yield respectively.

A third sulfenyl derivative which may be employed is the thiolsulfonate (87,58). Unlike the previously mentioned sulfenyl derivatives, thiolsulfonates are stable compounds, conveniently prepared by either the oxidation of disulfides (or thiols) by

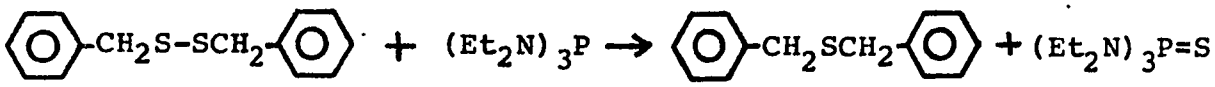


hydrogen peroxide (18) or the reaction of alkyl halides with thiolsulfonate salts (58,88). This method permitted the preparation of several disulfides in reasonable yield: benzyl p-nitrobenzyl disulfide (35%), benzyl p-bromobenzyl disulfide (58%) and benzyl p-tolyl disulfide (74%).

Several other disulfides were prepared for this desulfurization study; however, a discussion of the synthetic methods used for specific disulfides is best deferred until the discussion of the particular disulfide reaction.

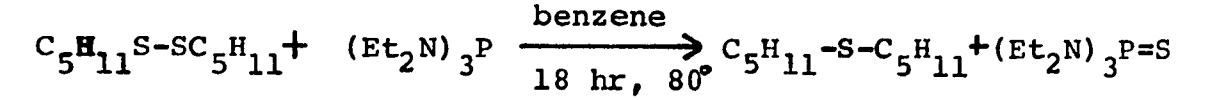
Desulfurization of Alkyl Disulfides.

The desulfurization of a variety of alkyl and aralkyl disulfides by tris(diethylamino)phosphine was found to proceed cleanly under mild conditions[1]. These results are summarized in Table II. Thus, the desulfurization of benzyl disulfide (2)



2 1 3 4

was effected in 18 hours at room temperature to afford the sulfide 3 in 85% yield or at 80° for 4 hours affording a 92% yield of 3. A much slower reaction obtains in the case of disulfide 5. After refluxing a benzene solution of 5 and



5 1 6 4

the aminophosphine 1 for 18 hours, the presence of unreacted disulfide was detected by vpc ; a 58% yield of diamyl sulfide (6) was obtained in this reaction.

The reaction of ethyl and iso-propyl disulfides (7) and (8) with the aminophosphine in refluxing benzene was found to

[1]A preliminary account of this work has been published: D.N.Harpp, J.G.Gleason and J.P.Snyder, J. Am. Chem Soc., 90, 4181 (1968)

TABLE II

DESULFURIZATION OF ALKYL DISULFIDES

$$R\text{-}S\text{-}S\text{-}R' + \underset{\underline{1}}{(Et_2N)_3P} \longrightarrow R\text{-}S\text{-}R' + \underset{\underline{4}}{(Et_2N)_3P{=}S}$$

Disulfides	Reaction time, hr	Reaction temp.[a]	% RSR'[b]	% 4[b]
$C_6H_5CH_2SSCH_2C_6H_5$ (2)	4	80°	92	86[c]
$C_5H_{11}SSC_5H_{11}$ (5)	18	80°	58	-
$C_6H_5SSCH_3$ (10)	0.01	exothermic	86	70
$CH_3C_6H_4SSCH_2C_6H_5$ (12)	0.01	exothermic	86	-
$CH_3OOCCH_2SSCH_2COOCH_3$ (14)	0.01	exothermic	85	-
$C_2H_5SSC_2H_5$ (7)	48	80°	-	75[d]
	24	90°[e]	17[f]	-
	22	80°[e]	-	80[g]
i-C_3H_7SS-i-C_3H_7 (8)	48	80°	-	50[d]
t-C_4H_9SS-t-C_4H_9 (9)	96	80°	-	5[d]
	48	80°[f]	1[d]	1[g]
Z-$NHC_2H_5SSC_2H_5$NH-Z[h] (37)	4	80°	68	-

(a) Benzene solvent, 1-2 M. (b) Unless otherwise noted, yields are of crystallized or distilled product. (c) Crude yield. (d) vpc analysis by peak height. (e) In neat excess phosphine 1 (100 mole excess). (f) Isolated as sulfone. (g) Quantitative vpc analysis with internal standards. (h) Z = carbobenzoxy.

proceed extremely slowly; after 48 hours of refluxing in benzene,

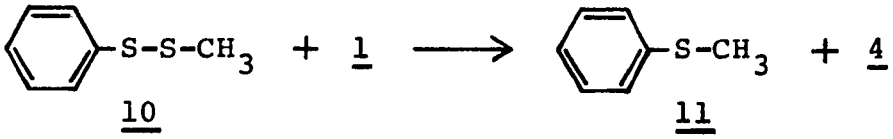
$$C_2H_5S\text{-}SC_2H_5 \ (\underline{7}) + \underline{1} \longrightarrow C_2H_5\text{-}S\text{-}C_2H_5 + (Et_2N)_3P\,S \ (\underline{4})$$

$$(CH_3)_2CH\text{-}S\text{-}S\text{-}CH(CH_3)_2 \ (\underline{8}) + \underline{1} \longrightarrow (CH_3)_2CH\text{-}S\text{-}CH(CH_3)_2 + \underline{4}$$

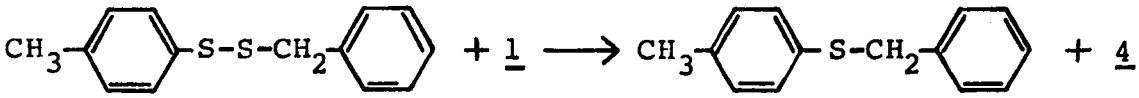
$$(CH_3)_3C\text{-}S\text{-}S\text{-}C(CH_3)_3 \ (\underline{9}) + \underline{1} \longrightarrow (CH_3)_3C\text{-}S\text{-}C(CH_3)_3 + \underline{4}$$

a 75% and 50% yield (vpc) respectively of phosphine sulfide 4 was obtained. Under similar conditions, di-t-butyl disulfide (9) was unreactive. The desulfurization of 7 could be accomplished by heating the disulfide in an excess of 1 at 80-100° for 22 hours. While oxidation of the reaction mixture with hydrogen peroxide permitted the isolation of only 20% diethyl sulfone, quantitative analysis of the desulfurization products showed an 80% yield of the phosphine sulfide 4. Even under these extreme conditions, no desulfurization of 9 was observed.

In contrast to these extremely slow reactions, the desulfurization of aralkyl disulfides proceeds exothermically at room temperature. For example, the reaction of phenyl methyl



10 + 1 → 11 + 4

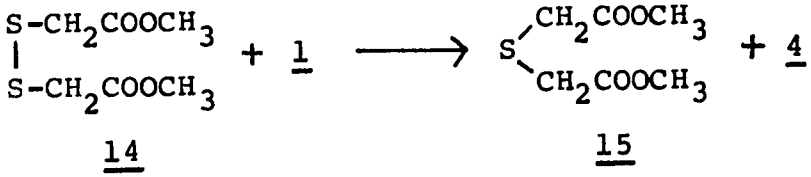


12 + 1 → 13 + 4

disulfide (10) with 1 is complete in under 2 minutes to afford an 86% yield of phenyl methyl sulfide (11). Examination of the crude reaction mixture by gas chromatography showed phosphine sulfide 4 and sulfide 11 to be the only products; no

diphenyl sulfide or dimethyl sulfide (or disulfides) was present. In a similar experiment, benzyl tolyl disulfide (12) was desulfurized in less than 2 minutes to afford an 86% yield of benzyl tolyl sulfide (13); again, no other products were detected by vpc.

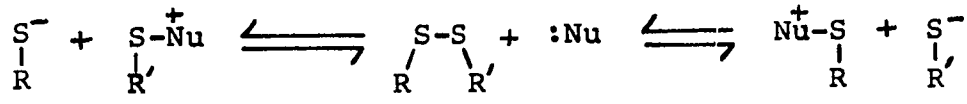
Very rapid desulfurization reactions may be realized not only for unsymmetrical disulfides, but for some symmetrical disulfides as well. Dicarbomethoxymethyl disulfide (14), on treatment with the phosphine 1, afforded the corresponding



14 15

sulfide 15 in 84% yield.

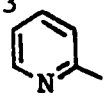
In both phenyl methyl disulfide (10) and tolyl benzyl disulfide (12), a large difference (3-4 pKa units) exists between the ionization constants of the two mercaptide halves of the disulfide (typical acid dissociation constants for several thiols are presented in Table III). This large difference would be expected to cause considerable polarization of the disulfide bond. Sulfur-sulfur cleavage of the disulfides should therefore occur in the direction of this polarization, and as a result, one of the possible mercaptides will be preferentially displaced. This hyphothesis is supported by



the observation of only one sulfide in the desulfurization of disulfides 10 and 12; in both reactions, no products were

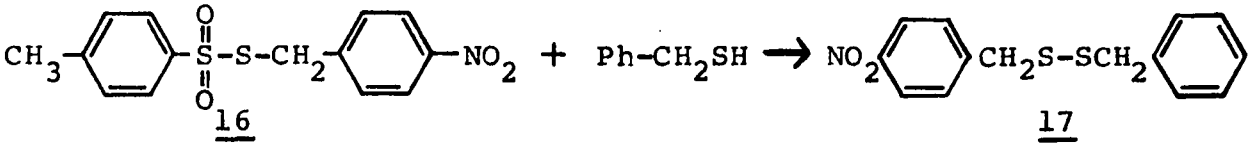
TABLE III

ACID DISSOCIATION CONSTANTS OF THIOLS[a]

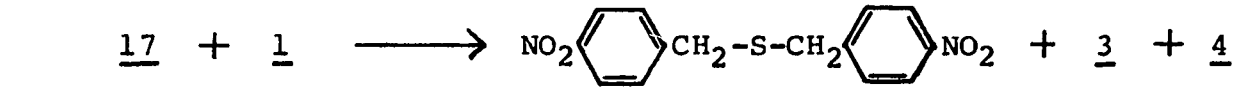
Thiol	pKa	ref.
C_6H_5-SH	8.6	89,90
p-$CH_3C_6H_4$-SH	9.3	89
CH_3OOC-CH_2-SH	9.9	90
	10.6	89
$C_6H_5CH_2$-SH	11.8	89,90
$CH_3(CH_2)_3$-SH	12.6	89,90
$CH_3CH(C_2H_5)$-SH	12.9	89
$(CH_3)_3C$-SH	13.1	89,90

(a) Acid dissociation constants for thiols have been measured in a variety of solvents. It was found that the values determined in dilute aqueous solution (90) and those determined in acetone/water (89) exhibited a simple linear correlation. The data presented in this table refer to acetone/water media; where necessary, an extrapolation to this solvent system was made.

observed which would result from initial displacement of the more basic mercaptide[2]. If this large pKa difference is reduced, the polarization of the disulfide bond will be diminished and, consequently, little selectivity should be observed. To test this hypothesis, the unsymmetrical disulfide,benzyl p-nitrobenzyl disulfide (17), was synthesized from p-nitrobenzyl p-tolylthiolsulfonate (16) and α-toluenethiol. When this disulfide was



16 17



17 + 1 → 18 + 3 + 4

mixed with the aminophosphine 1, a deep red color developed, heat was evolved, and the symmetrical bis-p-nitrobenzyl sulfide 18 separated out as colorless crystals. This material was obtained in 66% yield; benzyl sulfide (3), and tris(diethylamino)phosphine sulfide (4) were detected on tlc but not isolated. The red color observed during this reaction was observed in the reactions of 1 with other nitro compounds (16 for example); Ramirez (91) has attributed this red color to the formation of a charge-transfer complex.

To avoid any abnormality which might develop from the formation of this complex, a second unsymmetrical disulfide, benzyl

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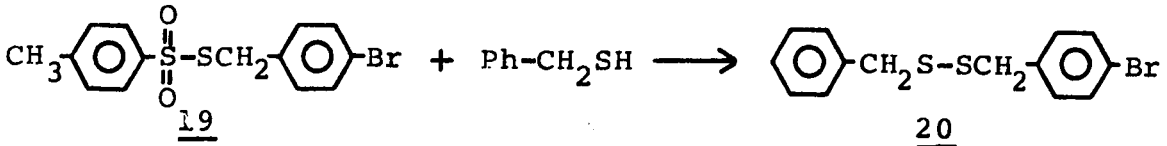
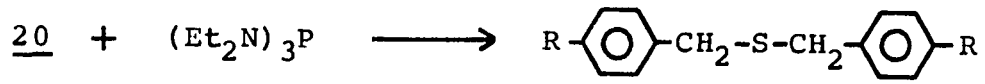
[2]For example, if the more basic benzyl mercaptide were initially displaced in the reaction of 12 with 1, it could react with 12 to yield dibenzyl disulfide and ditolyl disulfide. Neither of these disulfides nor their desulfurization products were observed in this reaction.

p-bromobenzyl disulfide (20) was prepared in a similar manner from p-bromobenzyl p-tolylthiolsulfonate (19). Desulfurization



19 20



	R	R	Yield
3	H	H	11%
21	Br	H	35%
22	Br	Br	22%

(3 hr., 80°) of this disulfide afforded all three of the possible sulfides, 3, 21 and 22, although not in statistical (1:2:1) amounts[3]. Mixing of ions (or mercaptide ligands) has occurred in the desulfurization of 20, a disulfide in which the pKa difference is very small. The non-statistical nature of this product distribution, however, would suggest that a process more complex than cation exchange is occurring.

As the degree of polarization of the disulfide bond is increased, the yield of unsymmetrical sulfide should increase at the expense of the symmetrical sulfides. At one extreme (disulfides 10 or 12), only unsymmetrical sulfides are formed; at the other extreme (disulfide 20), a near statistical distribution of the three possible sulfides is observed. Benzyl ethyl disulfide (23) should lie between these extremes (1 pKa unit difference between the mercaptide halves). Desulfurization of this disulfide at room temperature (18 hours) afforded not the expected benzyl ethyl sulfide, but a near-

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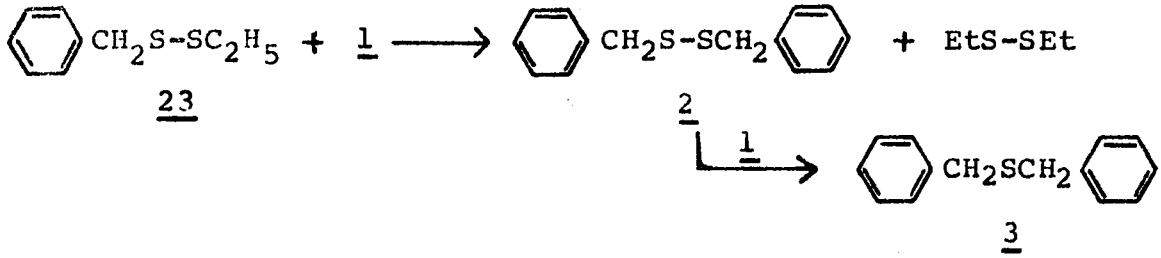
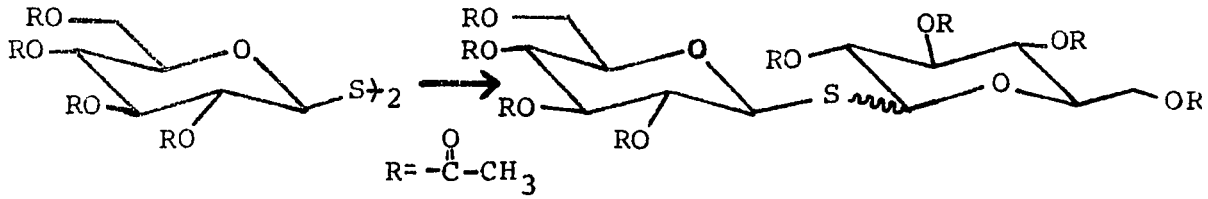
[3] Yields of 3, 21 and 22 were determined by quantitative vpc with internal standards.

quantitative yield of benzyl sulfide (3), as well as substantial amounts of diethyl disulfide! This reaction was monitored by vpc;



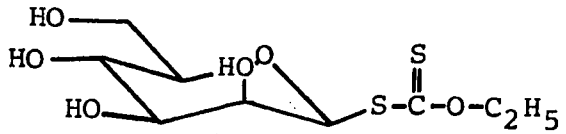
a significant (20%) amount of benzyl disulfide was initially formed in the reaction. A rough scheme for the formation of these products is shown above. Clearly the mixing of mercaptide ligands is not a process which is dependent on the degree of polarization of the disulfide bond. The non-statistical nature of the ligand exchange process and the observation of symmetrical disulfides during these reactions would suggest that a phosphine catalyzed equilibration of symmetrical and unsymmetrical disulfides may, in some cases, preceed desulfurization. This problem will be discussed in more detail during a consideration of the mechanism of desulfurization.

One attractive use of this desulfurization reaction is in the synthesis of thiosugars. For example, the conversion of β-D-glucopyranosyl disulfide to its corresponding sulfide with stereochemical control at the anomeric carbon atom would provide



a direct synthesis of thiotrehaloses (92). Such compounds are of considerable biochemical interest; their similarity to naturally occurring trehaloses render them attractive substrates for

glycosidase enzymes. Moreover, some thiosugars, β-D-mannopyranosyl ethyl xanthate (24) for example, have shown significant antitumor



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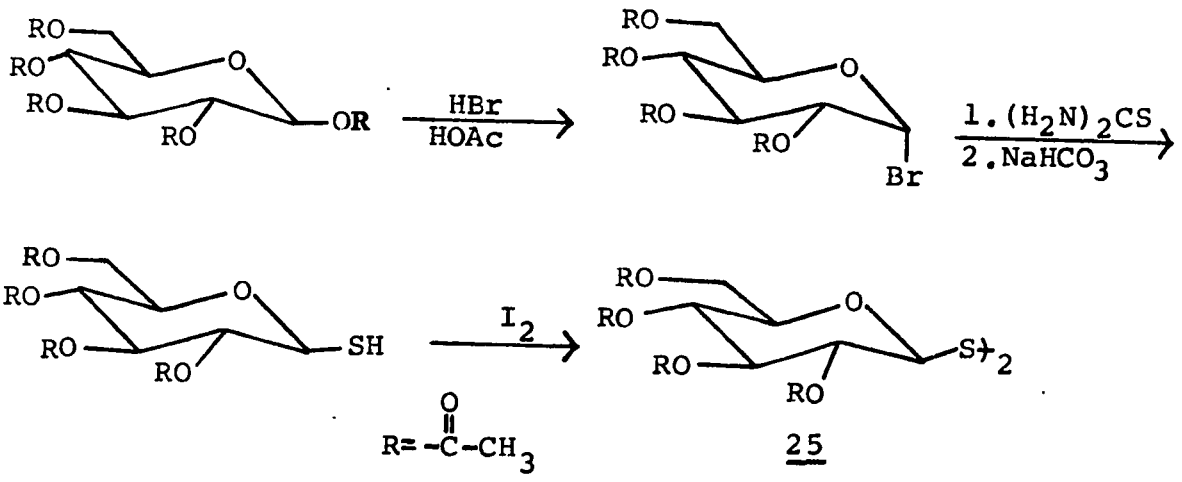
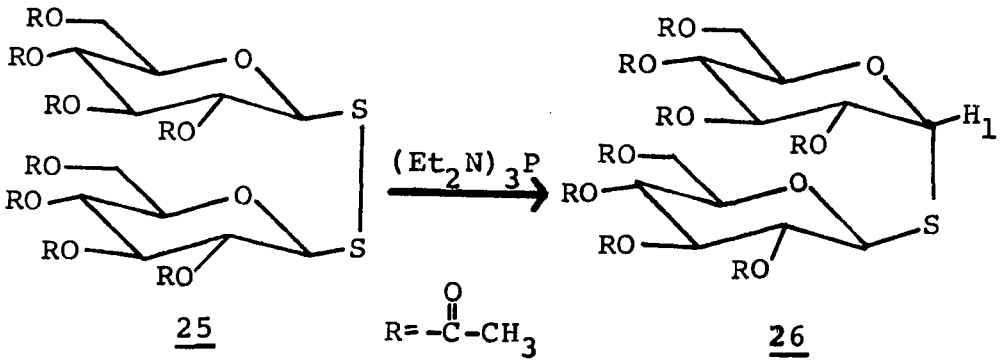
activity (92). The requisite disulfide, β-D-glucopyranosyl disulfide octa-acetate (25), for this study was prepared in several steps from glucose penta-acetate (93). Desulfurization of this



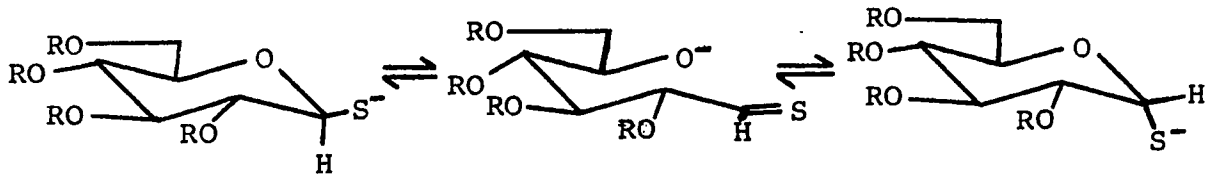
disulfide was effected by refluxing with phosphine 1 for 30



25 26

minutes. The product, obtained in 50% yield, was α-D-glucopyranosyl-1-thio-β-D-glucopyranoside octa-O-acetate (26). The stereochemistry of this product was verified (the mp of this product corresponds to that previously reported (92)) by the observation of a single proton as a low field doublet (4.0τ, J = 5 Hz) may be assigned to the equatorial anomeric proton (H_1 above),

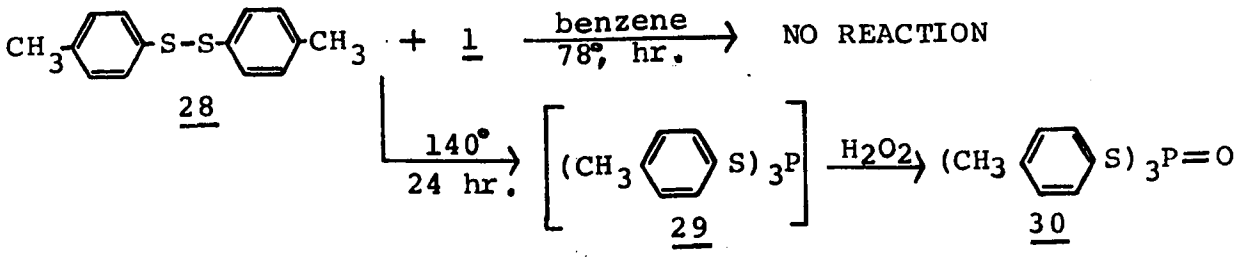
a resonance which is absent in the corresponding disulfide. The desulfurization reaction, then, has proceeded with inversion of configuration at one of the anomeric centers. This inversion of configuration may be a stereochemical consequence of the mechanism of desulfurization or may result from the epimerization of a glucopyranosidyl mercaptide:



While the isolated yield (50%) of this sulfide is somewhat low, an 80% yield of crude sulfide could be realized; the infrared spectrum of this material was identical to pure recrystallized sulfide. A variety of sugar disulfides have been reported (94); application of this reaction could provide a general route to thiotrehaloses.

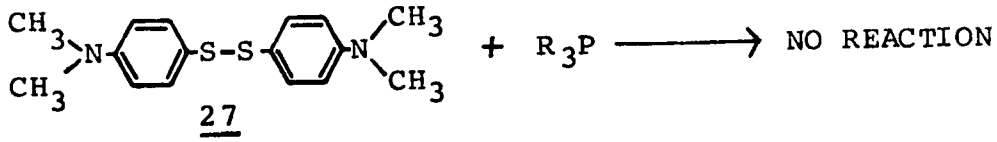
All of the disulfides discussed thus far have been those in which at least one of the substituents is an alkyl or substituted alkyl moiety. As was seen earlier, Schönberg (54) reported a desulfurization of bis(N,N-dimethylamino)phenyl disulfide (27)[4]. It was of interest to study the desulfurization of this and other diaryl disulfides. The desulfurization of di-p-tolyl disulfide 28 was attempted under a variety of conditions without success. No phosphine sulfide could be detected after refluxing a benzene solution of 28 with the aminophosphine 1 for 24 hours. Heating a neat mixture of 1 and 28 at 90° for 18 hours under a

[4]This result could not be duplicated. Refluxing 27 with Ph_3P in benzene for 24 hours did not result in any desulfurization; a 86% yield of 27 was recovered from the reaction.



nitrogen atmosphere caused some decomposition; however, no sulfide or phosphine sulfide could be detected. At still higher temperatures, 135 -140°C for 24 hours, a new compound was detected on tlc. Careful chromatography over a silica gel column permitted the isolation of 29 as colorless oil (10% of the reaction mixture). Oxidation of this oil with hydrogen peroxide afforded tri-p-toluene phosphotrithioate 30 as the only product. Thus the oil obtained from the column could be assigned the structure 29. The phosphotrithioate 30 was also isolated directly from the reaction mixture by chromatographic workup; it is most probable that this material results from the oxidation of 29 during the reaction and isolation procedure. Compound 30 exhibited a long range P-CH_3 coupling of 2.5 Hz; such a coupling has been observed in several phosphines and phosphites (95). The fate of the amino portion of the phosphine 1 in the above reaction is unknown.

The desulfurization of bis(N,N'-dimethylamino)phenyl disulfide (27) was also attempted. Neither triphenylphosphine nor tris-(diethylamino)phosphine entered into a reaction with 27; in both



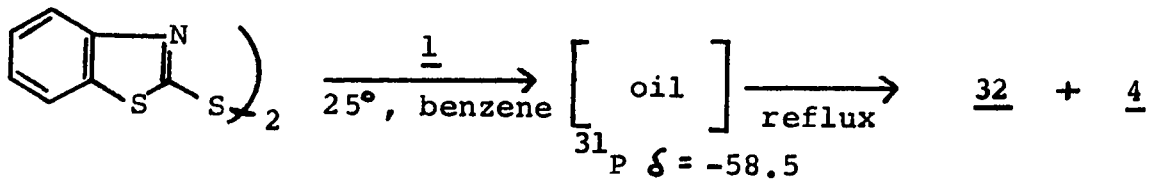
R = Ph, $N(C_2H_5)_2$

cases, the disulfide was recovered in high yield.

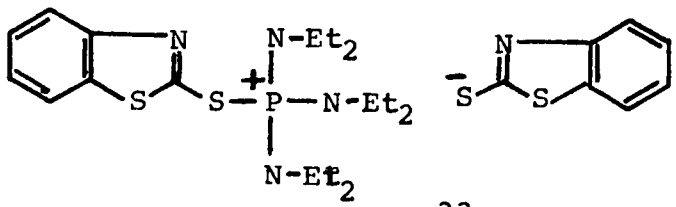
In contrast to the lack of reactivity of the diaryl disulfides, a heterocyclic disulfide, dibenzothiazole disulfide (31), could be desulfurized in refluxing benzene. The product of this reaction, dibenzothiazole sulfide (32), was isolated in 61% yield . If the reaction was performed at room temper-

31 32

ature, an oil formed upon addition of the phosphine; this oil



redissolved upon refluxing for 2-3 hours and sulfide 32 and phosphine sulfide 4 appeared. The ^{31}P nmr spectrum of this oil showed a resonance at -58.5 ppm (relative to H_3PO_4); a comparison of this chemical shift with a variety of aminophosphine



33

standards (Table IV) indicated that this oil was the phosphonium salt 33. The use of ^{31}P nmr for the identification of organophosphorus compounds has been discussed in several reviews (96, 97) and has been used to identify phosphines, phosphites,

TABLE IV

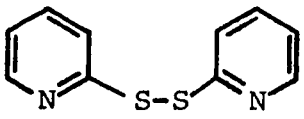
^{31}P NMR CHEMICAL SHIFTS

COMPOUND	δ ^{31}P (relative to H_3PO_4)
$(Et_2N)_3P$ (1)	-117.7
$(Et_2N)_3P{=}O$ [a]	-23.5
$(Et_2N)_3P{=}S$ (4)	-78.3
$(Et_2N)_3\overset{+}{P}\text{-S-}CH_2Ph\ \ BF_4^-$ [b]	-61.9
$(Et_2N)_3\overset{+}{P}\text{-S-}C_6H_4CH_3\ \ {}^-SO_2C_6H_4CH_3$ [b]	-61.6
33	-58.5
35	-60.4

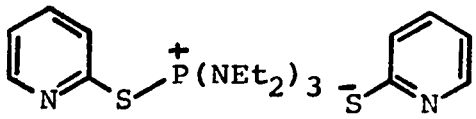
a) data obtained from reference 97.
b) the synthesis of this compound will be described later.

phosphoranes and phosphonium salts.

An attempt was made to desulfurize another heterocyclic disulfide, di-2-pyridyl disulfide (34). Upon mixing the disulfide 34 with tris(diethylamino)phosphine (1), a bright yellow oil was formed which would not react further on refluxing in benzene for 48 hours. On the basis of the ^{31}P nmr chemical shift (δ= -60.4 ppm), the phosphonium salt structure 35 was



34



35

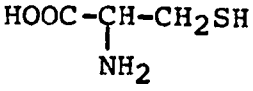
$^{31}P\ \delta$ = -60.4

assigned to this oil.

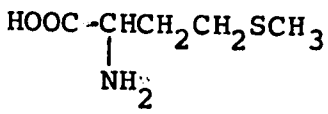
Amino Acid and Peptide Disulfides

Of the many naturally occurring sulfur compounds, three of the most common are the sulfur-containing amino acids,

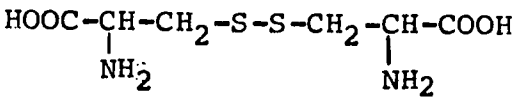
cysteine, cystine and methionine. Methionine, an amino acid



CYSTEINE



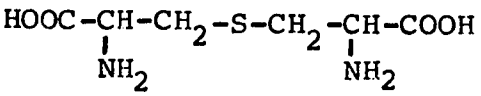
METHIONINE



CYSTINE

which is essential in the human diet for proper maintanance of the nitrogen balance in the body, serves as the major source of labile methyl groups in the synthesis of other important biological compounds. In addition, it may serve as a precursor to cystine and cysteine, although only the sulfur atom is transfered to these amino acids (98). Cystine and its reduced counterpart, cysteine, as amino acids, are of considerable interest because of their special role in biological systems. Cystine is found in the wool and hair of most mammals (99) and in several important hormones including insulin (5), oxytocin (4), vasopressin (100), vasotocin (101) and the human pituitary growth hormone (HGH)(102).

The sulfide analog of cystine, lanthionine (36), was first isolated from wool hydrolysates as a mixture of isomers



36

in 1941 (103) and synthesized by du Vigneaud and Brown in the same year (104). Subsequently it was demonstrated that lanthionine does not naturally occur in wool, but rather

results as an artifact of alkaline treatment during isolation (105). The first report of naturally occurring lanthionine was made in 1966 by Sloane and Untch (106). They isolated both L-and meso-lanthionine from the free amino acid pool of chick embryo. Subsequently, L-lanthionine has been found in the deprotonized haemolymph of various insects (107), most notably the silkworm and Japanese Oak Moth, and in plant pollen (108). The absence of the major sulfur-containing amino acids (cystine, cysteine and methionine) in these sources is interesting.

While several synthetic schemes for meso and DL-lanthionine have been reported (109), the only stereospecific synthesis of L-lanthionine involves the condensation of L-cysteine with methyl L-β-chloroalanate followed by strong alkaline hydrolysis. Low yields, coupled with problems of racemization[5] render this approach unattractive for the synthesis of larger lanthionine peptides.

It would appear that selective removal of a sulfur atom from appropriate cystine derivatives would afford a convenient synthetic route to optically pure lanthionine and its derivatives. Since carboxylic acids are known to react with aminophosphines (71), it was necessary to use cystine derivatives protected as methyl or ethyl esters for this study[6]. Preliminary work showed that the amide function would not interfere in the desulfurization reaction as dicarbobenzoxy-cysteamine (37) was

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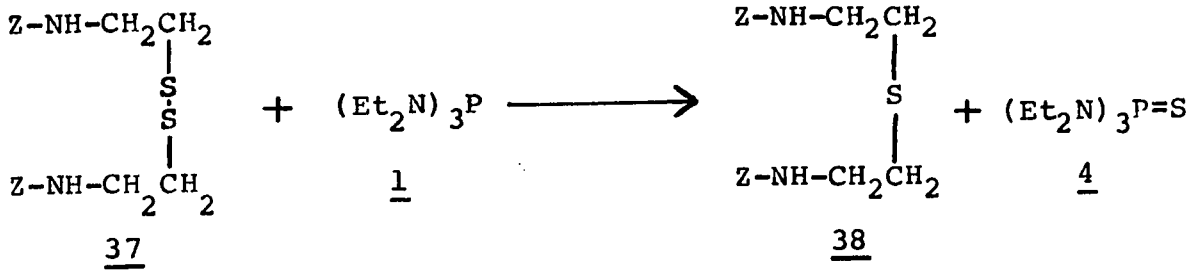
[5]Lanthionine undergoes complete racemization in 3-4 hours in 2.4N NaOH solution; this reaction is much faster than previously reported (106).

[6]See pg.52 for phosphine-carboxylic acid reaction.



37 + $(Et_2N)_3P$ (1) → 38 + $(Et_2N)_3P{=}S$ (4)

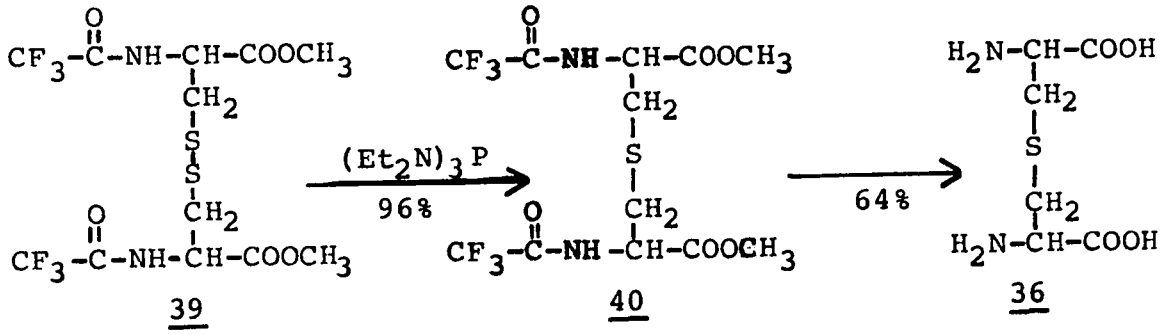
$Z = -COOCH_2C_6H_5$

desulfurized in 70% yield in refluxing benxene.

One cystine derivative chosen for this study was N,N'-bis-(trifluoroactly)-L-cystine methyl ester (39). The trifluoroacetyl group was selected since it may be removed under mild alkaline conditions (0.1N NaOH). In addition, the enhanced volatility of the TFA group (110) would allow for a mass spectral study of the cystine and lanthionine derivatives.

Disulfide 39 was prepared in 96% yield by reaction of L-cystine methyl ester hydrochloride with trifluoroacetic anhydride in trifluoroacetic acid at 0°C.

The desulfurization of disulfide 39 could be conveniently effected by addition of tris (diethylamino)phosphine (1) to a

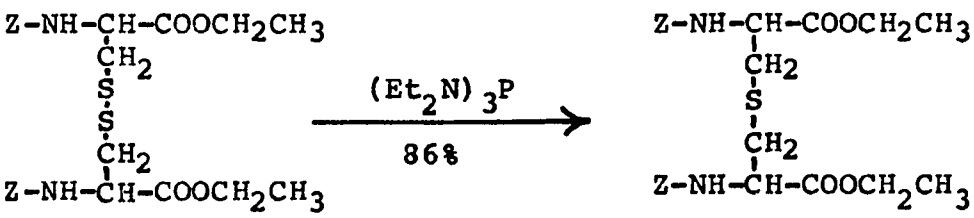


39 —$(Et_2N)_3P$, 96%→ 40 —64%→ 36

L-(+)-LANTHIONINE

suspension of 39 in dry benzene. After 4 to 5 minutes, the disulfide passed into solution followed immediately by precipitation of a white solid. Dilution with hexane and fitration afforded the corresponding lanthionine derivative 40 in 96% yield, $[\alpha]_D^{25}$ -21.6°. Structure proof of 40 obtains from its elemental analysis and mass spectrum (vide infra). Mild alkaline hydrolysis of 40 gave a 64% yield of L-(+)- lanthionine (36). The infared spectrum of 36 was identical to that reported (106) for L-(+)-lanthionine and completely different from both meso and racemic lanthionine. The optical rotation of 36 in acid, $[\alpha]_{578}^{25}$ +4.0°, compares favorably with that previously reported (107) ($[\alpha]_{578}^{25}$ + 2.36°, + 5.75°). Measurements of the optical rotation (2.4 N NaOH) gave a value of +9.4° (lit. $[\alpha]_D$ +8.4° (104)). On the basis of the spectroscopic and optical data, it was concluded that this material is of high optical purity. It was found that optically pure 36 underwent complete racemization over a period of several hours.

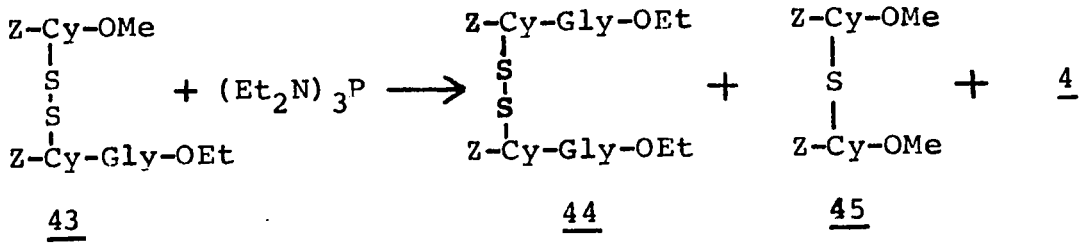
The high selectivity in removal of the carbobenzoxy group would make the lanthionine derivative 42 a useful starting material for peptide synthesis. This compound could be prepared in 86% yield by desulfurization of N,N'-dicarbobenzoxy-L-cystine diethyl ester (41)[7].



41 42

[7]The gift of this compound from Prof. R.G. Hiskey is gratefully acknowledged.

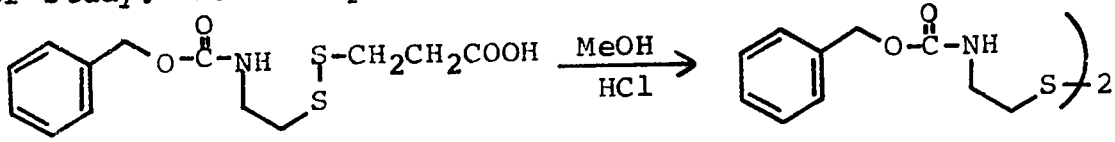
Of considerable interest was the desulfurization of some unsymmetrical disulfides since most naturally occurring cystine peptides are of this type. An attempt was made to desulfurize



43 44 45

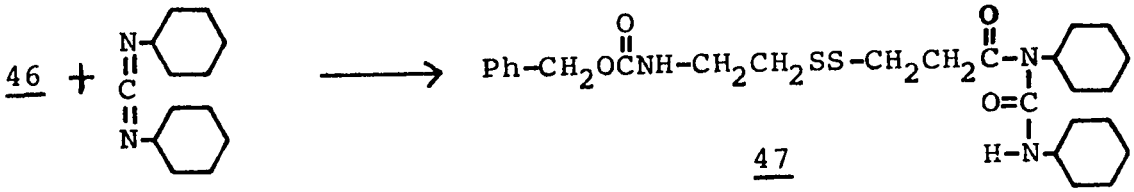
the unsymmetrical peptide[7] 43 ; however, the symmetrical disulfide 44 was isolated in 82% yield. In addition, significant amounts of phosphine sulfide 4 and sulfide 45 were detected by tlc.

It was desirable to repeat this reaction on a simpler, model disulfide. Since the mixed disulfide N-carbobenzoxy-2-amino-2'-carboxy ethyl disulfide (46) was available[7], conversion of it to the methyl ester would afford a suitable model compound for study. An attempt to esterify this acid with methanolic



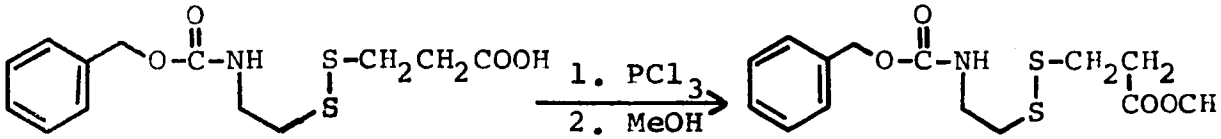
46 37

hydrochloric acid did not afford the desired ester, but rather a 65% yield of the symmetrical disulfide 37. The use of N,N'-dicyclohexylcarbodiimide to effect this esterification led to the formation of a highly insoluble white solid, mp 210-220°,



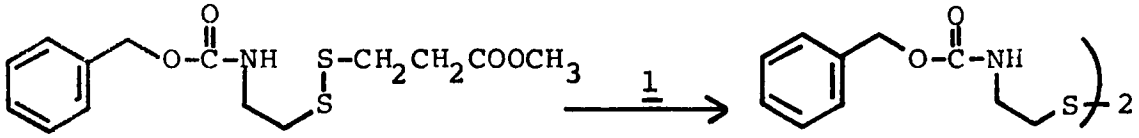
47

tentatively assigned the N-acyl urea structure 47 on the basis of its NMR spectrum. The desired ester could be obtained by the treatment of 46 with phosphorus trichloride at room temperature followed by the addition of methanol. After chromatography, the ester 48 was obtained in 70% yield.



46 48

An attempt to desulfurize this disulfide at room temperature led to the immediate formation of the symmetrical disulfide 37

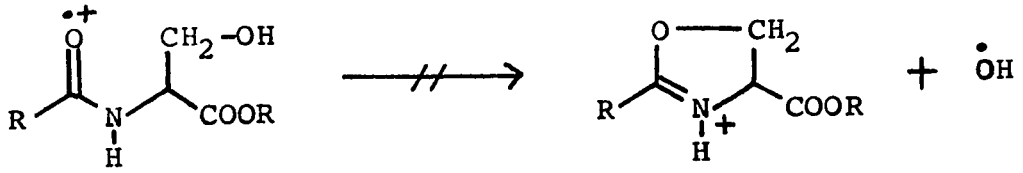


48 37, 88%

in 88% yield. Thus for both disulfides 43 and 48 , the formation of symmetrical disulfides is proceeding at a much faster rate than is the desulfurization reaction.

As might be expected, many of the spectral properties of the cystine and lanthionine derivatives are very similar. However, the fragmentation reactions which occur under electron impact in the mass spectrometer should be quite different (111). To determine the effect of the sulfide and disulfide groups on the fragmentation of cystine and lanthionine derivatives, a detailed examination of the mass spectra of the TFA derivatives 39 and 40, the carbobenzoxy derivatives 41 and42 and cysteamine derivatives 37, 38 and 48 was undertaken. The mass spectrum of

trifluoroacetyl cystine dimethyl ester (39) showed an intense molecular ion at m/e 460 (20%) with the base peak at m/e 198 arising from cleavage α to the disulfide (Fig. 3)[8]. While this ion may be formulated as either an open chain ion a_1 or as an oxazoline ion a_2, the latter formulation is preferred since the subsequent loss from it of methyl formate leads to the formation of the protonated oxazole ion b at m/e 138 (40%). The formation of the oxazoline ion appears unique in that it is not observed in other acetyl and trifluoroacetyl amino acid esters (112). This includes acetyl serine ethyl ester (49), where the loss of an OH radical would not be unexpected. The mass spectrum of the trifluoroacetyl lanthionine ester 40 is radically different from the cystine derivative 39. Here the major fragmentation (Fig. 4) occurs β to the sulfide to form ion c, a process which is common to most acylamino acid esters (112).



49

[8]The fragmentation processes were verified by the observation of appropriate metastables peaks. Where pertinent, these processes will be indicated by the presence of an asterisk (*) placed over the appropriate arrows in the fragmentation schemes.

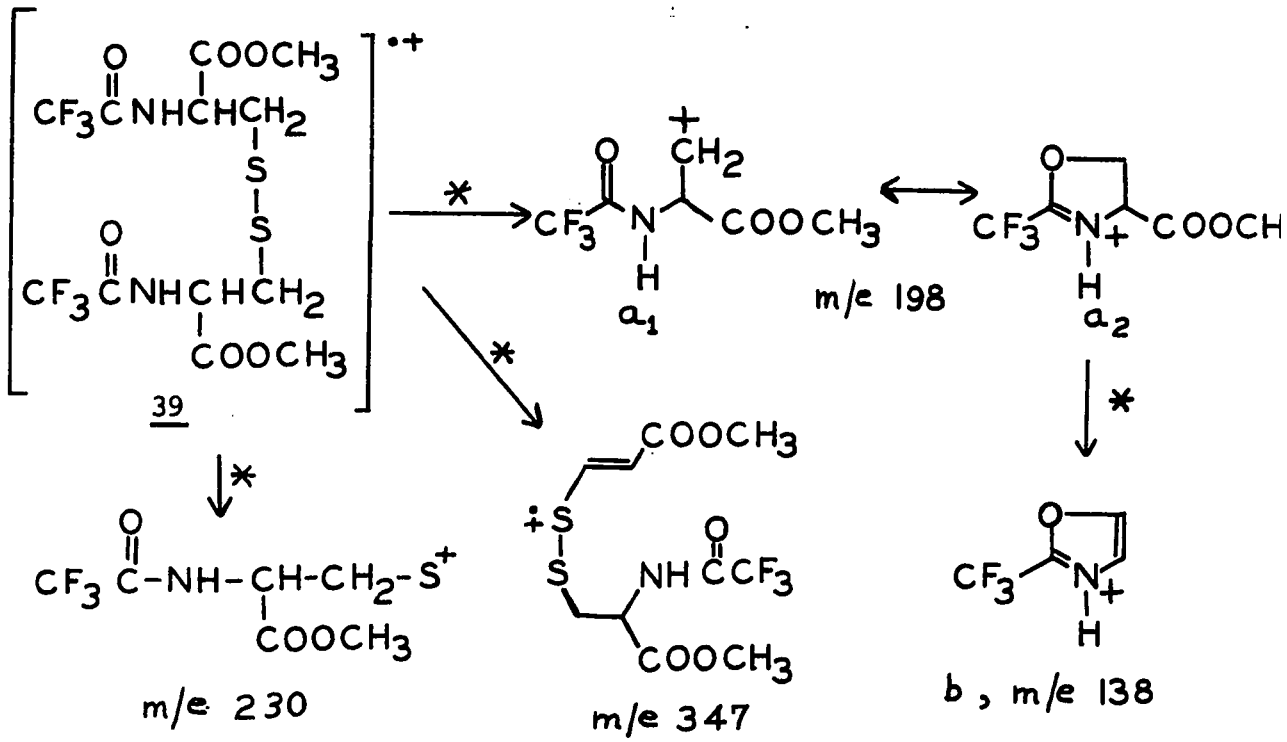


Figure 3. Mass spectral fragmentation of N,N'-Bis(trifluoroacetyl)-L-cystine dimethyl ester (39).

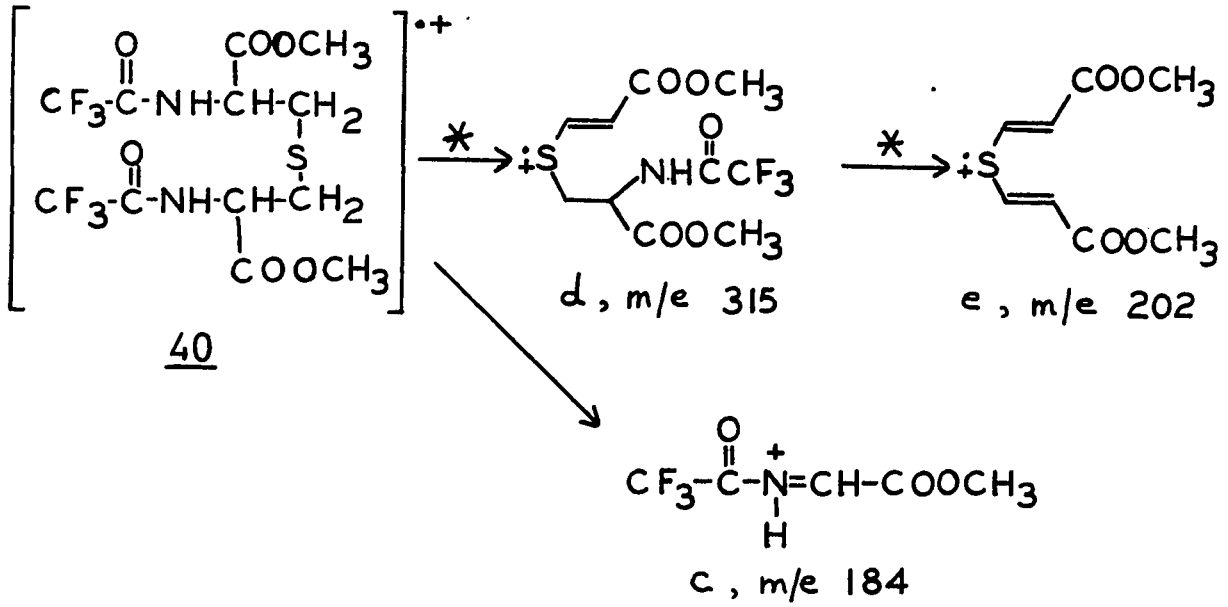
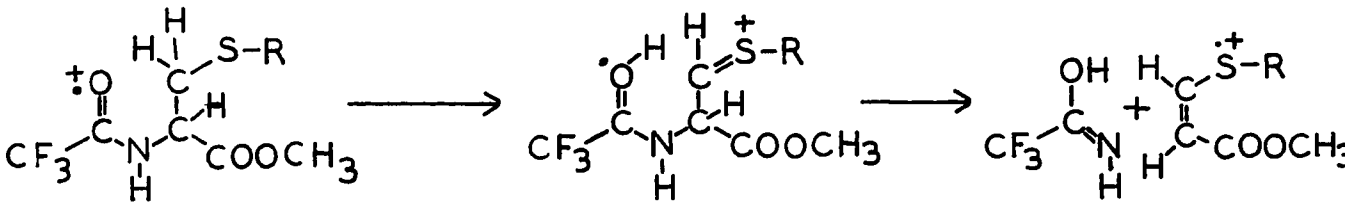


Figure 4. Mass spectral fragmentation of N,N'-Bis(trifluoroacetyl)-L-lanthionine dimethyl ester (40).

Of more interest in the spectrum of 40 is the loss of the elements of trifluoroacetamide to form ion d of m/e 315 which is 40% of the base peak. This ion subsequently loses another trifluoroacetamide molecule to form an intense ion e at m/e 202. The formation of d presumably results from hydrogen migration and cleavage of the C-N bond. This fragmentation is analogous to a



McLafferty rearrangement (113); however, unlike the McLafferty rearrangement the charge is retained on the olefin fragment. It should be noted that no normal McLafferty rearrangement occurs as evidenced by the lack of an ion at m/e 113, $(CF_3CONH_2)^{\cdot+}$. This unusual fragmentation is observed only in special circumstances, as, for example, in the fragmentation of N-acetyl β-phenylalanine esters to form styrene esters (112,114).

While the formation of the oxazoline ion is the major pathway for the trifluoroacetyl disulfide 39 with this "reversed" McLafferty rearrangement[9] occurring to a small degree, exactly the opposite behavior is observed for the sulfide. This dichotomy

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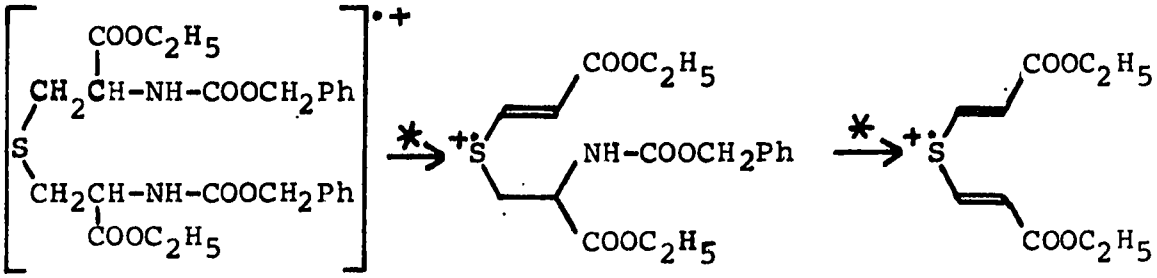
[9]The term "reversed" is used here to emphasize that the charge resides on the olefin fragment in contrast to the normal McLafferty rearrangement.

of behavior must be due to an inherent difference between sulfide and disulfide groups. To further explore this mass spectral behavior, the spectra of several analogous N-carbobenzoxy derivatives were examined. The mass spectrum of N,N'-dicarbobenzoxy-cystine ethyl ester 41 exhibited both oxazoline formation (ion f, m/e 250, 9%) and reversed McLafferty rearrangement (ion g, m/e 413, 3%) (Fig. 5). As was the case for disulfide 39, oxazoline formation predominates; here in the ratio of about 3:1.

In contrast, relatively little oxazoline formation is observed in the mass spectrum of the lanthionine derivative 42; the reversed McLafferty rearrangement is the major fragmentation process (h,m/e 381 and i, m/e 230). This parallels the observations in the TFA derivatives.



42 h, m/e 381 i, m/e 230

The mass spectra of several structurally analogous cysteamine derivatives were studied to further explore this sulfide-disulfide dichotomy. The mass spectrum of dicarbobenzoxy-cysteamine 37 exhibited a strong ion at m/e 178 (8%) corresponding to the oxazoline ion (Fig. 6) and a much smaller ion at m/e 269 (1%) corresponding to a reversed McLafferty rearrangement. The predominance of oxazoline formation again parallels the observation in the cystine series. Other ions observed in this spectrum and their origins are shown in Fig. 6. Note that the oxazoline ion

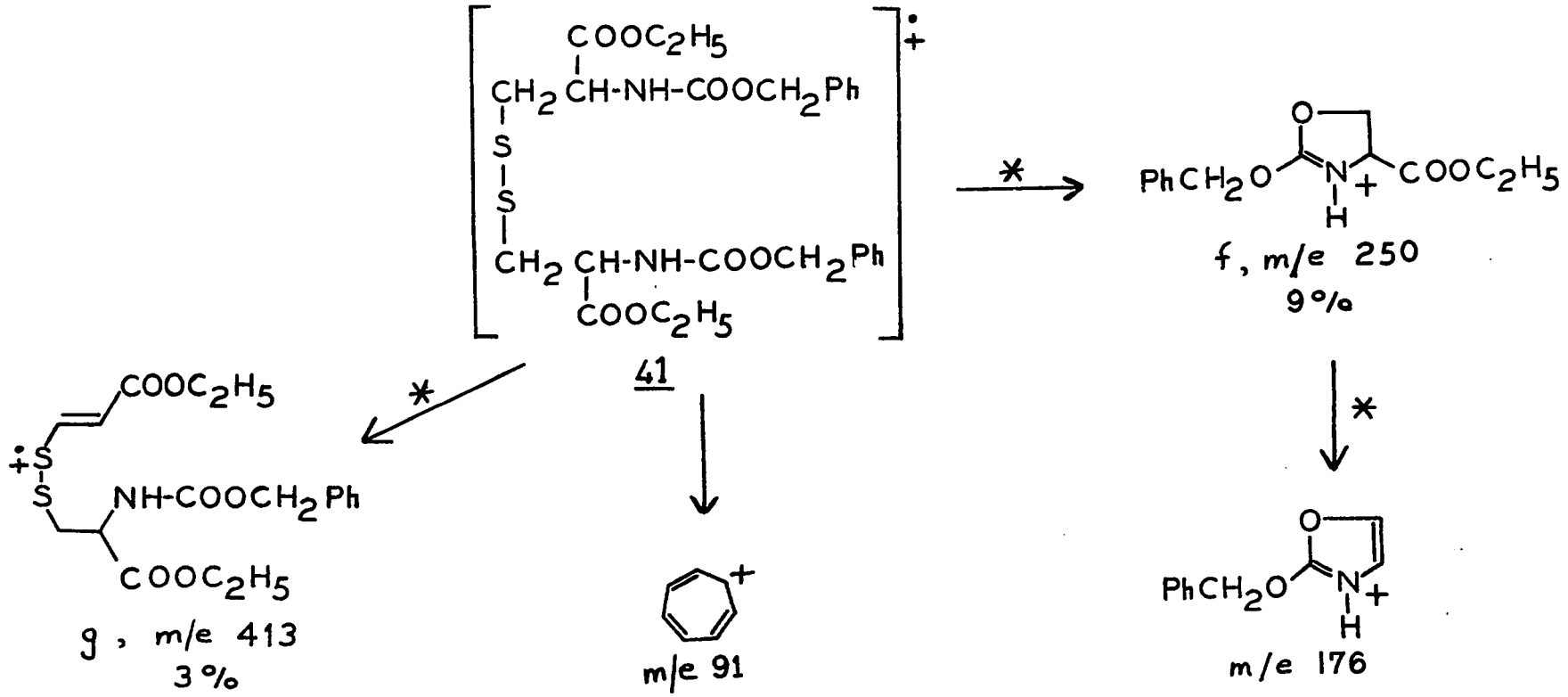


Figure 5. Mass spectral fragmentation of N,N'-Dicarbobenzoxy-L-cystine diethyl ester (41).

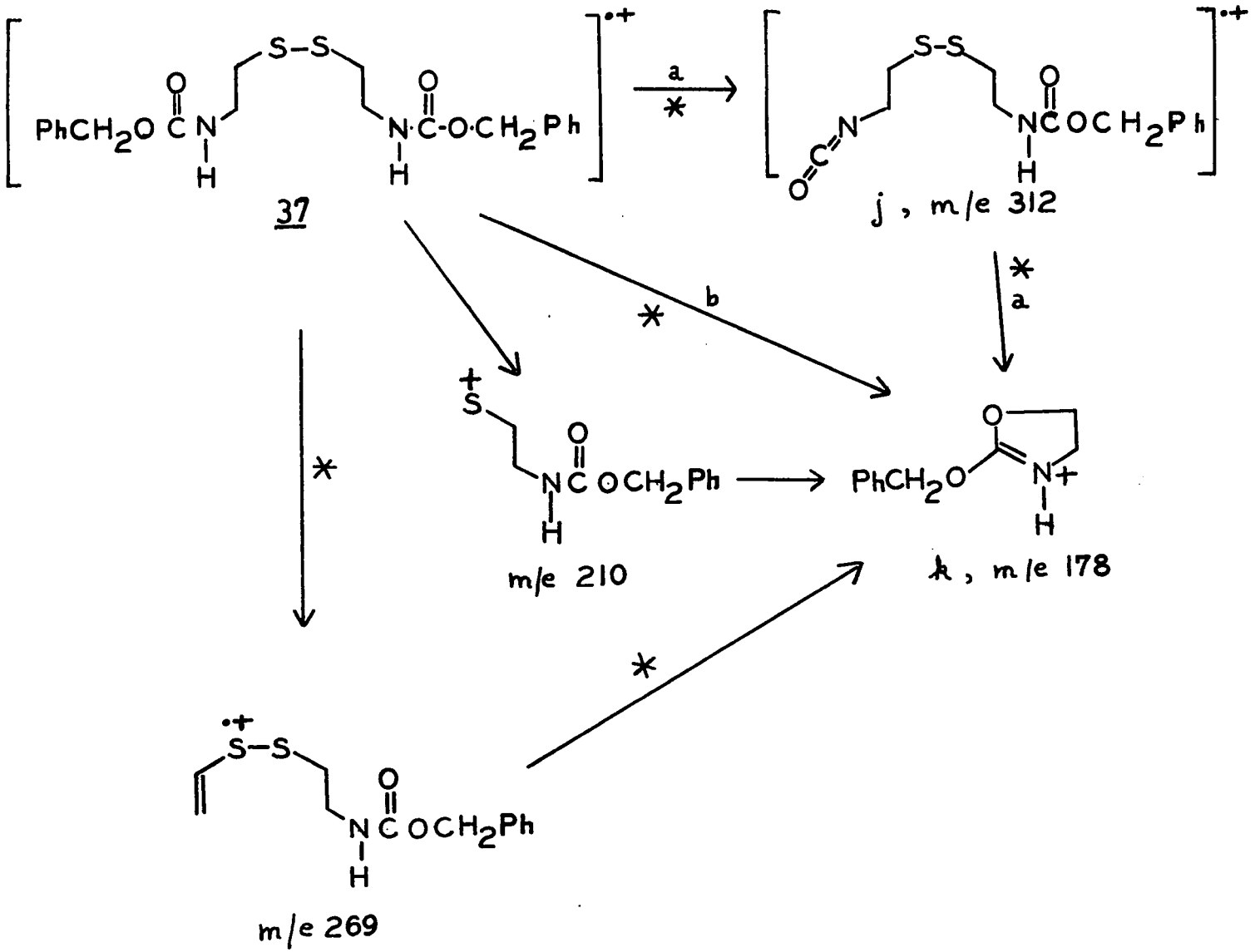


Figure 6. Mass spectral fragmentation of N,N'-Dicarbobenzoxycysteamine (37)

may arise from several pathways, although judging from the intensity of the various metastable peaks, only path a (2→j→k) and b (2→k) appear to be of major importance.

The mass spectrum of the unsymmetrical disulfide, N-carbobenzoxy-2-amino-2'-carbomethoxy-diethyl disulfide (48), possessed a strong peak at m/e 178. This peak may be ascribed to either oxazoline ion ℓ or ion m (resulting from reversed McLafferty rearrangement). A high resolution spectrum of m/e 178 showed clearly the presence of two ions; the major ion at m/e 178.0879 (85%) was the oxazoline ion ℓ (calcd. for $C_{10}H_{12}NO_2$: 178.0868), while the minor ion (15%), m/e 178.0128 (calcd. for $C_6H_{10}O_2S_2$: 178.0122) corresponded to the fragment m resulting from the reversed McLafferty rearrangement (Figure 7).

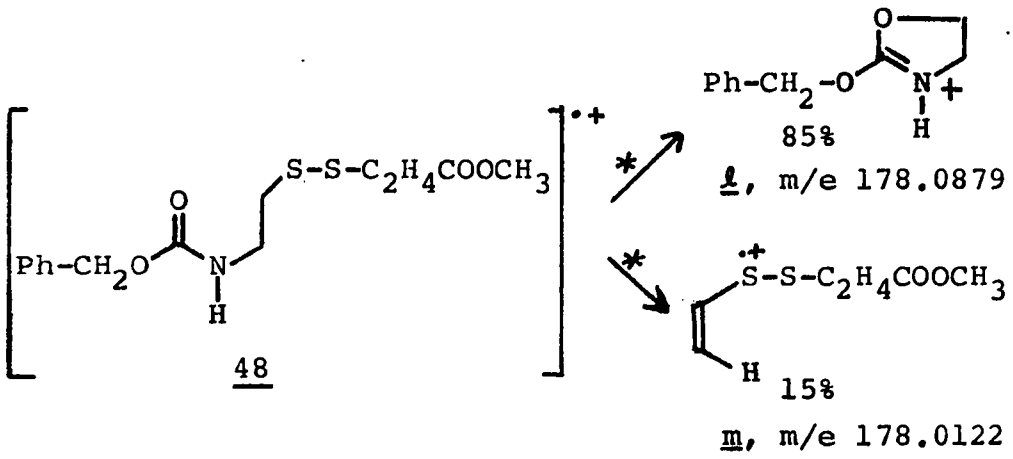
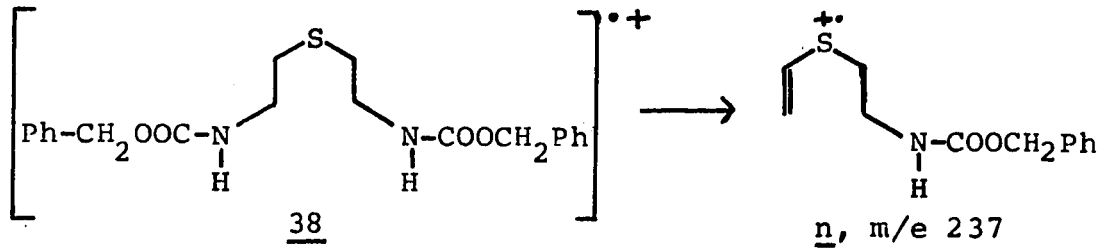


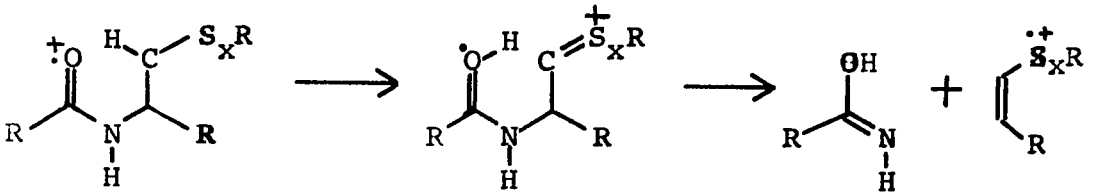
Figure 7. Mass spectral fragmentation of N-carbobenzoxy-2-amino-2'-carbomethoxy-diethyl disulfide (48)

In contrast to the behavior of 37 and 48, the sulfide derivative of 37, N,N'-dicarbobenzoxy-2,2'-diaminodiethyl sulfide 38 showed very little oxazoline formation, but again showed only the formation of the vinyl sulfide ion n at m/e 237 (5%).



38 n, m/e 237

The major difference in the spectra of the sulfides as compared with the corresponding disulfides lies in the relative amounts of the oxazoline to reversed McLafferty processes (Table V). The ratio is high for the disulfides and low for the sulfides. This difference between disulfides and sulfides could be the result of two additive effects. The electron donor ability of sulfur would assist in the transfer of a hydrogen to the carbonyl oxygen during vinyl sulfide (disulfide) formation. Sulfides, better electron donors than disulfides(115), would be more likely



x = 1,2

to undergo this reversed McLafferty rearrangement. In contrast, the increased stability of the sulfthiyl radical (RSS•) over the thiyl radical (RS•) (which has been attributed to both

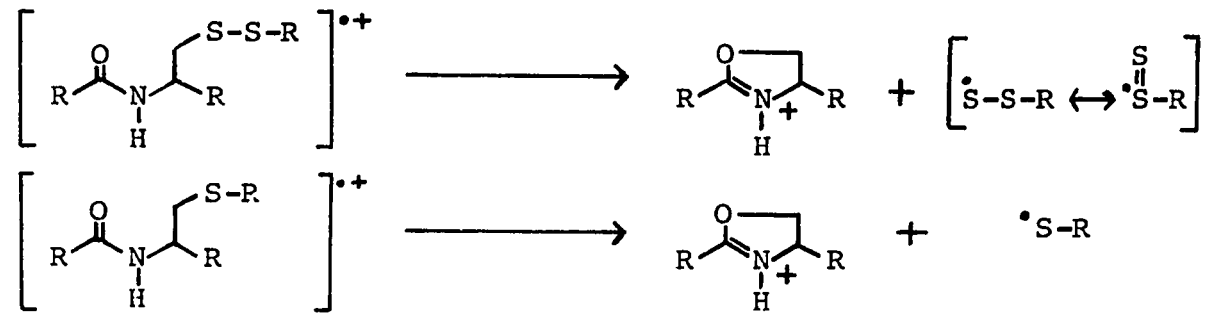


TABLE V

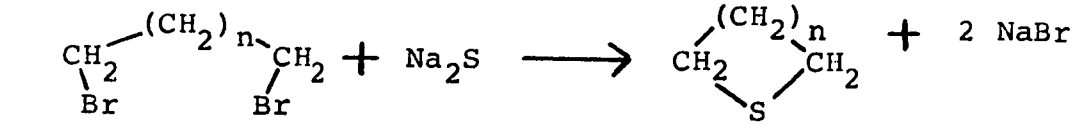
ION ABUNDANCES

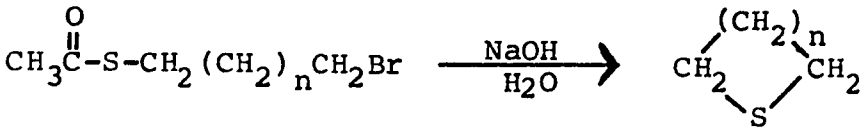
Compound	Parent ion, %	Oxazoline ion (X), %	Vinyl sulfide (disulfide) ion (Y), %	X/Y
Disulfides				
39	19	100	9	11
41	7	9	3	3
37	0.4	8	2	4
48	3	4	0.7	6
Sulfides				
40	4	15	42	0.35
42	0.005	0.5	3	0.2
38	-	0.5	5	0.1

inductive and resonance effects) (116) would result in the preferred formation of the oxazoline ion from disulfides rather than from sulfides.

Alicyclic Disulfides

As part of this study on the selective desulfurization of disulfides, it appeared to us that this reaction could provide a new synthetic approach to cyclic sulfides. The synthesis of cyclic sulfides may be accomplished by the action of sodium sulfide on alkyl dihalides (117,118) or by a variation of this approach, for example, the hydrolysis of halo-alkyl thioacetates



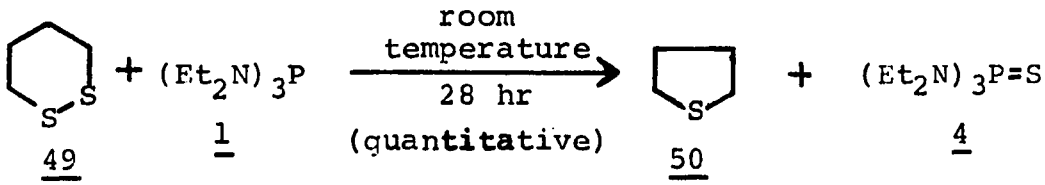


(119). While the formation of five and six membered sulfides generally proceeds in good yield, the formation of polymer is always competitive; this side reaction is a serious problem in the synthesis of four, seven and larger membered rings (117).

In contrast, the formation of cyclic disulfides by oxidation of the corresponding dithiol may, under suitable conditions, approach quantitative yields. For example, the oxidation of 1,4—butanedithiol under dilute conditions affords 1,2-dithiane

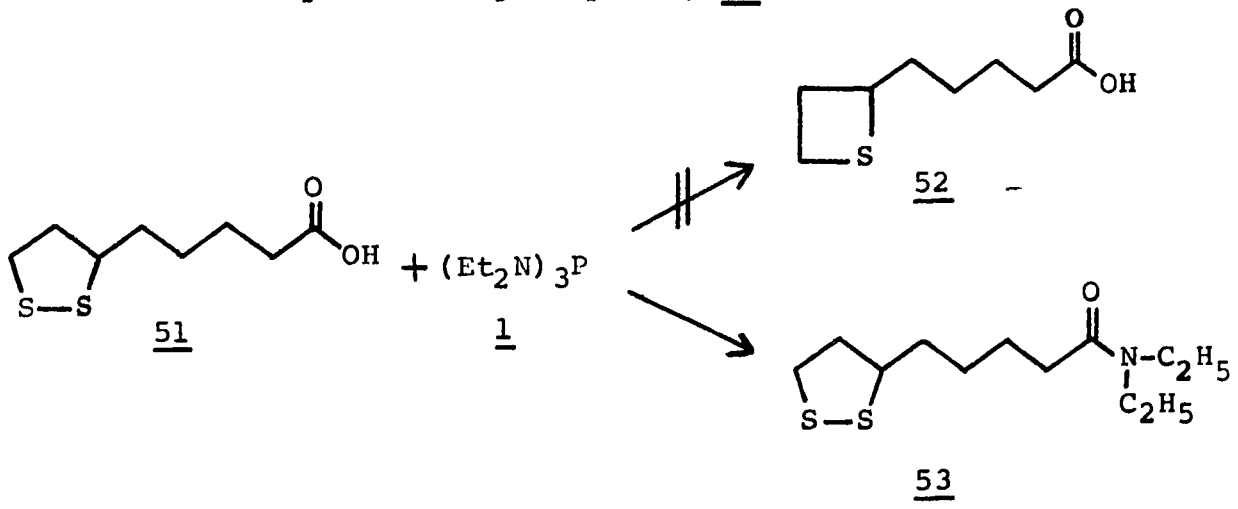
(49) in 93% yield (84). If the desulfurization reaction were to proceed with reasonable yields, this synthetic approach to cyclic sulfides would be competitive with known methods.

The desulfurization of 1,2-dithiane (49) occurred at room temperature to afford, after 28 hours, a quantitative (vpc)



yield of tetrahydrothiophene (50). This long reaction time could be significantly reduced with little loss in yield (see page 101).

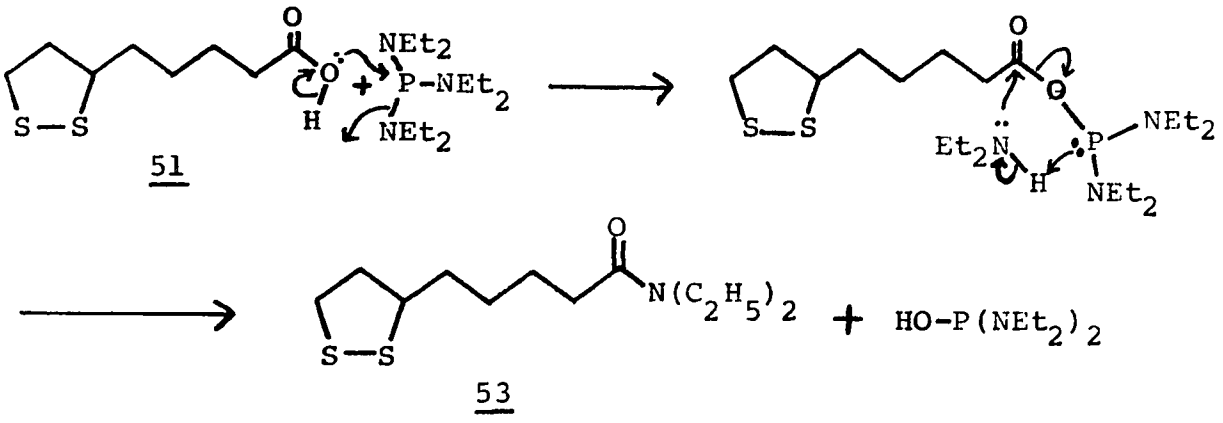
Of greater interest is the desulfurization of five membered disulfides (dithiolanes). One dithiolane, α-lipoic acid (51) an important vitamin, is readily available from natural sources (7). The corresponding thietane derivative, thietane-2-valeric acid (52) has only recently been prepared via a multi-step synthesis (120). An attempt was made to prepare this thietane from the naturally occurring compound, 51. However, when this



disulfide was treated with the aminophosphine 1, no thietane

derivative was obtained; the main product, isolated in 78% yield, was the diethylamide 53 of α-lipoic acid. The structure of 53 obtains from the observation of an ethyl moiety (8.90τ, triplet; 6.70τ, quartet; J = 7 Hz.) in its nmr spectrum and from its mass spectral fragmentation (Fig. 8). A parent ion at m/e 261 was observed. The fragments at m/e 115, 100 and 72 are in accord with the diethylamide structure and are characteristic fragmentations for amides (121). The ion fragment o of m/e 128, which results from cleavage γ to the amide function is of particular interest since α, β and δ cleavage does not occur to any significant extent. This cleavage appears to be general for α-lipoic acid derivatives.

The formation of amides from the reaction of carboxylic acids with 1 has been reported (71); a likely mechanism for this reaction is outlined below:



When the carboxylic acid was protected by conversion to the anilide 54 , the desulfurization reaction proceeded cleanly.

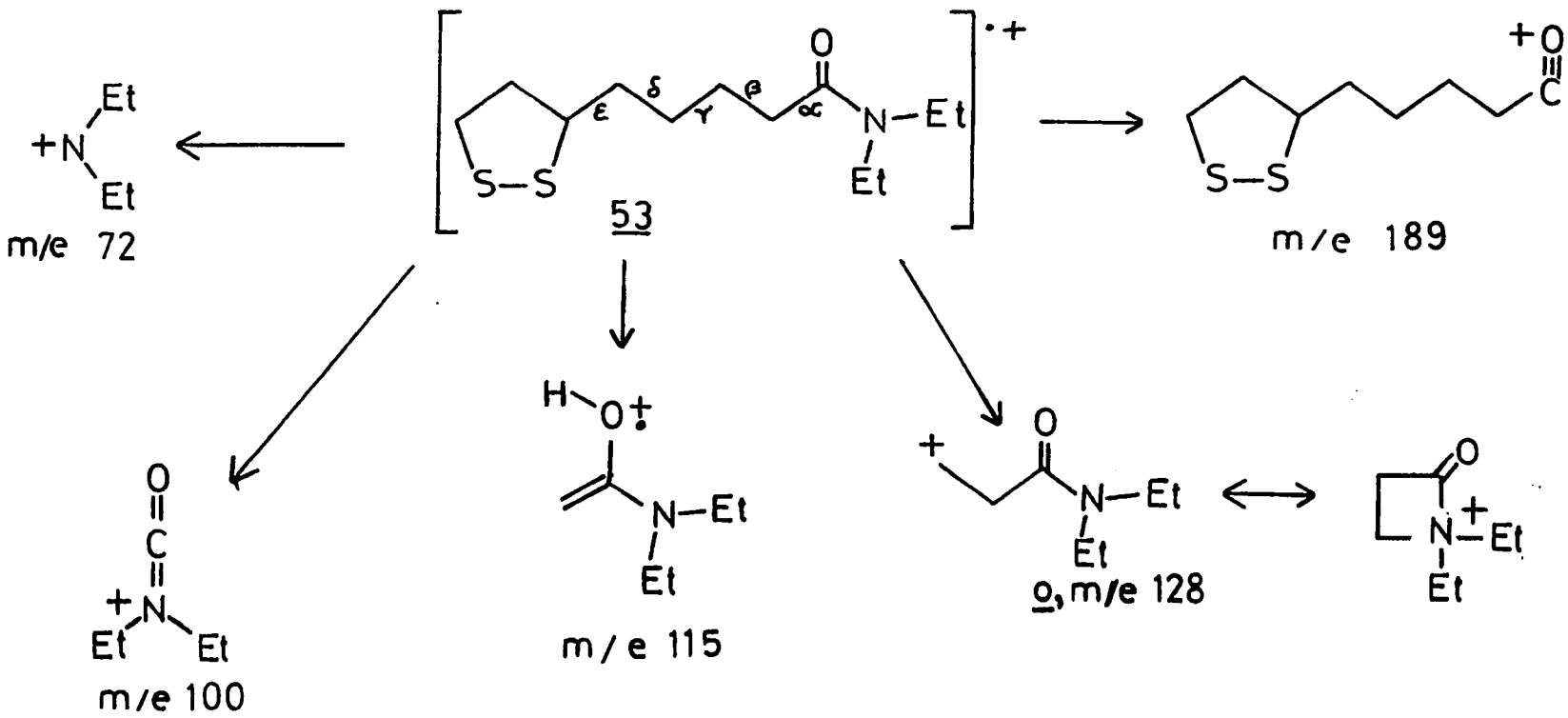
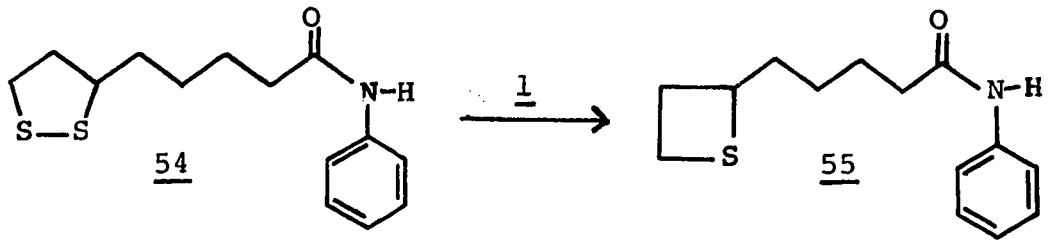


Figure 8. Mass spectral fragmentation of α-Lipoic acid diethylamide (53).

Thus, after stirring 54 for one hour with the aminophosphine,



the yellow color of the disulfide was completely discharged and the absorption maxima at 330 mμ (characteristic of 1,2-dithiolanes (122)) disappeared. A new compound, 55, was obtained in 68% yield. While the ir and nmr spectra of this compound were very similar to 54, the mass spectrum exhibited a parent ion at m/e 249.1180 (calcd. for $C_{14}H_{19}NOS$, 249.1198) consistent with the assigned thietane structure 55. The fragmentation pattern of this sulfide was similar to that of disulfide 53. The appearance of of several metastable ions (indicated by an * in the fragmentation schemes) permitted the deliniation of many of the fragmentation pathways. These are shown in Figure 9.

The formation of ion p (m/e 135) by a McLafferty rearrangement (114) and the aniline radical ion q (m/e 93) by C-N cleavage parallel fragmentations observed in the mass spectrum of α-lipoic acid diethylamide (53). Although the formation of an acylium ion (ion r, m/e 157) is not unusual for amides (123), it is possible that, for this compound, C-N cleavage is facilitated by cyclization. The postulation of a cyclic structure, s, for this ion is also not unreasonable, since, as will be seen later,

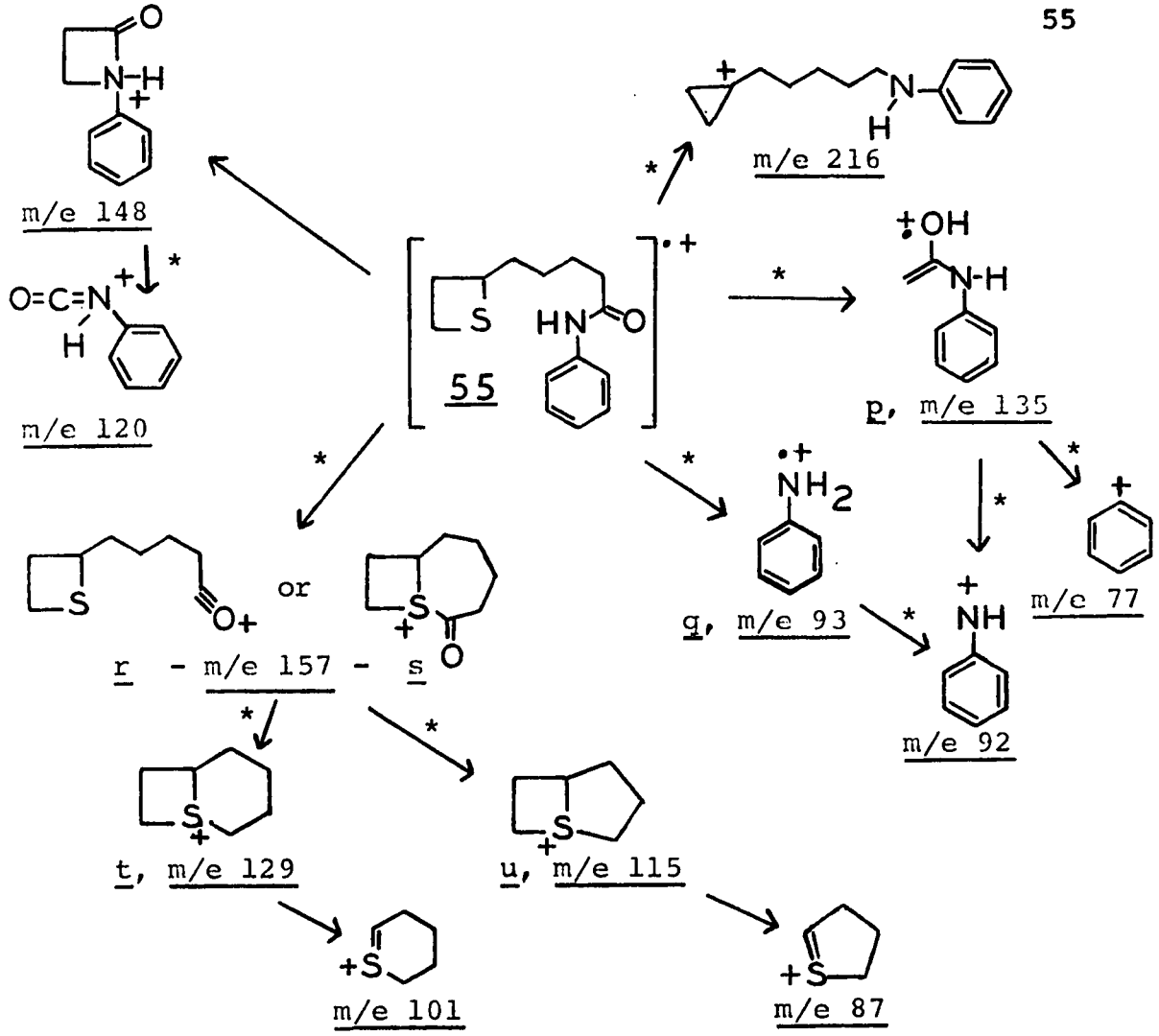


Figure 9. Mass spectral fragmentation of thietane-2-valeric acid anilide (55).

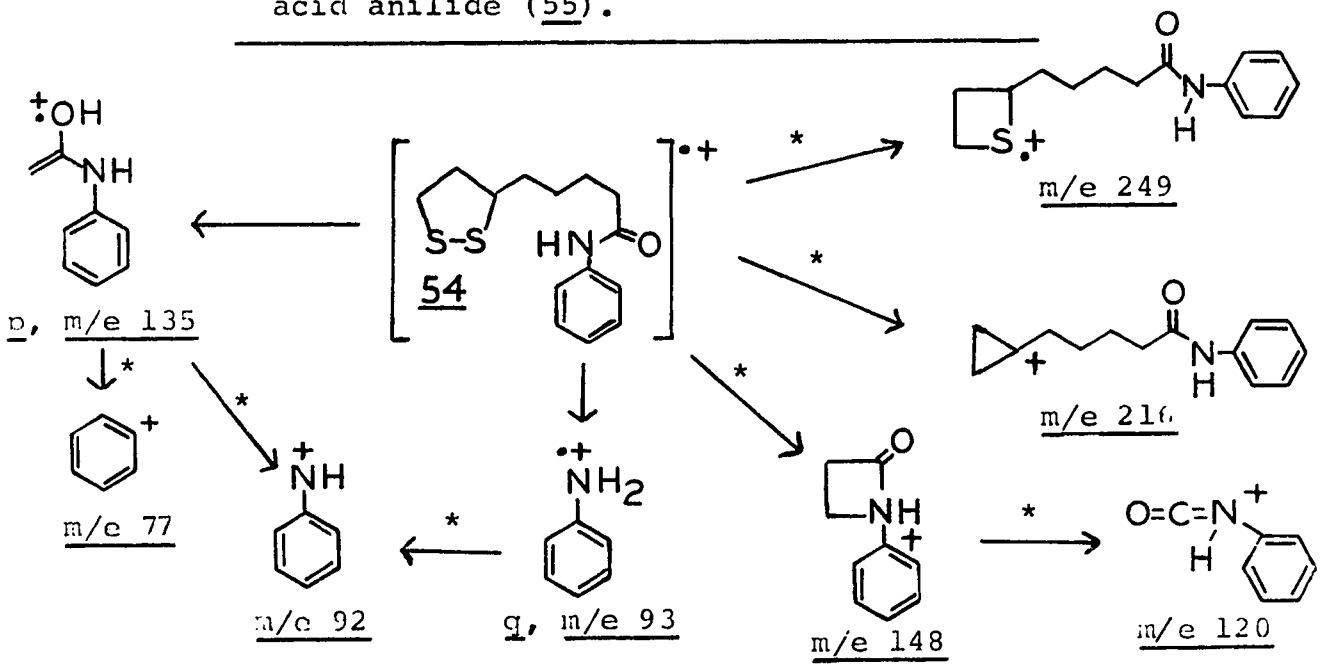
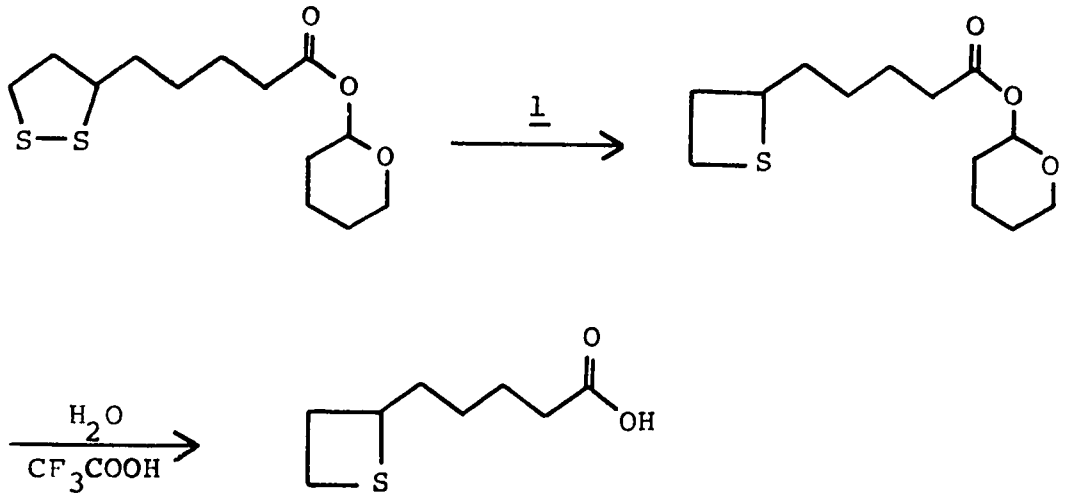


Figure 10. Mass spectral fragmentation of 1,2-dithiolane-3-valeric acid anilide (54)

the presence of the sulfide group is essential for its formation. This cyclic ion may extrude carbon monoxide to form t, m/e 129, or ketene to form u, m/e 115. The loss of ethylene from both t and u was also observed.

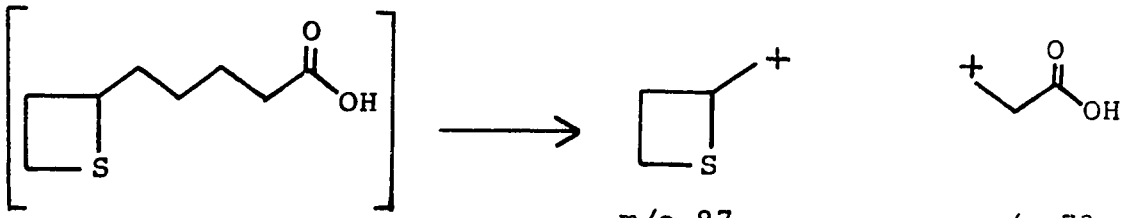
The mass spectrum of the analogous disulfide, α-lipoic acid anilide (54) was similar to that of 53. The formation of ions p, m/e 135, and q, m/e 93, were the major fragmentation processes (Figure 10). However, the formation of an acylium ion u was not observed. The presence of an acylium ion (or its cyclic counterpart) in the mass spectrum of 55 but not in the spectrum of the corresponding disulfide 54 would suggest that participation by sulfur is of considerable importance in the formation of this ion. This participation of sulfur would suggest that this ion exists as the cyclic ion s. Such a cyclization would be more likely observable in the spectrum of 55 since sulfides are better electron donors than are disulfides (115). The effect of this difference in donor ability between disulfides and sulfides has been observed in the mass spectra of several cystine derivatives (p. 49).

To obtain thietane-2-valeric acid (52) by desulfurization, it was desirable to use an acid protecting group which was readily removable. Thus, the acid labile (124) tetrahydropyranyl ester of α-lipoic acid was prepared and subjected to the aminophosphine desulfurization. After stirring the crude ester with the aminophosphine for 24 hours and subsequent hydrolysis of the reaction mixture, thietane-2-valeric acid (52) was



52

obtained in 82% yield. This material was converted to its anilide 54 which was identical in all respects to that anilide which had been prepared via desulfurization of α-lipoic anilide (53). The mass spectrum of thietane-2-valeric acid 52 exhibited a parent ion at m/e 174 consistent with the assigned structure.



52 m/e 174 m/e 87 m/e 73

The base peak, m/e 87, corresponded to δ cleavage. In addition, γ cleavage was also observed. The sequence of reactions performed on the lipoic acid derivatives is summarized in Figure 11.

To examine the generality of this novel ring contraction, it was desirable to prepare several 1,2-dithiolanes. Examina-

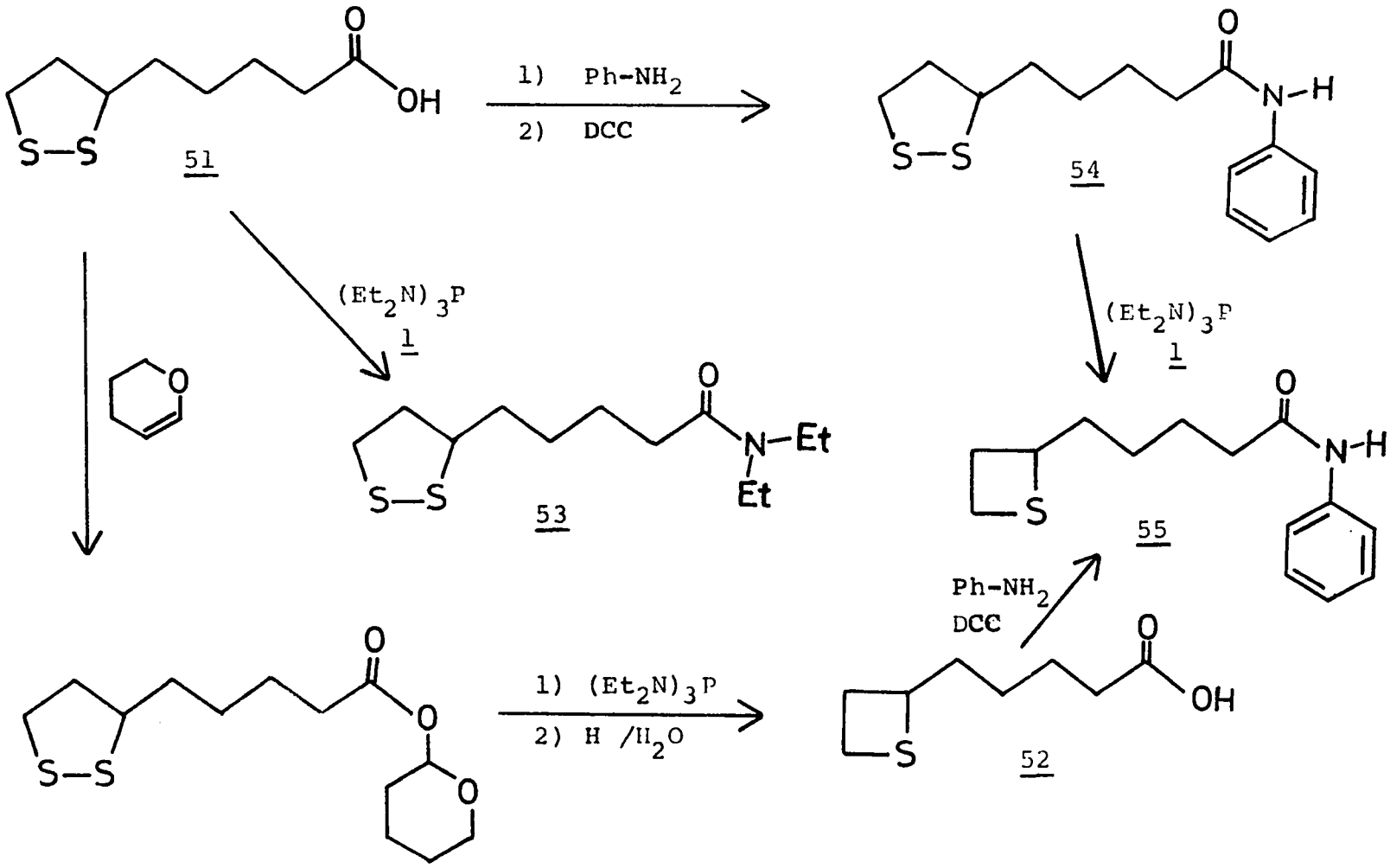
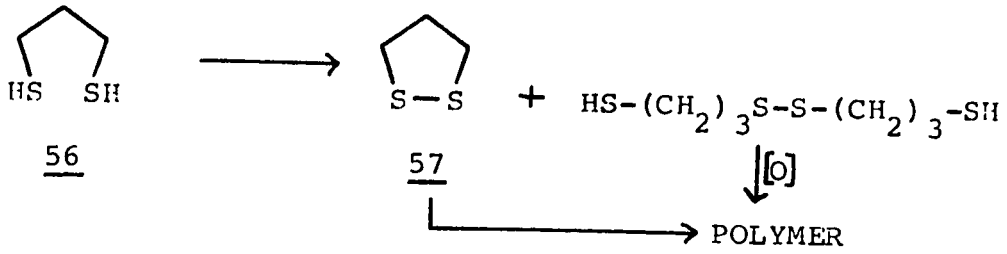


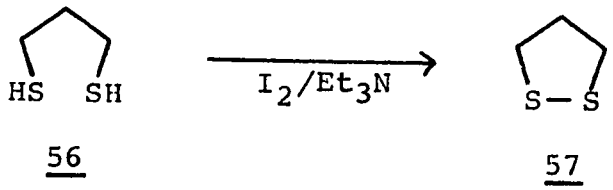
Figure 11. Transformations of α-lipoic acid (51)

tion of the literature revealed that, with the exception of a few alkyl substituted dithiolanes, oxidation of bis-thiols leads to extensive polymerization (125). Three factors are important in this oxidization. First, high dilution is necessary



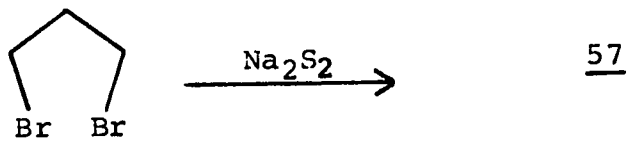
to reduce the amount of bimolecular oxidation; second, careful pH control is necessary to prevent base catalyzed polymerization, and third, an excess of thiol must be avoided to prevent thiol-disulfide exchange which also leads to polymerization. The use of triethylamine to maintain neutrality during iodometric oxidation of bis-thiols was found to greatly reduce polymerization (126). Slow addition of a solution of triethylamine and bis-thiol to a methanolic iodine solution provided high dilution, neutrality and excess iodine (therefore no free thiol), all which are desirable for such an oxidation. By this method, a variety of 1,2-dithiolanes were prepared.

The oxidation of 1,3-propanedithiol (56) by iodine/triethylamine as outlined above afforded a benzene solution of monomeric 1,2-dithiolane (57), free of polymer. In this reaction,



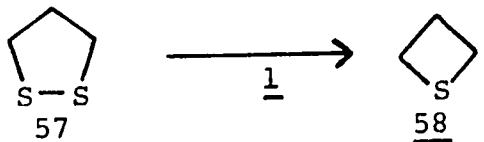
a yield of 56% was realized. This disulfide has been the subject of considerable controversy (125, 127, 128, 129, 130, 131). Oxida-

tion of 1,3-propanedithiol (56) by a variety of reagents yielded an insoluble white solid (125, 127) which was originally thought to be monomeric (128). More recent molecular weight determinations have shown this material to be dimeric (129). Schöberl and Gräfje (130) prepared what was believed to be monomeric 57 by careful oxidation of 56 by ferric chloride in butanol. This disulfide was not isolated, but was obtained as a butanol solution containing 28-30% disulfide. This solution deposited polymer on standing 10-12 hours in the dark. Calvin (131) prepared a solution of monomeric disulfide 57 by reacting 1,3-dibromopropane with sodium disulfide. Pure monomeric 57 could



be isolated at low temperature in vacuum; this disulfide was very unstable, undergoing rapid polymerization at room temperature. The yield of 57 prepared in this way was 9% (131). Thus, the realization of a 56% yield in the preparation of this very unstable disulfide is a considerable improvement over existing methods. Moreover, 0.1M solutions of 57 so prepared showed no tendency to polymerize if stored in the dark for several weeks.

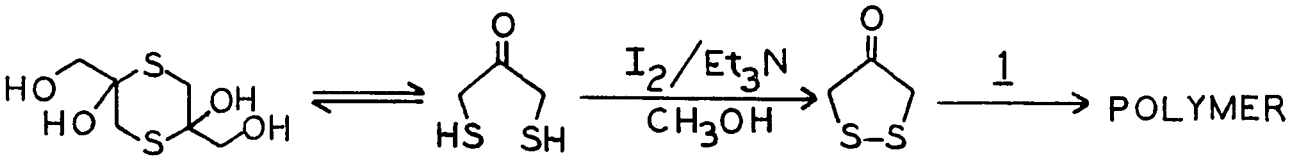
Desulfurization of a 0.1M solution of 1,2-ditholane proceeded very slowly at room temperature. After 432 hours, 87% of 57



had reacted and an 82% yield of thietane (58) (isolated as its mercuric chloride adduct) was obtained. That this reaction proceeds very slowly is surprising. Schöberl and Gräfje (130)

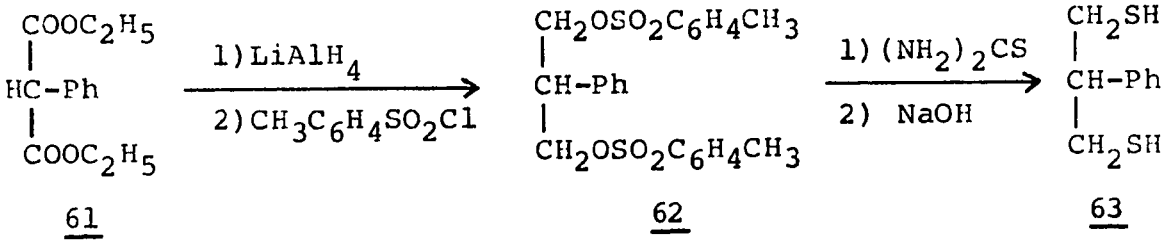
report this disulfide to be very reactive, both with respect to polymerization and to nucleophilic cleavage. The ring strain in 1,2-dithiolane has been estimated at 14-18 kcal/mole (130).

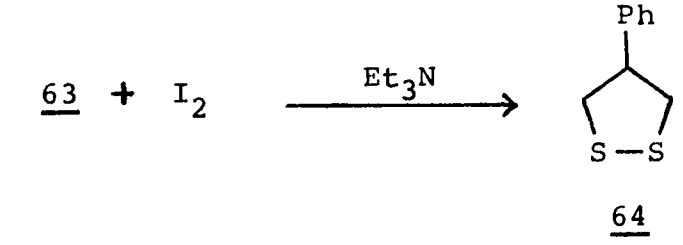
In a similar manner, the dimer of dimercaptoacetone (59) was oxidized to 1,2-dithiolane-4-one (60). Addition of the



aminophosphine 1, however, effected immediate polymerization of this disulfide and no characterizable products were obtained.

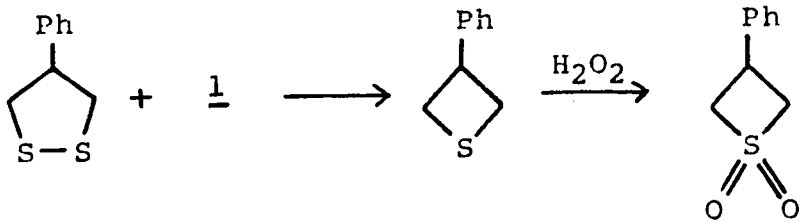
In contrast, 3-phenylthietane (65) was prepared from 4-phenyl-1,2-dithiolane (64) by reductive desulfurization. The requisite disulfide 64 was synthesized from diethyl phenylmalonate (61) in four steps. Reduction of this ester with lithium aluminum hydride and tosylation of the resulting diol afforded the ditosylate 62 (132). Reaction of 62 with an excess





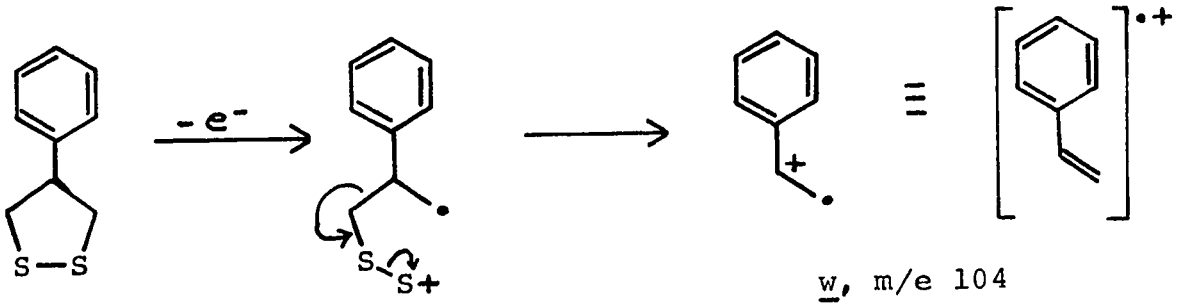
(10 fold) of thiourea and decomposition of the thiouronium salt

with base afforded 2-phenyl-1,3-propanedithiol (63) in 55% yield. Oxidation of 63 with iodine/triethylamine by the procedure outlined earlier afforded 4-phenyl-1,2-dithiolane (64) in 73% yield. This disulfide was desulfurized in four hours in refluxing benzene to provide thietane 65 in 87% yield. The



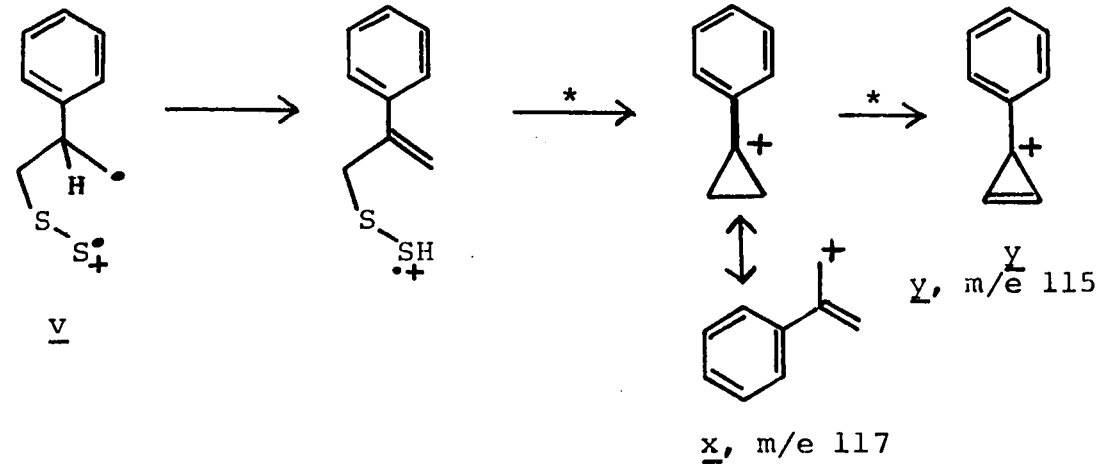
64 65 66

thietane 65 was oxidized and characterized as the sulfone 66. The mass spectra of 64 and 65 both exhibited strong molecular ions. The major fragmentation processes observed in these spectra may be explained in terms of bond cleavage α to sulfur. Thus, for 64, α cleavage followed by loss of thioformaldehyde and sulfur would give rise to the styrene ion w, m/e 104, which



64 v w, m/e 104

is the base peak of the spectrum. In addition, ion v resulting from α cleavage may undergo hydrogen migration and loss of $HS_2^{\bullet}$ to yield ion x, m/e 117. Loss of hydrogen from x affords the phenyl cyclopropenium cation y, m/e 115.

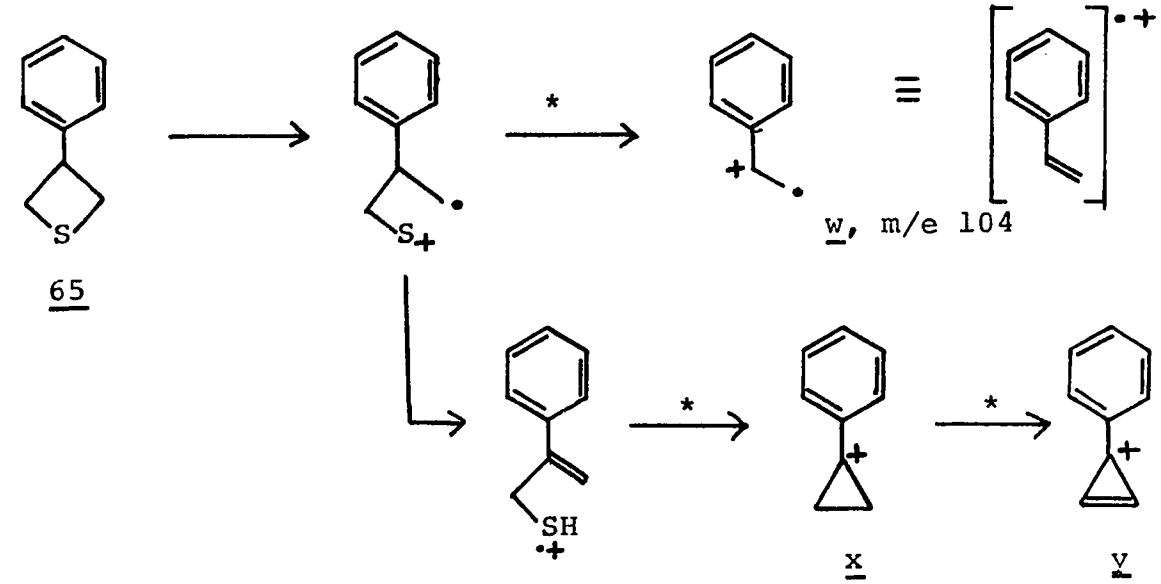


v

x, m/e 117

y, m/e 115

Similar fragmentation schemes may be proposed for 65. Thus, cleavage α to sulfur in 65 would lead to the styrene ion w, the phenylcyclopropane ion x and the phenylcyclopropenium ion y. Here, however, migration would be much less likely than



65

w, m/e 104

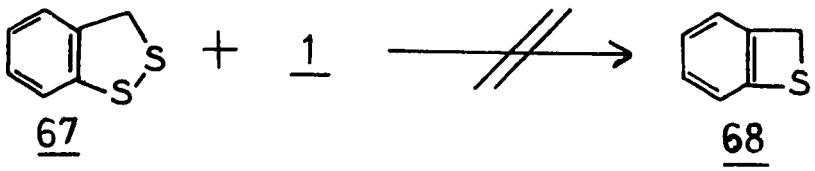
x

y

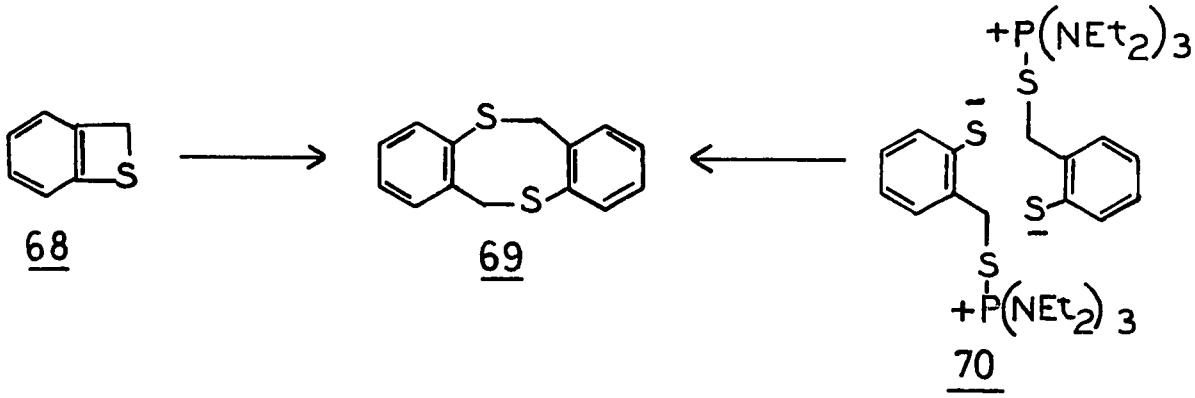
for 64 (4-center vs 5-center rearrangement) and hence ions x and y are observed to lesser extent.

It was hoped that the desulfurization of 3H-1,2-benzo[c]-dithiole 67 would provide a simple synthesis of the unknown heterocycle, benzo[b]thiete (68). This molecule has special

interest since removal of one of the methylene proton by base could provide a new non-benzoid aromatic (10 π electrons) species. The requisite disulfide 67 was prepared by the procedure of Lüttringhaus (77); desulfurization of 67, however, did not yield the desired benzo[b]thiete. The only isolable product was the



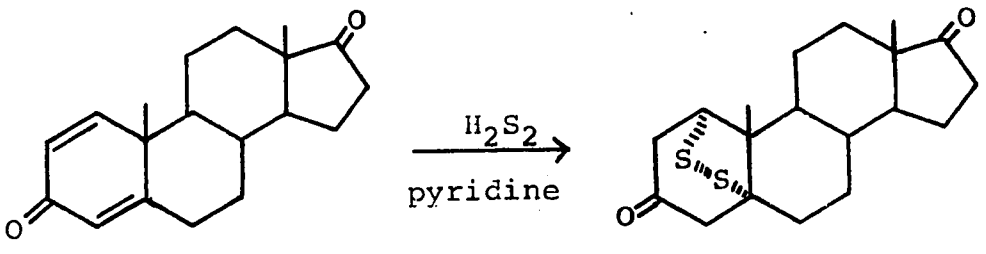
67 68



68 69 70

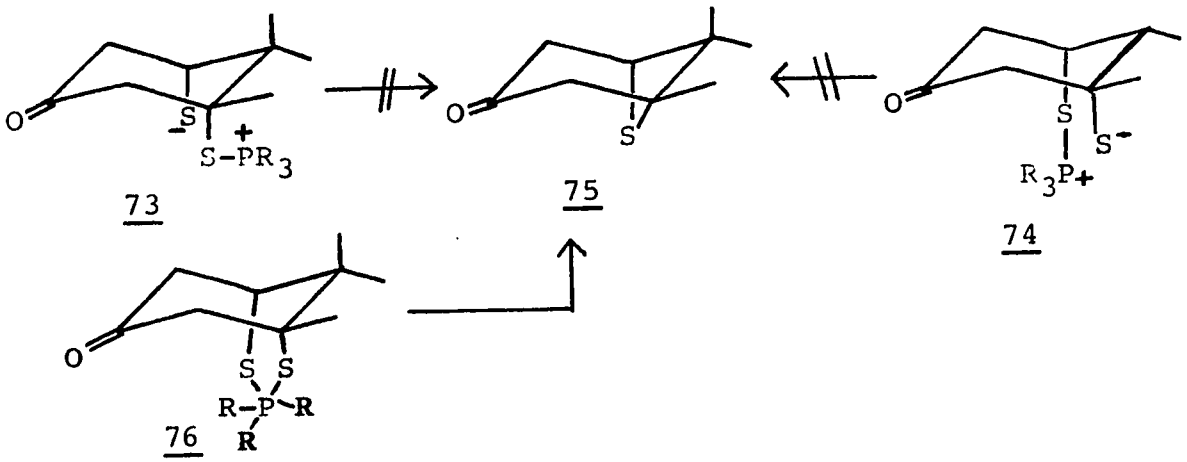
dimer of 68, 6H,12H-5,11-dibenzo[b,f]-dithioöcin 69. This dimer may arise from the dimerization of 68 or the phosphonium salt 70. Although two different phosphonium salts may be formed in the reaction of 67 with the aminophosphine (attack on the benzylic or aryl sulfur), only one of these salts, the more stable aryl mercaptide 70, could result in dimerization.

One of the few bicyclic disulfides reported in the literature is the steroidal disulfide 72 (133). The desulfurization of this disulfide was of interest since such a reaction would have strict stereochemical requirements. The formation of of phosphonium salts 73 and 74 from 72 is possible; however,



71 72

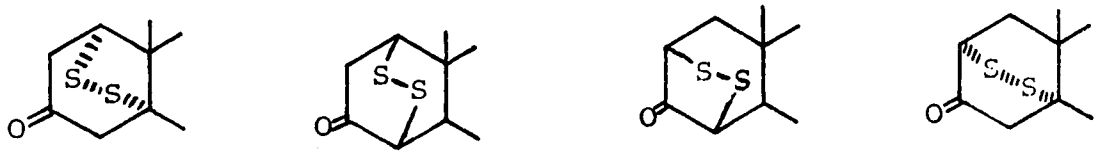
the decomposition of the salts to the cyclic sulfide 75 is most unlikely since this would require front-side displacement



73 75 74

76

of phosphine sulfide. A pentacovalent intermediate 76 , however, could decompose to afford 75. The requisite disulfide 72 was prepared from 71 by a modification of the procedure of Dodson (133). It was necessary to determine unambiguously the position of the disulfide bridge. The 1,5-disulfide suggested by Tweit and Dodson (133) is most reasonable from mechanistic considerations; the disulfide presumably is formed by double addition of hydrogen disulfide to the dieneone 71. However, four di-



72 77 78 79

sulfides (72, 77, 78, and 79) are possible from the addition of H_2S_2 to 71. That the product was the 1,5-disulfide was demonstrated by an examination of the spin-decoupled 100 MHz. nmr spectrum. A single proton was observed in the undecoupled spectrum as a quartet at 6.15τ and was assigned to the methine proton α to the disulfide bridge. Thus, both 77 and 78 are ruled out as possible structures; disulfide 78 possesses two similar methine protons while the methine proton of 77 would be a doublet, coupled only to the bridgehead proton. Both disulfides 72 and 77, however, have methine protons as part of an ABX spin system and hence would appear as a quartet. When this resonance at 6.15τ was irradiated in a double resonance experiment (Fig. 12), eight of the lines observed in the 6.9-7.4τ region collapsed to a quartet. In this way, the chemical shifts for the two protons adjacent to the methine were found to be 7.05 and 7.25τ. This chemical shift is that expected for protons adjacent to a ketone function and 1.0-1.5 ppm too low for aliphatic protons. This result is consistent only with disulfide 72 and not with disulfide 77.

Having rigorously demonstrated the presence of a 1,5-disulfide bridge, an attempt was made to desulfurize this compound. Treatment of 72 with the aminophosphine 1 did not afford either the sulfide 75 or the phosphonium salts 73 and 74, but a new compound, 80, $C_{27}H_{45}N_2O_2PS$ (exact mass calcd. for $C_{27}H_{45}N_2O_2PS$: 492.2939; found: 492.2960). The presence of an α,β-unsaturated ketone was indicated by the ir (1670 cm^{-1}) and uv spectrum ($\lambda_{Max.}^{MeOH}$ 228 mμ, ε = 650). The presence of only one

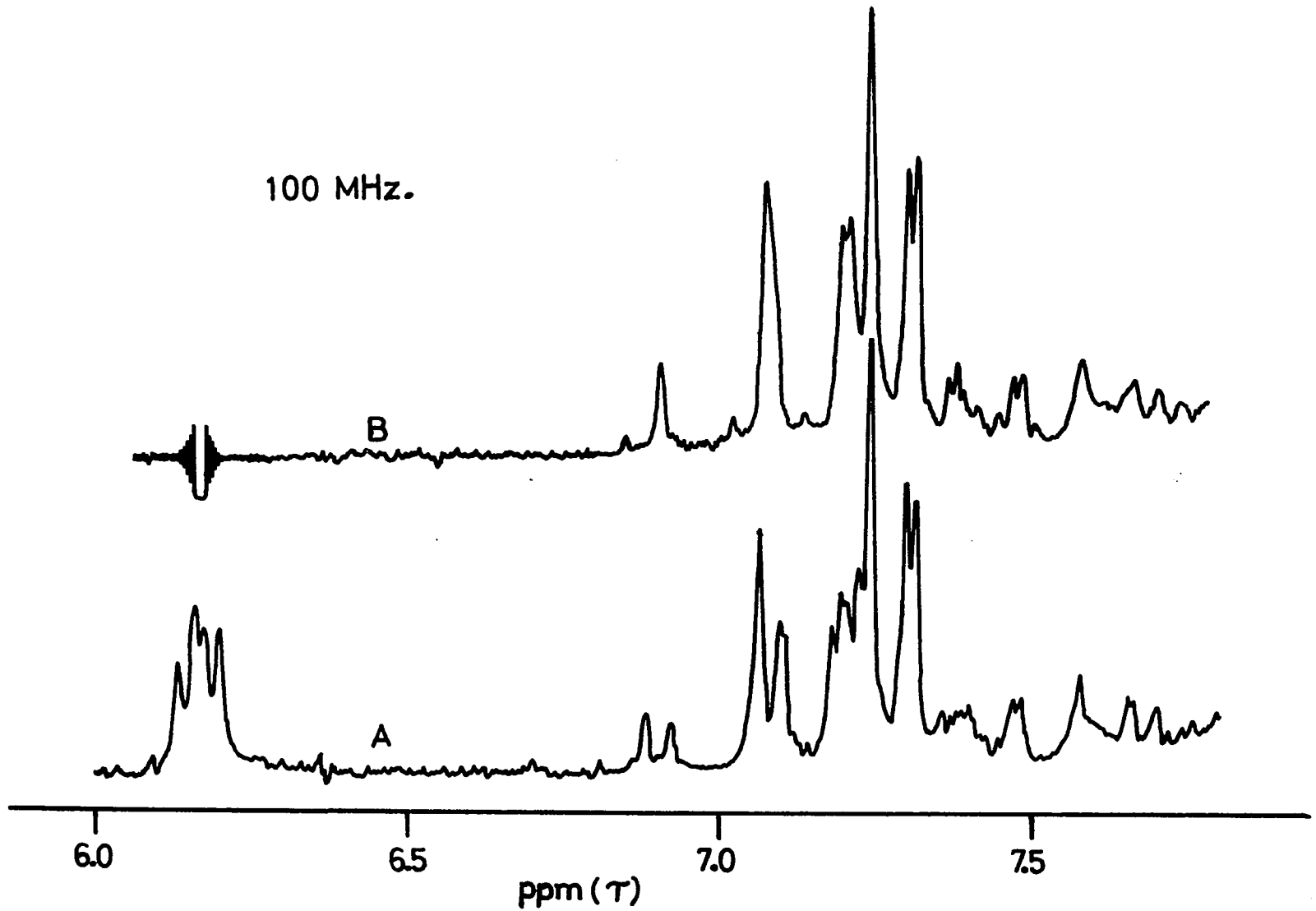
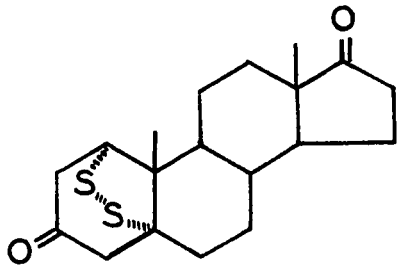


Figure 12. 100 MHz. Nuclear Magnetic resonance spectrum of 1α,5α-Epidithio-androstane-3,17-dione (72). A) Normal spectrum. B) Spin decoupled spectrum.

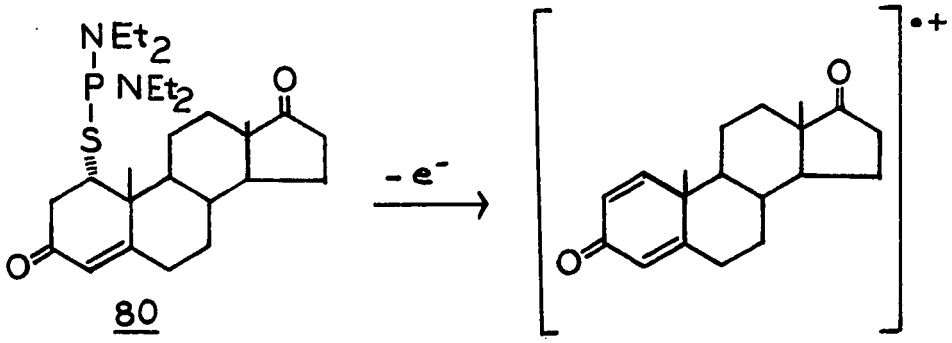


72

$\xrightarrow{1}$ $C_{27}H_{45}N_2O_2PS$

80

olefinic proton at 4.2τ in the nmr suggested that 80 possessed the $\Delta^{4,5}$-androstan-3-17-dione ring system. The loss of a bis-(diethylamino)phosphine sulfide fragment z upon electron impact



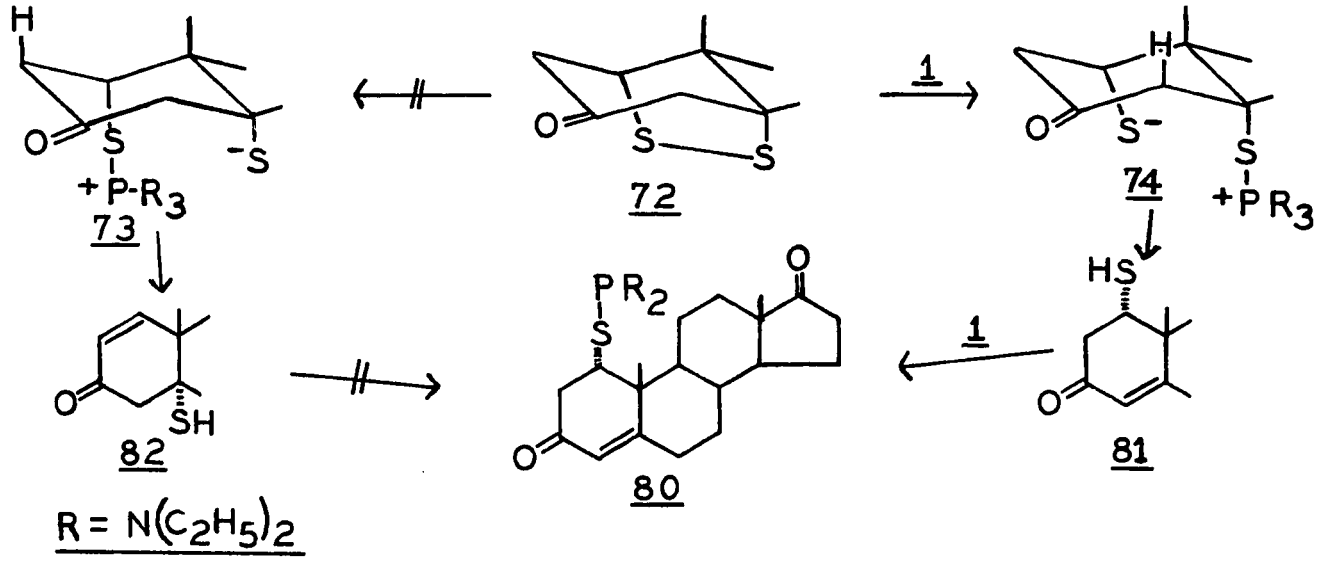
80

$\xrightarrow{-e^-}$

$+ \quad HS\text{-}P(NEt_2)_2$

z

permitted the assignment of structure 80 for this compound. A mechanistic rationalization for the formation of 80 is depicted below:



R = $N(C_2H_5)_2$

The phosphonium salt initially formed by ionic scission of the disulfide may undergo an elimination reaction to afford the intermediate thiol 81. This thiol would likely react with the aminophosphine to provide 80; such a reaction has been reported (134). Although cleavage of 72 could provide both phosphonium salts 73 and 74, the absence of 82 or a derivative of 82 in the reaction mixture would indicate that the predominant direction of cleavage is to afford 73. This preference is predictable both on steric and pKa considerations (Table III). Since no sulfide or phosphonium salt was obtained in this reaction, it is not possible to draw any conclusions as to the general steric requirements for desulfurization.

The preparation of two cyclic disulfide acids of known stereochemistry has been reported (135). The reaction of meso-dibromoadipic acid (prepared from adipic acid and N-bromosuccinimide, see appendix III) with potassium ethyl xanthate and subsequent ammonolysis afforded meso-dimercaptoadipic acid which could be oxidized by iodine to meso-1,2-dithiane-3,6-dicarboxylic acid (86) (Fig. 13). Heating this acid at 230°C for 10 minutes completely isomerized this acid to the more stable dl isomer 87. The corresponding sulfides 84 and 85 could be prepared from the meso and dl-dibromoadipic acid by reaction with sodium sulfide (Fig. 13) (136). So that desulfurization could be attempted, the meso acid was converted to its tetrahydropyranyl ester 88. This ester was very hygroscopic and therefore difficult to purify. Desulfurization of the crude ester afforded, after chromatography, an oil which

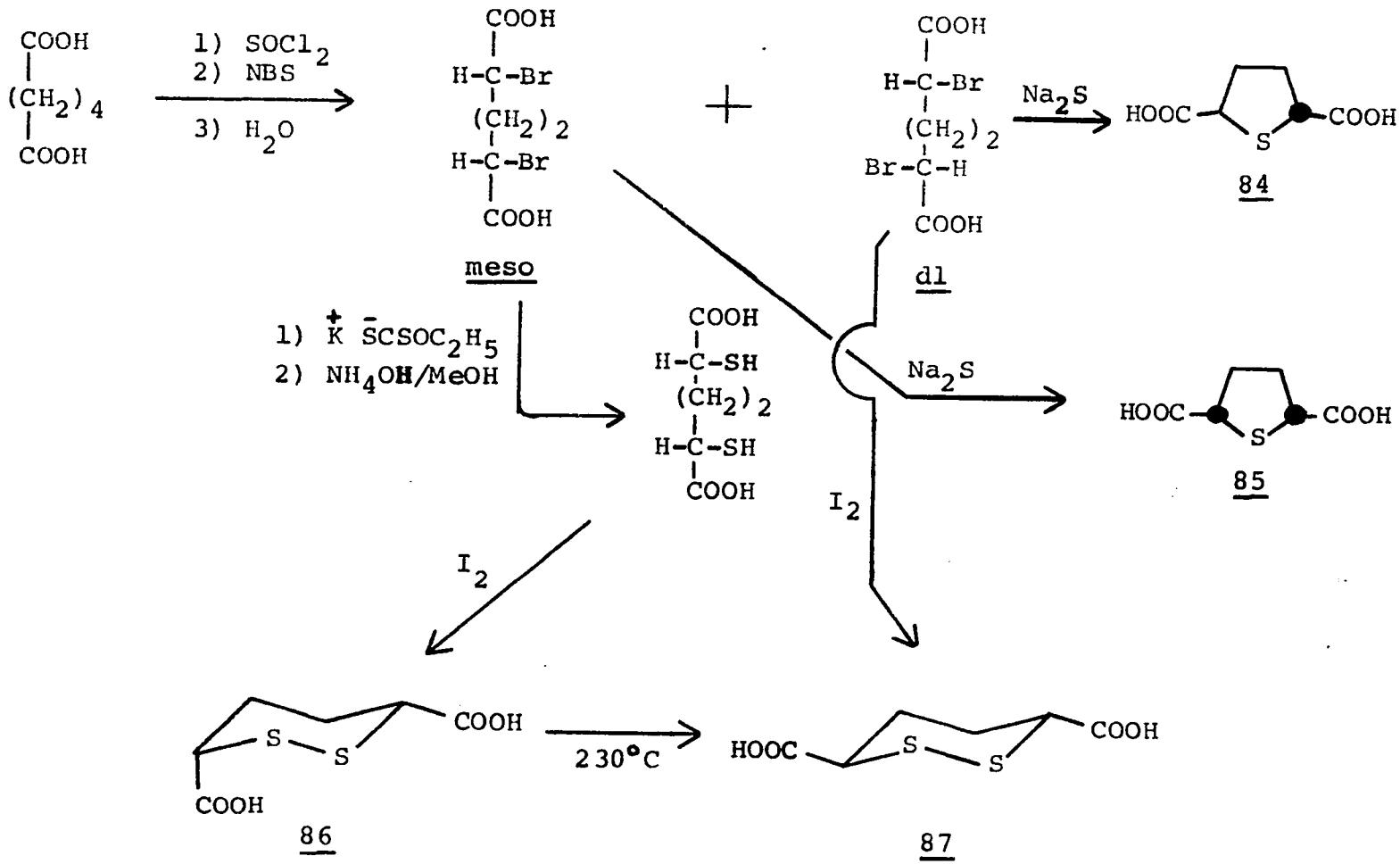
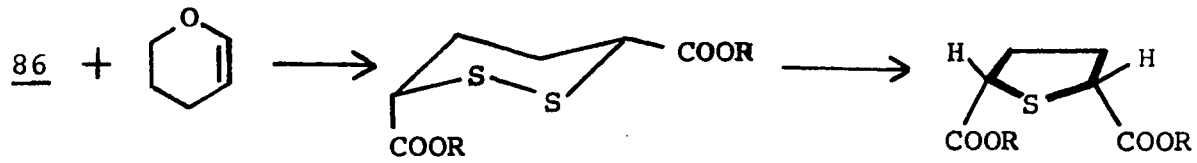


Figure 13. Preparation of the cyclic disulfide acids 86 and 87, and the cyclic sulfide acids 84 and 85

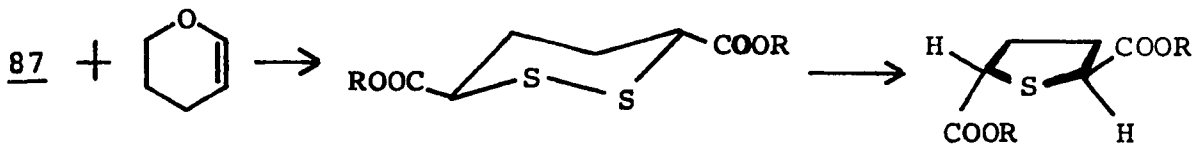
was hydrolyzed to trans-thiolane-2,5-dicarboxylic acid (85) in 48% yield. A similar attempt to esterify, desulfurize, and hydrolyze trans-1,2-dithiane dicarboxylic acid (87) afforded only a 17% yield of cis-thiolane-dicarboxylic acid 85 . The



88, R = THP

89, R = THP

85, R = H



90, R = THP

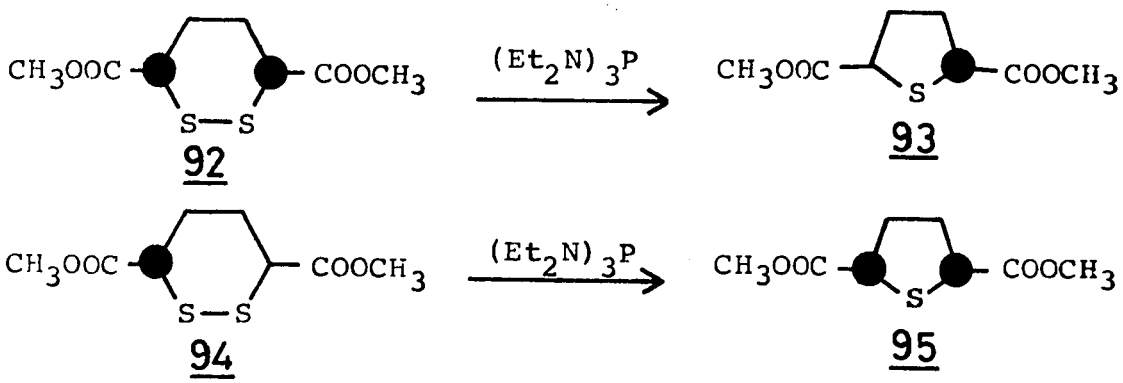
91, R = THP

84, R = H

low yields in these experiments might be attributable to the instability of the THP esters 88 and 90 and to problems of isolation. Because of the low yields, however, no firm stereochemical conclusions could be made.

Attempts using the methyl ester of 86 and 87 were much more successful. Both disulfide acids were converted into their methyl esters 92 and 94 by treatment with methanolic hydrochloric acid. Similarly, the two sulfide acids 84 and 85 were converted to their methyl esters 93 and 95. The stereochemical purity of these esters was confirmed by quantitative gas chromatography. Desulfurization of cis-3,6-dicarbomethoxy-1,2-dithiane (92) afforded a 102% yield (vpc) of trans-2,5-

dicarbomethoxy-thiolane (93). Similarly, trans-3,6-dicarbomethoxy-1,2-dithiane (94) afforded a quantitative yield of

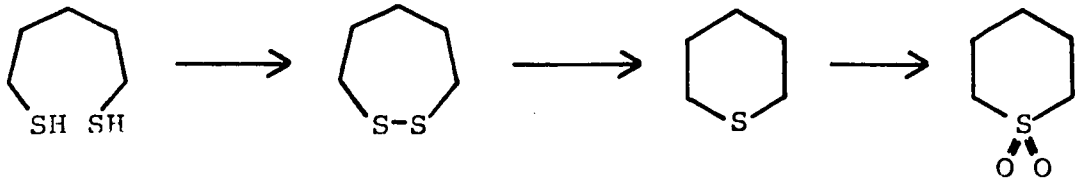


92 93

94 95

cis-2,5-dicarbomethoxy-thiolane (95). Thus, in the desulfurization of both disulfides 92 and 94, inversion of configuration at one of the carbon atoms α to the disulfide bridge has occurred. This observation has important mechanistic implications (vide infra). In view of this stereochemical result, it may be concluded that the inversion process observed in the desulfurization of the sugar disulfide 25 (p. 30) is a result of the stereospecificity of this desulfurization and not due to an anomeric effect. Moreover, the observation of an elimination reaction in the attempted desulfurization of the steroidal disulfide 72 (p. 66) is not unexpected since for 72, desulfurization must proceed with retention of configuration.

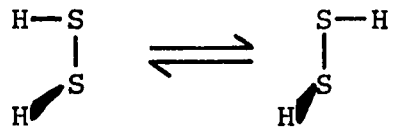
This desulfurization reaction was extended to seven and eight membered ring systems. The seven membered disulfide 1,2-dithiepin (96), generated by oxidation of 1,5-pentanedithiol, was desulfurized in refluxing benzene to yield, after oxidation with hydrogen peroxide, thiane-1,1-dioxide (98) in 40% yield.



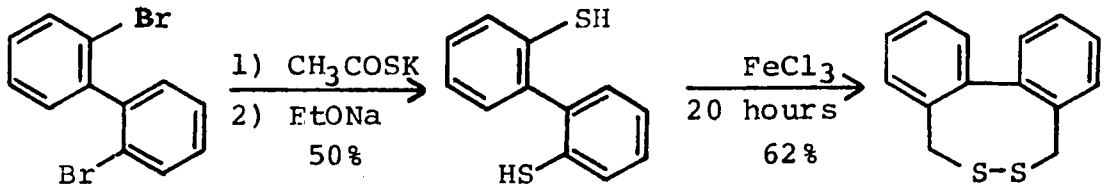
96 97 98

The major material loss was incurred in oxidation of the bis-thiol; both desulfurization of 96 and oxidation of 97 appeared by vpc to proceed to completion.

As was discussed earlier, disulfides possess a barrier to rotation about the sulfur-sulfur bond of 10-14 kcal/mole. Consider the two rotomers for the simplest disulfide, hydrogen disulfide:

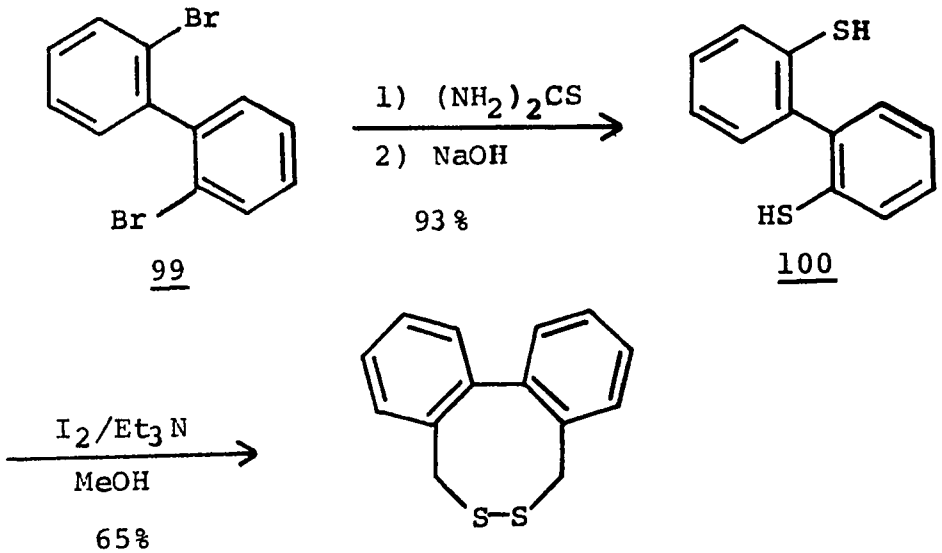


Hydrogen disulfide possesses C_2 symmetry (137). Thus, these two rotomers bear an enantomeric relationship to each other. For most disulfides, interconversion of these rotomers is rapid at room temperature; some disulfides, however, may exhibit conformational enantomerism as a result of the chirality of the disulfide rotomers. Such conformational enantomerism has been reported by Lüttringhaus (138, 139) for 5H,8H-6,7-dibenzo-[d,f] dithiocin (101). This disulfide has been synthesized (138) in 31% yield from 2,2-bis(bromomethyl) biphenyl (99):



99 100 101

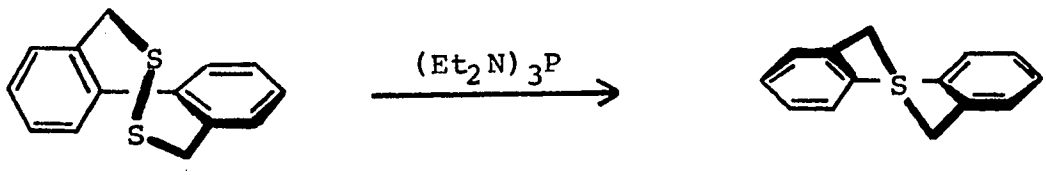
A modification of this technique has increased the overall yield for the conversion of 99 into 101 to 60%. Thus, treatment of 99 with thiourea and hydrolysis of the resulting salt afforded 100 in 93% yield. Oxidation of 100 with iodine/tri-



99 100 101

ethylamine gave a 65% yield of 101. The nmr of 101, as expected exhibited an AB quartet (J_{AB}=13Hz) for the benzylic protons; the interconversion of the conformational isomers of 101 is slow on the nmr time scale even at 150° (139).

The desulfurization of 101 proceeded rapidly at room temperature, the reaction being complete in less than three minutes. The product, 5H,7H-dibenzo[c,e]thiepin (102), isolated from the reaction in 97% yield, was identical in all respects to an



101 102

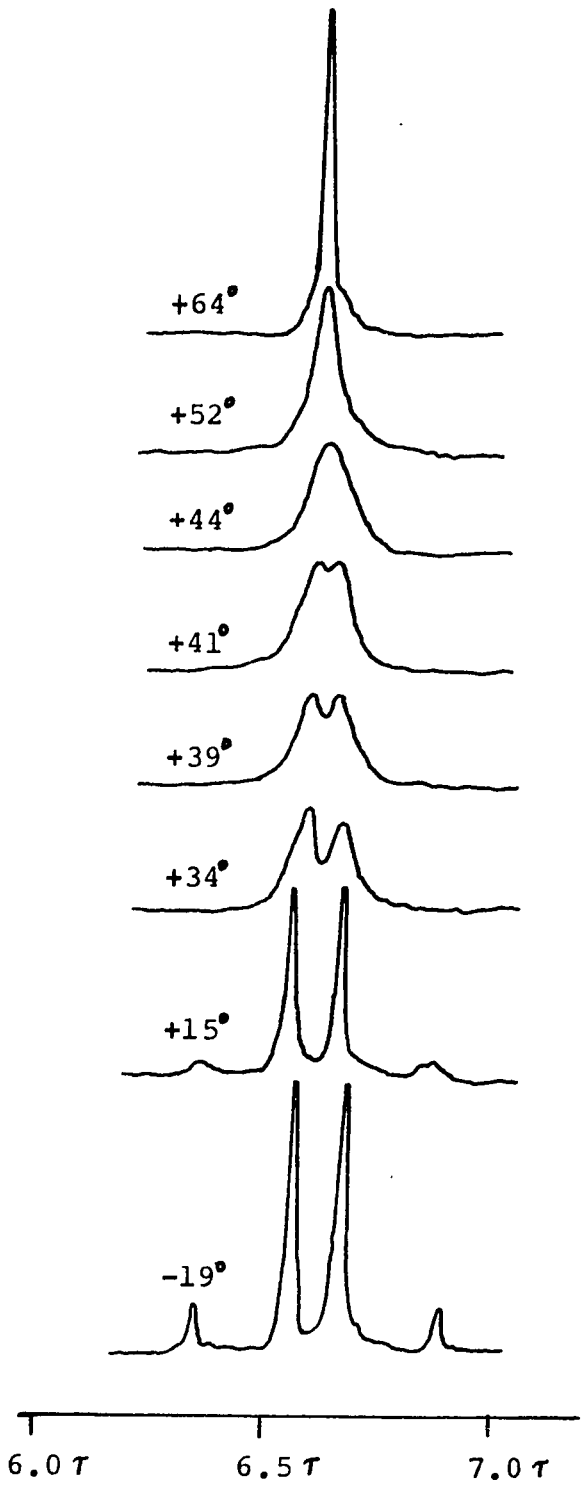


Figure 14. Temperature dependence of the nmr spectrum of 5H,7H-dibenzo[c,e]-thiepin (102).

authentic sample of this sulfide[10]. The nmr spectrum of 102 was recorded at several temperatures and the benzylic resonance is shown in Fig.14 as a function of temperature. At 64°, the benzylic protons appeared as a sharp singlet. Upon lowering the temperature, this resonance broadened; at -124° this resonance appeared as a sharp quartet (J_{AB} = 13Hz.). The coalescence point for this spectrum was 43° which is in good agreement with that reported (45°C) for this compound (140). This coalescence temperature is equivalent to a rotational barrier of 17 kcal/mole. Conformational enantomerism in this and other similar compounds has been studied by Mislow (141) and Sutherland (140).

Summary

Before entering upon a detailed consideration of the mechanism of these desulfurization reactions, it would be useful to review the findings thus far. It has been demonstrated that a wide variety of alkyl, aralkyl and alicyclic disulfides are desulfurized by tris(diethylamino)phosphine (1). These results are summarized in Table VI. Many of the more common functional groups do not interfere in this reaction and most of those that do may be suitably masked. For example, a side reaction may occur with acids (72) and alcohols (72), while amides including ureides, esters, ethers and acetates may be used without interference. A limitation does exist in that aryl nitro groups form charge transfer complexes with the amino-

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[10]The gift of a sample of this compound from Professor G. Wahl is gratefully acknowledged.

TABLE VI

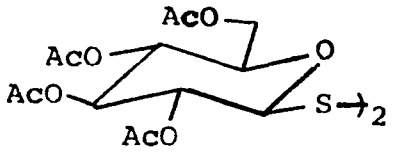
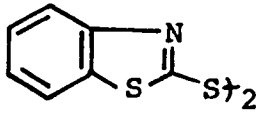
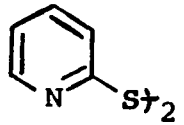
DESULFURIZATION OF ORGANIC DISULFIDES

$$R\text{-}S\text{-}S\text{-}R' + (Et_2N)_3P \longrightarrow R\text{-}S\text{-}R' + (Et_2N)_3P{=}S$$

	Disulfide	Reaction time[a], hr	% Yield R-S-R'	% Yield Other
2	$(C_6H_5CH_2\text{-}S)_2$	4[b]	92	86[h] (4)
5	$(C_5H_{11}S)_2$	18[b]	58	-
10	$Ph\text{-}SS\text{-}CH_3$	0.01	86	70 (4)
12	$Ph\text{-}CH_2SS\text{-}Ph\text{-}CH_3$	0.01	86	-
14	$(CH_3OOC\text{-}CH_2S)_2$	0.01	85	-
7	$(C_2H_5S)_2$	48[b]	-	75[c] (4)
		22[b,d]	-	80[e] (4)
		24[f]	17[g]	-
8	$(i\text{-}C_3H_7S)_2$	48[b]	-	50[c] (4)
9	$(t\text{-}C_4H_9S)_2$	96[b]	1[c]	1[c] (4)
		48[b,d]	1[c]	1[e] (4)
16	$Ph\text{-}CH_2SS\text{-}CH_2Ph\text{-}NO_2$	0.5	-	66 $(NO_2Ph\text{-}CH_2)_2S$
20	$Ph\text{-}CH_2SS\text{-}CH_2Ph\text{-}Br$	3[b]	35[e]	11[e] $(Ph\text{-}CH_2)_2S$
				22[e] $(Br\text{-}Ph\text{-}CH_2)_2S$

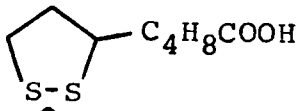
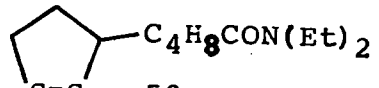
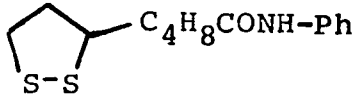
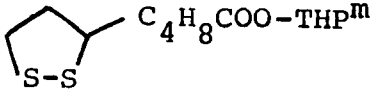
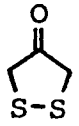
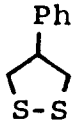
(continued)

TABLE VI (continued)

	Disulfide	Reaction time[a], hr	% Yield R-S-R	% Yield Other
23	$Ph-CH_2SS-CH_2CH_3$	18[b]	5	90[e] $(Ph-CH_2)_2S$
25		0.5[b]	47 (84[h])	-
28	$CH_3Ph-SS-Ph-CH_3$	24 (140)	1	5 $(CH_3Ph-S)_3P=O$
27	$((CH_3)_2N-Ph-S\rightarrow)_2$	8[b]	-	80 27 recovered
31		4[b]	61	-
34		18[b]	-	70 salt 35
37	$(Z-NH-CH_2CH_2S\rightarrow)_2$	4[b]	68	-
39	$(CF_3CONH-CH(COOCH_3)-CH_2S\rightarrow)_2$	0.2	96	-
41	$(Z-NH-CH(COOC_2H_5)-CH_2S)_2$	1	86	99 (4)

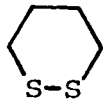
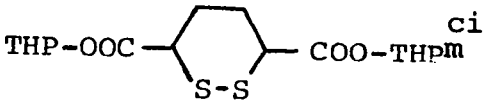
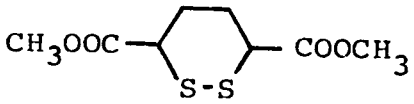
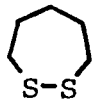
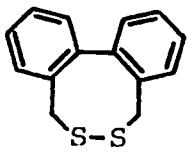
(continued)

TABLE VI (continued)

	Disulfide	Reaction time[a], hr	% Yield R-S-R	% Yield Other
43	Z-Cy-OMe (S, S) Z-Cy-Gly-OEt	0.1	-	88 Z-Cy-Gly-OEt (S-)$_2$
48	Z-NH-C_2H_4SS-C_2H_4COOCH$_3$	1	-	70 (Z-NH-C_2H_4S-)$_2$ (37)
51		4	-	80  53
54		1	64	-
		24	82[i]	-
57		432	82[j]	-
60		0.1	-	polymer
64		4[b]	87	-

(continued)

TABLE VI (continued)

	Disulfide		Reaction time[a], hr	% Yield R-S-R	% Yield Other
49			28	101[e]	-
88		cis	0.1[k]	65	105 (4)
90		trans	0.8	17[i]	-
92		cis	0.1	102[e]	-
94		trans	0.1	108±10[e]	-
96			16[b]	38[g]	-
101			0.1	97	-

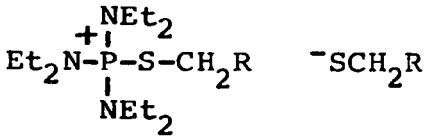
(a) In benzene solution at room temperature, unless otherwise noted. (b) At 80 C. (c) vpc analysis by peak height. (d) In neat excess 1 (100 mole excess). (e) quantitative vpc analysis with internal standards. (f) At 90 C. (g) Isolated as sulfone. (h) Crude yield. (i) Isolated as the corresponding acid. (j) Isolated as the mercuric chloride adduct. (k) In ether as solvent. (m) THP = tetrahydropyranyl

phosphines (91). Alkyl halides also react with the amino-phosphine, in this case, affording phosphonium salts (142). Cystine derivatives, when suitably protected, undergo desulfurization to afford lanthionine derivatives in high yield. Cyclic disulfides (five to eight membered rings) are desulfurized in 40-97% yield. The reaction, moreover, was shown to proceed with inversion of configuration at one of the carbon atoms α to the disulfide group.

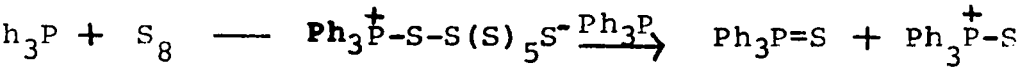
While some heterocyclic disulfides may be desulfurized aryl disulfides are unreactive. Unsymmetrical disulfides in which the sulfur-sulfur bond is highly polarized undergo desulfurization without rearrangement. However, if this polarization is not great, varing amounts of symmetrical sulfides are formed.

Mechanism of Desulfurization

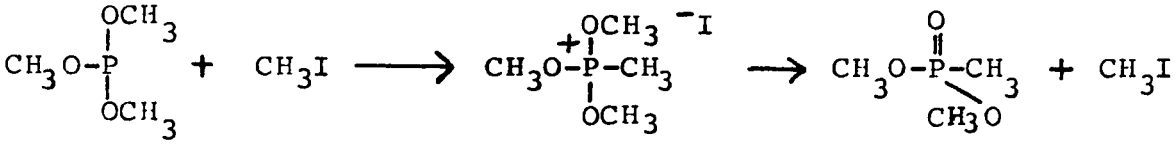
The postulation of a phosphonium salt as an intermediate in the desulfurization of organic disulfides has



been invoked several times in this thesis to account for specific experimental facts (for example, the formation of the steroidal phosphine 80 from the reaction of 1α,5α-epidithioandrostane-3,17-dione (72) with 1). Moreover, the aminophosphines were felt to be ideal desulfurizing agents since electromeric release from the alkylamino groups would help stabilize a phosphonium cation. The postulation of such a salt is not unreasonable; they have been suggested as intermediates in several reaction involving organo-phosphorus compounds. Bartlett and Meguerian (49) have suggested that the reaction of triphenylphosphine with sulfur proceeds by way of a series of ionic intermediates. Phosphonium salts



have been identified as intermediates in the Michaelis-



Arbuzov Reaction (143). In some cases, stable phosphonium salts may be prepared by the reaction of alkyl halides with

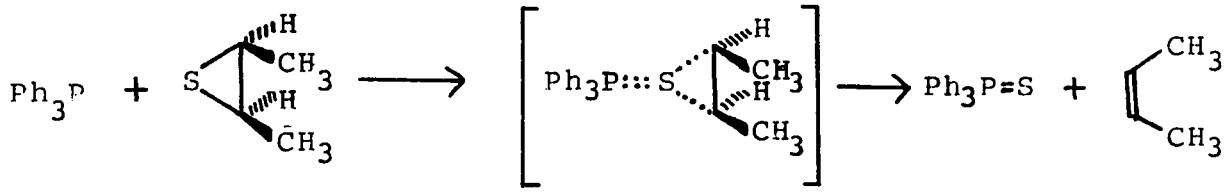
$$PH_3P + R\text{-}CH_2\text{-}X \longrightarrow Ph_3\overset{+}{P}\text{-}CH_2R\ \bar{X} + EtOEt$$

$$Ph_3P{=}S + Et_3\overset{+}{O}\ \bar{B}F_4 \longrightarrow Ph_3\overset{+}{P}\text{-}S\text{-}Et\ \bar{B}F_4 + EtOEt$$

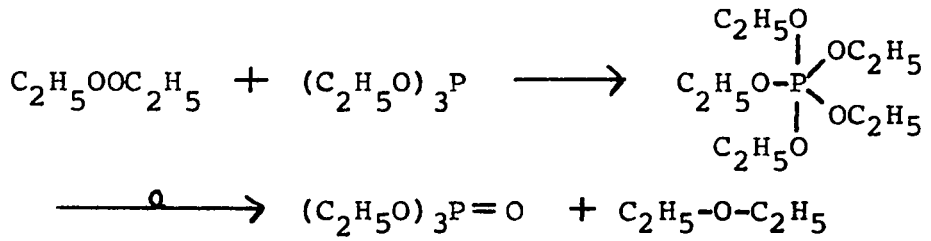
$$R_3P{=}O + Et_3\overset{+}{O}\ \bar{B}F_4 \longrightarrow R_3\overset{+}{P}\text{-}O\text{-}Et\ \bar{B}F_4$$

phosphines (144) or alkylation of phosphine sulfides (145) and oxides (146).

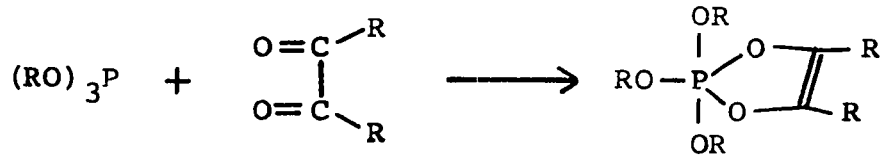
Not all reactions involving phosphorus nucleophiles proceed by way of phosphonium salts. For example, the desulfurization of cis-2-butene episulfide affords exclusively



cis-2-butene (50). A nonpolar transition state has been suggested for this reaction as evidenced by the lack of a kinetic solvent effect. The deoxygenation of peroxides has

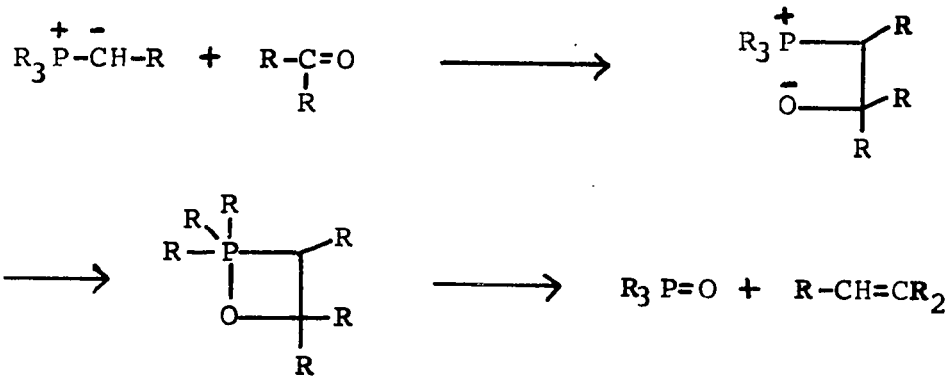


been shown to proceed by way of a pentacovalent intermediate (147). Similar intermediates have been detected by Ramirez (45)

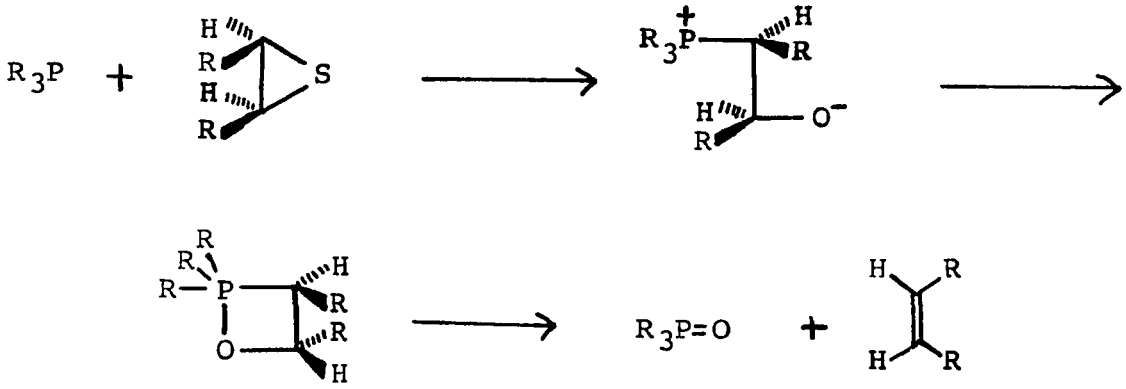


in the reaction of α-diketones with phosphites.

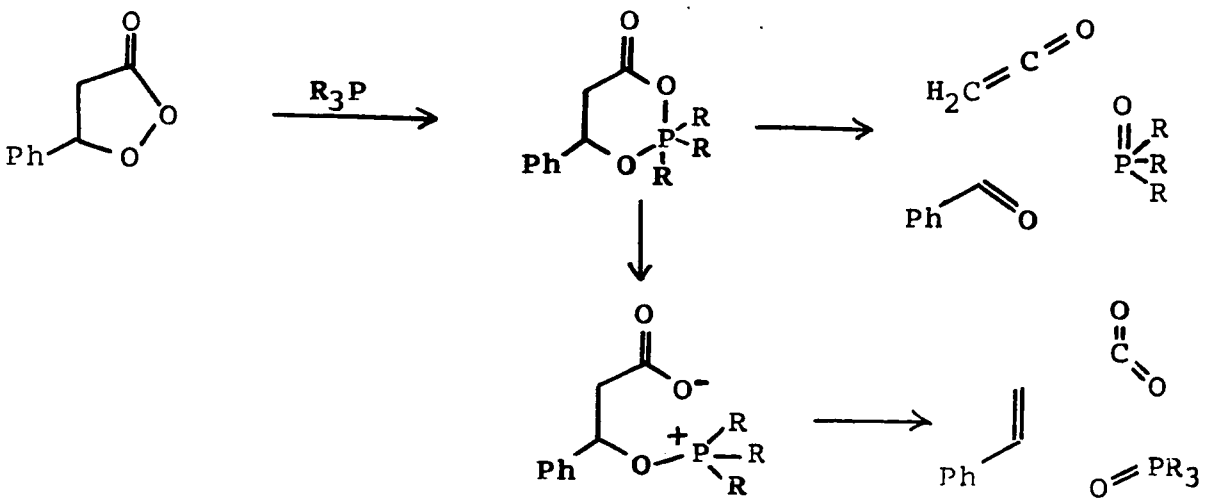
It is possible to have both phosphonium salts and pentacovalent intermediates in the same reaction. For example, in the well-known Wittig reaction (148), a dipolar intermediate



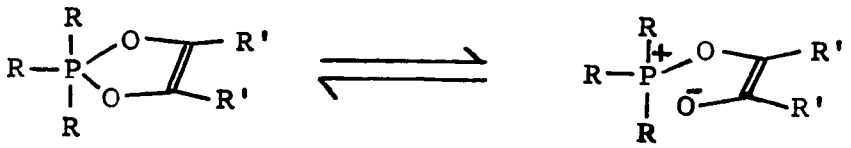
cyclizes to a pentacovalent intermediate. This latter material decomposes to afford an olefin and phosphine oxide. Similar intermediates have been postulated (52) for the deoxygenation



of cis-2-butene epoxide. There is, as well, literature precedent for the ionization of a pentacovalent intermediate to a phosphonium salt. Adam (64b) has postulated such a process



in the deoxygenation of cyclic peroxyesters. Ramirez (45) has shown the phosphorane-phosphonium salt equilibrium

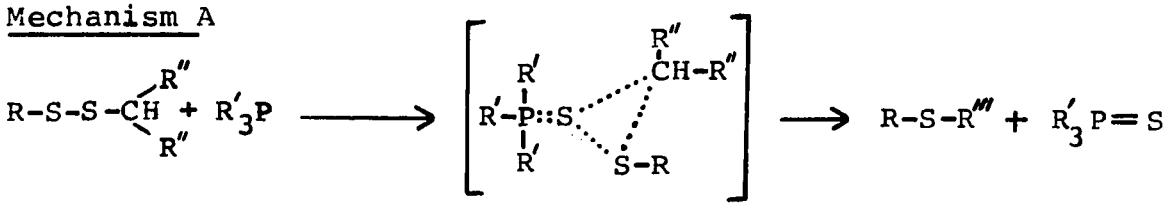


to be solvent dependent.

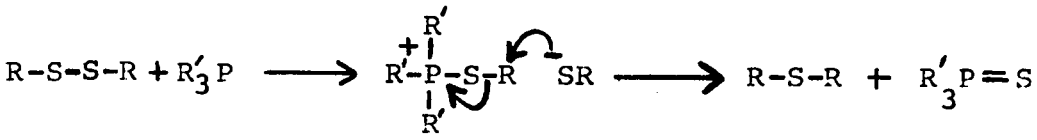
Several mechanistic pathways appear possible for the desulfurization of organic disulfides: (a) a direct abstraction process in which one of the sulfur atoms is removed via a non-polar transition state (Mechanism A), (b) an ionic mechanism in which the disulfide reacts with the phosphine to afford sulfide via a phosphonium salt intermediate (Mechanism B), (c) an insertion process in which the phosphine adds to the disulfide bond affording a pentacovalent intermediate which then decomposes to products (Mechanism C), or (d) a combination of (b) and (c) which involves both pentacovalent and phosphonium salt intermediates (Mechanism D). In mech-

anisms B,C, and D the various steps may be reversible; this

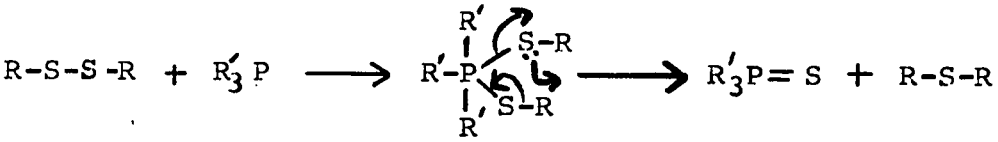
Mechanism A



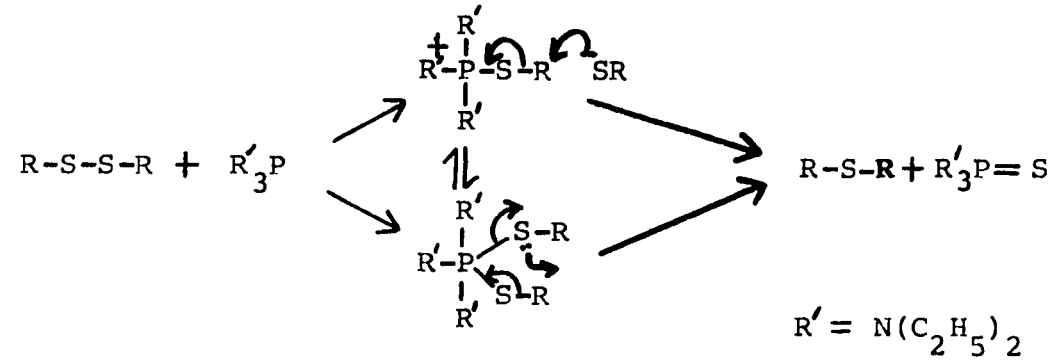
Mechanism B



Mechanism C



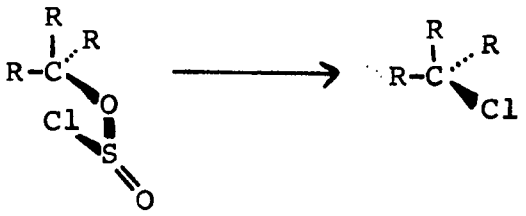
Mechanism D



possibility will be considered in the mechanistic discussion.

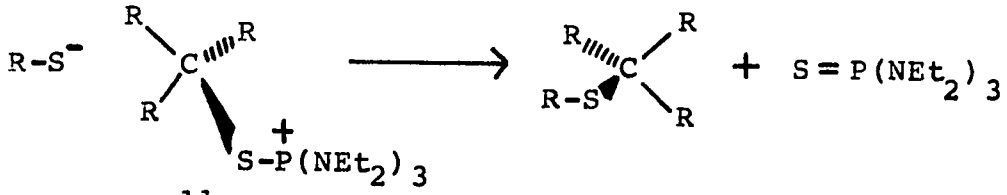
The number of possible mechanisms for this reaction may be considerably reduced by a consideration of the stereochemical consequences of the various pathways. Mechanisms A and C both would predict retention of configuration at both of the carbon atoms ∝ to the disulfide group. The mechanism outlined in A is analogous to the desulfurization of episulfides which proceed with retention of configuration (50). The decomposition

step in mechanism C is analogous to the decomposition of alkyl chlorosulfites in which retention of configuration is



is observed (149). Such S_Ni[11] type reactions have been observed in several other systems (149, 150).

Mechanism B, however, predicts inversion of configuration at one of the carbon atoms ∝ to the disulfide group since decomposition of the phosphonium salt intermediate would be a



bimolecular S_N2[11] substitution reaction. Since mechanism D is a combination of B and C, partial inversion of configuration should be observed. The proportion of inverted product would reflect the relative amounts of product resulting from the two intermediates involved in the reaction.

The desulfurization reaction has been shown to proceed with inversion of configuration at one of the carbon atoms ∝ to the disulfide bond. This was demonstrated in the desulfurization of 1β-D-glucopyranosyl disulfide octa-O-acetate (25).

Similarly, inversion was observed in the the desulfurization of the diastereomeric esters 92 and 94. In both reactions,

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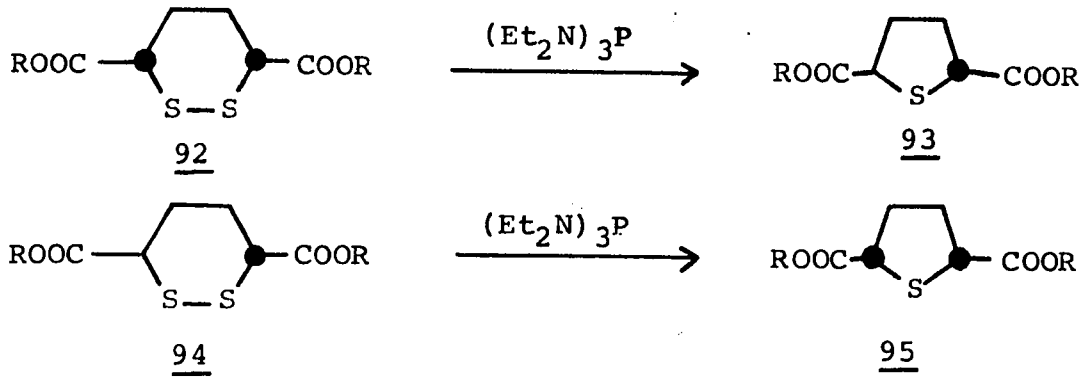
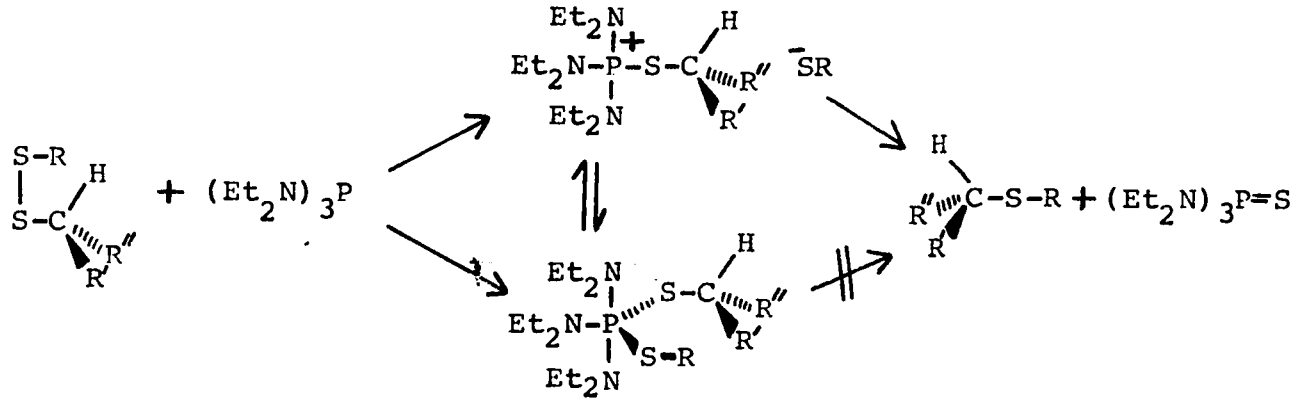
[11]Terminology is that of Gould (149).



quantitative yields of the inverted products were obtained. For example, the trans-diester 94 afforded only the cis-sulfide 95 on desulfurization; no trans-sulfide 93 was detected (limit of detection, 2%) in this reaction. Thus, the product forming step must be one in which inversion of configuration occurs. This observation is consistent only with **mechanisms** B and D. In the latter case, no product may arise from decomposition of the pentacovalent intermediate. A mechanistic scheme which incorporates mechanisms **B** and D, and has been modified to accomodate these stereochemical results, is outlined below. The validation of the remaining steps in this mechanism must now be undertaken.



Kinetics of Desulfurization

Considerable information concerning this desulfurization process was obtained from a study of the kinetics and energetics of this reaction[12]. The desulfurization of benzyl disulfide (2) was chosen as a model system. This reaction was free from side reactions, had an intermediate rate (see Table II for approximate reaction times or Table XVII to come for relative rate constants) and could be conveniently monitored by gas chromatography.

For any mono- or bimolecular reaction (equation 1) the

$$x\,A + y\,B \longrightarrow z\,P + w\,Q + \cdots\cdots \qquad \text{eq. 1}$$

rate of reaction at any time t is given by

$$-\frac{dA}{dt} = \frac{dP}{dt} = k(A)^{x}(B)^{y} \qquad \text{eq. 2}$$

where k is the kinetic rate constant (151, 152). Thus, at time t=o, this expression may be rewritten as

$$\log\left\{\frac{dP}{dt}\right\}_{t=0} = \log(k) + x\,\log(A_o) + y\,\log(B_o) \qquad \text{eq. 3}$$

where A_o and B_o are the initial concentrations of A and B respectively. If the initial concentration of one of the reactants is maintained constant, this equation may be simplified:

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[12] For the sake of clarity, the kinetic data has been grouped according to the technique employed for measuring the rate constants (vpc or uv). All the kinetic results will be presented together and this will be followed by a discussion of these results.

A_o = Constant

$$\log\left\{\frac{d[P]}{dt}\right\}_{t=0} = y \log(B_o) + C \qquad \text{eq. 4}$$

$$C = x \log(A_o) + \log(k) = \text{Constant}$$

Thus, a plot of the log of the initial reaction velocity vs the log of the initial concentration should be linear with slope y, the partial order of reaction, and intercept ($x \log(A_o) + \log(k)$). In this manner, the coefficients x and y of eq. 3 may be evaluated. The overall reaction order, n, is given by

$$n = x + y \qquad \text{eq. 5}$$

The desulfurization of benzyl disulfide (2) by tris(diethylamino)phosphine (1) was conducted in benzene solution with

$$\underset{\underline{2}}{Ph\text{-}CH_2\text{-}S\text{-}S\text{-}CH_2\text{-}Ph} + \underset{\underline{1}}{(Et_2N)_3P} \longrightarrow \underset{\underline{3}}{Ph\text{-}CH_2\text{-}S\text{-}CH_2\text{-}Ph} + \underline{4}$$

several initial concentrations of disulfide and phosphine[13]. The concentration of sulfide was measured as a function of time; these results are presented graphically in Figures 15a and 15b. The initial reaction velocities (Table VII) were measured as the slope of the tangent to these curves drawn at t=0. From a plot of log(initial velocity) vs log(initial concen-

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[13]Experimentally, it was found that consistant vpc analyses were obtained if an aliquot of the reaction mixture was quenched with sulfur before vpc analysis. The reaction of 1 with S_8 is much faster than any of these desulfurizations (134). In this way, analyses were reproducibile to ±1%.

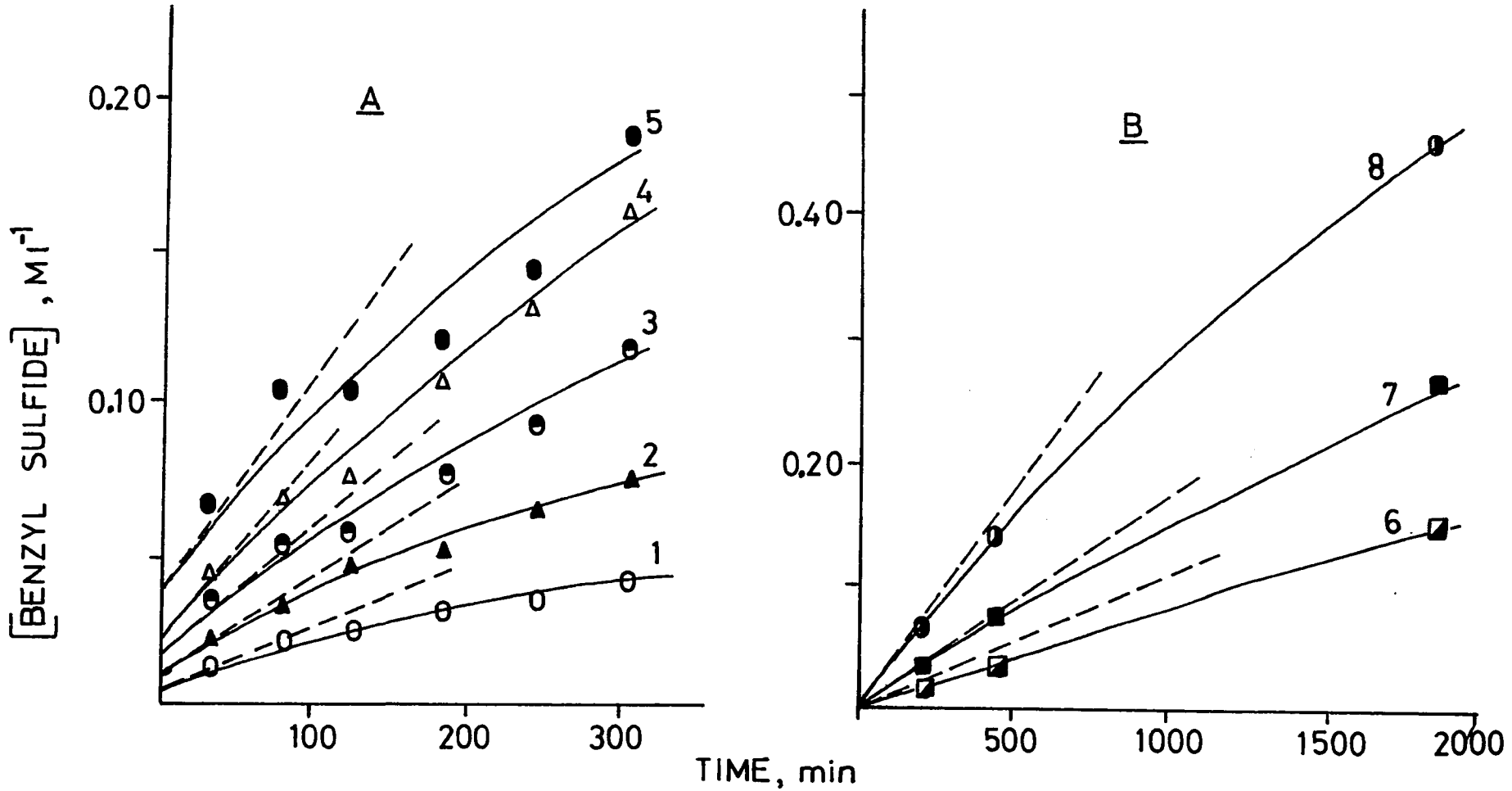


Figure 15a. A plot of Benzyl sulfide (3) concentration vs time. Initial disulfide conc.: 1) 0.152 M; 2) 0.320 M; 3) 0.457 M; 4) 0.610 M; 5) 0.763 M. Initial phosphine concentration was 0.50 M. in all cases.

Figure 15b. A plot of Benzyl sulfide (3) concentration vs time. Initial phosphine conc.: 6) 0.05 M; 7) 0.10 M; 3) 0.20 M. Initial disulfide concentration in all cases was 0.10 M.

TABLE VII

INITIAL REACTION VELOCITIES OF THE DESULFURIZATION OF BENZYL DISULFIDE (25°C)

REACTION	INITIAL CONCENTRATION (Ml^{-1}) PHOSPHINE (1)	DISULFIDE (2)	INITIAL REACTION VELOCITY,[a] ($Ml^{-1}min^{-1}$)	k_2[a] ($1M^{-1}sec^{-1}$)
1	0.50	0.152	2.3×10^{-4}	3.4×10^{-5}
2	0.50	0.320	3.0×10^{-4}	3.0×10^{-5}
3	0.50	0.457	4.4×10^{-4}	3.1×10^{-5}
4	0.50	0.610	6.4×10^{-4}	3.1×10^{-5}
5	0.50	0.763	7.4×10^{-4}	3.1×10^{-5}
6	0.05	0.10	0.9×10^{-5}	3.4×10^{-5}
7	0.10	0.10	1.6×10^{-5}	3.2×10^{-5}
8	0.20	0.10	3.4×10^{-5}	3.0×10^{-5}

a) Initial reaction velocities and rate constants are accurate to ±10%.

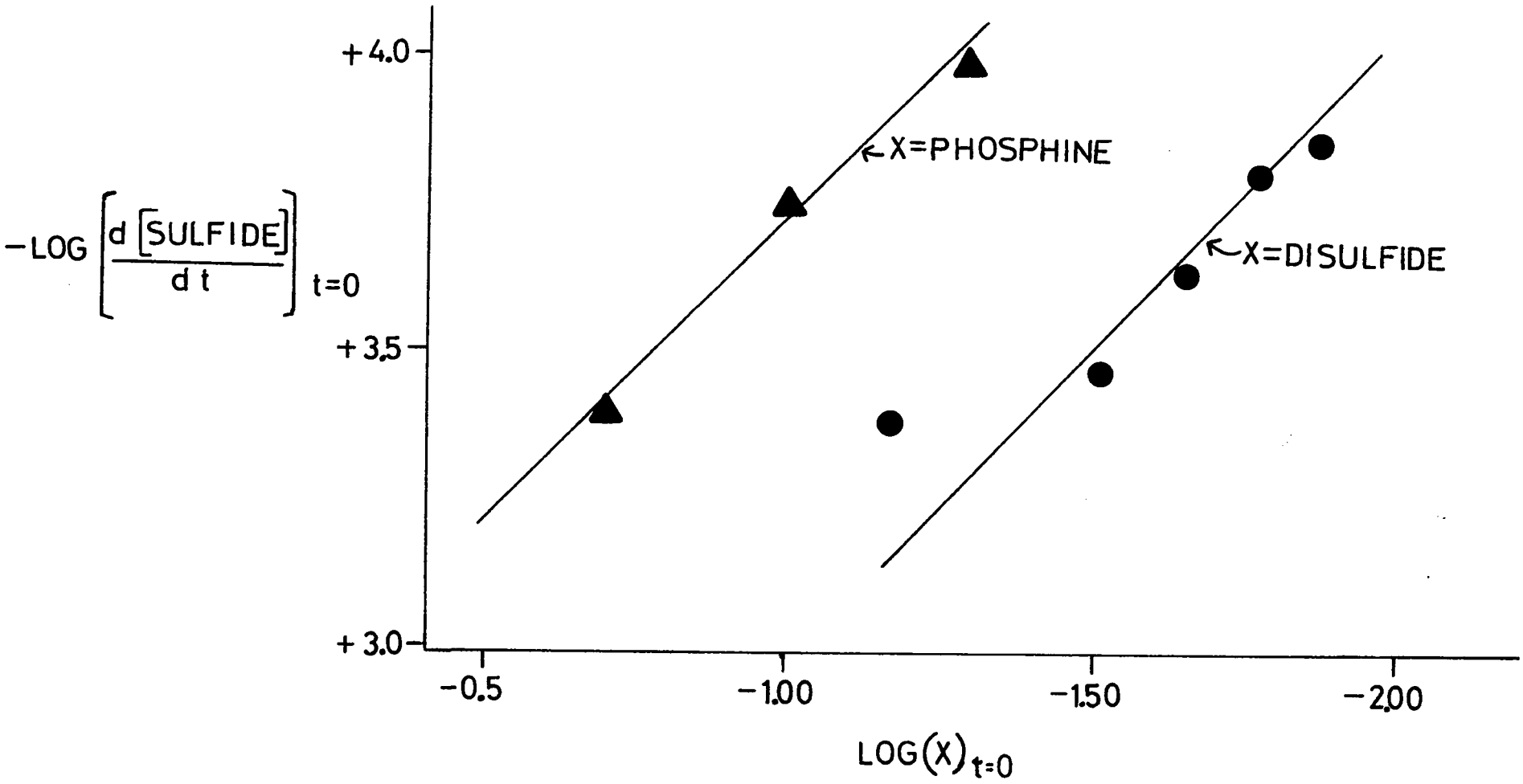


Figure 16. A plot of -log(initial reaction velocity) against log(initial concentration)

tration) (Figure 16), the partial reaction orders of 0.96 for phosphine and 1.01 for disulfide were obtained. Thus, the desulfurization of benzyl disulfide by tris(diethylamino)phosphine is a second order reaction, first order each in phosphine and disulfide.

Integration of the general second order rate equation (equation 2, x=y=1) affords the integrated rate expressions:

$A_o \neq B_o$

$$t = \frac{1}{k_2(A_o - B_o)} \ln\left(\frac{A \cdot B_o}{B \cdot A_o}\right) \qquad \text{eq. 6}$$

$A_o = B_o$

$$t = \left(\frac{1}{k_2 A} - \frac{1}{k_2 A_o}\right) \qquad \text{eq. 7}$$

Thus, when $A_o \neq B_o$, a plot of $\log(A \cdot B_o / B \cdot A_o)$ vs time will be linear with a slope of $2.303/k_2(A_o - B_o)$ from which the second order rate constant, k_2, may be calculated(152). If $A_o = B_o$, then, from equation 7, a plot of 1/A vs time will be linear with a slope of $1/k_2$, and, from this, k_2 may be evaluated. The second order rate plots (based on eq. 6 and 7) for these desulfurizations are linear (Fig. 17); the rate constants calculated from these experiments are summarized in Table VII. However, because of the lack of close temperature control, the error in these rate constants is somewhat greater than in those to be presented later.

For bimolecular second order reactions, the kinetic expression is considerably simplified if the initial concentration of reactants are equal. The integrated rate equation (equation 7)

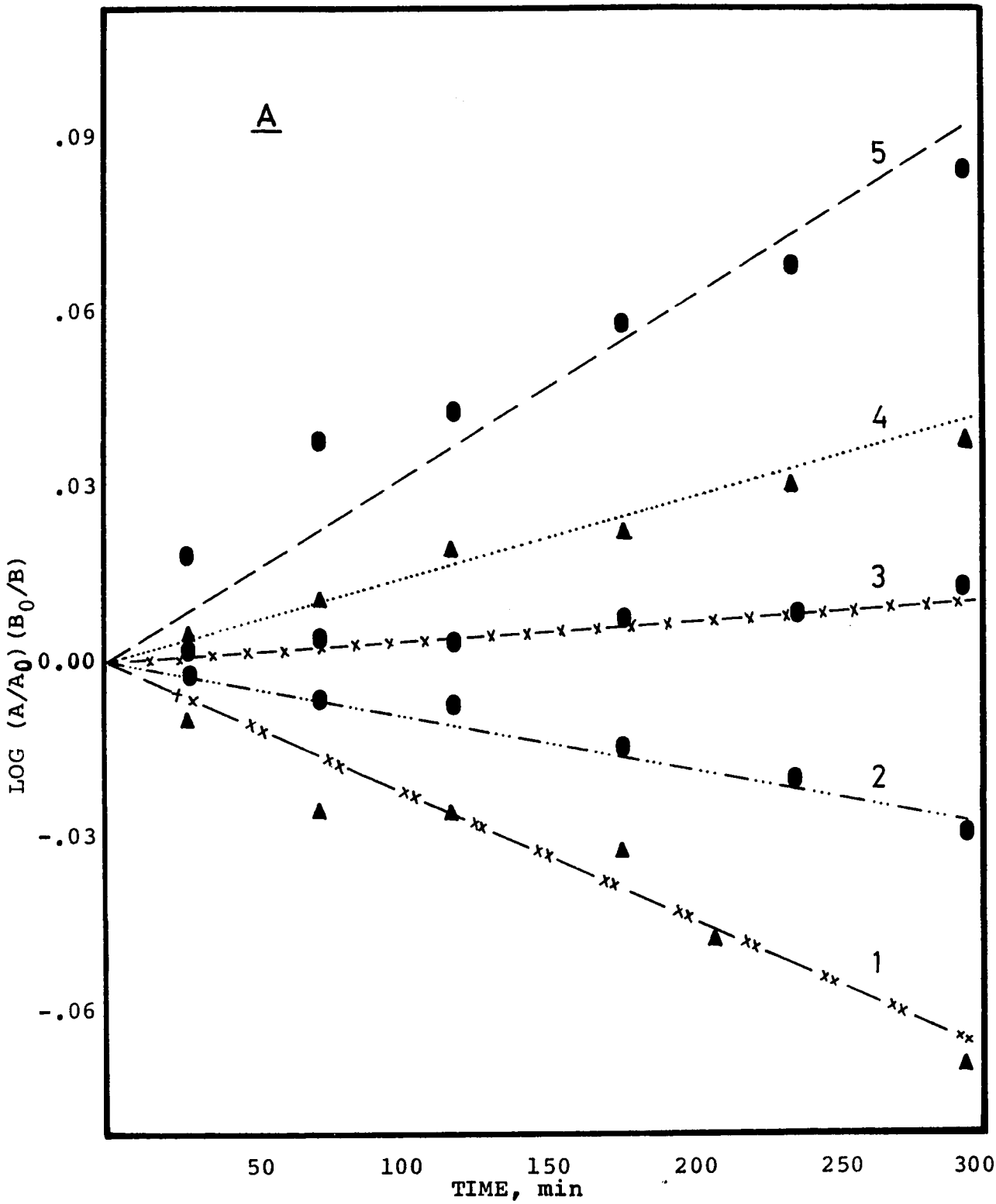


Figure 17a. Second order plot for the desulfurization of benzyl disulfide (2). Initial concentration of 2: (1) 0.152 M (2) 0.320 M; (3) 0.457 M; (4) 0.610 M; (5) 0.763 M. Initial concentration of tris(diethylamino)phosphine (1) was 0.500 M in all cases.

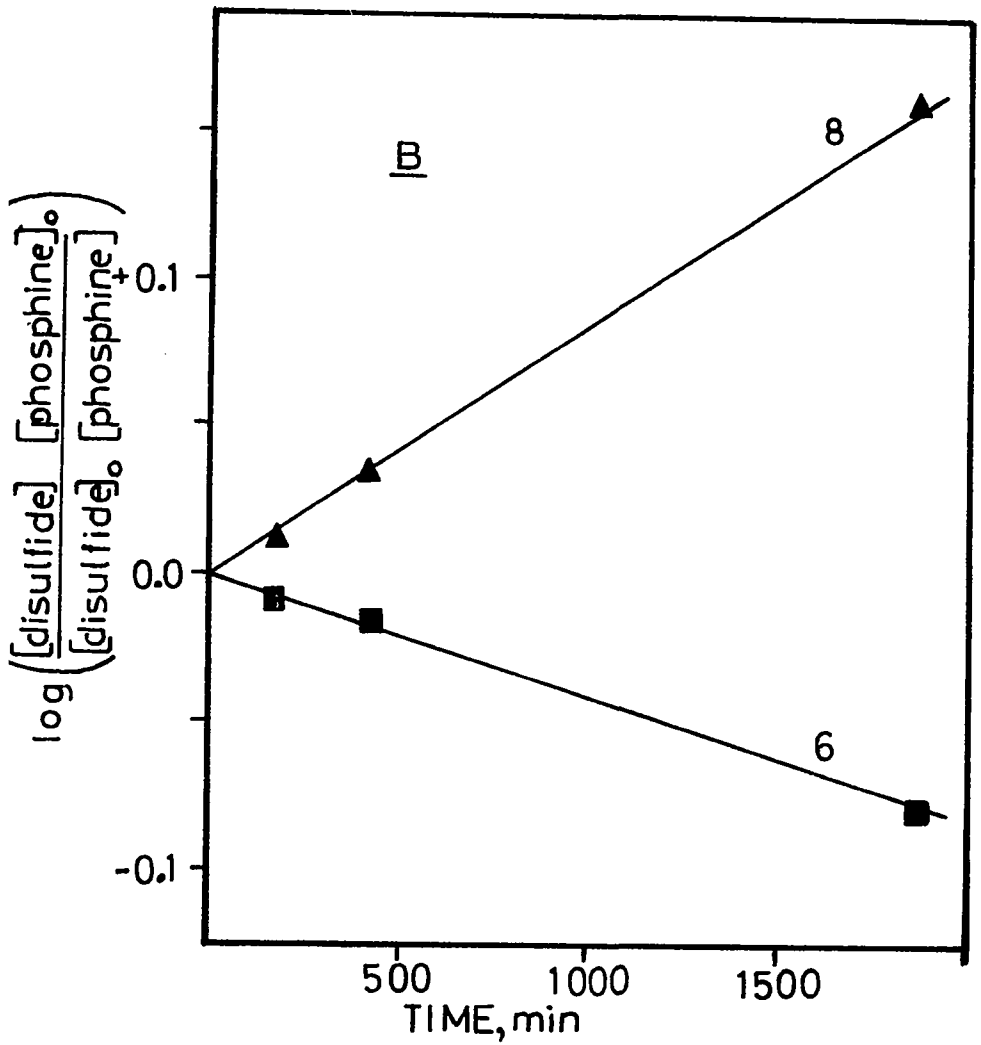


Figure 17b. Second order plot for the desulfurization of benzyl disulfide (2). Initial conc. of phosphine: 6) 0.05 M; 8) 0.20 M. Initial conc. of disulfide 2 was 0.10 M in both cases.

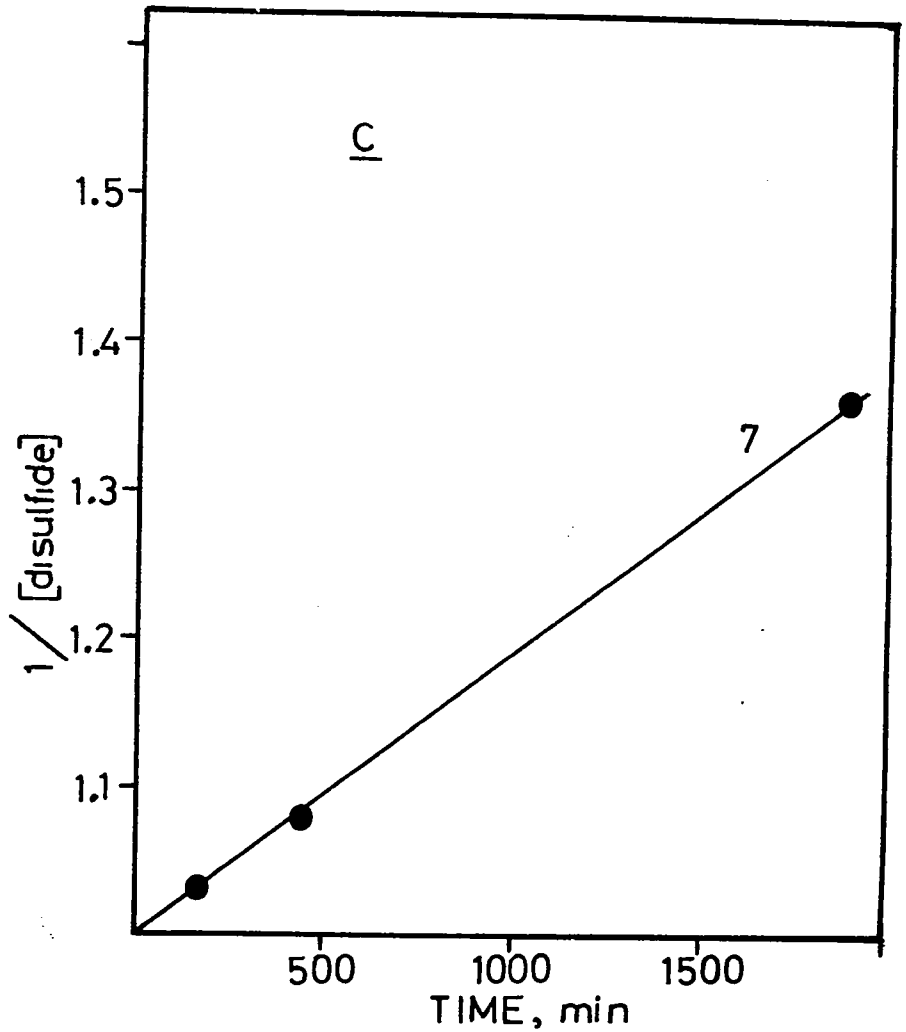


Figure 17c. Second order plot for the desulfurization of 2. Initial conc. of both phosphine and disulfide was 0.10 M.

may be written in the form

$$t = \frac{1}{k_2 A_o} \cdot \frac{m}{A} \qquad A_o = B_o \qquad \text{eq. 8}$$

where m is the amount of product formed in time t (152). This form of the rate equation is of particular convenience for gas chromatographic monitoring of kinetic experiments. Equation 8 may be rewritten as

$$t = \frac{\underset{\sim}{f}}{k_2 A_o}\left(\frac{\text{Product Area}}{\text{Reactant Area}}\right) = \frac{1}{k_2 A_o}\,\frac{[\text{Product}]}{[\text{Reactant}]} \qquad \text{eq. 9}$$

where $$\underset{\sim}{f} = \frac{(\text{Product Concentration}) \times (\text{Reactant Area})}{(\text{Reactant Concentration}) \times (\text{Product Area})} \qquad \text{eq. 10}$$

where the product and reactant areas are the integrated peak areas for one reactant and one product as obtained by vpc analysis. The required constant $\underset{\sim}{f}$, defined in equation 10, is obtained by calibration of the gas chromatograph with suitable standards. Thus a plot of [Product]/[Reactant] vs time, or (Product Area)/(Reactant Area) vs time, should be linear with a slope of $1/k_2A_o$ or $\underset{\sim}{f}/k_2A_o$ respectively. From such a plot, the second order rate constant may be calculated.

The desulfurization of benzyl disulfide (2) was conducted at 30.1°, 38.0° and 45.0° in a variety of solvents. In all of these experiments, initial concentrations of 0.10 M in both tris(diethylamino)phosphine (1) and benzyl disulfide (2) respectively. After appropriate time intervals (at least five per run), aliquots of these reactions were analyzed by vpc. The second order rate constants, standard deviations, activation

enthalpy ($\Delta H^{\ddagger}$) and activation entropy ($\Delta S^{\ddagger}$) were calculated by computer (IBM-360/50) using a least squares program designed to permit gas chromatographic data as input (Appendix II). The results of these experiments are summarized in Table VIII. Second order plots for those reactions performed at 30.1° are illustrated in Figure 18. The average standard deviation in each run was found to be ± 3%; the reproducibility, ± 4%.

In these reactions, a substantial solvent dependence was observed. For example, a 1400 fold acceleration in rate is observed in transferring the reaction from cyclohexane to o-dichlorobenzene. Since both the aminophosphine and aminophosphine sulfide are highly polar molecules, in high concentration, they would likely make a substantial contribution to the polarity of the reaction medium (59). For this reason, experiments were carried out with low phosphine concentrations (0.1-0.01 M).

It was of interest to evaluate the effect of the alkyl portion of the aminophosphine. The rate of desulfurization of benzyl disulfide (2) with tris(diethylamino)phosphine 1 may be compared with that for the desulfurization of 2 with the corresponding methyl-aminophosphine 103 (Table IX). It was found

TABLE IX

COMPARISON OF ETHYL- AND METHYL-AMINOPHOSPHINES

PHOSPHINE		$10^5 k_2$ ($l.M^{-1}sec^{-1}$)
$((CH_3)_2N)_3P$	(103)	4.1 ± 0.2
$((CH_3CH_2)N)_3P$	(1)	4.7 ± 0.2

that tris(dimethylamino)phosphine reacts with benzyl disulfide at

TABLE XVIII

DESULFURIZATION OF BENZYL DISULFIDE (2)

SOLVENT	TEMP. °C.	k_2 ($l.M^{-1}sec^{-1}$) a	$\Delta H^{\ddagger}$ b kcal/mole	$\Delta S^{\ddagger}$ b eu.
Cyclohexane	30.1	$1.5 \pm 0.1 \times 10^{-6}$		
Cyclohexane	38.0	$2.3 \pm 0.1 \times 10^{-6}$	15.6	-24
Cyclohexane	45.0	$5.3 \pm 0.1 \times 10^{-6}$		
Benzene	30.1	$4.7 \pm 0.2 \times 10^{-5}$		
Benzene	38.0	$7.1 \pm 0.2 \times 10^{-5}$	13.5	-24
Benzene	45.0	$1.4 \pm 0.1 \times 10^{-4}$		
Ethyl acetate	30.1	$1.2 \pm 0.05 \times 10^{-4}$		
Ethyl acetate	38.0	$2.0 \pm 0.1 \times 10^{-4}$	10.2	-34
Ethyl acetate	45.0	$3.0 \pm 0.1 \times 10^{-4}$		
o-Dichlorobenzene	30.1	$2.1 \pm 0.1 \times 10^{-3}$		
o-Dichlorobenzene	38.0	$3.6 \pm 0.2 \times 10^{-3}$	9.7	-28
o-Dichlorobenzene	45.0	$5.2 \pm 0.2 \times 10^{-3}$		

a) Average of two runs; errors are standard deviations. Reproducibility, ±4%. b) Error ±10%.

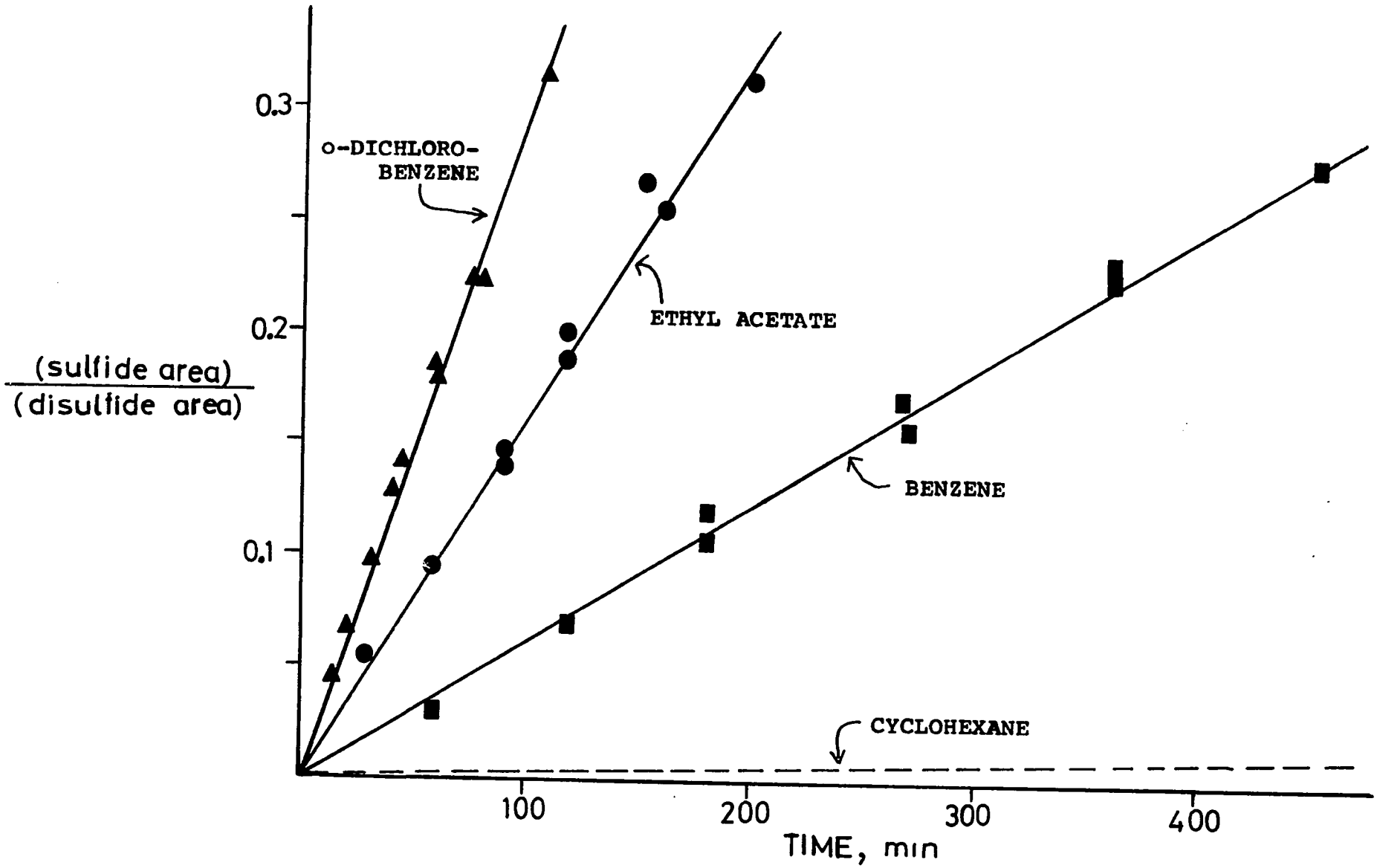
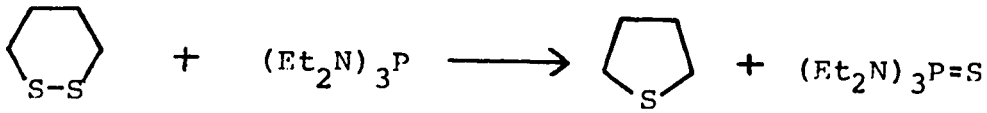


Figure 18. Second order plot for the desulfurization of Benzyl Disulfide (2) by Tris(diethylamino)phosphine (1) in several solvents at 30.1°.

a rate comparable to that of the ethyl derivative (1). Thus, from kinetic considerations, either of the aminophosphines could be effectively used to desulfurize disulfides.

The desulfurization of 1,2-dithiane (49) proceeds at a rate comparable to that of benzyl disulfide and the reaction could



49 1 50 4

be followed by gas chromatography. The desulfurizations were performed at 30.0°, 37.8° and 50.0° in benzene, and at 30.0°, 38.3° and 44.9° in ethyl acetate. The results of these experiments are summarized in Table X. A second order plot for the desulfurization of 49 in benzene is shown in Figure 19 and the corresponding Arrhenius plot in Figure 20. Since all calculations were performed by computer, these plots are presented only to illustrate the close fit of experimental data to the theoretical expressions.

It was desirable, for comparison, to measure the rate of desulfurization of a simple alkyl disulfide. The desulfurization of diamyl disulfide (5) proceeded at a measurable rate in refluxing benzene. Although some loss of solvent occurred during the reaction, a second order rate plot (Figure 21)

$$\underset{5}{C_5H_{11}S\text{-}SC_5H_{11}} \xrightarrow[k_2 \simeq 10^{-9}]{(Et_2N)_3P} \underset{6}{C_5H_{11}\text{-}S\text{-}C_5H_{11}}$$

for the first 50% of the reaction was linear and from it, a rate constant of $4.6 \pm 0.3 \times 10^{-6}$ $1M^{-1}sec^{-1}$ was calculated.

TABLE X

DESULFURIZATION OF 1,2-DITHIANE (49)

Solvent	Temp. °C.	10^5 k_2 ($l.M^{-1}sec^{-1}$)[a]	$\Delta H^{\ddagger}$[b] kcal/mole	$\Delta S^{\ddagger}$[b] eu
Benzene	30.0	4.5 ± 0.2		
Benzene	37.8	7.0 ± 0.2	12.3	-28
Benzene	50.0	16.8 ± 0.9		
Ethyl Acetate	30.0	11.6 ± 0.5		
Ethyl Acetate	38.3	17.2 ± 0.4	8.8	-38
Ethyl Acetate	44.9	24.1 ± 0.5		

a) Average of two runs; errors are standard deviations. Reproducibility, ± 4%. b) Error, ± 10%.

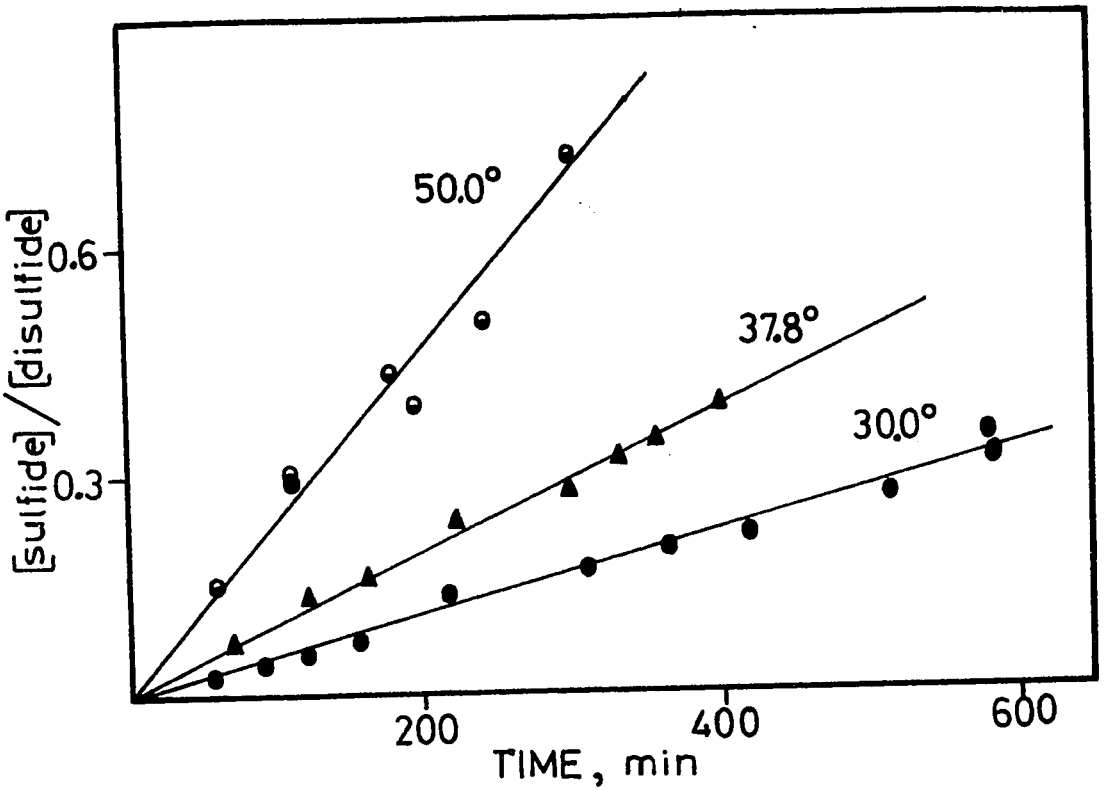


Figure 19. Second order plots for the desulfurization of 1,2-Dithiane (49) in benzene solution.

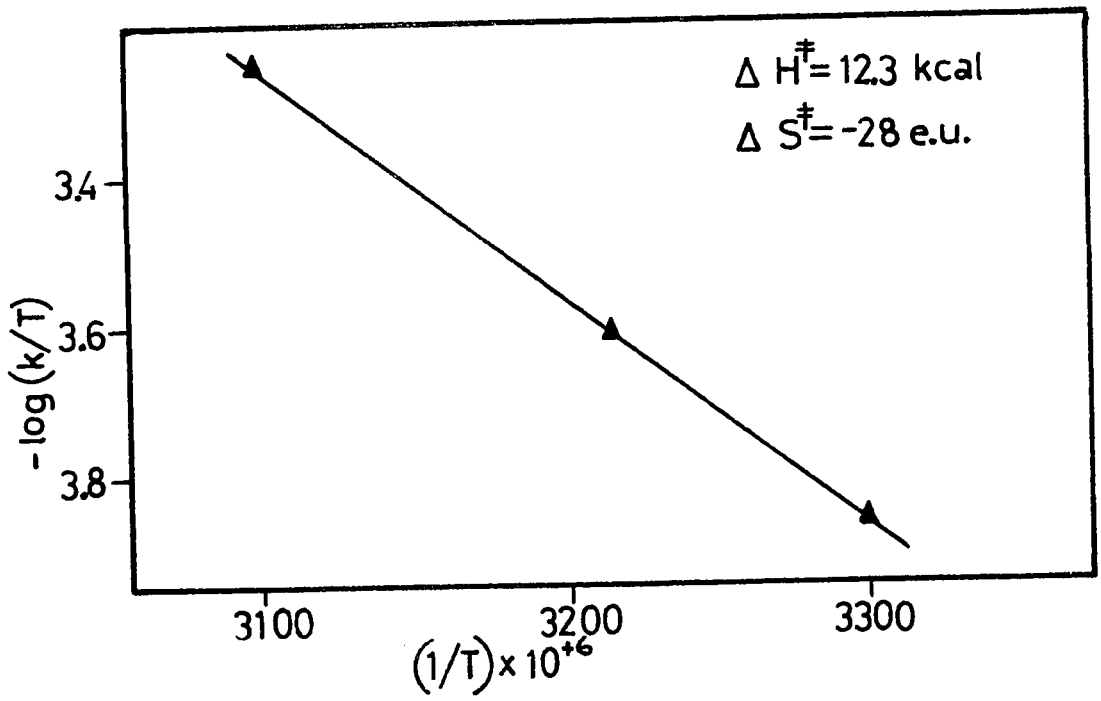


Figure 20. Arrhenius plot for the desulfurization of 1,2-Dithiane (49) in benzene solution.

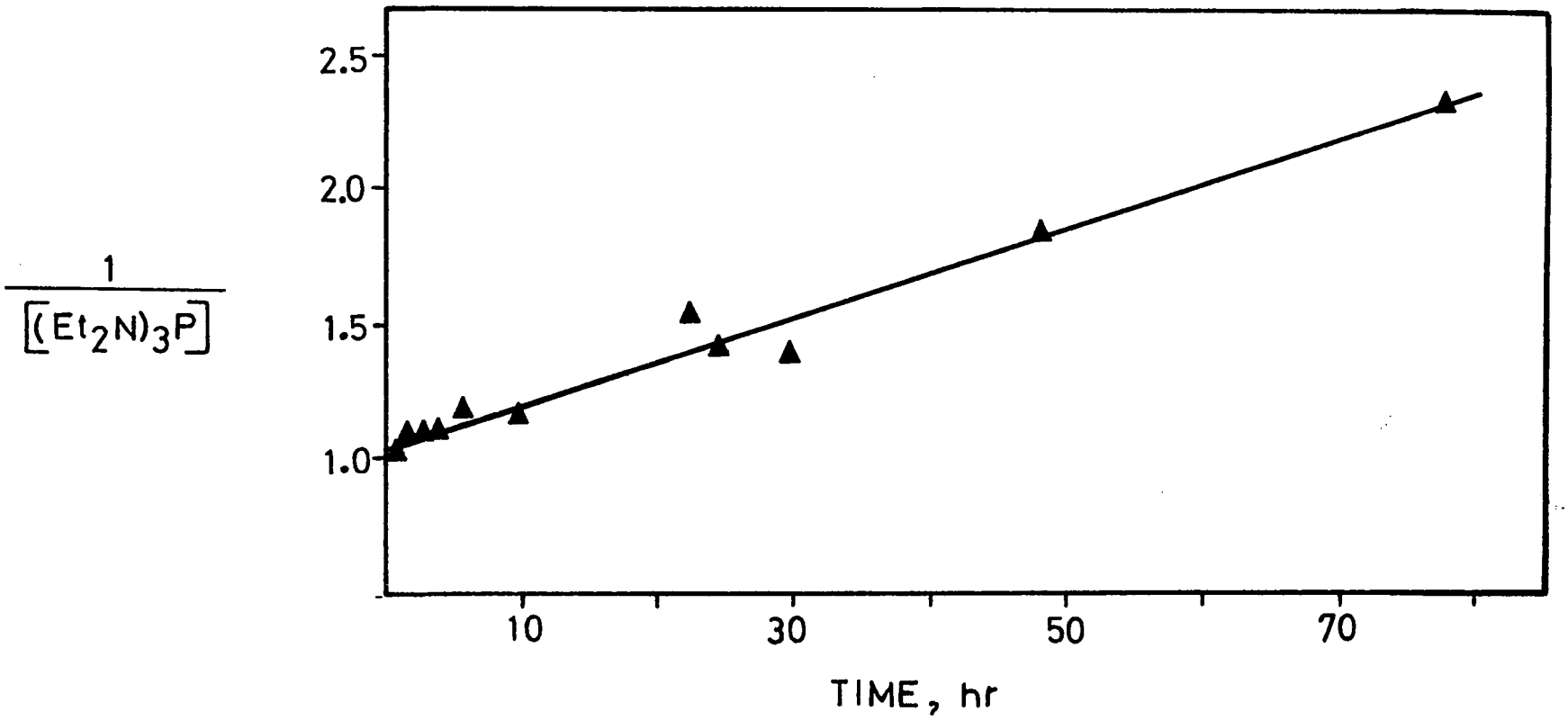
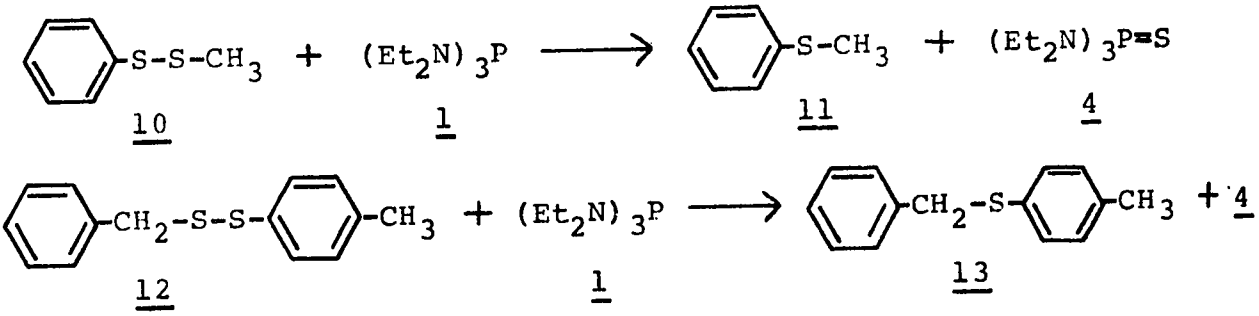


Figure 21. Second order plot for the desulfurization of Diamyl Disulfide (5) in benzene solution at 80 ± 3°.

This rate constant, however, refers to a reaction at 80±3° and at a phosphine concentration of 1 Molar. An extrapolation of this rate constant based upon the energetics of the desulfurization of 1,2-dithiane (49) results in a rate constant of 1.6×10^{-9} $1M^{-1}sec^{-1}$ at 30°C. The error in this rate constant is very large (an estimate of ±100% is not unreasonable); nevertheless, for comparison purposes, it is acceptable provided this error is noted.

The desulfurization of the unsymmetrical disulfides proceeded too rapidly to be followed by gas chromatography. However, the uv spectra of most disulfides show a broad absorption at 240-260 mμ(153) which, in many cases, extends well beyond 300 mμ. Although the ultraviolet maxima could not be used to monitor the desulfurization since the aminophosphines exhibit a very strong end absorption at ca. 270-280 mμ, it was possible to follow the desulfurization of several disulfides using that part of the disulfide absorption which extended beyond this cut-off wavelength.

The desulfurization of phenyl methyl disulfide (10) and benzyl tolyl disulfide (12) were carried out under pseudo-first order conditions with aminophosphine 1 in 10-100 fold



10 + 1 → 11 + 4

12 + 1 → 13 + 4

excess. The desulfurization of 10 was conducted in benzene, cyclohexane and ethyl acetate at 30°C. The decrease in absorption at 315 mμ was measured as a function of time, and, from this data, the pseudo-first order rate constant (k') and the true second order rate constant (k_2) were calculated. The computer program used for these calculations (Appendix II) was based on the following equations:

$$k' = \frac{1}{t} \ln\left(\frac{A_o - A_\infty}{A_t - A_\infty}\right) \qquad \text{eq.11}$$

$$k_2 = \frac{1}{tC_o} \ln\left(\frac{A_o - A_\infty}{A_t - A_\infty}\right) \qquad \text{eq.12}$$

where C_o is the initial concentration of excess reagent, in this case, phosphine; A_o, A_t and A_∞ are the optical densities at t=0, t=t and t=∞ respectively. The rate constants thus obtained are summarized in Table XI.

TABLE XI

DESULFURIZATION OF PHENYL METHYL DISULFIDE (10) AT 30.0°C

SOLVENT	10^2 k_2[a] ($LM^{-1}sec^{-1}$)
CYCLOHEXANE	1.14 ± .02
BENZENE	45.0 ± .3
ETHYL ACETATE	151. ± 3

a) average of two runs; errors are standard deviations.

Similarly, the rate constants for the desulfurization of benzyl tolyl disulfide (12) were measured in cyclohexane,

benzene and ethyl acetate. This desulfurization was conducted

TABLE XII

DESULFURIZATION OF BENZYL TOLYL DISULFIDE (12)

SOLVENT	$10^2 k_2{}^a$ ($LM^{-1}sec^{-1}$) (at 30.0°C)	
	$(Et_2N)_3P$	$(Me_2N)_3P$
CYCLOHEXANE	0.446 ± 0.003	—
BENZENE	12.0 ± 0.3	21.6 ± 0.4
ETHYL ACETATE	61.5 ± 0.3	—

a) average of two runs

at 30°, 38° and 46° in benzene solution. The second order rate constants and activation parameters are summarized in Tables XII and XIII.

TABLE XIII

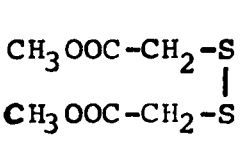
ENTHALPY AND ENTROPY OF DESULFURIZATION

OF BENZYL TOLYL DISULFIDE IN BENZENE

TEMPERATURE (°C)	$10^1 k_2{}^a$ ($LM^{-1}sec^{-1}$)	$\Delta H^{\ddagger}$ (kcal/Mole)	$\Delta S^{\ddagger}$ (eu.)
30.0°	1.20 ± 0.03	5.4 ± 0.1	-35
38.0°	1.55 ± 0.02		
46.0°	1.99 ± 0.02		

a) average of two runs.

This uv technique was used, as well, for the measurement of the rate constants for the desulfurization of di(carbomethoxymethyl)disulfide (14) and α-lipoic acid anilide (54). Thus, the second order rate constant for the desulfurization of 14 in benzene was found to be $1.03 \pm 0.02 \times 10^{-1}$ while for 54, the

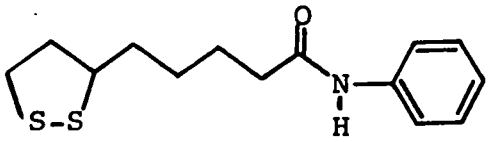


14

$k_2 = 1.03 \pm 0.02 \times 10^{-1}$

57

$k_2 = 1.68 \times 10^{-5}$



54

$k_2 = 4.18 \pm 0.08 \times 10^{-4}$

rate constant was $4.18 \pm 0.08 \times 10^{-4}$. In the latter case, the absorption maxima at 330 mμ could be used to monitor the reaction.

The desulfurization of 1,2-dithiolane (57) was followed by the disappearance of the uv absorption maximum at 315 mμ. This desulfurization, however, was not performed under pseudo-first order conditions, but rather under true second order conditions in benzene solution at 25°C with a slight excess of phosphine. The initial disulfide concentration was 0.112M. This reaction was performed in the dark so as to prevent light-induced polymerization of the disulfide. From the reported extinction coefficient (λ_{max}^{MeOH} 315, $\varepsilon = 147$ (131)), the disulfide concentration and hence the phosphine concentration could be computed. From the resulting second order rate plot (Figure 22) the rate constant (at 25°) of $1.68 \times 10^{-5} LM^{-1} sec^{-1}$ was obtained. No polymerization was observed during this 430 hour (12 day) reaction as evidenced by the lack of any precipitate forming during this reaction. More concentrated disulfide solutions (0.5-1.0 M) produced significant amounts of polymer in 3-8 hours in the dark at room temperature.

Discussion of Kinetic Results

A summary of all the kinetic results obtained are presented in Table XIV. These rates vary over a range of 10^9. A striking

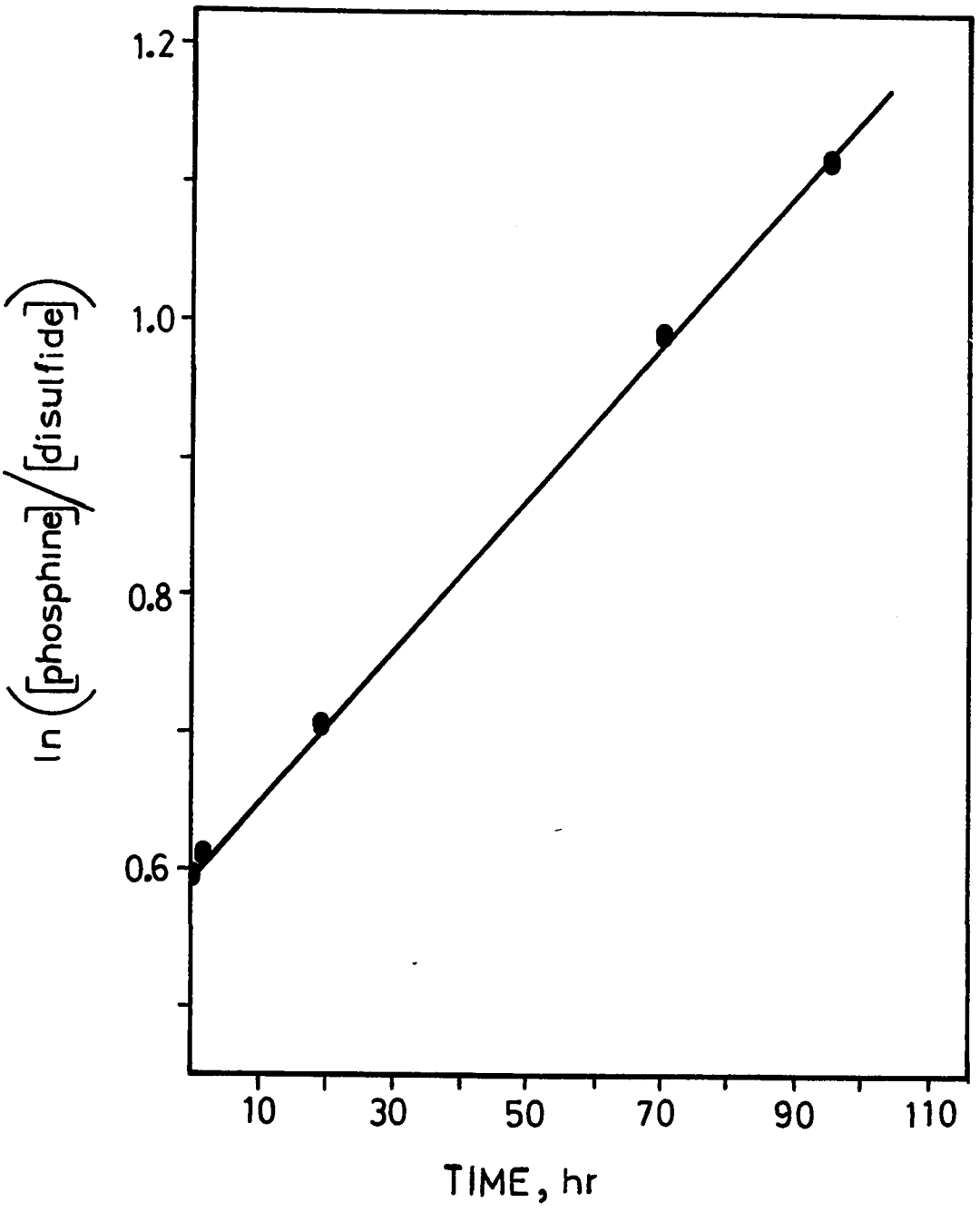


Figure 22. Second order plot for the desulfurization of 1,2-Dithiolane (57) in benzene solution at 25°C.

TABLE XIV

SECOND ORDER RATE CONSTANTS OF DESULFURIZATION

Disulfide	Solvent[a]	k_2 at 30° ($l.M^{-1}sec^{-1}$)[b]	$\Delta H^{\ddagger}$[c]	$\Delta S^{\ddagger}$[c]
Benzyl Disulfide	cyclohexane	$1.5 \pm 0.1 \times 10^{-6}$	15.6	-24
	benzene	$4.7 \pm 0.2 \times 10^{-5}$	13.5	-24
	ethyl acetate	$1.2 \pm 0.1 \times 10^{-4}$	10.2	-34
	o-dichlorobenzene	$2.1 \pm 0.1 \times 10^{-3}$	9.7	-28
1,2-Dithiane	benzene	$4.5 \pm 0.2 \times 10^{-5}$	12.3	-28
	ethyl acetate	$1.2 \pm 0.1 \times 10^{-4}$	8.8	-38
Diamyl Disulfide	benzene[d]	$1.6 \pm 1. \times 10^{-9}$	-	-
1,2-Dithiolane	benzene	$1.68 \pm 0.03 \times 10^{-5}$	-	-
α-Lipoic Acid Anilide	benzene	$4.18 \pm 0.08 \times 10^{-4}$	-	-
Phenyl Methyl Disulfide	cyclohexane	$1.14 \pm 0.02 \times 10^{-2}$	-	-
	benzene	$4.50 \pm 0.03 \times 10^{-1}$	-	-
	ethyl acetate	1.51 ± 0.03	-	-
Benzyl Tolyl Disulfide	cyclohexane	$4.46 \pm 0.03 \times 10^{-3}$	-	-
	benzene	$1.20 \pm 0.03 \times 10^{-1}$	5.4	-35
	ethyl acetate	$6.15 \pm 0.03 \times 10^{-1}$	-	-
Dicarbomethoxy-methyl Disulfide	benzene	$1.03 \pm 0.02 \times 10^{-1}$	-	-

a) All reactions were performed or extrapolated to 30°C.
b) Average of two runs; errors are standard deviations.
c) Error, ± 10%. d) Concentration, 1.0 M.

feature of these results is the marked dependence of the rate constant on the polarity of the reaction medium. This dependence is seen from a plot of log (k) against $E_t(30)$, a solvent polarity parameter[14] (154). Such a plot is shown in Figure 23.

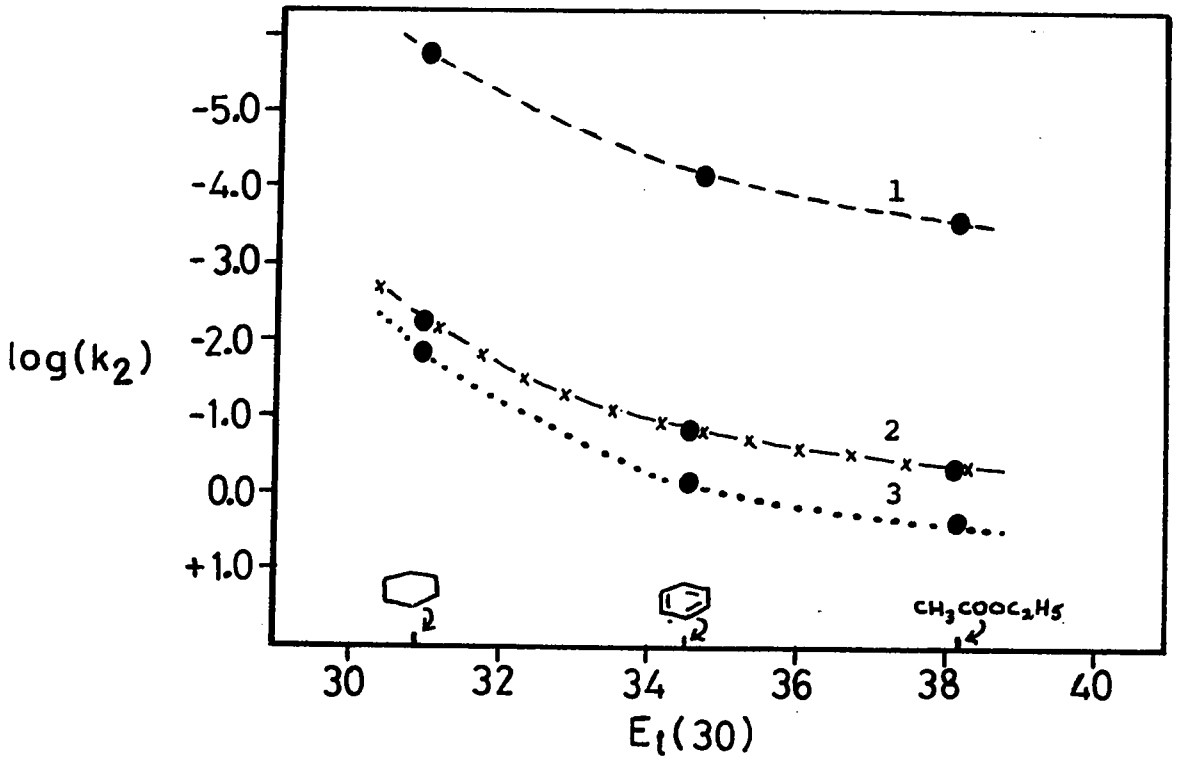


Figure 23. Plot of $\log(k_2)$ vs $E_t(30)$. 1) Dibenzyl Disulfide; 2) Benzyl Tolyl Disulfide; 3) Phenyl Methyl Disulfide.

The solvent effect for dibenzyl disulfide (2), phenyl methyl disulfide (10) and benzyl tolyl disulfide (12) may be compared with that observed in other ionic reactions (Table XV). From this comparison, it may be seen that the solvent effect is at least as great as that observed in the Menschutkin Reaction (155) (the reaction of tertiary amine with an alkyl halide) where nearly 50% ionization has occurred in the transition state (49). Moreover, the solvent effect is of the same order

[14] $E_t(30)$ is a solvent polarity parameter based upon the solvation effect of a given solvent upon the energy of the intramolecular charge transfer band of a pyridinium-phenol betaine.

TABLE XV

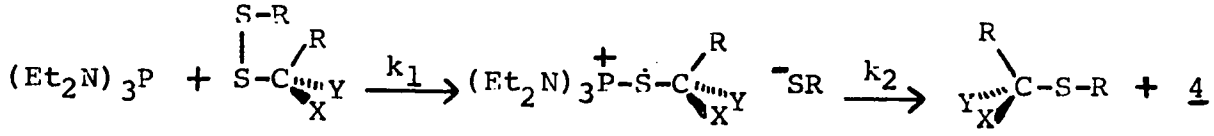
COMPARISON OF SOLVENT EFFECTS OF SELECTED REACTIONS

Solvent	ε_{25}	RELATIVE RATE OF REACTION (BENZENE = 1.0) Benzyl Disulfide + 1	Benzyl Tolyl Disulfide + 1	Phenyl Methyl Disulfide + 1	Ph_3P[a] + S_8	Menschutkin Reaction[b]
Hexane	1.89	-	-	-	-	0.01
Cyclohexane	2.02	0.03	0.03	0.04	0.01	-
Benzene	2.28	1.0	1.0	1.0	1.0	1.0
Chlorobenzene	5.62	-	-	-	2.6	3.5
Ethyl acetate	6.02	2.6	3.3	5.1	-	-
o-Dichlorobenzene	9.93	43.	-	-	-	-
Benzonitrile	25.2	-	-	-	-	28.

a) Data from Bartlett and Meguerian (49).

b) Data from Grimm, Ruf and Wolff (155a).

of magnitude as that observed by Bartlett in the reaction of sulfur with triphenylphosphine (49). The observed solvent effect in the desulfurization of these disulfides would suggest that a charged intermediate is being formed during the reaction. The stereochemical results presented earlier suggested that the product forming step was an S_N2 decomposition of a phos-



104

phonium salt. The observed solvent effect is consistent with the formation of a phosphonium salt during the reaction. This solvent effect does not, however, necessarily demand that charge separation is occurring in the rate limiting step. If the formation of 104 were a reversible process, the effect of solvent could be to shift the equilibrium in favor of this salt and thus increase the overall rate of reaction. This effect would be observed regardless of which step (k_1 or k_2) is rate limiting.

The activation parameters ($\Delta H^{\ddagger}$,$\Delta S^{\ddagger}$), however, reflect the energy required to form the activated complex for the rate limiting step (Fig. 24). Therefore, the effect of solvent on

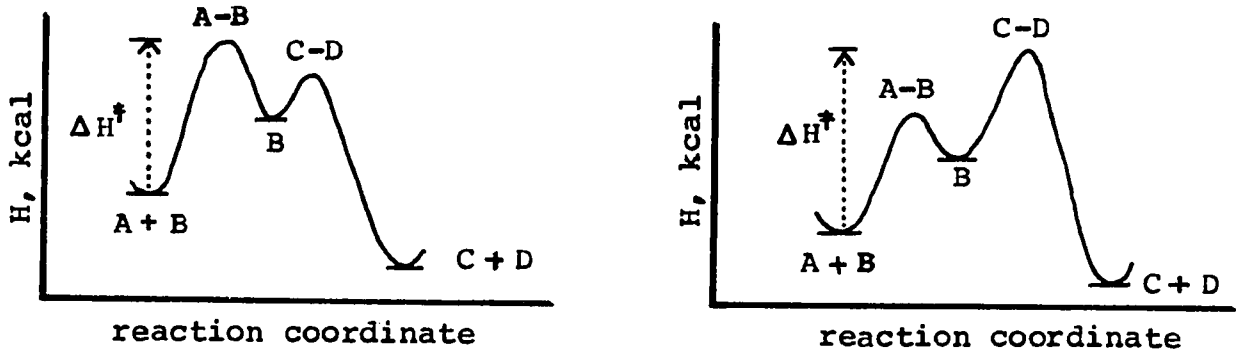


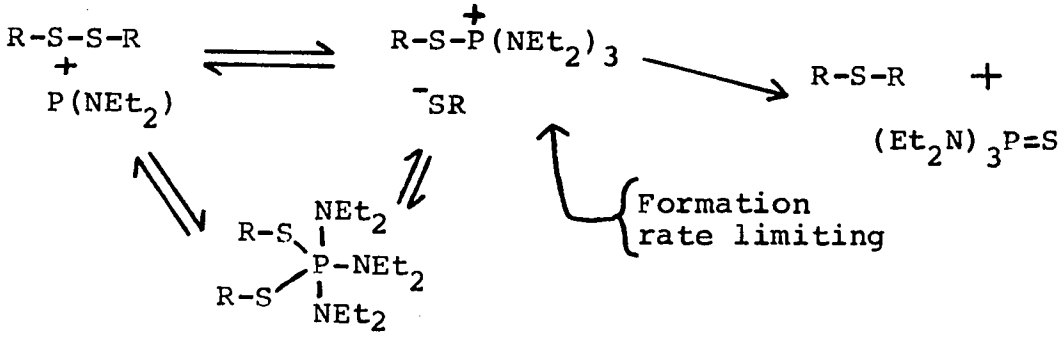
Figure 24. Energetics of a two step reaction.

these parameters should reflect the solvation effects on this activated complex and hence on the rate limiting step. The desulfurization of benzyl disulfide is accelerated by increasing the polarity of the reaction. More important, this solvent effect is reflected in a decrease in the activation enthalpy $\Delta H^{\ddagger}$ of this reaction (Table XVI). From this, it may be concluded that charge separation is occurring in the transition state of the rate determining step (that step in which the activated complex of highest energy is being formed). Thus, the formation of the phosphonium salt is rate limiting. The formation of this salt, however, may arise from the ionization of a pentacovalent intermediate or by direct ionic scission

TABLE XVI

DEPENDENCE OF $\Delta H^{\ddagger}$ ON SOLVENT POLARITY

SOLVENT	ε	$10^5 k_2(30)$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
cyclohexane	2.02	0.15±0.01	15.6	-24
benzene	2.28	4.7 ± 0.2	13.5	-24
ethyl acetate	6.02	12.1 ± 0.2	10.2	-34
o-dichlorobenzene	9.93	209. ± 4.	9.7	-28



of the disulfide bond. These two possibilities are not readily distinguishable .

Those factors which would promote the formation of a phosphonium salt should have a considerable effect on the rate of desulfurization. The effect of solvent has been discussed. Other related factors are the stability of the mercaptide which is formed, the degree and direction of polarization of the disulfide bond, and the sulfur-sulfur bond strength.

To facilitate comparison of rate data, the rate constants of desulfurization of several disulfides at 30°C in benzene are tabulated in Table XVII along with the relative rate constants (k_r) (1,2-dithiane = 1.0) and approximate pKa values (89, 90) for the mercaptide ions which would be formed on desulfurization. The rate of desulfurization of these disulfides

TABLE XVII

DESULFURIZATION OF DISULFIDES

KINETIC SUMMARY

DISULFIDE	k_2 ($1M^{-1}sec^{-1}$)	k_r	pK_a (89,90)
$C_5H_{11}S\text{-}S\text{-}C_5H_{11}$ (5)	$\sim 10^{-9}$ [a]	0.0001 [a]	12.6
1,2-dithiolane (57)	1.7×10^{-5} [b]	0.44 [b] (0.6 [c])	-
$(Ph\text{-}CH_2\text{-}S)_2$ (2)	4.7×10^{-5}	1.1	11.8
1,2-dithiane (49)	4.2×10^{-5}	1.0	-
α-Lipoic acid anilide	4.6×10^{-4}	11.	-
$(CH_3OOC\text{-}CH_2S)_2$ (14) (54)	1.0×10^{-1}	2,470.	9.8
$Ph\text{-}CH_2S\text{-}S\text{-}Ph\text{-}CH_3$ (12)	1.2×10^{-1}	2,800.	9.3
$Ph\text{-}S\text{-}S\text{-}CH_3$ (10)	4.4×10^{-1}	10,550.	8.6

(a) extrapolated from 80°; (b) at 25°; (c) relative to 1,2-dithiane (49) at 25°, by extrapolation.

shows a definite dependence on the pKa of the mercaptide being formed. (The cyclic disulfides are excluded from this consideration for reasons of ring strain and entropy effects). This dependence is clearly seen by the near linearity of a plot of log (k_2) vs pKa (Fig. 25). Thus it may be concluded

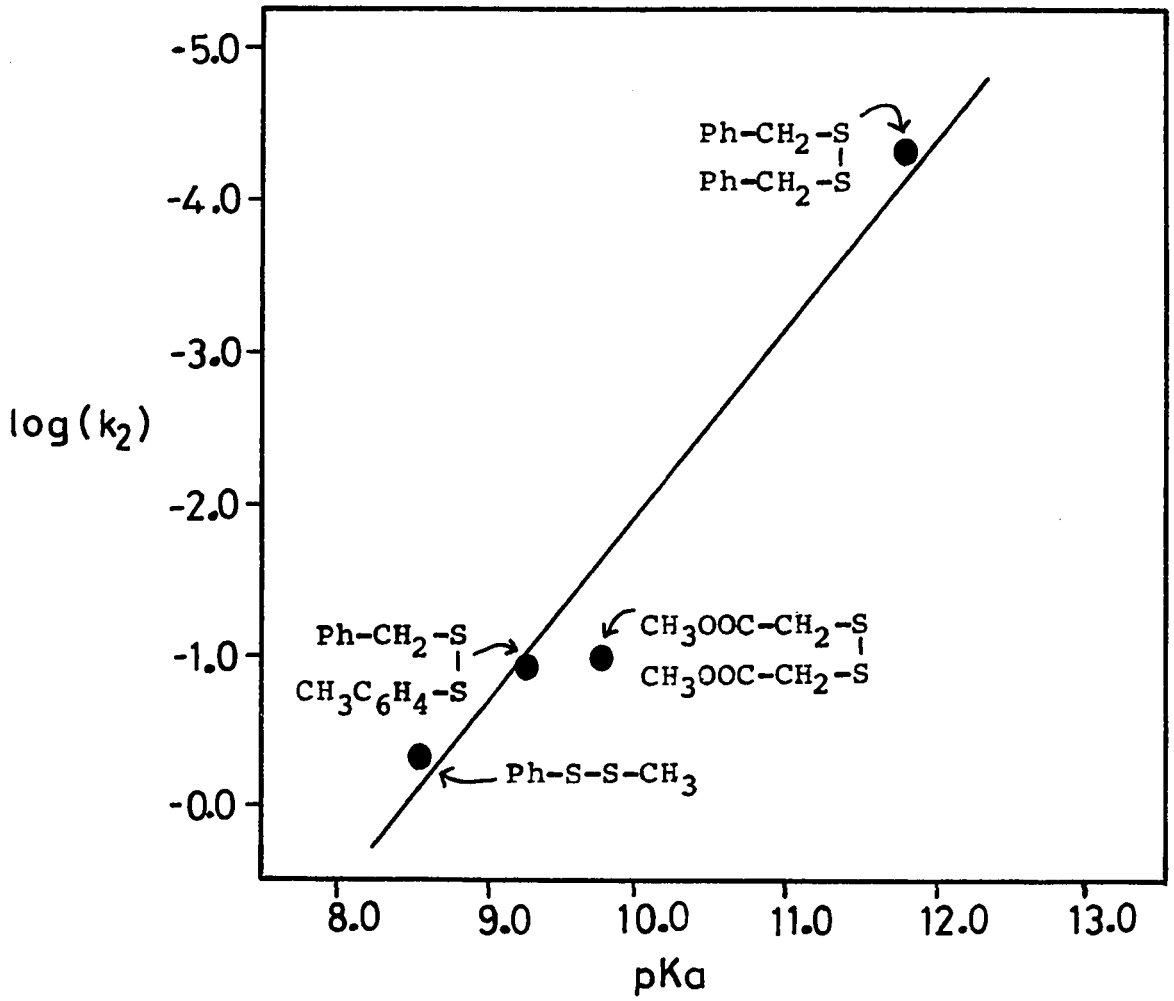
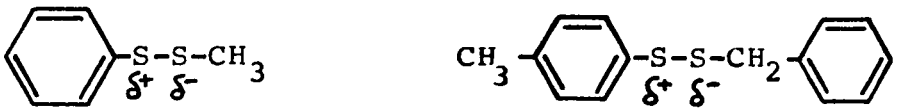


Figure 25. Plot of log (k_2) vs pKa. Data from Table XVII.

that the rate of desulfurization is a logarithmic function of mercaptide stability. This observation is consistent with

the postulation of a phosphonium salt being formed in the rate limiting step.

The polarization of the sulfur-sulfur bond in an unsymmetrical disulfide would be such as to provide the highest electron density about that sulfur atom which is attached to the more electronegative substituent (61). For benzyl tolyl and phenyl methyl disulfides, the polarization would then be:



Such a polarization is consistent with attack of electrophilic agents on the more negative sulfur atom (156). Nucleophilic substitution should, however, occur on the more positive sulfur atom (34). This would result in displacement of the least stable mercaptide. In these desulfurizations, however, the more stable mercaptide is displaced (or ionized) in the rate limiting step. This would suggest that either ionization from a pentacovalent intermediate is occurring (hence unaffected by polarization of the disulfide), or a high degree of P-S bond formation has occurred in the transition complex. In the latter case, polarization effects would be secondary to mercaptide stability. This postulation of a high degree of bond formation (hence a high degree of charge formation) in the transition state complex receives some support from the large solvent effect which was observed. This solvent effect was indicative of considerable charge separation(formation) in the activated complex.

The rate of ionic scission of disulfides by nucleophiles

is dependent on the sulfur-sulfur bond strength (157). This effect is readily detected in the ionic scission of cyclic disulfides. For example, the reaction of n-butyl mercaptide-^{35}S with 1,2-dithiolane (57) proceeds 10,000 times as fast as with

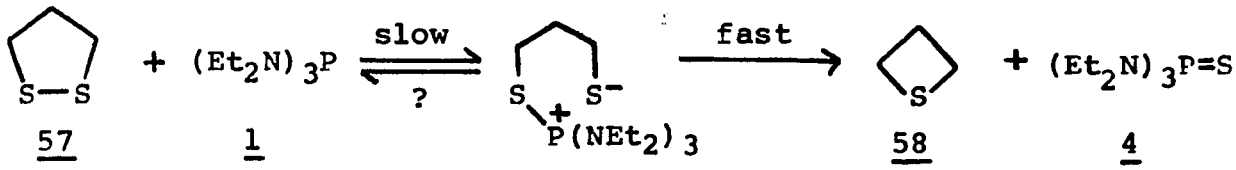
$$\text{n-Bu-S-S-(CH}_2\text{)}_3\text{-S}^-$$

57

$$\text{nBu-S-S-nBu} + \text{nBu-}^{35}\text{S}^- \longrightarrow \text{n-Bu-}^{35}\text{S-S-nBu} + \text{nBuS}^-$$

its open chain analogue (32). This acceleration results from the release of ring strain in 1,2-dithiolane. The origin of this ring strain (15 kcal/mole) has been discussed earlier.

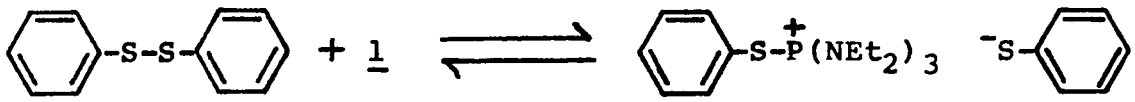
If the formation of a phosphonium salt in the desulfurization reaction results from an ionic scission of the disulfide bond, it should exhibit a similar accelerating effect. A comparison of the rate of desulfurization of diamyl disulfide ($k_2 = 10^{-9}\,1M^{-1}sec^{-1}$) with 1,2-dithiolane shows that the cyclic disulfide reacts at a rate 10^4 times faster than amyl disulfide. This acceleration is of the same magnitude as that observed for the reaction of 57 with n-butyl mercaptide. This observation is consistent with the formation of the phosphonium salt from disulfide via ionic scission. An acceleration of this magnitude would not be anticipated if the salt intermediate results from ionization of a pentacovalent intermediate. Although the formation of the pentacovalent intermediate would be accelerated, its decomposition, the rate limiting step, would not be significantly affected, and, hence, the overall rate would be close to that of an aliphatic disulfide.



57 1 58 4

It is most probable, therefore, that the phosphonium salt is formed by direct ionic scission of the disulfide bond[15]. Since all the evidence presented thus far strongly favors the ionic scission mechanism, and no evidence was found which would implicate a pentacovalent intermediate — it is not formed in the rate limiting step nor involved in the product determining step — its role in the reaction, if it is indeed present, is negligible.

A more important problem was raised earlier in the discussion. Although the product forming step is irreversible, this need not be true of the formation of the intermediate phosphonium salt. To detect such an equilibrium process, it would be necessary to prepare a stable phosphonium salt and investigate its reaction with a mercaptide ion. It was expected that the reaction of diphenyl disulfide 105 with tris(diethylamino)phosphine (1) would provide a stable phosphonium salt. However, when equimolar amounts of di-p-tolyl disulfide 28 and 1 were



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[15]The possibility of a pre-equilibration of a pentacovalent intermediate with starting material has not been rigorously excluded. Further proof might be obtained were an optically active aminophosphine used in this reaction. The pentacovalent intermediate, if it were formed, would rapidly racemize via pseudo-rotation. However, no optically active aminophosphines have been reported; the synthesis and resolution of simple phosphines and phosphites present considerable difficulties (158).

mixed in the nmr tube and the ^{31}P spectrum observed, the only resonance present was that due to unreacted 1 (-118 ppm). However, if a mixture of phenyl disulfide (105) and tolyl disulfide (28) are mixed with 1, a significant amount of tolyl phenyl disulfide (106) was formed immediately. This would

$$\underset{105}{Ph\text{-}S\text{-}S\text{-}Ph} + \underset{28}{CH_3\text{-}Ph\text{-}S\text{-}S\text{-}Ph\text{-}CH_3} \longrightarrow \underset{106}{Ph\text{-}S\text{-}S\text{-}Ph\text{-}CH_3}$$

$$Ph\text{-}S\text{-}S\text{-}Ph + 1 \rightleftharpoons \underset{107}{Ph\text{-}S\text{-}\overset{+}{P}(NEt_2)_3} + \bar{S}\text{-}Ph$$

$$CH_3\text{-}Ph\text{-}S\text{-}S\text{-}Ph\text{-}CH_3 + 1 \rightleftharpoons \underset{108}{CH_3\text{-}Ph\text{-}S\text{-}\overset{+}{P}(NEt_2)_3} + \bar{S}\text{-}Ph\text{-}CH_3$$

$$Ph\text{-}S\text{-}\overset{+}{P}(NEt_2)_3 + \bar{S}\text{-}Ph\text{-}CH_3 \rightleftharpoons Ph\text{-}S\text{-}S\text{-}Ph\text{-}CH_3 + 1$$

suggest that the phosphonium salts 107 and 108 are being formed in a rapid equilibrium process.

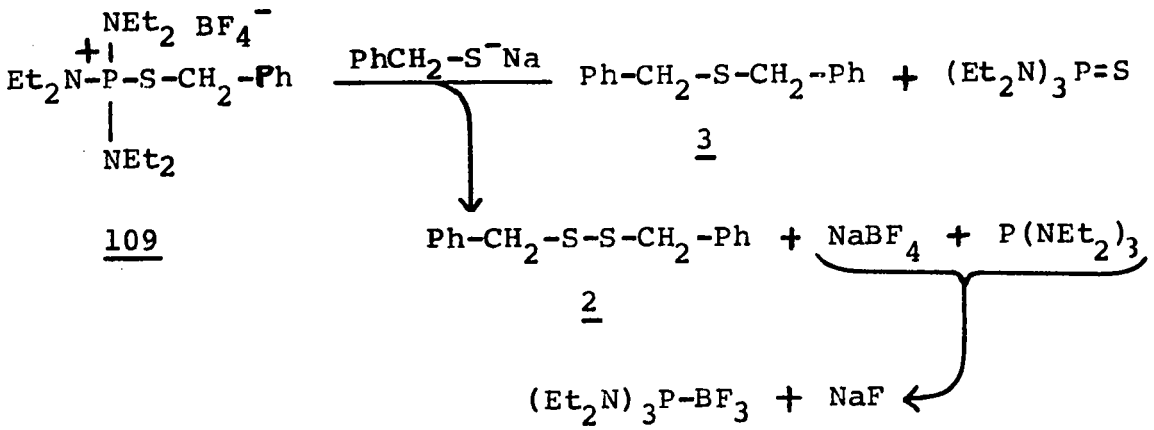
It was possible to prepare an authentic phosphonium salt by alkylation of tris(diethylamino)phosphine sulfide (4). Similar reactions have been reported for phosphine oxides (146). Reaction of this phosphine sulfide with benzyl bromide in the presence of silver tetrafluoroborate yielded the phosphonium

$$(Et_2N)_3P{=}S + \text{C}_6\text{H}_4(CH_2Br) + AgBF_4 \longrightarrow \underset{109}{Et_2N\text{-}\overset{+}{P}(NEt_2)\text{-}S\text{-}CH_2\text{-}C_6H_5}\ BF_4^-$$

$^{31}P\ \delta = -61.9$ ppm

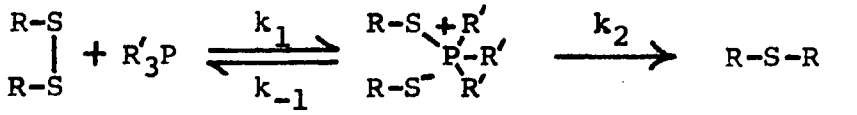
salt 109. This salt was isolated as a hygroscopic, viscous oil. All attempts to induce crystallization of this oil were unsuccessful. This salt exhibited a doublet for the benzylic proton (J_{PH}=8 Hz). The ^{31}P nmr of this oil exhibited a resonance at -61.9 ppm relative to H_3PO_4. The position of this resonance is consistent with the phosphonium salt structure (97) .

When sodium benzyl mercaptide was added to a benzene solution of this phosphonium salt, a black solid formed immediatly. Analysis of the benzene solution by vpc revealed the presence of disulfide 2 and sulfide 3 in the ratio 6:4. The nmr of this solution lacked the benzylic doublet of the salt, but showed singlets for both the sulfide and disulfide. Stirring this reaction for several hours had no effect upon the product ratio; presumably, the phosphine reacted further with the fluoroborate ion to form an addition complex. The formation of a complex was observed as well in the reaction of 1 with silver tetrafluoroborate. The question of phosphine-boron complexes has been discussed in a review article (159). This complexation may have a considerable effect upon the amount of disulfide which is formed in this reaction. However, this



experiment does provide proof of the reversibility of the formation of a phosphonium salt in the desulfurization of disulfides.

Since the formation of a phosphonium salt is a reversible process, the kinetic expression for this reaction may now be written:



$$-\frac{d[RSSR]}{dt} = k_1 \frac{k_2}{k_{-1}+k_2}[RSSR]\left[(Et_2N)_3P\right]$$

$$R' = Et_2N-$$

This expression is based upon a steady state approximation (152) which appears to be justifiable since no intermediates were detected (nmr, vpc, uv, ir) during the reaction. The solvent effect and mercaptide pKa dependence would require that k_1 be rate limiting. However, if k_2 is not very much greater than k_{-1} (ie. $(k_{-1}+k_2) \cong k_2$), it may not be neglected in considering the overall rate of reaction. This effect is most clearly evident in the relative rates of desulfurization of cyclic disulfides. Since the rate controlling step in the desulfurization of these disulfides is the ionic scission of the disulfide bond, the release of ring strain (due in part to the interaction of the lone pairs of electrons on adjacent sulfur atoms) should result in an acceleration in the rate of desulfurization of these cyclic molecules.

The most stable conformation for disulfides is that in which the dihedral angle (CSS-SSC) is near 90° (17). In six-membered disulfides, this dihedral angle is reduced to 70° (160).

This distortion of the dihedral angle results in a ring strain of 2 kcal/mole (130). In five-membered disulfides, this dihedral angle is reduced to 26° and the ring strain increases to 10-14 kcal/mole (130). As would be expected, the tendency for cyclic disulfides to undergo nucleophilic scission of the sulfur-sulfur bond increases with decreasing ring size (130). In view of this, it is surprising to find that the most highly strained disulfide,

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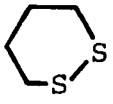

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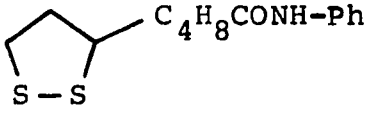

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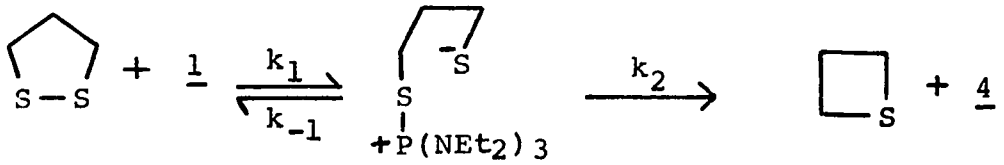
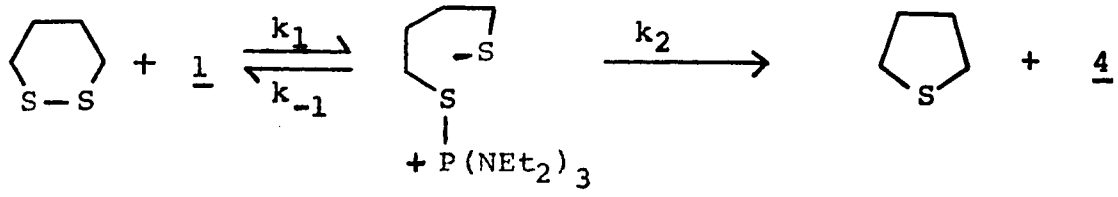
Ring strain	15 kcal	2 kcal	10 kcal
k_r	0.6	1.0	11

1,2-dithiolane (57) reacts the slowest while 1,2-dithiane (49), the least strained, reacts 3 times faster. This difference results from the relative magnitudes of k_1, k_{-1} and k_2. The five membered disulfide is highly strained; hence, ionic scission (k_1) is very rapid. Recyclization of the phosphonium salt to form sulfide (k_2) proceeds via a four centered transition state, a process which would be expected to be slow (161). Reversal to starting materials (k_{-1}), however, proceeds via a five centered transition state. In contrast, disulfide 49





is not highly strained. Therefore k_1, ionic scission, would be slower than for disulfide 57. The reverse of this process (k_{-1}) will be of a comparable rate to that of 57. However, recyclization to afford products (k_2) would proceed through a five-centered transition state as compared to the four-centered transition state of disulfide 57. Cyclization reactions leading to the formation of five-membered rings may occur 10^3-10^5 times faster than the analogous processes forming four-membered rings (162). Thus, for 57, the acceleration due to ring strain is partially counteracted by a decrease in k_2 due to the steric effects of a four-centered transition state. Disulfide 49, however, does not encounter this latter decelerating effect and hence the full effect of ring strain is observed.

The increased reactivity of α-lipoic anilide may be the result of a substituent effect on the recyclization of the intermediate phosphonium salt. It has been observed that the presence of alkyl substituents may aid in cyclization reactions which lead to the formation of 3- and 4-membered rings (161). The origin of this effect, however, is not fully understood (161, 163).

It was noted earlier that the desulfurization of several unsymmetrical disulfides afforded a variety of disulfides and sulfides as products. For example, in the desulfurization of benzyl ethyl disulfide (23), a substantial amount (~20%) of dibenzyl disulfide (2) was observed in the early stages of the reaction. The final products of the reaction were dibenzyl sulfide (3) and diethyl disulfide (7). This result may be rationalized in terms of a series of disulfide equilibration processes (Fig 26).

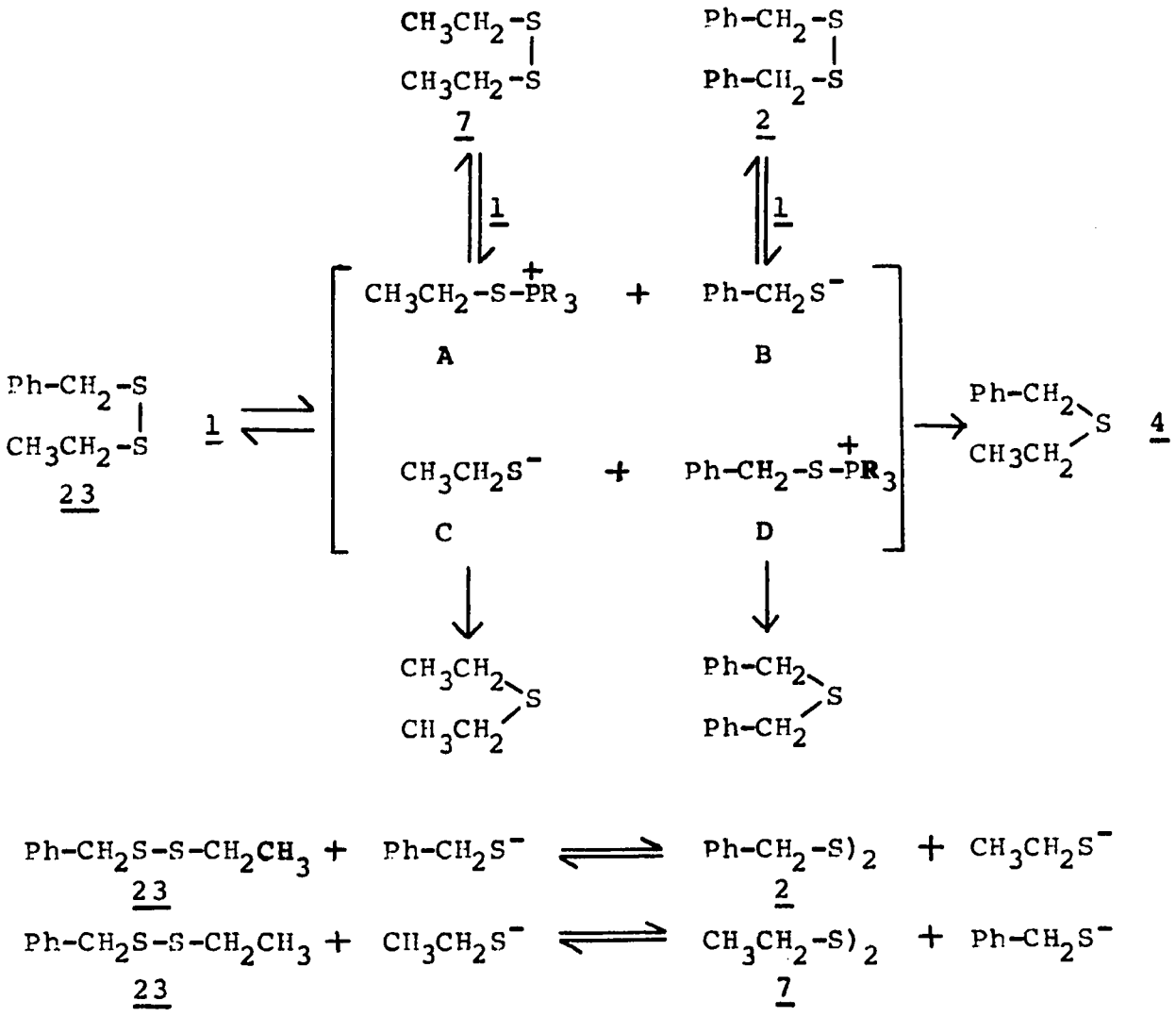


Figure 26. Proposed mechanism for the desulfurization of Benzyl Ethyl Disulfide (23).

A reversable ionic scission of the disulfide bond may occur in the two ways illustrated; recombination of the ions so formed would afford the two symmetrical disulfides. However, the formation of 2 and 7 occurs at a much faster rate than does desulfurization. If this were not so, substantial amounts of diethyl sulfide and benzyl ethyl sulfide should be formed during the reaction. It has been demonstrated by Dalman that the equilibration of disulfides by mercaptides (B or C for example) occurs very rapidly (164). That a similar process may be operative in these desulfurizations was demonstrated in that the reaction of benzyl mercaptide with a mixture of tolyl disulfide (28)

$$(Et_2N)_3\overset{+}{P}\text{-S-CH}_2\text{-Ph}\ BF_4^- \quad (109) \;+\; (CH_3\text{-Ph-S})_2 \quad (28) \xrightarrow{Ph\text{-}CH_2S^-\ \overset{+}{Na}} CH_3\text{-Ph-S-S-CH}_2\text{-Ph} \;+\; Ph\text{-}CH_2S_xCH_2\text{-Ph}\ (x=1,2)$$

and tris(diethylamino)benzylthio-phosphonium fluoroborate (109) afforded benzyl tolyl disulfide as a major reaction product. Hence, the disulfide may effectively compete with a phosphonium salt for the mercaptide ion. Thus, all the equilibria processes outlined in Figure 26 may occur in the desulfurization of disulfides. Since the reaction of 7 with the aminophosphine does not take place to a significant extent under conditions (25°, 18 hr) in which the desulfurization of 2 (and 23) is complete (see Table II, p. 23), the products which would be expected in this reaction are the disulfide 7 and benzyl sulfide 3. These are the products which were observed in the desulfurization experiment.

A similar explanation would account for the products observed in the desulfurization of the peptide 43 (p. 39). The equilibria

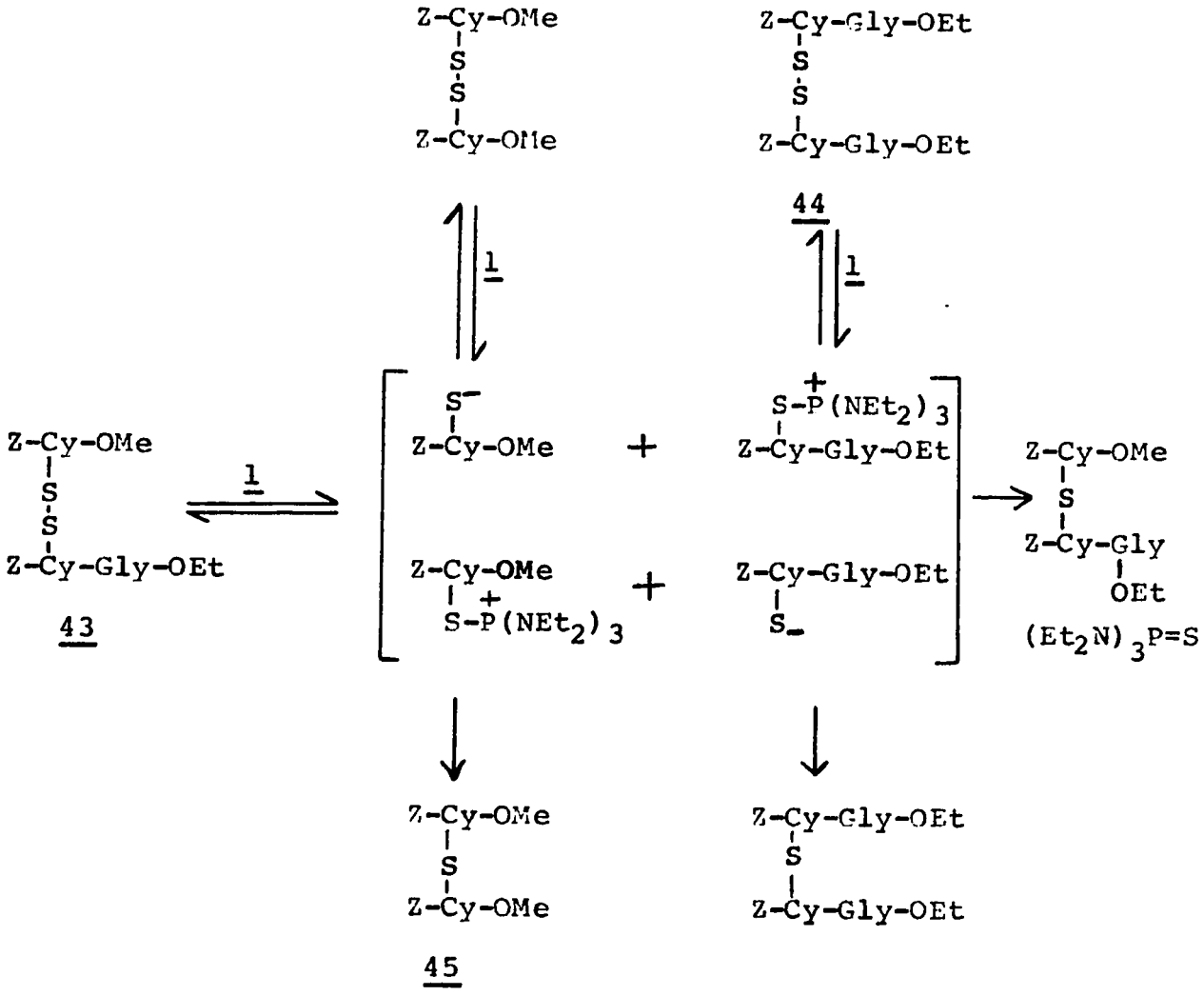


Figure 27. A mechanistic scheme for the desulfurization of Ethyl N,N'-dicarbobenzoxy-O-methyl-L-cystinyl-glycinate (43).

which are implicated in this desulfurization are illustrated in Fig. 27.

Thiolsulfonates and Thiolsulfinates

A major test of a proposed reaction mechanism is in its ability to anticipate the outcome of other analogous reactions. The mechanism which has been forwarded for the desulfurization of disulfides may be summarized: a highly polarizable sulfur-sulfur bond is cleaved by nucleophilic attack of a phosphine on one of the sulfur atoms with a concomitant displacement of

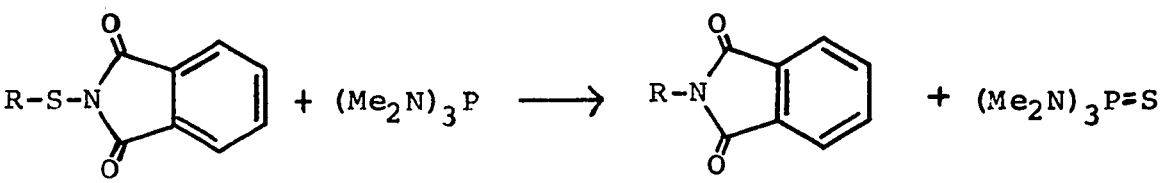
$$R_3P + \overset{R'}{\underset{|}{S}}\text{-S-R}'' \rightleftharpoons \left[R_3\overset{+}{P}\text{-}\overset{R'}{\underset{|}{S}}\ \overset{-}{S}\text{-R}''\right] \longrightarrow R_3P{=}S + R'\text{-S-R}''$$

a relatively acidic anion. The phosphonium salt which is thereby generated decomposes to products via an S_N2 type displacement of phosphine sulfide by this anion. This mechanism would suggest that other sulfenyl compounds which possess a highly polarizable S-X bond and a good potential anion (X^-) be subject to such a desulfurization. Thus, this reaction may be generalized:

$$R\text{-S-X-}R' + (Et_2N)_3P \longrightarrow R\text{-X-}R' + (Et_2N)_3P{=}S$$

$$X = S,\ S_x,\ NR''_2,\ SO,\ SO_2,\ SSO_2,\ O.$$

Several of these sulfenyl derivatives have been subjected to the desulfurization reaction. Sulfenimides readily lose a sulfur atom to the aminophosphine (165). This reaction provides an



alternate route to N-alkyl phthalimides, important intermediates in the Gabriel systhesis of primary amines (166).

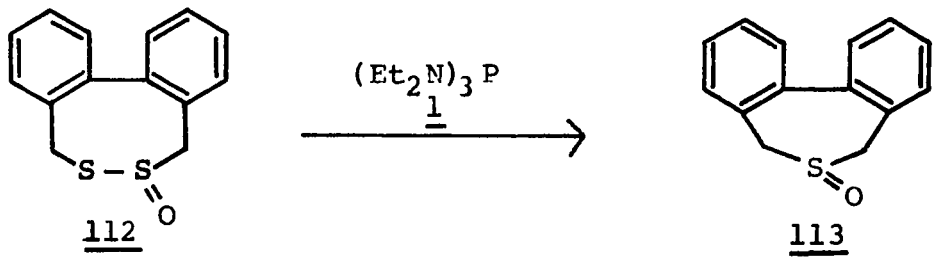
Trisulfides have been shown by Harpp and Ash (167, 168) to undergo desulfurization much more readily than the corresponding disulfides. It has further been demonstrated (168) that, while diphenyl trisulfide (111) loses the central sulfur atom,

$$\underset{\underline{110}}{Ph\text{-}CH_2\text{-}S\text{-}{}^{35}S\text{-}S\text{-}CH_2\text{-}Ph} + \underset{\underline{1}}{(Et_2N)_3P} \longrightarrow Ph\text{-}CH_2\text{-}S\text{-}{}^{35}S\text{-}CH_2\text{-}Ph + \underline{4}$$

$$\underset{\underline{111}}{Ph\text{-}S\text{-}{}^{35}S\text{-}S\text{-}Ph} + \underset{\underline{1}}{(Et_2N)_3P} \longrightarrow Ph\text{-}S\text{-}S\text{-}Ph + (Et_2N)_3P{=}{}^{35}S$$

dibenzyl trisulfide (110) loses a terminal sulfur atom. This mechanistic dichotomy is not fully understood (167, 168).

The desulfurization of thiolsulfinates (R-S-SO-R) has not been studied extensively. That such compounds may be desulfurized by aminophosphines, however, was demonstrated in that 5H,8H-dibenzo[d,f]-1,2-dithiepine-1-oxide (112) afforded the



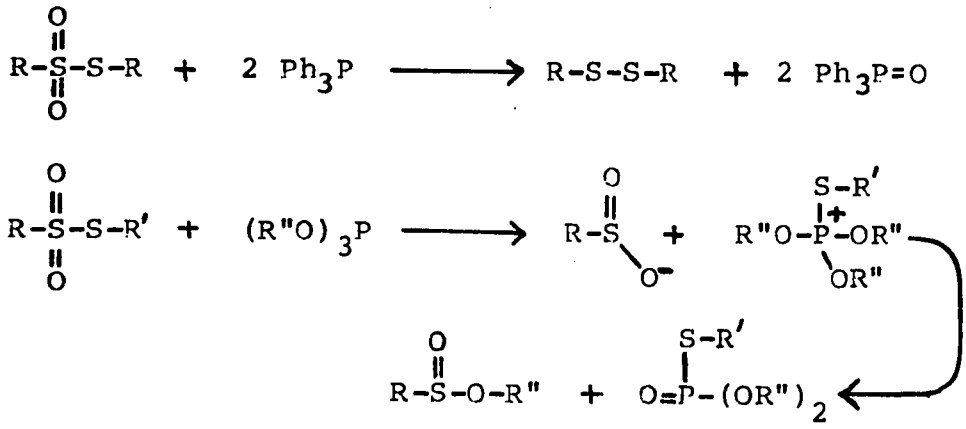
112 113

corresponding sulfoxide (113) in 65% yield on treatment with aminophosphine 1. It has been reported by Carson and Wong (169) that thiolsulfinates do not undergo desulfurization with triphenylphosphine, but rather are reduced to disulfides in high

$$R\text{-}\overset{\overset{O}{\|}}{S}\text{-}S\text{-}R + Ph_3P \longrightarrow R\text{-}S\text{-}S\text{-}R + Ph_3P{=}O$$

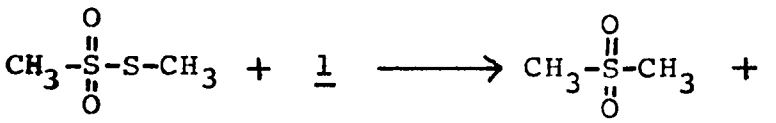
yield. Further work in this area is anticipated.

Thiolsulfonates have been reported to undergo deoxygenation with triphenylphosphine (170) or desulfurization with trialkyl

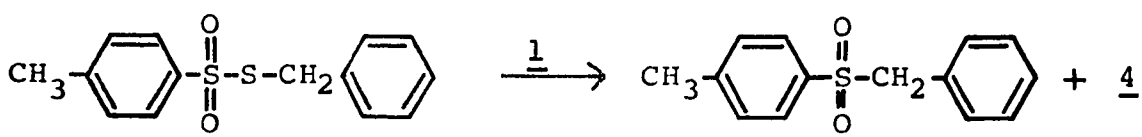


phosphites (171). In this latter case, the sulfinate anion which is formed, may react through oxygen to afford sulfinate esters or through sulfur to afford sulfones. However, only products resulting from O-alkylation in an Arbuzov rearrangement are observed. While the Arbuzov rearangement would not be possible for aminophosphines, both O and S substitution products are possible.

A variety of thiolsulfonates were prepared and subjected to the desulfurization reaction. In most of the reactions, investigated, sulfone was the only product observed (Table XVIII). For example, methyl methanethiolsulfonate (114) and benzyl toluenethiolsulfonate (116) afforded dimethyl sulfone (115) and

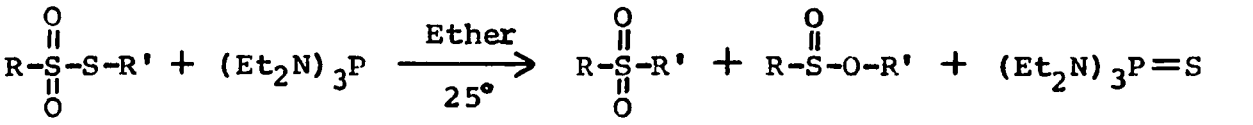


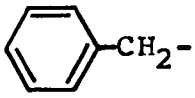
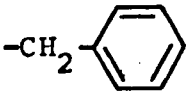
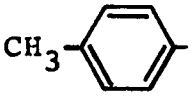
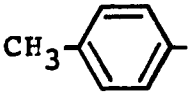
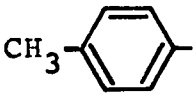
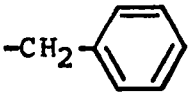
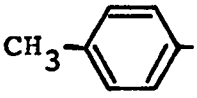
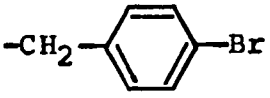
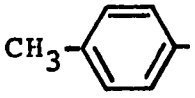
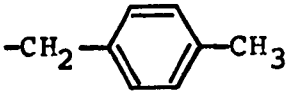
114 115



116 117

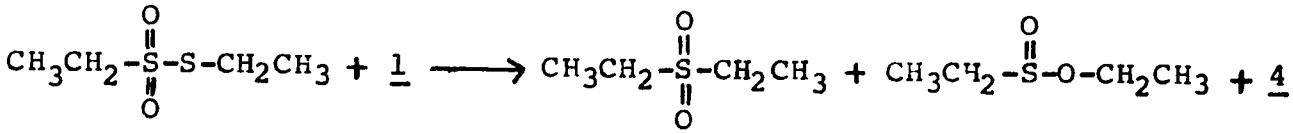
TABLE XVIII



	R	R'	Product Composition[a] R-S(=O)-R'	R-S-O-R'
114	CH_3-	$-CH_3$	100	0
118	C_2H_5-	$-C_2H_5$	66	33
121			100	0
122		$-CH_3$	66	33
123		$-C_2H_5$	61	39
116			100	0
20			100	0
124			100	0

a) Product composition expressed as the sulfone / sulfinate ester ratio of the crude product mixture. In all cases, unless otherwise noted, isolated yields were better than 60%.
b) No products were isolated.

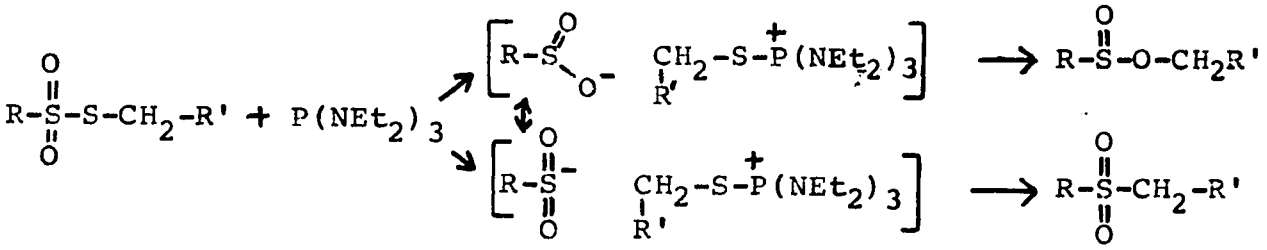
tolyl benzyl sulfone (117) in 80% and 70% yield respectively. In both reactions, the absence of sulfinate ester (R-S(O)-O-R) was demonstrated by vpc. In a few cases, sulfinate esters were observed as minor byproducts (10%-30%) of the desulfurization reaction. For example, ethyl ethanethiolsulfonate (118) afforded both diethyl sulfone (119) (50%) and ethyl ethanesulfinate (120) (15%) on reaction with 1. The results of these



118 119, 50% 120, 15%

desulfurization reactions are summarized in Table XVIII. In all cases, isolated yields were in excess of 65%; where only one product was formed, the absence of sulfinate was demonstrated by vpc analysis of the reaction mixture.

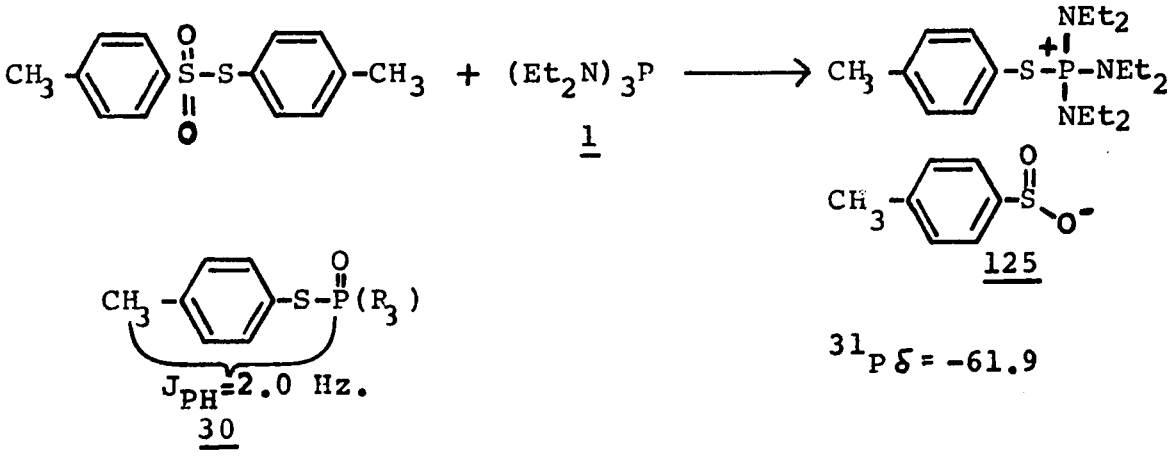
The formation of both sulfone and sulfinate ester during desulfurization is indicative of the formation of the ambident sulfinate anion. The negative charge of this anion would be



expected to reside largely on the more electronegative oxygen atom. It is not uncommon, however, for ambident anions to react through the less electronegative site in bimolecular S_N2 reactions (149). Meek and Fowler (172) have demonstrated that O

and S alkylation of the ambident p-toluenesulfinate anion is very sensitive to the structure of the alkylating agent. It is not possible, however, to make any definite conclusions as to the sulfinate/sulfone ratio since sulfinate esters were observed in only three reactions.

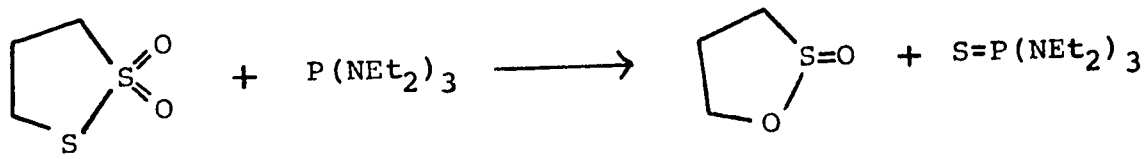
The reaction of diaryl thiolsulfonates are of special interest since neither sulfone nor sulfinate ester may be formed. When the phosphine 1 was added to an ethereal solution of tolyl p-toluenethiolsulfonate, a 1:1 thiolsulfonate-phosphine adduct (125) separated out of the reaction as a viscous, hygroscopic oil. The 60 MHz nmr spectrum of this oil exhibited a singlet



and a doublet (J_{PH} = 2.5 Hz) for the p-tolyl methyl resonances. The doublet results from 7-bond long range coupling with the phosphorus nucleus. Such a coupling has been observed in the spectrum of tri-p-tolylphosphotrithioate (30) and for several other phosphines, phosphine oxides and phosphonium salts (95). The phosphonium salt structure of this adduct was confirmed by ^{31}P nmr spectroscopy in that adduct 125 exhibited a resonance at -61.9 ppm relative to H_3PO_4, consistent with that observed

for other phosphonium salts (see Table IV).

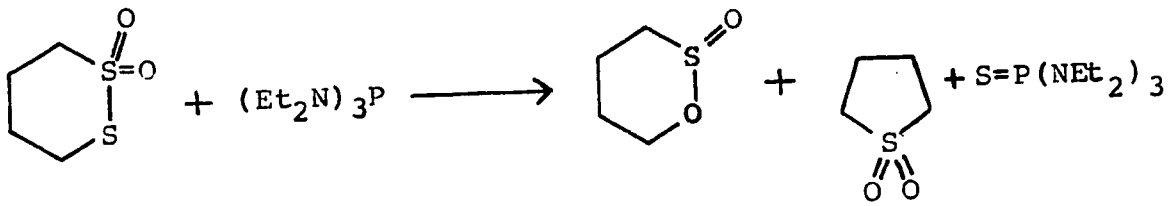
Cyclic thiolsulfonates were subjected to this desulfurization reaction. Here, however, sulfinate esters and not sulfones were the major reaction products (173). Thus, addition of the aminophosphine 1 to a benzene solution of 1,2-dithiolan-1,1-dioxide (126) effected an exothermic reaction which on chromatographic workup, provided 1,2-oxathiolan-2-oxide (127) in 92%



126 1 127 4

yield.

Similarly, the reaction of 1,2-dithian-1,1-dioxide (128) with 1 afforded a mixture consisting of 10% tetrahydrothiophene-



128 129 130

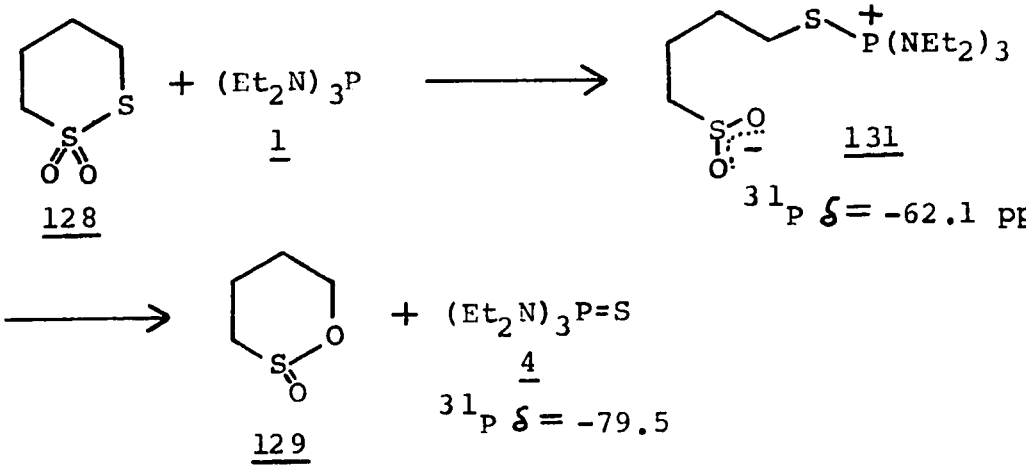
1,1-dioxide (130) and 90% 1,2-oxathian-2-oxide (129). This alicyclic sulfinate ester was subsequently isolated in 62% yield.

Proof of structure of sulfinates 127 and 129 obtained from their ready oxidation by permanganate to the corresponding sultones. The presence of a strong infrared band at 1120 cm^{-1} (-O-SO-) further confirmed the presence of the sulfinate ester

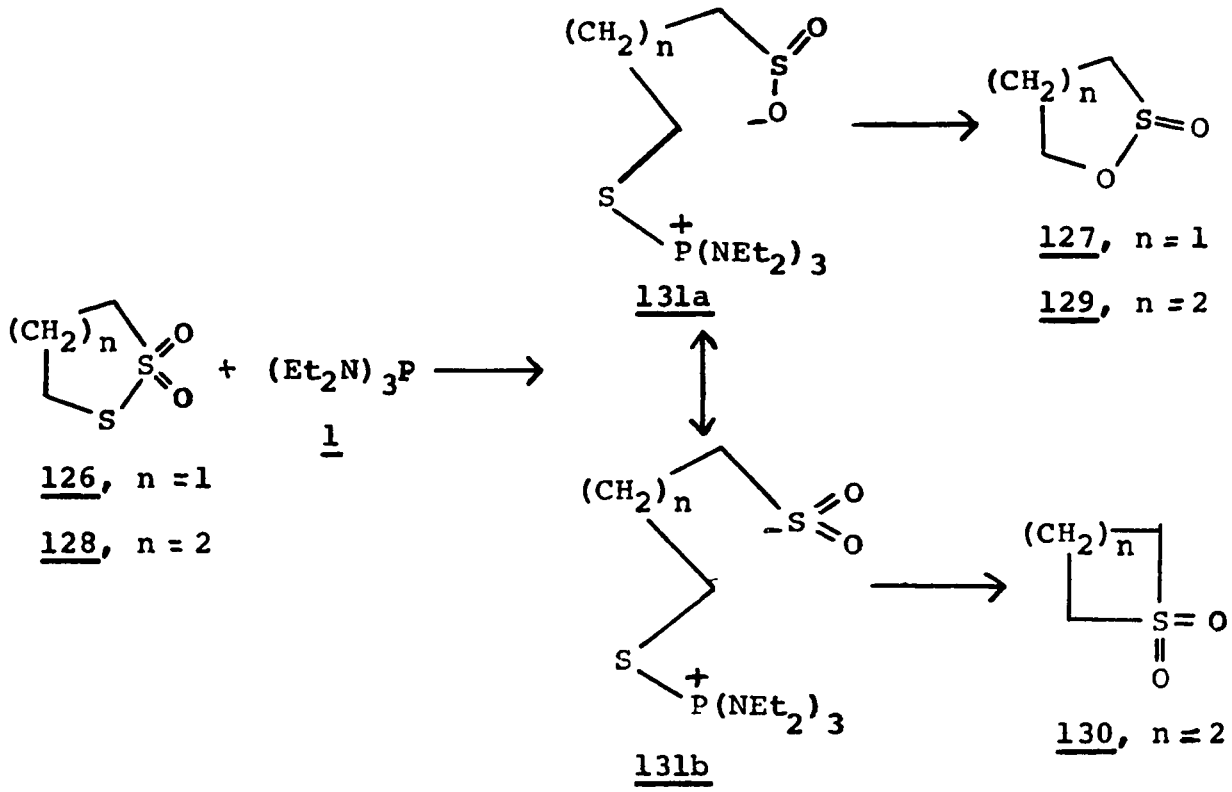
grouping. In addition, the nmr and mass spectra of 127 and 129 were consistent with the proposed structures. The nmr spectrum of 129 was of special interest; it will be discussed later.

Whereas cyclic sulfonic acid esters, sultones, have been studied extensively, cyclic sulfinate esters have remained relatively unknown. They have been synthesized via thermal isomerization of thietane dioxides at 300°-400° (174), controlled chlorine oxidation of mercapto-alcohols (174a) and the action of thionyl chloride on 3-butene-1-ols (175). In all cases, the esters so prepared were highly substituted; the parent members, 127 and 129, of these heterocycles were unknown. Thus, this method appears to be a general approach to the synthesis of these novel heterocycles under exceptionally mild conditions.

The formation of both sulfone 130 and sulfinate 129 during desulfurization of 128 would indicate that the reaction proceeds via an ionic intermediate of the type 131. Such a phosphonium salt was observable in the ^{31}P nmr. Thus, when equimolar amounts of thiolsulfonate 128 and 1 were mixed in an nmr tube, an oil appeared immediately. This oil exhibited a



resonance at -62.1 ppm (relative to H_3PO_4), consistent with a phosphonium salt structure. This signal slowly (5 min.) disappeared and was replaced by a new resonance at -79.5 ppm, consistent with that observed for the aminophosphine sulfide 4, -78.6 ppm (50% benzene solution) (lit. -77.8 ppm (176)). Thus, it may be concluded that a phosphonium salt of the type 131 is formed as an intermediate in this reaction. The preferred

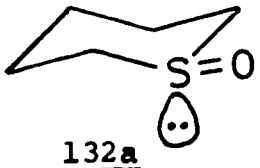


formation of sulfinate may reflect the effect of ring size on the course of reaction.

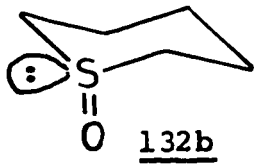
Conformational Preferences of the S=O Group in Cyclic Systems.

The conformational preferences for substituents on cyclohexane ring systems are well studied (178). However, when heteroatoms containing non-bonded lone-pair electrons are

present, conformational preferences may be altered considerably (179). It has been predicted that in the case of thian—1-oxide 132, there should exist a slight preference (0.5 kcal) for



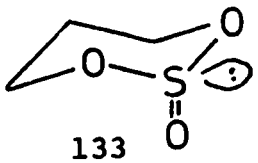
132a



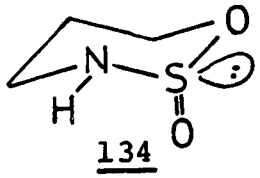
132b

an axial oxygen (180). It has been demonstrated by low temperature nmr that there exists a very small energy difference (0.17 kcal) between the two conformations, although it is not clear which isomer is, in fact, preferred (181).

Whereas the conformational isomers of 132 may only be observed at -70° in the nmr (181), propylene sulfite (133) exists at room temperature only as the isomer in which the S=O oxygen is axial (182); the conformational energy of this



133

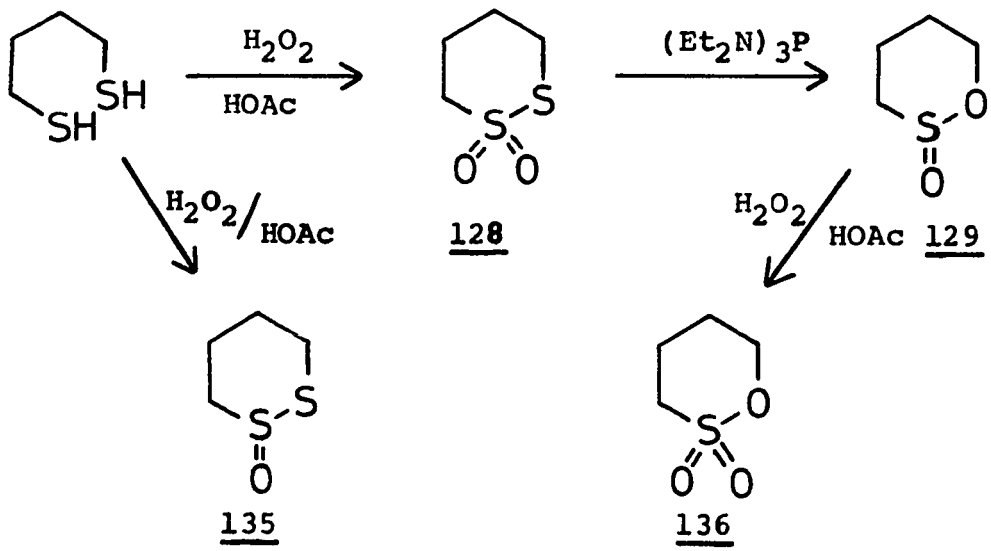


134

system has been estimated at 3.75 kcal/mole (183). This strong preference for a sulfoxide oxygen to take an axial position is also observed for 1,2,3-oxathiazine-2-oxide (134)(184). These observations are surprising since one would expect that the conformational energy of 133 and 134 should be less than 132 and not greater. The substitution of a heteroatom for a methylene group in cyclohexane should lower the barrier to chair-chair interconversion by reducing 1-2 rotational interactions (185). Moreover, Eliel (179a) has demonstrated that sulfur (and

presumably oxygen as well) with its lone pairs has a smaller space requirement than a methylene group. No satisfactory explanation has been advanced for this unusual, high conformational preference. It was felt that further insight might be gained by an analysis of other similar heterocycles.

Simple syntheses of some missing members of this series, 1,2-dithiane-1,1-dioxide (128), 1,2-oxathian-2-oxide (129), its thio analog, 1,2-dithian-1-oxide (135), and 1,2-oxathian-2,2-dioxide (136), have been developed (173) and a detailed analysis has been undertaken of the nmr spectra of these



compounds to further investigate this conformational preference.

The low temperature nmr spectra of both sultone 136 and thiosultone 128 indicated that these compounds are undergoing very rapid chair-chair interconversion as low as -90°. This was evidenced by the observation of triplets at 5.50τ and 6.87τ (J = 5 and 5.5 Hz.) for 136 and 3.02τ and 6.85τ (J=2.0 and 3.5 Hz.) for 128 in spectra which were invarient over the temperature range of -90° to +30° C. In contrast, the conformational isomers

98

of thian-1,1-dioxide 98 are observable at -60° (181). The second heteroatom, as expected, significantly lowers the barrier to chair-chair interconversion.

The spectrum of 1,2-dithian-1-oxide (135) (Fig. 28) was extremely complex; however, irradiation of the high field multiplet caused the collapse of the low field lines to two AB quartets thus indicating the non-equivalence of the pairs of protons α to the S and S=O groups. While it was not possible to definitively assign the conformation of the S=O bond in this molecule, clearly, this ring is not undergoing interconversion.

The nmr (100 MHz.) spectrum of 1,2-oxathian-2-oxide (129) (Fig. 29) was interpretable only in terms of a single conformational isomer. The multiplet at 5.58τ may be assigned to the axial proton H_1 adjacent to the ring oxygen on the basis of the observed 11.5 Hz. coupling which is consistent with a trans-diaxial coupling to the adjacent protons (186). The multiplet at 6.28τ was assigned to the corresponding equatorial proton H_2. This assignment was confirmed by double resonance. Similarly, the multiplet at 7.13τ was assigned to the axial proton H_3.

This interpretation has placed both axial protons H_1 and H_3 to low field relative to their equatorial counterparts H_2

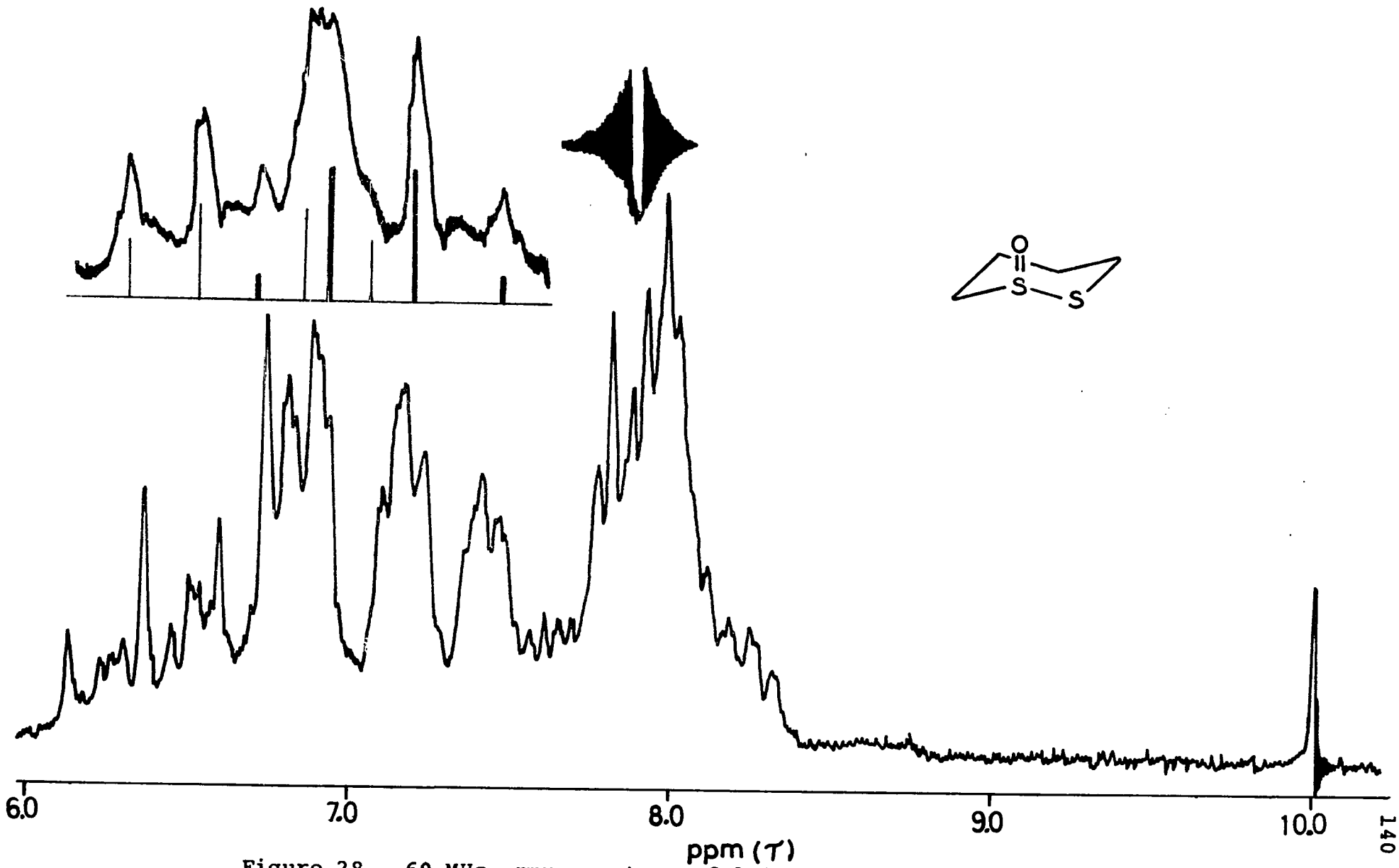


Figure 28. 60 MHz. nmr spectrum of 1,2-Dithian-1-oxide (135).

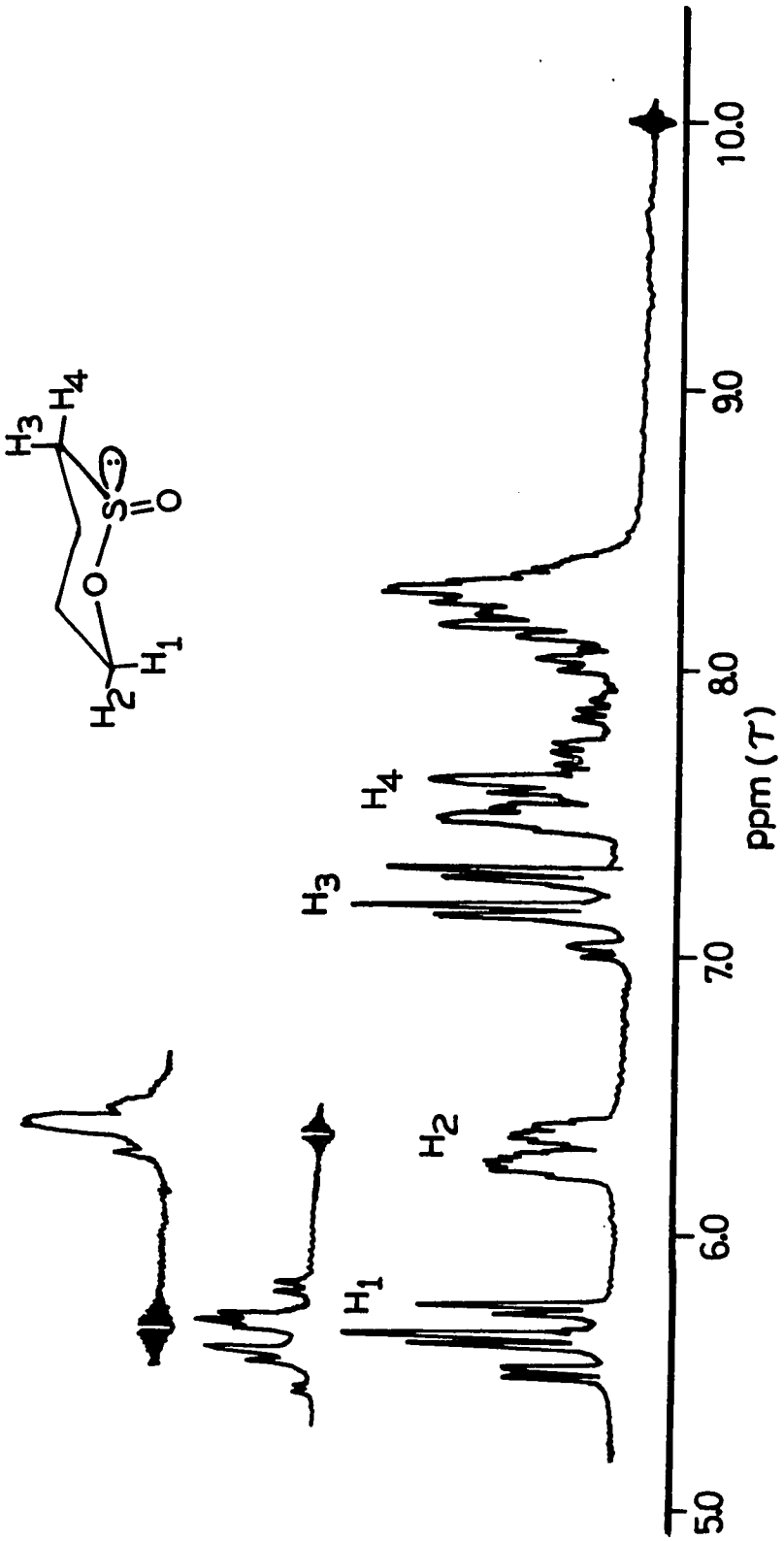
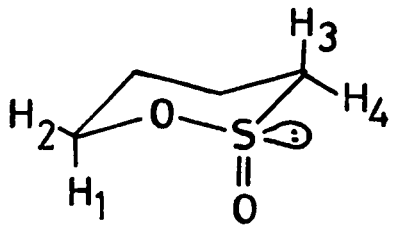


Figure 29. 100 MHz. nmr spectrum of 1,2-Oxathian-2-oxide (129).

and H_4. In alicyclic systems, axial protons are normally displaced to high field relative to equatorial protons (187). Previous studies have shown that protons in a 1,3 diaxial relationship to a sulfinyl oxygen experience a deshielding effect (188,189,190,191,192), the so-called syn-axial effect, (191,189c) due to a proximity effect (191,193) and/or an acetylene-like anisotropy (191,192,194) of the S=O bond. Thus, the deshielding of H_1 relative to H_2 would imply that H_1 is in a 1,3 cis-diaxial relationship to the S=O bond as illustrated below. In addition, the deshielding of proton



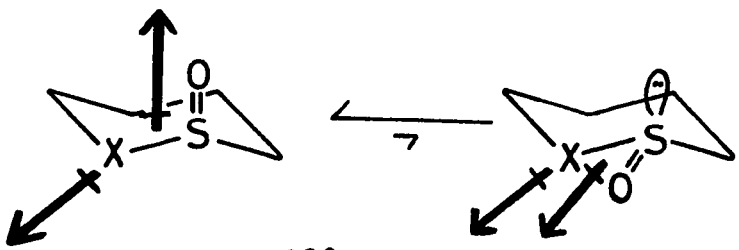
129a

H_3 relative to H_4 is consistent with that observed for other sulfoxide systems (195). This deshielding of H_3 relative to H_4 is not, however, consistent with the assumed acetylenic anisotropy of the S=O bond (192) (vide infra.).

Since the nmr spectra of both 129 and 135 are unchanged over a wide temperature range (-90° to +150°), it may be concluded that both these compounds are conformationally pure. Thus, 129 (and presumably 135) adopt the same axial sulfoxide conformation as do the sulfites. Since only one isomer is observed at room temperature for sulfite 133, the oxides of 1,2-oxathiane 129 , 1,2,3-oxathiazine 134, and 1,2-dithiane 135

under conditions where less than 5% of the minor isomer would be detectable, a conformational barrier in excess of 2 kcal/mole exists for these compounds. This is more than 1.8 kcal greater than the barrier observed for sulfoxide 132.

This strong preference for an axial S=O configuration may result from a dipolar interaction analogous to the anomeric effect observed in carbohydrate systems (196). The conformation in which the S=O bond is in an equatorial position possesses an unfavorable dipolar arrangement, since the net dipole resulting from the non-bonded lone pair electrons of oxygen is nearly parallel to that of the S=O bond. This unfavorable arrangement

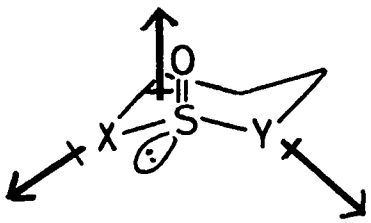


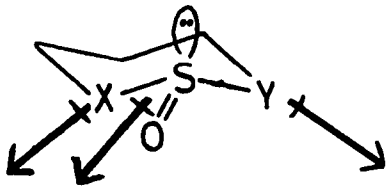
129, X=O

135, X=S

is relieved with the S=O bond adopting an axial configuration. Such a dipolar effect has been used to explain the conformational preference (0.5 kcal) of the trans diaxial conformation of trans-1,2-dibromocyclohexane over the corresponding diequatorial isomer (197). For methyl glycosides, the dipolar or anomeric effect is approximately 1.5 kcal (198); for a highly polar group such as a sulfoxide, this effect should be even greater.

A similar argument may be advanced for the conformational preference of an axial S=O bond in the sulfite 133, and the oxathiazine oxide 134. Thus, in all of these cases (133, 134, 126, 135), the sulfoxide bond is adjacent to at least one





133, X=Y=O

134, X=O, Y=NH

heteroatom bearing lone pair electrons and therefore should experience an electrostatic dipole repulsion when the S=O bond is in an equatorial conformation.

Anisotropy of the S=O Bond.

The unusual 1,3-diaxial deshielding effect of an S=O bond has been attributed to an acetylene-like anisotropy of the S=O bond (189a, 191, 192). While the deshielding effect is well established (188,189,190,191,192), the validity of the acetylene-like anisotropy approximation may be questioned. For a bond which electronically exhibits cylindrical symmetry about the bond axis, the McConnell point dipole approximation (199) (eq. 13) may be used to calculate the sign and magnitude of the nuclear screening of a proton in a given spatial position by a sulfoxide group where R=the distance between the proton

$$\sigma = \Delta X \left(\frac{1-3\cos^2\theta}{3R^3}\right) \qquad \text{eq. 13}$$

under consideration and the electrical center of gravity of the anisotropic bond[16], θ = the angle between the direction of

[16]The electrical center of gravity of the S=O bond is assumed to be the midpoint of the bond (192).

R and the symmetry axis of the anisotropic bond, and ΔX = a constant characteristic of the bond under consideration. This approximation has been used to explain the 1,3 syn-axial deshielding in sulfites (192) and sulfoxides (194). Utilizing the chemical shift difference of one of the pairs of protons of the molecule to calculate the required constant ΔX should allow the prediction of the effect of this anisotropy at any other point in the molecule. Using the appropriate parameters for protons H_1 and H_2, the anisotropy constant ΔX was calculated for the S=O bond in 1,2-oxathian-2-oxide 129a to be -22.6×10^{-30} $cm^3 molecule^{-1}$. This value is in good agreement with that calculated for an S=O bond in sulfites((192) and for acetylenes (194).

However, using this constant to calculate the effect of this acetylene-like anisotropy on the chemical shifts of protons H_3 and H_4 results in the prediction that the signal for H_3 should occur 0.66 ppm upfield from H_4. Such is not the case; the resonance for H_3 is 0.4 ppm downfield from H_4. Clearly, the acetylene approximation for the an S=O bond anisotropy is inadequate. The shift difference of -0.4 ppm is much closer to that which would be expected if the S=O bond anisotropy resembled a carbonyl bond and not an acetylene bond, an assumption for which there is some precedent (195). Thus, it is felt that this syn-axial effect is a proximity effect, while, at least for these molecules, the anisotropy of the S=O bond more resembles that of a carbonyl bond.

CONCLUSIONS AND CLAIMS TO ORIGINAL WORK

Thus, it has been demonstrated that tris(diethylamino) phosphine (as well as other aminophosphines) reacts with a wide variety of organic disulfides to afford the corresponding thioethers in high yield . This reaction was shown to be compatible with a wide variety of commonly encountered functional groups, and, in large part, free of side reactions. The reaction was demonstrated to be applicable to the desulfurization of alkyl, aralkyl and cyclic disulfides and thus provides a new general approach to the synthesis of organic thioethers. This reaction has a particularly noteworthy application in the synthesis of thioethers analogous to naturally occurring amino acid and peptide disulfides.

The desulfurization reaction was shown to be a general reaction applicable to a wide variety of organic sulfur compounds including sulfenate esters, sulfenimides, tri- and polysulfides, thiolsulfinates and thiolsulfonates. In the latter case, cyclic thiolsulfonates react with aminophosphines to afford cyclic sulfinate esters. This reaction provides a new general approach to the synthesis of these novel heterocycles. The conformational preference of an S=O bond for an axial configuration was discussed in terms of an electrostatic dipolar repulsion between the polar S=O bond and adjacent nonbonded lone pair electrons.

All of the desulfurization reactions investigated were found to proceed via a common intermediate phosphonium salt. Although this intermediate was never isolated and characterized, it was observed by ^{31}P nmr in several experiments. For disulfides, the formation of this intermediate by nucleophilic scission of the polarizable sulfur-sulfur bond by the aminophosphine was shown to be rate limiting. This salt decomposes in an S_N2 process to afford products. The stereochemistry of the reaction involves inversion of configuration at one of the carbon atoms α to the disulfide group.

Several findings encountered during the course of this investigation are worthy of special note. N-Bromosuccinimide was found to be an excellent reagent for the α bromination of acid halides. This process was found to be applicable to a wide variety of primary and secondary acids as well as diacids (see Appendix III for details of this reaction) and is therefore a new competitive general method for the synthesis of α bromo acid derivatives.

The use of iodine/triethylamine in a new modified procedure for the oxidation of propan-1,3-dithiols was found to be an excellent method of preparing 1,2-dithiolanes in high yield with minimal polymerization.

The mass spectra of a variety of sulfides and disulfides were compared and the difference interpreted in terms of the differences in electron donor ability between these groupings as well as the stability of the various sulfur radicals.

EXPERIMENTAL

EXPERIMENTAL

Common intermediates were obtained from commercial sources and were purified as necessary. Melting points were obtained on a Gallenkamp melting point apparatus and are corrected.

Infrared spectra were recorded on a Perkin-Elmer Infracord (Model 137) Spectrophotometer or a Perkin-Elmer Model 257 or Model 337 Grating Infrared Spectrophotometer. Spectra were calibrated with the 1602 cm^{-1} band of a polystyrene film reference. Refractive indices were measured on a Carl Zeiss 28241 Refractometer at 25°. A Unicam SP-800 ultraviolet spectrophotometer was used for routine spectra. For kinetic measurements, a Coleman 124 spectrophotometer equipped with a Coleman 165 recorder and a Neslab Constant Temperature Regulator was employed.

Nuclear magnetic resonance (nmr) spectra were recorded on Varian Associates A-60, HA-100 or T-60 spectrophotometers; ^{31}P nmr spectra were measured by Professor D.F.R. Gilson on a Varian Associates DP-60 spectrophotometer at an oscilator frequency of 19.3 MHz. All proton spectra are reported in tau (τ) units relative to tetramethylsilane (TMS); ^{31}P spectra were measured relative to 85% phosphoric acid. Abbreviations used in reporting of nmr spectra are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad; sh, shoulder.

Mass spectra were recorded on an AEI-MS-902 Mass Spectrometer equipped with a direct insertion probe. Spectra are reported in order of decreasing intensity.

Gas chromatographic (vpc) analyses were performed on an F & M Model 5750 Research Chromatograph equipped with a Perkin-Elmer Model 194B Printing Integrator. Three 6' x 1/8" stainless steel columns were used: 10% diethylene glycol succinate on Chromasorb W/AW-MCDS (LAC column), 10% silicone gum rubber UCC-W98 on Diatoport-S (UC-W98 column), and 10% Apiezon-L on Chromasorb W/AW-MCDS (Apiezon-L column). The LAC column was used extensively for kinetic experiments as was a Bronwill Thermomix constant temperature circulator.

Organic microanalyses were performed by Scandanavian Microanalytical Laboratories, Herlev, Denmark, and Organic Microanalyses (Dr. C. Daessle), Montreal, Canada.

Tris(diethylamino)phosphine (1) The proceedure used was a modification of the method of Mark (70). Thus, a solution of 43.0 g (3.4 mmol) of phosphorus trichloride in 3 l of anhydrous ether was flushed with nitrogen and cooled to 10°; 150 g (2.06 mmol) of diethylamine was added dropwise with vigorous stirring over 2 hours. The resulting suspension was stirred overnight, then refluxed for 0.5 hour. After cooling, the mixture was filtered and the filtrate evaporated to dryness. The residue was dissolved in 200 ml of hexane, treated with charcoal, and the hexane removed in vacuum. The resulting oil was fractionated in vacuum to afford 50.2 g (65%) of (1), bp (0.5 mm) 80-84°; n_D^{25} 1.469 (lit. n_D^{30} 1.465 (72)).

Benzyl Disulfide (2) (Fisher Scientific Co. Ltd.) was recrystalized from ethanol; mp 71-72° (lit. mp 71.5° (200)).

Amyl disulfide (5). was prepared by the procedure of Miller (201); n_D^{25} 1.485 (lit. n_D^{20} 1.488 (201)).

Ethyl disulfide (7), i-Propyl disulfide (8) and t-Butyl disulifde(9) (Aldrich Chem. Co.,Inc.) were redistilled before use.

Dicarbomethoxymethyl disulfide (14). To a solution of 25.0 g (99 mmol) of iodine and 50.0 g (336 mmol) of sodium iodide in 200 ml of water was added slowly 20.0 g (194 mmol) of carbomethoxymethanethiol. After stirring for 1 hour, the mixture was decolorized with sodium thiosulfate and extracted with chloroform. The extract was washed well with water, dried and the solvent removed in vacuum to afford a colorless oil. Distillation in vacuum yielded 10.5 g (53%) of 14, bp (0.5 mm) 104-106°; ir (film) 1730 cm^{-1} (C=O); n_D^{25} 1.512 (lit. n_D^{25} 1.511 (202)).

β-D-Glucopyranosyl disulfide octa-O-acetate (25) was prepared in 82% yield from sodium 1-thio-β-D-glucose[1] by the proceedure of Youngs and Perlin (203); mp 143-144° (lit. mp 145-146° (203)).

p-Tolyl disulfide (28) was prepared from 12.4 g (100 mmol) of p-toluenethiol and 19.5 g (250 mmol) of dimethyl sulfoxide according to the method described by Wallace (78); mp 46-48° (lit. mp 46°(204)).

Bis-N,N'-dimethylaminophenyl disulfide (27). To a solution of 3.0 g (25 mmol) of p-aminothiophenol in 10 ml of methanol was added 3.1 g (12.4 mmol) of iodine. After stirring 10 minutes, the mixture was diluted with water, neutralized with sodium

[1] The generous gift of this compound from Prof. A.S. Perlin is gratefully acknowledged.

carbonate and extracted with ether. The ether extract was dried and the solvent removed in vacuum. The residue was dissolved in 20 ml of N,N-dimethylformamide and 20 ml of ethanol and 8.0 g (57 mmol) of methyl iodide was added. After refluxing the mixture for three hours, 200 ml of water was added, the mixture neutralized with sodium carbonate and extracted with ether. Evaporation of the ether in vacuum and crystalization of the residue twice from ethanol afforded 0.7 g (10%) of 27, mp 116-117°(lit. mp 118°(205)).

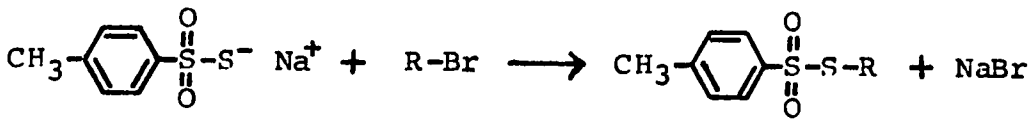
Di-2-benzothiazole disulfide (31) (Baker Chemical Co.) was recrystallized from benzene before use; mp 177-179°(lit mp.180° (206)).

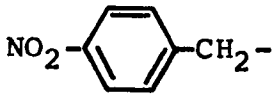
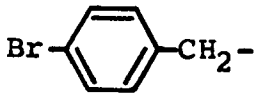
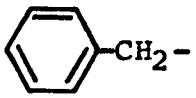
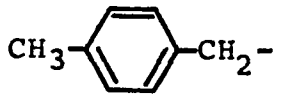
Di-2-pyridyl disulfide (34). A solution of 6.6 g (60 mmol) of 2-pyridinethiol in 50 ml of methanol was added to a solution of 7.5 g (30 mmol) of iodine in 50 ml of methanol. The solution was diluted with 500 ml of water. On neutralization with sodium bicarbonate, the crude disulfide precipitated. Crystallization of the crude material provided 4.5 g (68%) of 34 as colorless crystals, mp 60-62°(lit. mp 57-58°(207)).

Alkyl p-toluenethiolsulfonates were prepared by the proceedure described by Boldryev (88). A solution of equimolar quantities of potassium p-toluenethiolsulfonate (208) and alkyl halide in ethanol was refluxed 3-6 hours. The reaction was diluted with water and extracted with chloroform. The extract was dried and evaporated to dryness. The residue was crystallized from ethanol or distilled as appropriate. The alkyl p-toluenethiolsulfonates so prepared are summarized in Table XIX.

TABLE XIX

PREPARATION OF ALKYL p-TOLUENETHIOLSULFONATES



Thiolsulfonate	R	% Yield	mp	bp/mm
16		74[a]	120-123°	-
20		79[b]	84-85.5°	-
116		75	55-57°	-
122	CH_3-	23	55-57°	-
123	CH_3CH_2-	67	-	105°/0.5
124		60[c]	53-54°	-

a) Anal. Calcd. for $C_{14}H_{13}NO_4S_2$: C, 52.01; H, 4.05; N, 4.34; S, 19.82. Found: C, 52.14; H, 3.87; N, 4.27; S, 19.85.

b) Anal. Calcd, for $C_{14}H_{13}BrO_2S_2$: C, 47.06; H, 3.67; S, 17.95. Found: C, 47.04; H, 3.76; S, 17.79.

c) Anal. Calcd. for $C_{15}H_{13}O_2S_2$: C, 61.63; H, 5.51; S, 21.94. Found: C, 61.35; H, 5.45; S, 21.77.

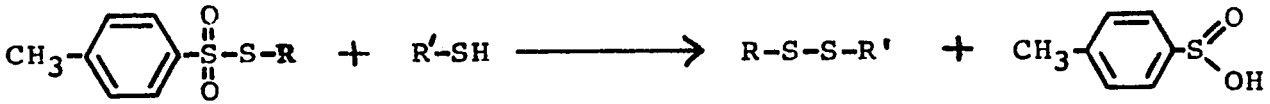
Preparation of Unsymmetrical Disulfides via Thiolsulfonates. An ethanol solution of equimolar quantities of the requisite thiolsulfonate (vide supra) and thiol was refluxed for 4-6 hours. The disulfide crystallized upon cooling the reaction mixture. The crude disulfide was collected by filtration and recrystallized from ethanol or hexane to afford pure product. The disulfides prepared by this method are summarized in Table XX.

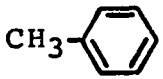
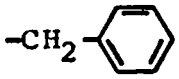
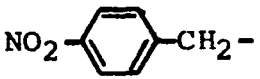
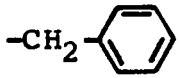
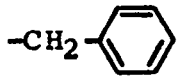
Benzyl ethyl disulfide (23). A solution of 0.10 mole of thiocyanogen in 500 ml ether was prepared as described by Hiskey (86). This solution was cooled to 0° and 12.4 g (0.10 mole) of α-toluenethiol in 200 ml of ether was added dropwise over a period of 2 hours. A solution of 6.2 g (0.10 mole) of ethanethiol in 200 ml of ether was then added slowly. After stirring for 1 hour, the mixture was filtered and the filtrate washed alternately with 100 ml of a 0.5% solution of sodium bicarbonate and 100 ml of water until a negative ferric chloride test for thiocyanic acid was obtained. The ether solution was dried and the solvent removed in vacuum to afford an oil which on distillation yielded 9.0 g (48%) of benzyl ethyl disulfide (23) as a colorless oil, bp (0.3 mm) 70-74°; n_D^{25} 1.585 (lit. n_D^{25} 1.582 (209)).

Benzyl tolyl disulfide (12) was prepared by the same method described above for benzyl ethyl disulfide (23). Thus, 53 mmoles of thiocyanogen, 5.4 g (42.5 mmol) of p-toluenethiol and 5.4 g (42.5 mmol) of α-toluenethiol afforded, after chromatographic

TABLE XX

UNSYMMETRICAL DISULFIDES PREPARED VIA THIOLSULFONATES



Disulfide	R	R'	% Yield	mp
12			74	34-36°
17			35[a]	53-54°
19			58[b]	54-55°

a) Anal. Calcd. for $C_{14}H_{13}NO_2S_2$: C, 57.71; H, 4.50; N, 4.81; S, 22.01. Found: C, 58.07; H, 4.43; N, 4.54; S, 21.90.

b) Anal. Calcd. for $C_{14}H_{13}BrS_2$: C, 51.66; H, 4.02; S, 19.71. Found: C, 51.64; H, 3.80; S, 19.90.

workup (silica gel, 9:1 hexane-dichloromethane) and crystallization (methanol), 3.0 g (28%) of benzyl tolyl disulfide (12) as colorless crystals, mp 36-37.5° (lit. mp 34-35° (210)).

Phenyl methyl disulfide (10) (Aldrich Chem. Corp.) was redistilled prior to use; bp (9 mm) 73-74°; n_D^{25} 1.618 (lit. bp (7 mm) 96°; n_D^{25} 1.161 (61)).

Desulfurization of benzyl disulfide (2). A solution of 3.69 g (15 mmol) of benzyl disulfide and 4.40 g (18 mmol) of tris(diethylamino)phosphine (1) in 20 ml of dry benzene was refluxed for 4 hours; the solvent was removed under vacuum and the residue chromatographed over a silica gel column. Elution with an 8:2 hexane-chloroform mixture afforded a colorless oil which crystallized on standing to yield 2.95 g (92%) of benzyl sulfide (3) as colorless crystals, mp 50° (lit. mp 50° (211)), which did not depress the melting point of an authentic sample and was identical in all respects (ir, nmr, vpc (3 columns), tlc, mp) to the authentic sulfide.

Further elution of the column with chloroform afforded 4.3 g (104%) of crude aminophosphine sulfide 4 which was identical (vpc, ir) to an authentic sample prepared by the procedure of Steube and Lankelma (134).

Desulfurization of 2 with the aminophosphine 1 at room temperature for 18 hours afforded, after a similar isolation procedure, an 85% yield of 3, mp 49-51°.

Desulfurization of Amyl disulfide (5). A solution of 2.08 g (10 mmol) of diamyl disulfide (5) and 2.8 g (11 mmol) of 1 in

5 ml of benzene was refluxed for 18 hours under nitrogen. The solvent was removed in vacuum and the residue distilled to afford 1.0 g (58%) of diamyl sulfide (6), bp (0.5 mm) 74°; n_D^{25} 1.459 (lit. n_D^{25} 1.456 (212)). This product was identical in vpc retention time (UC-W98) to an authentic sample prepared by the method described by Vogel (213).

Desulfurization of diethyl disulfide (7).

a) in benzene solution. A solution of 1.22 g (10 mmol) of diethyl disulfide (7) and 2.75 g (11 mmol) of tris(diethylamino) phosphine (1) in 5 ml of dry benzene was refluxed for 48 hours in a nitrogen atmosphere. Analysis (vpc) by peak height of the reaction mixture indicated that 75% conversion of the phosphine 1 to phosphine sulfide 4 had occurred. No products were isolated from the reaction.

b) in neat 1 at 80°. A mixture of 0.0483 g (0.396 mmol) of diethyl disulfide, 0.0292 g (0.157 mmol) of diphenyl sulfide (added as a standard) and 0.8161 g (3.50 mmol) of tris(diethylamino)phosphine 1 was heated under nitrogen for 22.5 hours at 80°. Quantitative vpc analysis (see Appendix I) indicated that 0.307 mmol (78%) of tris(diethylamino)phosphine sulfide (4) had been formed.

c) in neat 1 at 90°, isolation of diethyl sulfone. A mixture of 1.2 g (10 mmol) of 7 and 5.0 g (20 mmol) of 1 was heated under nitrogen for 18 hours at 90°. Vpc analysis showed the reaction to be complete. The mixture was diluted with 50 ml of a 7% solution of hydrogen peroxide in acetic acid. After

stirring overnight, the mixture was evaporated to dryness, neutralized with aqueous sodium carbonate and the mixture re-evaporated in dryness to afford a crystalline mass. This material was extracted in a soxlet apparatus with benzene for 12 hours. The benzene extract was evaporated to dryness and the residue crystallized from hexane to yield 200 mg (17%) of diethyl sulfone as colorless crystals, mp 72-73° (lit. mp 73- 74° (214)).

Desulfurization of i-propyl disulfide (8).

a) in benzene solution. In an identical experiment to that described for diethyl disulfide (above), a 50% conversion of the aminophosphine 1 to the phosphine sulfide 4 was observed upon refluxing 1.50 g (10 mmol) of i-propyl disulfide (8) with 2.75 g (11 mmol) of 1 in 10 ml of benzene for 48 hours.

b) in neat 1 at 80°. A mixture of 0.0553 g (0.369 mmol) of i-propyl disulfide, 0.0284 g (0.153 mmol) of diphenyl sulfide (added as a standard), and 0.8161 g (3.50 mmol) of tris(diethylamino)phosphine (1) was heated under nitrogen for 22.5 hours at 80°. Quantitative vpc analysis (Appendix I) indicated that 0.157 mmol (43%) of tris(diethylamino)phosphine sulfide (4) had been formed.

Attempted desulfurization of t-butyl disulfide (9).

a) in benzene solution. A solution of 1.78 g (10 mmol) of t-butyl disulfide (9) and 2.50 g (10 mmol) of tris(diethylamino)phosphine (1) in 10 ml of benzene was refluxed under nitrogen for 4 days. No phosphine sulfide 4 was formed during this period as determined by vpc.

b) in neat 1 at 80°. A mixture of 0.0699 g (0.393 mmol) of 9, 0.0288 g (0.155 mmol) of diphenyl sulfide (added as a standard) and 0.8289 g (3.31 mmol) of 1 was heated under nitrogen for 22.5 hours. No phosphine sulfide (4) was detected in the reaction mixture.

Desulfurization of Methyl Phenyl Disulfide (10). A solution of 4.72 g (30 mmol) of phenyl methyl disulfide (10) in 20 ml benzene was cooled in an ice bath and 11.2 g (45 mmol) of tris(diethylamino)phosphine (1) was slowly added. An exothermic reaction occurred and after 2 minutes at 10°, no disulfide was detected on the gas chromatograph (Silicone rubber UC-W-98 at 150-200°). The solvent was removed under vacuum and the residue fractionally distilled to yield 4.1 g (86%) of phenyl methyl sulfide (11), bp (0.5 mm) 36-37°; n_D^{25} 1.582 (lit. n_D^{25} 1.583 (215)), identical in the ir spectrum and vpc retention time to an authentic sample of this sulfide, and a second fraction, 7.5 g (70%) of tris(diethylamino)phosphine sulfide (4), bp (0.5 mm) 123-125°, identical (ir) to an authentic sample.

Desulfurization of Benzyl Tolyl Disulfide (12): To a solution of 3.75 g (15.2 mmol) of benzyl tolyl disulfide (12) in 10 ml of benzene was added slowly 4.29 g (17 mmol) of tris(diethylamino)phosphine (1). When the exothermic reaction ceased (about 5 minutes), the solvent was removed under vacuum and the residue applied to a silica gel column. Elution of the column with a 8:2 hexane-chloroform mixture afforded a color-

less oil which after crystallization from petroleum ether (bp 30-60°) provided 2.8 g (86%) of benzyl tolyl sulfide as white crystals, mp 44.5-46° (lit. mp 46° (216)); nmr (CCl_4) 2.80τ (s, 5H), 2.85τ (q, 4H), 6.18τ (s, 2H), 7.76τ (s, 3H).

Dicarbomethoxymethyl Sulfide (14). To a solution of 4.20 g (17.5 mmol) of di(carbomethoxymethyl)disulfide (14) in 10 ml of dry benzene was added slowly 6.0 g (24.3 mmol) of tris(diethylamino)phosphine. When the exothermic reaction was complete (about 2 minutes), the solvent was removed in vacuum and the residue distilled to afford 2.96 g (84%) of the sulfide 15, bp (0.1 mm) 82-84°; nmr (CCl_4) 6.24τ (s, 3H), 6.62τ (s, 2H), ir (film) 1730 cm^{-1} (-COO-); which on oxidation with hydrogen peroxide yielded a crystalline sulfone mp 111-112° (lit. mp 114-116°(217)).

Desulfurization of Benzyl p-Nitrobenzyl Disulfide (17). A solution of 0.873 g (3.0 mmol) of benzyl p-nitrobenzyl disulfide (17) in 5 ml of dry benzene containing 0.01 g (0.1 mmol) of hydroquinone was treated with 0.750 g (3.0 mmol) of 1. Upon addition of the phosphine, a blood-red color developed and a precipitate which formed immediately was obtained by filtration. Concentration of the filtrate and dilution with petroleum ether afforded more of this precipitate. Crystallization of this material from acetone/ethanol yielded 300 mg (66%, based on total conversion of 16 to 17) of di-p-nitrobenzyl sulfide (18), mp 158-160° (lit. mp 159° (218)); nmr ($CDCl_3$/$Cl_3CCOCCl_3$) 1.78τ (m, 2H), 2.50τ (m, 2H), 6.3τ (s, 2H). The

petroleum ether filtrate was concentrated in vacuum to afford a crude oil. A tlc analysis of this residue indicated the presence of phosphine sulfide 4 and dibenzyl sulfide (3).

Desulfurization of Benzyl p-Bromobenzyl Disulfide (20)

A) Preparation of Standards.

Benzyl p-Bromobenzyl Sulfide (21). A solution of 2.5 g (20 mmol) of α-toluenethiol, 2.22 g (20 mmol) of triethylamine and 5.0 g (20 mmol) of p-bromobenzyl bromide in 10 ml of ethanol was refluxed for 0.5 hour, cooled, diluted with water, and extracted with benzene. The benzene extract was evaporated to dryness and the residue distilled in vacuum to afford 3.0 g (53%) of 21, bp (0.007 mm) 130-132°; sulfone (H_2O_2/AcOH) mp 176-177° (lit. mp 174-176° (219)).

Di-p-bromobenzyl Sulfide (22). A solution of 2.50 g (10 mmol) of p-bromobenzyl bromide and 1.25 g (5 mmol) of sodium sulfide (nona-hydrate) in 20 ml of ethanol was refluxed for 6 hours, poured into water, the crude product filtered and recrystallized from ethanol to yield 1.7 g (80%) of 22, mp 59.5-61° (lit. mp 58-59° (220)).

B) Desulfurization of 20. A solution of 0.3400 g (1.04 mmol) of benzyl p-bromobenzyl disulfide (20), 0.2875 g (1.16 mmol) of tris(diethylamino)phosphine (1) and 0.0121 g (0.10 mmol) of hydroquinone in 2.5 ml of dry benzene was refluxed under nitrogen for 6 hours. To the reaction was added 0.0518 g (0.278 mmol) of diphenyl sulfide (vpc standard) and the reaction mixture was analyzed by quantitative vpc (Appendix I). Four products were detected and their concentrations measured:

tris(diethylamino)phosphine sulfide (4) (0,882 mmol, 85%), benzyl sulfide (3) (0.117 mmol, 11%), benzyl p-bromobenzyl sulfide (21) (0.399 mmol, 39%) and di-p-bromobenzyl sulfide (22) (0.228 mmol, 22%). The accuracy of these analyses was ± 2% (see Appendix I).

Desulfurization of Benzyl Ethyl Disulfide (23). A solution of 2.17 g (10 mmol) of benzyl ethyl disulfide (23) and 2.60 g (11 mmol) of tris(diethylamino)phosphine (1) in 20 ml of benzene was stirred at room temperature for 18 hours. The reaction was monitored by vpc (Apiezon-L); after 1 hour, 20% benzyl disulfide (2) had formed. This material disappeared and after 18 hours, 4.5 mmol (90%) of benzyl sulfide (3) was present. Also detected were diethyl disulfide (7) and trace amounts of benzyl disulfide (2), benzyl ethyl disulfide (23) and benzyl ethyl sulfide. All compounds were identified by comparison with authentic samples.

Desulfurization of β-D-glucopyranosyl Disulfide Octa-O-acetate (25) A suspension of 100 mg (0.137 mmol) of β-D-glucopyranosyl disulfide octa-O-acetate (25) in 5 ml of dry benzene was treated with 45 mg (0.180 mmol) of tris(diethylamino)phosphine (1), and the resulting solution refluxed 30 minutes. The solvent was removed in vacuum and the residue washed several times with hexane. The residue (80 mg, 84%, ir identical to recrystallized product) was crystallized twice from methanol to yield 45 mg (47%) of α-D-glucopyranosyl-1-thio-β-D-glucopyranoside octa-O-acetate (26) as white needles, mp 169-170° (lit. mp 170°

(92)); ir (KBr) 1740 cm^{-1} (O-CO-); nmr (100 MHz) ($CDCl_3$) 4.03 τ (d, 1H, J=5.5 Hz), 4.85τ(m, 6H), 5.60τ(m, 6H), 6.20τ(m, 1H), 7.88τ(s, 3H), 7.88τ(s, 3H), 7.95τ(m, 12H), 7.98τ(s, 3H), 7.98τ(s, 3H), mass spectrum (190°) (no parent ion observable) m/e 43 (CH_3CO^+), 332, 170.

Anal. Calcd. for $C_{28}H_{38}O_{18}S$: C, 48.41; H, 5.51. Found: C, 48.01; H, 5.42.

Attempted Desulfurization of Di-p-tolyl Disulfide (28).

A) In benzene solution. A solution of 2.14 g (8.7 mmol) of di-tolyl disulfide (28) and 2.61 g (11 mmol) of tris(diethylamino)phosphine (1) in 5 ml of dry benzene was refluxed for 12 hours in a nitrogen atmosphere. No new products were detected (tlc, vpc) in the reaction mixture.

B) In neat phosphine 1 at 90°. A mixture of 2.46 g (10 mmol) of ditolyl disulfide (28) and 3.5 g (14 mmol) of 1 was heated for 18 hours at 90° in a nitrogen atmosphere. Although the clear solution turned black after 3 hours, no new products were detected by tlc and vpc.

C) In neat phosphine at 140°. A mixture of 2.46 g (10 mmol) of disulfide 28 and 3.5 g (14 mmol) of 1 was heated for 24 hours at 140° in a nitrogen atmosphere. The reaction mixture was chromatographed over silica gel. Elution with 4:1 hexane-chloroform afforded 0.5 g of a clear viscous oil which partially crystallized on standing. Trituration of part of this oil with methanol afforded a few milligrams of di-p-tolyl sulfide as crystals, mp 54-57° (lit. mp 57° (221)) ir (KBr) 3010 cm^{-1},

1500, 810, 805, 485, 475. Evaporation of the methanol solution and crystallization from ethanol afforded 50 mg of tri-p-tolylphosphotrithioate (30), mp 134-137° (lit. mp 138-140°(222)), ir(KBr) 3010 cm^{-1} (Ph), 1500 (Ph), 1220 (P=O) 810 (Ph), 560, 550, 495; nmr (100 MHz)(CCl_4) 2.78 τ (m, 4H), 7.64 τ (d, 3H, J_{PH} = 2.5 Hz). This same material could be obtained by oxidation (H_2O_2/AcOH) of the crude oil obtained by chromatography.

Desulfurization of Bis-N,N'-dimethylaminophenyl Disulfide (27).

A) With triphenylphosphine. A solution of 101 mg (0.33 mmol) of bis-N,N'-dimethylaminophenyl disulfide (27) and 100 mg (0.33 mmol) of triphenylphosphine in dry benzene (2 ml) was refluxed for 96 hours. No new products were detected by tlc, and 86 mg (86%) of disulfide 27, mp 115-117°(lit. mp 118° (205)), were recovered from the reaction by extraction with 5% hydrochloric acid solution and subsequent neutralization.

B) With tris(diethylamino)phosphine (1). A solution of 50 mg (0.16 mmol) of bis-N,N'-dimethylaminophenyl disulfide (27) and 50 mg (0.20 mmol) of tris(diethylamino)phosphine (1) in 5 ml of benzene was refluxed for 8 hours. No new products were detected by tlc and 40 mg (80%) of 27 was recovered unchanged from the reaction.

Desulfurization of Di-2-benzothiazole Disulfide (31). A solution of 3.32 g (10 mmol) of di-2-benzothiazole disulfide (31) and 3.0 g (12 mmol) of tris(diethylamino)phosphine (1) in 25 ml of benzene was stirred at room temperature. A red oil formed immediately on mixing 31 with 1. After refluxing 4 hours,

this red oil redissolved and phosphine sulfide 4 was detected on tlc. The solvent was removed in vacuum and the residue chromatographed over silica gel. Elution with 9:1 ethyl acetate-hexane afforded an oil which, on stirring with hexane, deposited 1.83 g (61%) of di-2-benzothiazole sulfide 32 as colorless crystals, mp 96-98 , which on crystallization from ethanol afforded colorless needles, mp 97-98°, (lit. mp 99° (223)); ir (KBr) 1450 cm^{-1} (C=N), 760 (aromatic), 700 (C-S); nmr ($CDCl_3$) 1.9-2.8τ (m); mass spec: parent ion m/e 300, fragments at 167, 108, 242, 69.

In a similar experiment, benzothiazole disulfide (372 mg, 1.0 mmol), tris(diethylamino)phosphine (1) (250 mg, 1.0 mmol) and 0.5 ml of benzene were mixed in an nmr tube. The ^{31}P nmr spectrum exhibited a single resonance at -58.5 ppm (relative to H_3PO_4). The mixture was transferred to a 5 ml flask and refluxed under nitrogen for 3 hours. Analysis (tlc) of the reaction mixture indicated the presence of di-2-benzothiazole sulfide 32 and tris (diethylamino)phosphine sulfide (4).

Attempted Desulfurization of Di-2-pyridyl Disulfide (34).

A solution of 0.222 g (1.0 mmol) of di-2-pyridyl disulfide (34) and 0.30 g (1.2 mmol) of tris(diethylamino)phosphine (1) in 5 ml of dry benzene was refluxed for 18 hours in a nitrogen atmosphere. A yellow oil which formed immediately upon mixing 34 and 1 did not redissolve. This oil reacted exothermically with water; 2-mercaptopyridine was detected (tlc) as one of the hydrolysis products.

To characterize this yellow oil, the reaction was repeated.

Thus, 220 mg (1.0 mmol) of disulfide 34 and 0.25 g (1.0 mmol) of 1 were mixed with 0.5 ml of benzene in an nmr tube. A yellow oil formed immediately. The ^{31}P nmr spectrum of this oil exhibited a strong signal at -60.4 ppm relative to phosphoric acid.

N,N'-Bis(trifluoroacetyl)-L-cystine Dimethyl Ester (39).

A suspension of 4.50 g of cystine methyl ester hydrochloride in 15 ml of trifluoroacetic acid was cooled to -5°C and 10 ml of trifluoroacetic anhydride was added dropwise. The resulting solution was stirred for one hour at -5°C, then one hour at room temperature. The reaction mixture was poured over 200 ml of ice/H_2O and after stirring for ten minutes, filtered and the crystalline product washed well with water, then dried in vacuum to yield 6.2 g (95%) of white crystals, mp 152-154°; $[\alpha]_D^{25}$ -183° (MeOH, c 2.5) (lit. mp 152-153°; $[\alpha]_D^{25}$ -194° (110)).

N,N'-Bis(trifluoroacetyl)-L-lanthionine Dimethyl Ester (40).

To a suspension of 2.30 g (5.0 mmol) of 39 in 25 ml dry benzene was added slowly 1.40 g (5.5 mmol) of tris(diethylamino)phosphine. The resulting mixture was stirred under nitrogen for ten minutes. The suspended amide slowly dissolved, then reprecipitated as a gel. After addition of 50 ml of hexane the resulting suspension could be filtered and the white crystals were washed well with hexane to yield 2.07 g (96%) of white crystals, mp 103-109°C.

After three recrystallizations from aqueous methanol, an analytical sample was obtained, mp 117-118°; $[\alpha]_D^{25}$ -32.4°

(MeOH, c 0.4); ir (KBr) 3300 cm^{-1} (N-H), 1760 (-COO-), 1705 (CONH).

Anal. Calcd. for $C_{12}H_{14}N_2O_6SF_6$; C, 33.57; H, 3.30; N, 6.54; S, 7.49; F, 26.63. Found: C, 33.92; H, 2.91; N, 6.59; S, 7.61; F, 27.05.

L(+)-Lanthionine (36). A solution of 1.290 g (3.0 mmol) of bis(trifluoroacetyl)lanthionine methyl ester 40 in 15 ml of dioxane was cooled to 0° in an ice bath and 27 ml of 1.0N NaOH was added slowly. After 0.5 hour at 5°, the mixture was acidified with 12 ml of 2N HCl. After adjusting the pH to 6.0, the solvent was removed under vacuum. To the residue was added 15 ml of H_2O and the crystalline L-(+)-lanthionine was collected by filtration and dried in vacuum to yield 0.398 g (64%) white crystals, mp 295-296° dec; $[\alpha]_D^{25}$ +9.4° (2.4N NaOH, c 1.4) (lit. mp 295°dec; $[\alpha]_D^{25}$ +8.4°(104)); the infrared spectrum of this material was identical to that reported for L-(+)-lanthionine (107).

N,N'-Dicarbobenzoxy-L-Lanthionine Diethyl ester (42). To a suspension of 2.261 g (4.0 mmol) of N,N'-dicarbobenzoxycystine diethyl ester[2] in 10 ml of dry benzene was added slowly 1.20 g (4.8 mmol) of tris(diethylamino)phosphine (1). An exothermic reaction occurred and the peptide dissolved. After stirring for one hour, the solvent was removed under vacuum and the residue chromatographed over silica gel. The phosphine sulfide (1.09 g, 99%) was eluted with 9:1 hexane/ethyl acetate, followed

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[2]The generous gift of this compound from Professor Richard G. Hiskey is gratefully acknowledged.

by a small amount of impurities (0.05 g). Elution with 1:1 hexane/ethyl acetate afforded a colorless oil which on standing crystallized to give 1.83 g (86%) of white crystals, mp 63-67°, which after three recrystallizations from cyclohexane afforded an analytical sample, mp 67-68°; $[\alpha]_D^{25}$ -15.9 (MeOH, c 1.1); ir (KBr) 3320 cm^{-1} (N-H), 1750 (-COO-), 1690 (-O-CO-NH). The infrared spectrum of the analytical sample was identical to the crude (mp 63-67°) crystals obtained from the column.

Anal. Calcd. for $C_{26}H_{32}N_2O_8S$: C, 58.62; H, 6.06; N, 5.26 S, 6.02 Found: C, 58.68; H, 6.20; N, 5.37; S, 6.22.

Reaction of Ethyl N,N'-dicarbobenzoxy-O-methyl-L-Cystinylglycinate (43). A suspension of 131 mg (0.22 mmol) of 43 and 100 mg (0.4 mmol) of phosphine 1 in 100 ml of anhydrous ether was stirred for 2 hours, during which time the texture of the suspension changed. Filtration afforded a white crystalline material, 60 mg (82% based on complete conversion of 43 to 44, mp 165-170°, which was identical (mp, ir, nmr) to authentic disulfide[2] 44. The tlc of the filtrate of 44 showed the presence of tris(diethylamino)phosphine sulfide 4 and sulfide 45, both identified by comparison with authentic samples.

Esterification of N-Carbobenzoxy-2-aminodiethyl Disulfide-2'-Carboxylic Acid (46).

A) Methanolic Hydrochloric Acid; Preparation of N,N'-dicarbo-

benzoxy-2,2'-diamino-diethyl Disulfide (37). To a suspension of 3.5 g (15 mmol) of 46[2] in 25 ml of methanol was added 10 drops of thionyl chloride. After standing at 25° for 24 hours, the methanol was removed in vacuum and the residue crystallized from methanol to afford 1.5 g (65%) of N,N'-dicarbobenzoxy-2,2'-diamino-diethyl disulfide 37 as colorless plates, mp 125-126°; ir (KBr) 3170 cm^{-1} (NH), 1690 (O-CO-N); nmr ($CDCl_3$) 2.65 τ (s, 5H, aromatic), 4.8 τ (b, 1H, NH), 4.88 τ (s, 2H), 6.50 τ (m, 2H), 7.22 τ (m, 2H); mass spectrum: parent ion m/e 328, fragments at 91, 178.

Anal. Calcd. for $C_{20}H_{24}N_2O_4S_2$: C, 57.21; H, 5.78; N, 6.64; S, 15.25. Found: C, 56.99; H, 5.87; N, 6.58; S, 14.98.

B) Methanol/Dicyclohexylcarbodiimide. To a solution of 1.0 g (5 mmol) of dicyclohexylcarbodiimide in 10 ml of methanol was added 1.6 g (5 mmol) of 46[2]. After stirring for 15 minutes, the mixture was filtered and the methanol removed in vacuum. Dilution of the resulting oil with ether afforded 300 mg of a crystalline product, mp 210-220° which was not further characterized.

C) Phosphorus Trichloride/Methanol; N-carbobenzoxy-2-amino-2'-carbomethoxy-diethyl disulfide (48). A solution of 0.50 g (1.57 mmol) of 2-(N-carbobenzoxy)amino-diethyl-disulfide-2'-carboxylic acid[2] and 1.0 ml of phosphorus trichloride in 10 ml of chloroform was stirred at room temperature for 1 hour. The excess phosphorus trichloride and chloroform were removed under vacuum and the residue diluted with 10 ml of methanol. After stirring the mixture for 10 minutes, the solvent was

removed under vacuum and the residue diluted with 10 ml of methanol. After stirring the mixture for 10 minutes, the solvent was removed under vacuum and the residue chromatographed over silica gel. Elution with chloroform afforded an oil which resisted all attempts at crystallization. Removal of all traces of solvent in vacuum afforded a colorless oil, 0.405 g (70%), which was homogeneous on tlc (silica gel, $CHCl_3$); ir (film) 3180 cm^{-1} (N-H), 1720 broad (-O-CO- and O-CO-NH); nmr ($CDCl_3$) 2.58 τ (s, 5H, aromatic), 4.6 τ (b, 1H, NH), 4.80 τ (s, 2H, benzylic) 6.21 τ (s, 3H, $-OCH_3$), 6.40 τ (q, 2H, $-CH_2-N$), 7.1 τ (m, 6H); mass spectrum: parent ion at m/e 329.0757) (calcd for $C_{14}H_{19}NO_4S_2$: 329.0755)

Anal. Calcd for $C_{14}H_{19}NO_4S_2$: C, 51.05; H, 5.81; N, 4.25; S, 19.43. Found: C, 50.81; H, 5.59; N, 4.36; S, 19.22.

Reaction of N-carbobenzoxy-2-amino-2'-carbomethoxy-diethyl Disulfide(48)with Tris(diethylamino)phosphine (1). To a solution of 0.33 g (1.0 mmol) of 48 in 3 ml of dry benzene was added 0.30 g (1.2 mmol) of tris(diethylamino)phosphine (1). A white precipitate which formed immediately on addition of the phosphine was obtained by filtration as colorless crystals, 0.184 g (88% based on complete conversion of 48 to 37), mp 124-124.5°, mmp 124-125°, identical (ir, nmr) to authentic disulfide 37.

N,N'-Dicarbobenzoxy-2,2'-diamino-diethylsulfide (38). To a suspension of 0.210 g (0.5 mmol) of N,N'-dicarbobenzoxy-2,2'-diamino-diethyl disulfide (37) in 2 ml of dry benzene was added

0.20 g (0.8 mmol) of tris(diethylamino)phosphine (1). After refluxing the mixture for 4 hours, the reaction was diluted with 25 ml of hexane. On standing, colorless crystals were obtained, 0.131 g (68%) mp 99-100° which after crystallization from ethanol afforded an analytical sample, mp 99-100°, ir (KBr) 3150 cm^{-1} (N-H), 1680 (C-CO-NH).

Anal. Calcd for $C_{20}H_{24}N_2O_4S$: C, 61.83; H, 6.22; N, 7.21; S, 8.25. Found: C, 61.81; H, 6.25; N, 7.04; S, 8.39.

Preparation of 1,2-Dithiane (49). A mixture of 16.5 g (135 mmol) of 1,4-butanedithiol and 50 ml of a 20% aqueous sodium hydroxide solution was added dropwise with vigorous stirring to a solution of 34 g (136 mmol) of iodine and 30 g (200 mmol) of sodium iodide in 100 ml of water. The mixture was extracted with ethyl acetate, washed with sodium thiosulfate and evaporated to dryness. The residue was sublimed three times at 30° (15 mm) to yield 5.5 g (33%) of 1,2-dithiane, mp 30-32° (lit. mp 32-33° (131)), nmr (CS_2) 7.0 τ (m, 4H), 7.9 τ (m, 4H).

This disulfide has been subsequently prepared by Field (84) in 93% yield by oxidation of 1,4-butanedithiol with p-toluenesulfonyl chloride.

Desulfurization of 1,2-Dithiane (49).

A) Product Analysis by Gas Chromatography. A solution of 0.6039 g (5.03 mmol) of 1,2-dithiane (49), 1.2396 g (5.02 mmol) of tris(diethylamino)phosphine (1) and 0.1898 g (1.79 mmol) of xylene (redistilled) in 5.0 ml of dry benzene was stirred at room temperature for 48 hours. A yield of 5.10 mmol (101%)

(vpc analysis) of tetrahydrothiophene (50) was obtained. No products were isolated from this reaction.

B) Attempts to Isolate Tetrahydrothiophene (50) from the Desulfurization of 1,2-Dithiane (49). A mixture of 1.9 g (15.8 mmol) of 1,2-dithiane (49) and 4.0 g (16 mmol) of tris(diethylamino)phosphine (1) was stirred at room temperature for 4 hours. No disulfide remained unreacted at this time (vpc). The reaction mixture was slowly distilled to afford 1.4 g (100%) of crude tetrahydrothiophene, bp 120-140°, which contained 5-10% tris(diethylamino)phosphine sulfide (4) as an impurity. Redistillation of this material afforded 0.5 g (38%) of tetrahydrothiophene bp 124-128° (lit. bp 119-122° (224)), which was identical (nmr, vpc, ir) to an authentic sample.

1,2-Dithiolane-3-valeric Acid Diethylamide (53). A solution of 0.412 g (2.0 mmol) of 51 and 0.55 g (2.2 mmol) of tris-(diethylamino)phosphine (1) in 2.5 ml of dry benzene was stirred for 4 hours. An oil which formed immediately upon addition of the phosphine slowly redissolved on stirring and a solid precipitated. The solvent was removed under vacuum and the residue was chromatographed over silica gel. Elution with methylene chloride afforded the diethylamide as a yellow oil, 0.42 g (80%), homogeneous on thin-layer and gas chromatography, ir (film) 1640 cm^{-1} (tertiary amide); nmr (CCl_4) 6.70 τ (q, J=7Hz), 8.90 τ (t, J=7Hz), both observable above a broad envelope; mass spectrum: parent ion m/e 261, fragments at 58, 115, 72 (Et_2N^+), 100, 128, 189, 228.

dl-1, 2-Dithiolane-3- Valeric Acid Anilide (54). A solution of 1.0 g (4.8 mmol) of 51 and 0.5 g (5.4 mmol) of aniline in 10 ml of methylene chloride was cooled to 5° and 1.0 g (4.9 mmol) of dicyclohexylcarbodiimide was added with stirring. After stirring 0.5 hour, the dicyclohexylurea (0.9 g, 85%) was removed by filtration. The filtrate was concentrated in vacuum and the residue chromatographed over Florisil. Elution with 1:1 chloroform-petroleum ether (30-60°) afforded 1.0 g (75%) of yellow crystals, mp 60-65°C, which after crystallization from cyclohexane/methylene chloride gave yellow needles, mp 69-71° (lit. mp 72-73° (225)); λ_{max}^{EtOH} 242 mμ (ε=30,200), 332 (363); ir (KBr) 3290 cm^{-1} (N-H), 1660 (amide I), 1540 (amide II), 690 (aromatic); nmr ($CDCl_3$) 1.93 τ (b, 1H, NH), 2.7 τ (m, 5H, aromatic), 6.48 τ (m, 1H, methine), 6.9 τ (m, 2H, $-CH_2-S$), broad multiplets centered at 7.8 τ and 8.5 τ accounting for remaining aliphatic protons; mass spectrum (150°): molecular ion at m/e 281.0918 (calcd for $C_{14}H_{19}NOS_2$: 281.0907), fragments of m/e 93, 135, 41, 55, 56, 148, 155.

Thietane-2-Valeric Acid Anilide (55). A solution of 1.129 g (4 mmol) of the anilide 54 and 1.10 g (4.4 mmol) of tris-(diethylamino)phosphine (1) in 10 ml of benzene was stirred for 1 hour during which time the yellow color was discharged and the uv maximum at 332 mμ disappeared. The reaction mixture was allowed to stand overnight, the solvent removed under vacuum and the residue chromatographed over Florisil. The phosphine sulfide was eluted with 1:1 CH_2Cl_2- petroleum ether (60-80°). Elution with CH_2Cl_2 afforded 0.634 g (64%) of color-

less crystals, mp 51-54° which after 2 crystallizations from cyclohexane afforded an analytical sample, mp 55-57°; ir (KBr) 3290 cm^{-1} (N-H), 1660 (C=O), 1540 (amide II), 760 and 690 (aromatic); λ_{max}^{MeOH} 242 mμ (ε = 24,900); nmr (CCl_4) broad multiplet at 2.7τ (6H, aromatic + NH) and aliphatic protons from 6.5-9.0τ; mass spectrum (150°): molecular ion at m/e 249.1180 (calcd for $C_{14}H_{19}NOS$: 249.1198); fragments at m/e 93, 135, 41, 129.

Anal. Calcd for $C_{14}H_{19}NOS$: C, 67.44; H, 7.68; N, 5.62; S, 12.86. Found: C, 67.47; H, 7.64; N, 5.47; S, 12.85.

Thietane-2-valeric Acid (52). A solution of 4.04 g (20 mmol) of 54 in 20 ml of dihydropyran was refluxed for 3 hours. The solvent was removed in vacuum and the residue dissolved in 25 ml of ethyl acetate containing 5.5 g (22 mmol) of tris-(diethylamino)phosphine (1). After stirring at room temperature for 24 hours, the solvent was removed under vacuum, 25 ml of dioxane and 25 ml conc. HCl was added and the solution stirred 18 hours. The solution was diluted with 200 ml of water, extracted with ether; the ethereal layer was extracted with 100 ml of a 5% sodium bicarbonate solution; the bicarbonate solution was acidified and extracted with ether. After drying over anhydrous sodium sulfate, the ethereal solution was evaporated to dryness in vacuum to yield 2.82 g (80%) of 52 as a viscous yellow oil, bp (0.1 mm) 143°, n_D^{25} 1.5155; ir (film) 3020 cm^{-1} (b, OH), 1708 (COOH); nmr (CCl_4) -1.63τ(s, 1H COOH), multiplet from 6.0 - 9.2τ accounting for 13 protons; mass spectrum (50°): parent ion at m/e 174, fragments at m/e 87, 41, 45, 55, 73, 80. The acid 52 was characterized as its anilide 55 (aniline, dicyclohexylcarbodiimide), mp 55-57°. This material

was identical in all respects with the sample prepared by direct desulfurization of 54.

1,2-Dithiolane (57). A solution of 1.06 g (10 mmol) of 1,3-propanedithiol and 2.10 g (20 mmol) of triethylamine in 10 ml of methanol was added dropwise over 15 minutes to a solution of 2.66 g (10.5 mmol) of iodine in 25 ml of methanol. The resulting solution was diluted with 250 ml of benzene, decolorized with a 10% solution of sodium thiosulfate, washed with water, dried over magnesium sulfate and concentrated in vacuum at 30-35° to less than 50 ml volume, the solution transferred to a 50 ml volumetric flask and made up to volume with dry benzene. From the absorption at 331 mμ in the uv spectrum (lit. λ_{max}^{MeOH} 330 mμ, ε = 147 (131)) the concentration of this solution was found to be 0.112 M corresponding to a yield of 56%; nmr (benzene) 7.70τ (t, 2H, J=6Hz), 8.65τ (m, 4H).

Thietane (58). To 50 ml of a 0.112M solution of 57 in benzene was added 2.50 g (10 mmol) of tris(diethylamino)phosphine(1). After standing in the dark for 18 days, the clear solution was added to 25 ml of a 20% solution of mercuric chloride in ethanol. After standing overnight, 1.6 g (82%) of a crystalline solid was obtained, mp 94-99° dec (lit. mp 93-95° dec (226)).

1,2-Dithiolane-4-one (60). A solution of 1.22 g (10 mmol) of dimercaptoacetone (as its dimer) (227) and 2.10 g (20 mmol) of triethylamine in 25 ml of methanol was added dropwise to a solution of 2.66 g (10.5 mmol) of iodine in 50 ml of methanol. The reaction mixture was filtered to remove 200 mg of polymer

and the filtrate was diluted with 200 ml of benzene. After decolorization with a 10% solution of sodium thiosulfate and several washings with water, the solution was dried over magnesium sulfate and concentrated in vacuum to 50 ml to afford a golden yellow solution of 1,2-dithiolane-4-one in benzene; nmr (benzene) 7.15 τ (s); $\lambda_{max}^{benzene}$ 340 mμ (sh) (ε·50), 325 (65), 312 (74), 300 (80).

Desulfurization of 1,2-Dithiolane-4-one (60). To 50 ml of the benzene solution of 60, prepared above, was added 2.50 g (10 mmol) of tris(diethylamino)phosphine (1). Immediately upon addition of the phosphine, the color changed from yellow to dark brown, and a dark brown tar separated out of the solution. This tar was insoluble in all organic solvents tried.

2-Phenyl-1,3-Propanedithiol (63). A solution of 4.6 g (10 mmol) of 2-phenyl-1,3-propanediol ditosylate[3] and 10 g (130 mmol) of thiourea in 50 ml of ethanol was refluxed for 4 hours; the ethanol was removed under vacuum and the residue refluxed under nitrogen with 10 g of sodium hydroxide in 50 ml of water for 12 hours. After careful acidification, the mixture was extracted with chloroform, the extract washed well with water, dried and evaporated to dryness. The crude oil was fractionally distilled in vacuum to afford 1.0 g (55%) of a pale yellow oil, bp (0.005 mm) 76-78°; nmr ($CDCl_3$) 2.70 τ (m, 5H, aromatic), 6.0-7.4 τ (m, 5H), 8.7 τ (m, 3H S-H). This crude dithiol was used without further purification.

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[3]For the preparation of 2-phenyl-1,3-propanediol ditosylate, see C. Beard and A. Burger (132).

4-Phenyl-1,2-Dithiolane (64). A solution of 1.4 g (7.6 mmol) of the dithiol 63 and 1.8 g (1.8 mmol) of triethylamine in 20 ml of methanol was added dropwise with stirring in a nitrogen atmosphere to a solution of 1.95 g (8 mmol) of iodine in 50 ml of methanol. The resulting solution was rapidly filtered and the filtrate cooled in dry ice until crystals formed. The crystals were filtered and washed well with cold methanol to afford 1.0 g (73%) of yellow crystals, mp 77-83°. Sublimation at 75° and 25μ pressure afforded 488 mg of yellow crystals, mp 82-84°; ir (KBr) 1600, 1490, 1460, 775 and 705 cm^{-1} (aromatic); $\lambda_{max}^{benzene}$ 335 mμ (ε=143); nmr ($CDCl_3$) 2.66τ (m, 5H, aromatic), 6.5τ (m, 5H).

Anal. Calcd for $C_9H_{10}S_2$: C, 59.29; H, 5.53; S, 35.19. Found: C, 59.09; H, 5.50; S, 34.83.

3-Phenylthietane (65). A solution of 400 mg (2.2 mmol) of 64 and 600 mg (2.4 mmol) of tris(diethylamino)phosphine (1) in 10 ml benzene was refluxed 4 hours during which time the yellow color was discharged. The reaction mixture was evaporated to dryness and the residue chromatographed over silica gel. Elution with 1:1 hexane-chloroform afforded 280 mg (87%) of a colorless oil, homogeneous on thin layer and gas chromatography (LAC column at 190°), n_D^{25} 1.5895; ir (film) 1610 cm^{-1}, 1500, 1465, 760, 705 (aromatic); nmr (CCl_4) 2.78τ (5H), 5.50τ (m, 1H), 6.62τ (m, 4H).

This material was characterized as its sulfone (H_2O_2, AcOH), mp 101-101.5°, ir (KBr) 1320 cm^{-1}, 1140 (SO_2).

Anal. Calcd for $C_9H_{10}SO_2$: C, 59.29; H, 5.53 S, 17.59. Found: C, 59.67; H, 5.60; S, 17.84.

Desulfurization of 3H-Benzo[b]—1,2—Dithiole (67). To a solution of 0.9 g (6.35 mmol) of 3H-benzo[b]—1,2—dithiole [4] in 15 ml of benzene was added slowly 1.88 g (7.6 mmol) of tris-(diethylamino)phosphine (1). After 10 minutes, the benzene was removed under vacuum and the residue chromatographed over silica gel. Elution with 10% chloroform in hexane afforded 50 mg (7%) of 6H,12H-dibenzo[b,f]—1,5—dithiocin as colorless crystals, mp 172-178° which after crystallization from ethanol afforded colorless needles, mp 173-175° (lit. mp 174-176° (228)).

1α,5α-Epidithioandrostane-3-17-dione (72). The method used was a modification of the procedure of Tweit and Dodson (133). Thus, a solution of 3.0 g (10.5 mmol) of 1.4-androstadiene-3,17-dione and 0.5 g (15 mmol) of sulfur in 100 ml of pyridine was saturated with hydrogen sulfide over 3 hours. After stirring the resulting solution for 18 hours at room temperature, the solvent was removed under vacuum, 50 ml xylene was added and evaporated under vacuum. The residual solid was suspended in benzene and triphenylphosphine was slowly added until unreacted triphenylphosphine could be detected on thin layer[5]. The benzene was removed under vacuum and the resulting solid mass washed several times with cold acetone. The insoluble material could be recrystallized from hot acetone to yield 1.2 g (33%) yellow needles, mp 210-214° (lit. mp 210-214° (133)); ir (KBr) 1730 cm^{-1} (C=O); λ_{max}^{MeOH} 364 mμ (ε=51), 280 sh (650), 262 (730); nmr ($CDCl_3$)

[4]For the preparation of 3H-benzo[b]-1,2-dithiole, see A. Lüttringhaus and K. Hägle (77).

[5]Triphenylphosphine was used to remove occluded sulfur from this steriod.

(100 MHz) 6.15τ (q, 1H, $J_{AX} + J_{BX} = 7Hz$, $J_{AX} - J_{BX} = 1Hz$), 9.10τ (s, 3H), 8.59τ (s, 3H), and a multiplet centered about 7.5-6.9τ.

S-Bis(diethylamino)phosphino-1α-thioandrostan-4-ene-3,17-dione (80). A suspension of 348 mg (1 mmol) of 1α,5α-epidithioandrostan-3,17-dione (72) in 5 ml of dry benzene containing 1.0 g (4 mmol) of tris (diethylamino)phosphine (1) was stirred overnight. The solvent was removed under vacuum and the residue chromatographed over silica gel. After elution of tris(diethylamino)phosphine sulfide (4) with 95:5 CH_2Cl_2-acetone, the product was eluted with 85:15 CH_2Cl_2-acetone. Crystallization from hexane afforded 100 mg (20%) colorless crystals, mp 201-202°; ir (KBr) 1740 cm^{-1} (C_{17} C=O), 1670 cm^{-1} (C=C-C=O); λ_{max}^{MeOH} 228 mμ (ε=6450), 280 (1470); mass spectrum: parent ion at m/e 492.2959 (Calcd for $C_{27}H_{45}N_2O_2PS$ 492.2939) with a fragment ion at m/e 284.1785 ($p^+ - (Et_2N)_2PSH$); (Calcd for $C_{19}H_{24}O_2$: 284.1776).

Anal. Calcd for $C_{27}H_{45}N_2O_2PS$: C, 65.81; H, 9.21; N, 5.69. Found: C, 65.75; H, 9.02; N, 5.61.

Preparation and Desulfurization of dl- and meso-1,2-Dithiane-3,6-Dicarboxylic Acid.

α,α'-Dibromoadipic Acid. A mixture of 36.5 g (250 mmol) of adipic acid and 50 ml of thionyl chloride was refluxed for 3 hours at which time all the acid had passed into solution. The mixture was diluted with 250 ml of carbon tetrachloride and 87 g (500 mmol) of N-bromosuccinimide was added. The mixture was heated to reflux, and 3-5 drops of water was added. After refluxing 2 hours, the mixture was cooled, the succinimide

removed by filtration, the filtrate evaporated in vacuum, the residue mixed with 250 ml of water and heated to reflux for 20 min. Crystals deposited on cooling. These crystals were obtained by filtration and recrystallized from hot water to afford 22.5 g (60%) of meso-dibromoadipic acid as white crystals, mp 185-190° (lit. mp 192-193° (229)). The mother liquors were concentrated in vacuum and crystallized from formic acid to afford 10.2 g (29%) of dl-α,α'-dibromoadipic acid as white crystals, mp 125-129° (lit. mp 139° (229)).

Meso-1,2-Dithiane-3,6-Dicarboxylic Acid (86) was prepared in 28% yield from meso-α,α'-dibromoadipic acid by the procedure of Fregda (135); mp 196-198° (lit. mp 199° (135)).

dl-1,2-Dithiane-3,6-Dicarboxylic Acid (87) was prepared in 60% yield from meso-1,2-dithiane-3,6-carboxylic acid 86 by the procedure of Fregda (135); mp 270°(lit. mp 275° (135)).

Meso- and dl-Thiophane-2,5-Dicarboxylic Acids were prepared in 70% and 55% respectively by the procedure of Schotte (136); meso- mp 143-145° (lit. mp 144-146° (136)); dl- mp 162-164° (lit. mp 164-165° (136)).

Tetrahydropyranyl meso-1,2-Dithiane-3,6-Dicarboxylate (88). A suspension of 4.0 g (22.8 mmol) of the meso-diacid 86 in 20 ml of redistilled dihydropyran was refluxed for 0.5 hr, cooled, and the excess dihydropyran removed in vacuum. The residual mass was crystallized from ether to afford 4.6 g (53%) of 88 as highly hygroscopic material; mp 98-101 ; ir (KBr) 1730 cm^{-1} (COO); nmr (CCl_4) 3.96τ (b, 2H), 6.2τ (b, 6H), 7.4-8.7τ (b, 16H). Attempts to recrystallize this material were not

successful. This crude diester was therefore used without further purification.

Desulfurization of bis-tetrahydropyranyl meso-1,2-dithiane-3,6-dicarboxylate (88). A suspension of 2.5 g (6.6 mmol) of 88 in 10 ml of dry benzene and 10 ml of dry ether was treated with 1.8 g (7.2 mmol) of tris(diethylamino)phosphine (1). After 15 minutes, the solvent was removed in vacuum and the residue chromatographed over Florisil with 10% ether in hexane as elluant. After 1.9 g (105%) of crude aminophosphine sulfide (4) was eluted, a fraction containing 1.5 g (65%) of a colorless oil was collected which resisted attempts at crystallization.

A mixture of 0.5 g of this crude oil in 5 ml of water and 1 ml of trifluoroacetic acid was stirred for 5 minutes, the solvent removed in vacuum, and the residue crystallized from ether/hexane to afford 0.12 g (38% based on 88 as starting material) of dl-thiophane-2,5-dicarboxylic acid (84), mp 160-164°, mixed mp 159-163° (lit. mp 164-165° (136)).

Preparation and Desulfurization of Tetrahydropyranyl dl-1,2-Dithiane-3,6-dicarboxylate (90). To a suspension of 0.7 g (4 mmol) of dl-1,2-dithiane-3,6-dicarboxylic acid (87) in 5 ml of ether was added 5 ml of dihydropyran and 1 drop of phosphorus oxychloride. After refluxing 2 hours, the solvent was removed in vacuum to afford the crude tetrahydropyranyl ester. This ester was dissolved in 10 ml of dry benzene and 1.25 g (5 mmol) of tris(diethylamino)phosphine (1) was added. After stirring the mixture for 45 minutes, the solvent was removed in vacuum and the residue dissolved in 5 ml of a 50% trifluoroacetic

acid solution. The mixture was stirred for 1 hour. The solvent was removed in vacuum, the residue washed several times with hexane, and the residue crystallized from acetone/hexane to yield 100 mg (17%) of colorless crystals mp 133-138°. Recrystallization from water afforded crystals mp 141-145°, mixed mp 140-143° (lit. mp 144-146° (136)).

Preparation and Desulfurization of meso- and dl-3,6-dicarbomethoxy-1,2-Dithiane.

meso-3,6-Dicarbomethoxy-1,2-Dithiane (92). To a solution of 400 mg (2.3 mmol) of meso-1,2-dithiane-3,6-dicarboxylic acid in 5 ml of methanol was added 3 drops of thionyl chloride. After standing 24 hours, the solvent was removed in vacuum and the residue crystallized from cyclohexane to afford 300 mg (65%) of colorless needles, mp 72-76° , ir (KBr) 1720 cm^{-1} (COO); mass spectrum: parent ion at m/e 236.0145 (calcd for $C_8H_{12}O_4S_2$: 236.0177).

dl-3,6-Dicarbomethoxy-1,2-Dithiane (94). In a similar manner, 50 mg (0.28 mmol) of dl-1,2-dithiane-3,6-dicarboxylic acid was esterified in methanol to yield 50 mg of crude oil which could not be crystallized but which was judged to be greater than 98% pure by vpc; ir (film) 1730 cm^{-1} (COO); mass spectrum: parent ion at m/e 236.0143 (calcd for $C_8H_{12}O_4S_2$: 236.0177).

Desulfurization of meso-3,6-Dicarbomethoxy-1,2-Dithiane (92). A solution of 0.149 mmol of the meso-diester 92, 0.0715 mmol of tris(dimethylamino)phosphine oxide (internal standard for vpc analysis) and 0.230 mmol of tris(diethylamino)phosphine(1) in 1 ml of dry benzene was shaken for 10 minutes. Sulfur was added to destroy the excess phosphine, and the resulting mixture

analyzed by vpc. The reaction products consisted of a mixture of 0.005 mmol of unreacted disulfide 92 and 0.147 mmol of dl-2,5-dicarbomethoxythiophane(93). Thus, the yield of dl-diester was 101.8% (based on recovered 92). No meso-2,5-dicarbomethoxythiophane (95) was detected in the product mixture.

Desulfurization of dl-3,6-dicarbomethoxy-1,2-dithiane (94). The desulfurization of dl-3,6-dicarbomethoxy-1,2-dithiane (94) was performed as described for the meso isomer 92 above. Thus, from 0.0146 mmol of 94 was obtained 0.0158 mmol (108% ± 10%) of meso-2,5-dicarbomethoxythiophane (95). No dl isomer was detected in the product mixture.

For both of the above desulfurizations, vpc standards were prepared by esterification (methanol, thionyl chloride) of the appropriate acids 84 and 85. Neither of these esters were crystalline, but both were judged to be greater than 98% pure (vpc-tlc). Mass spectrum: for ester 84, parent ion at m/e 204.0437 (Calcd for $C_8H_{12}O_4S$: 204.0456) for ester 85, parent ion at m/e 204.0426 (Calcd for $C_8H_{12}O_4S$: 204.0456)

Preparation and Desulfurization of 1,2-Dithiepane (96). A solution of 1.5 g (11 mmol) of 1,5-pentanedithiol and 2.5 g (25 mmol) of triethylamine in 50 ml of methanol was added dropwise to a solution of 3.3 g (13 mmol) of iodine in 100 ml of methanol. The mixture was diluted with benzene, washed with water, decolorized with sodium thiolsulfate, and concentrated in vacuum to 50 ml volume. Complete removal of solvent and vacuum distillation lead to extensive polymerization. The benzene solu-

tion of 1,2-dithiepane showed no tendency to polymerize on standing; the disulfide was pure as judged by vpc; nmr (benzene) 7.45τ (m, 4H), 8.4τ (m, 6H).

This solution of 11 mmol of 96 in 50 ml benzene was treated with 4.0 g (16 mmol) of tris(diethylamino)phosphine and the resulting solution refluxed for 16 hours. Vpc analysis of the mixture showed the reaction to be complete. The mixture was diluted with 50 ml of acetic acid and 10 ml of a 30% aqueous hydrogen peroxide solution. After stirring for 24 hours, the reaction was concentrated in vacuum, the residue carefully neutralized with sodium carbonate and then concentrated in vacuum to afford a crystalline mass. This material was extracted with benzene in a soxhlet apparatus for 24 hours. Removal of the solvent in vacuum and crystallization from benzene afforded 550 mg (38%) of thiane-1,1-dioxide 98, mp 95-97° (lit. mp 98° (230)).

5H,8H,-dibenzo[d,f]-1,2-dithiocin (101). A solution of 4 g (1.17 mmol) of 2,2'-di(bromomethyl)biphenyl[6] and 15 g (21 mmol) of thiourea in 50 ml of ethanol was refluxed for 4 hours; the ethanol was removed in vacuum and the residue dissolved in 50 ml of a 20% sodium hydroxide solution. After refluxing under nitrogen for 4 hours, the solution was carefully acidified (a large amount of H_2S was evolved) and extracted with ether. After drying the extract over magnesium sulfate, the ether was removed in vacuum to yield 2.7 g (93%) of a yellow oil;

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[6] The gift of this compound from Professor G. Wahl is gratefully acknowledged.

ir (film) 2500 cm^{-1} (SH), 1480, 1440 and 765 (aromatic); nmr (CCl_4) 2.6τ (m, 10H, aromatic), 6.5τ (d, 4H, J=8Hz, $-CH_2-S$), 8.5τ (t, 2H, SH).

The crude dithiol was dissolved in 50 ml methanol containing 2.6 g (2.6 mmol) of triethylamine; this solution was added dropwise to 3.0 g (1.19 mmol) of iodine in 50 ml of methanol. When addition was complete, the solution was diluted with 350 ml of benzene, washed with water, decolorized by sodium thiosulfate, dried and the benzene removed in vacuum to afford a crude product which was crystallized from ethanol to afford 1.84 g (65%) of light brown crystals, mp 160-165° (lit. mp 161°(138)); ir (KBr) 770 cm^{-1}, 745; nmr (CCl_4) 2.75τ (m, 8H, aromatic), 4.25τ (q, 4H, J_{AB}= 13Hz, CH_2-S).

5H,7H-dibenzo[c,e]thiepin (102). A solution of 0.70 g (0.28 mmol) of 5H,8H-dibenzo[d,f]-1,2-dithiocin and 0.90 g (0.36 mmol) of tris(diethylamino)phosphine (1) in 10 ml benzene was stirred at room temperature for 10 minutes. The solvent was removed in vacuum and the residue chromatographed over silica gel. Elution with 1:1 hexane-chloroform afforded after drying 0.580 g (97%) of white crystals, mp 91-92°; mmp 90-92° (lit. mp 89° (231)); nmr (CCl_4) 2.6τ (m, 8H, aromatic), 6.6τ (broad doublet, 4H, J=10Hz). The temperature dependence of this spectrum is shown in Figure 14, p. 75.

Attempts to Prepare a Phosphonium Salt. RS^- $RS-\overset{+}{P}(NEt_2)_3$.

A) Reaction of Diphenyl Disulfide (105) with the Aminophosphine 1. A mixture of 0.218 g (1.0 mmol) of diphenyl disulfide (105)

and 2.50 g (1.0 mmol) of tris(diethylamino)phosphine (1) was mixed in an nmr tube. After standing 0.5 hour, the ^{31}P nmr spectrum was recorded. A strong resonance at -118.4 ppm (lit. -118.2 ppm (177)), characteristic of unreacted 1 was observed. No other phosphorus species were detected. The chemical shift of pure aminophosphine 1 was found to be -117.7 ppm (50% in benzene solution).

B) Reaction of Diphenyl Disulfide and Di-p-tolyl Disulfide with the Aminophosphine 1. A mixture of 0.1 g (0.45 mmol) of diphenyl disulfide (105) and 0.1 g (0.40 mmol) of di-p-tolyl disulfide (28) was dissolved in 5 ml of benzene and 0.1 g (0.4 mmol) of 1 was added. The resulting solution was analyzed by vpc. In addition to the disulfides added, a new peak was observed. This new compound was identified as p-tolyl phenyl disulfide (106) by comparison with an authentic sample. The three disulfides, 105, 106, and 28 were present in near equal amounts.

Preparation of Tris(diethylamino)benzyl Thiophosphonium Fluoroborate (109). A suspension of 1.95 g (10 mmol) of silver tetrafluoroborate and 2.78 g (10 mmol) of tris(diethylamino)phosphine sulfide (4) in 50 ml of dry dichloromethane was stirred in a nitrogen atmosphere at -78° while 1.71 g (10 mmol) of benzyl bromide in 10 ml of dry dichloromethane was added dropwise. The resulting mixture was allowed to warm up to room temperature. After stirring the mixture for 0.5 hour, the silver bromide was removed by filtration and the crude salt precipitated as an oil by dilution with hexane. The oil was

separated and washed 10 times with hexane, precipitated from dichloromethane with hexane and washed as before. The oil was dried in vacuum in the dark to yield 4.0 g(83%) of a viscous hygroscopic oil. When prepared in this manner, the salt contained 5-15% (nmr) occluded phosphine sulfide 4. The nmr spectrum of this salt showed aromatic protons as a singlet at 2.55τ, benzylic protons as a doublet (J_{PH} = 8.0 Hz) at 5.77τ, methylene protons as a multiplet at 6.7τ, and methyl protons as a triplet (J_{HH} = 7.5 Hz) at 8.75τ; ir (film) 1460 cm^{-1}, 1400, 1015 (broad), 800.

Reaction of Tris(diethylamino)benzylthiophosphonium Fluoroborate (109) with Sodium Benzyl Mercaptide. A suspension of 0.073 g (0.5 mmol) of sodium benzyl mercaptide in 2 ml of dry benzene was shown by vpc to be free of benzyl disulfide and benzyl sulfide. To this suspension was added 0.244 g (0.5 mmol) of the phosphonium salt 109 in 2 ml of dry benzene. A reaction occurred immediately; a brown solid precipitated and the solution turned black. After allowing the mixture to settle for 1 minute, the supernatant liquid was analyzed by vpc; both benzyl disulfide and benzyl sulfide were observed as products, in the ratio of 6:4 . A large amount of phosphine sulfide 4 was also present in the mixture. On standing 18 hours, the product ratio was unchanged. No phosphine 1 was detected by vpc.

When silver tetrafluoroborate (0.1 g) was mixed in benzene solution with the aminophosphine 1, the colorless solution turned black and a fine black solid deposited. A tlc chromatogram of this solution showed several spots on development with iodine.

Desulfurization of Thiolsulfinates.

Preparation of 5H,8H-Dibenzo[d,f]-1,2-Dithiocin-6-oxide (112).

To 245 mg (1.0 mmol) of 5H,8H-dibenzo[d,f]-1,2-dithiocin (101) suspended in 10 ml of acetic acid was added 2 ml of a 3.5% hydrogen peroxide solution and 5 ml of dichloromethane. The mixture was stirred until solution occurred (18 hours). The reaction was diluted with water (50 ml), the precipitated solid filtered and crystallized from ethanol to afford 233 mg (90%) of the thiolsulfinate 112 as colorless crystals, mp 154-155°; ir (KBr) 1085 cm^{-1} (S=O); nmr ($CDCl_3$) 2.53 τ (m, 8H, aromatic), 5.62 τ (q, 2H, J_{AB} = 13.0 Hz), 6.08 τ (q, 2H, J_{AB} = 15.0 Hz).

Anal. Calcd for $C_{14}H_{12}S_2O$: C, 64.59; H, 4.65; S, 24.63. Found: C, 64.85; H, 4.41; S, 24.58.

Desulfurization of 112; 5H,7H-Dibenzo[c,e]-Thiepin-6-oxide (113).

A solution of 50 mg (0.19 mmol) of 112 in 2 ml of benzene was treated with 100 mg (0.4 mmol) of tris(diethylamino)phosphine (1). After stirring the mixture for 1 hour, the solvent was removed in vacuum and the residue chromatographed over silica gel. Elution with chloroform afforded after crystallization from hexane, 28 mg (64%) of 5H,7H-dibenzo[c,e]-thiepin-6-oxide (113), mp 127-129°, ir (KBr) 1085 cm^{-1} (S=O), nmr ($CDCl_3$) 2.47 τ (m, 8H, aromatic), 6.32 τ (q, 2H, J_{AB} = 11.5 Hz), 6.30 τ (q, 2H, J_{AB} = 14.5 Hz).

Anal. Calcd for $C_{14}H_{12}SO$: C, 73.64; H, 5.30; S, 14.08. Found: C, 73.30; H, 5.09; S, 14.39.

Desulfurization of Thiolsulfonates:

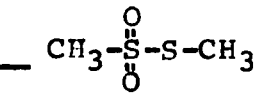
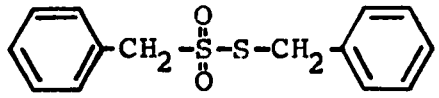
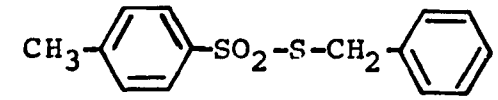
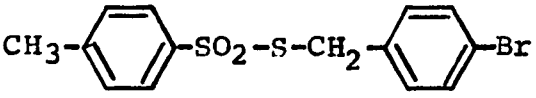
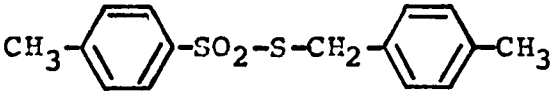
A) Thiolsulfonates which Yield Sulfone as the Only Product.

To a solution of the thiolsulfonate in dry ether was added the

requisite amount (10% excess) of tris(diethylamino)phosphine (1) in dry ether. An oil which deposited immediately on stirring and cooling, slowly crystallized. Filtration and recrystallization of the crude sulfone afforded pure product. The thiolsulfonates which were desulfurized in this manner are summarized in Table XXI.

TABLE XXI

$$R\text{-}SO_2\text{-}S\text{-}R' + (Et_2N)_3P \longrightarrow R\text{-}SO_2\text{-}R' + (Et_2N)_3P{=}S$$

$R\text{-}SO_2\text{-}S\text{-}R'$	% Yield $R\text{-}SO_2\text{-}R'$	mp	lit.	ref.
114 	80	108-109°	109°	232
121 	65	154-155°	151°	233
116 	70	140-141°	145°	234
20 	72	177-180°	172°	235
124 	58	156-157°	157°	236

B) Thiolsulfonates which Yield Both Sulfinate Ester and Sulfone. Desulfurization of Ethyl Ethanethiolsulfonate (118). To a solution of 1.54 g (10 mmol) of ethyl ethanethiolsulfonate (118) in 10 ml of ether was treated with 2.60 g (11 mmol) of tris-(diethylamino)phosphine (1). After stirring the mixture for

10 minutes, the solvent was removed in vacuum and the residue distilled in vacuum to afford 176 mg (14.5%) of ethyl ethanesulfinate (120), bp (10 mm) 61-63° (lit. bp (16 mm) 62° (237)). The residue from the distillation was diluted with hexane upon which diethyl sulfone precipitated as fine crystals. The product was filtered and washed with hexane to yield 0.60 g (50%) of diethyl sulfone, mp 70-73° (lit. mp 73-74° (214)).

Desulfurization of Methyl p-Tolylthiolsulfonate (122). To a solution of 0.808 g (4.0 mmol) of methyl p-tolylthiolsulfonate (122) in 10 ml of anhydrous ether was added slowly 1.10 g (4.4 mmol) of the aminophosphine 1. After stirring the mixture for 2 hours, the solvent was removed in vacuum. The residue was analyzed by vpc; by comparison of peak areas, the sulfone/sulfinate ester ratio was calculated to be 2/1. The residue was distilled to afford two fractions; 0.50 g, bp (0.1 mm) 80-100°, and a high boiling fraction, 0.65 g, bp (0.1 mm) 120-127°. Redistillation of the lower fraction afforded 0.10 g (13%) of methyl p-tolylsulfinate, bp (0.1 mm) 100-104°, n_D^{25} 1.548 (lit. n_D^{20} 1.543 (238)). The high boiling fraction, on dilution with cyclohexane, deposited 0.04 g (6%) of methyl p-tolyl sulfone as colorless crystals, mp 85-87° (lit. mp 86-87° (239)).

Desulfurization of Ethyl p-Tolylthiolsulfonate (123). A solution of 2.16 g (10 mmol) of ethyl p-tolylthiolsulfonate (123) and 2.75 g (11 mmol) of the aminophosphine 1 in 10 ml of dry ether was stirred for 3 hours. The solvent was removed in vacuum and the residue was analyzed by vpc. By comparison of

peak areas, the sulfone/sulfinate ester ratio was calculated to be 3/1. No pure products, however, were isolated from this reaction.

1,2-Dithiolan-1,1-dioxide (126). A solution of 20.1 g (200 mmol) of 1,3-propanedithiol in 450 ml of acetic acid was cooled to 5° and 60 ml (600 mmol) of a 35% aqueous hydrogen peroxide solution was added dropwise. The mixture was stirred overnight, the acetic acid removed in vacuum (below 40°), the residue diluted with water and extracted with ethyl acetate. After neutralization with sodium carbonate, the extract was dried and concentrated in vacuum. The residue was crystallized from ethyl acetate/ether to afford 7.3 g (26%) of colorless crystals, mp 24.5-26°; ir (KBr) 1325 and 1110 cm^{-1}; nmr ($CDCl_3$) 6.25 τ (t, 2H, J = 6.5 Hz), 6.53 τ (t, 2H, J = 7 Hz), 7.46 τ (m, 2H); mass spectum: parent ion at m/e 138, fragments at 46, 45, 74, 64.

Anal. Calcd for $C_3H_6S_2O_2$: C, 26.07; H, 4.38; S, 46.40. Found: C, 26.09; H, 4.58; S, 45.96.

1,2-Oxathiolan-2-oxide (127). To a solution of 1.38 g (10 mmol) of 1,2-dithiolan-1,1-dioxide (126) in 25 ml of benzene was added dropwise 2.60 g (11 mmol) of tris(diethylamino)-phosphine (1). An exothermic reaction occurred immediately upon addition of 1. The mixture was stirred for 15 minutes, the solvent removed in vacuum and the residue distilled in vacuum to yield 0.80 g (80%) of 127, bp (0.2 mm) 48-49°; n_D^{25} 1.4862, ir (film) 1105 cm^{-1} (S=O); nmr ($CDCl_3$) 6.55 τ (m, 2H), 8.65 τ (m, 4H); mass spectrum: parent ion at m/e 106, fragments

at 43, 58, 42, 78.

Anal. Calcd for $C_3H_6SO_2$: C, 33.93; H, 5.70; S, 30.19. Found: C, 33.08; H, 5.92; S, 29.36.

1,2-Dithian-1,1-Dioxide (128). A solution of 30.5 g (250 mmol) of 1,4-butanedithiol in 250 ml of acetic acid was cooled in an ice bath and 75 ml (770 mmol) of a 35% aqueous peroxide solution was added slowly such that the reaction temperature did not rise above 35°. After stirring for 18 hours, the solvent was removed under vacuum, the residue diluted with water, neutralized with sodium bicarbonate and extracted with benzene; the benzene extract was dried and the solvent removed under vacuum to yield a viscous oil which was crystallized from ether to provide 10.5 g (28%) of white crystals, mp 52-55°, which after two crystallizations from ether provided an analytical sample, mp 54-56°, (lit. mp 54.5-55°(84)); nmr (CCl_4) 7.0τ (m, 4H), 7.9τ (broad multiplet, 4H).

Anal. Calcd for $C_4H_8S_2O_2$: C, 31.56; H, 5.30; S, 42.12. Found: C, 31.83; H, 5.38; S, 41.67.

1,2-Oxathian-2-Oxide (129). A solution of 4.50 g (29.6 mmol) of 1,2-dithian-1,1-dioxide (128) in 50 ml of dry benzene was cooled in an ice bath and 7.80 g (31.6 mmol) of tris(diethylamino)phosphine (1) was added slowly. After stirring the mixture for 10 minutes, the solvent was removed under vacuum and the residue fractionally distilled in vacuum to yield

2.25 g (64%) of a colorless oil, bp (0.2 mm) 58-64°, which on redistillation afforded an analytical sample, bp (0.5 mm) 60-61°; n_D^{25} 1.4862; ir(film) 1125 cm^{-1} (S=O).

Anal. Calcd for $C_4H_8O_2S$: C, 39.97; H, 6.70; S, 26.68. Found: C, 39.68; H, 6.73; S, 26.33.

1,2-Oxathian-2,2-Dioxide (136). To a solution of 100 mg (0.84 mmol) of 1,2-oxathian-2-oxide (129) in 5 ml of water was added in aqueous potassium permanganate solution until the permanganate color persisted. The solution was filtered, acidified with concentrated hydrochloric acid and the solvent removed under vacuum; the residue was dissolved in ether, dried and the ether removed under vacuum to provide a clear oil identical in its ir and nmr spectrum to an authentic sample.

1,2-Dithian-1-Oxide (135). A solution of 10.0 g (82 mmol) of 1,4-butanedithiol in 200 ml of acetic acid was cooled to 10° and 17 ml (175 mmol) of a 35% hydrogen peroxide solution was slowly added. To maintain solution, 25-40 ml of methylene chloride was added as necessary. After stirring 24 hours, the solvent was removed under vacuum, the residue diluted with water, extracted with ether, washed with water, dried and the solvent removed under vacuum to afford a viscous oil which on distillation provided a fraction bp (0.1 mm) 100-105° which crystallized on cooling to yield 0.6 g (5%) of a wax-like material, mp 67-74°. This material could be sublimed in vacuum (70-90° at 0.1 mm) to provide pure product, mp 74-76°. This material

was homogeneous by vpc analysis; ir (KBr) 1060 cm^{-1} (S=O). The mass spectrum of this material exhibited a parent ion at m/e 136.0007 (calcd for $C_4H_8OS_2$: m/e 136.0016).

Attempted Desulfurization of p-Toluene p-Tolylthiolsulfonate; the Isolation of Adduct 125. To a solution of 2.78 g (10 mmol) of p-toluene p-tolylthiolsulfonate in 10 ml of ether was added dropwise 2.50 g (10 mmol) of tris(diethylamino)phosphine (1). No heat was evolved; however, an oil precipitated immediately. The supernatant liquid was removed and the oil was washed eight times with fresh ether. The resulting oil was dried in vacuum for 24 hours to yield 5.0 g (92%) of adduct 125 as a tan, viscous, hygroscopic oil; nmr (benzene) 2.5τ (m,8H, aromatic), 6.87τ (m, 12H, J_{HH}=7 Hz, J_{PH}=13 Hz), 7.60τ (d, 3H, J_{PH}=2.5 Hz), 7.69τ (s, 3H), 8.85τ (t, 3H, J_{HH}=7 Hz). The ^{31}P nmr of this adduct exhibited a strong resonance at -61.6 ppm relative to phosphoric acid.

Anal. Calcd for $C_{26}H_{44}N_3O_2PS_2 \cdot H_2O$: C, 58.08; H, 8.63; N, 7.81; P, 5.76; S, 11.92. Found: C, 56.63; H, 8.93; N, 8.08; P, 5.45; S, 13.07. (Sample was reported to be highly hygroscopic).

Kinetics of Desulfurization

Method A. Gas Chromatography. All materials were recrystallized or redistilled prior to use in these kinetic experiments. An F&M 5750 Research Chromatograph equipped with a Perkin Elmer Model 194B Printing Integrator and a flame ionization detector was employed to monitor the reactions. The gas chromatographic analyses were reproducable to better than ± 2%. For all exper-

iments, a 6' × 1/8" stainless steel column packed with 10% diethylene glycol succinate on Chromasorb W/AW-MCDS maintained at an oven temperature of 220° (injection port temperature, 330°; detector port temperature, 350°) was employed. Helium was used as a carrier gas at a flow rate of 50 ml/min. The solutions of disulfide and phosphine were equilibrated for 15 minutes in a constant temperature bath (Bronwill Thermomix Constant Temperature Circulator employed for temperature control) at the desired temperature before each run. (All thermometers employed in these kinetic experiments were calibrated against an Erco #57478 thermometer).

The requisite amounts of reactants were volumetrically transferred to a flask, stoppered, shaken quickly and immersed in a constant temperature bath. After appropriate time intervals (at least 4 per run), aliquots of the reaction mixture were removed, the reaction quenched with excess sulfur, and the resulting mixture analyzed by vpc. All experiments were performed in duplicate.

In those experiments in which stoichiometric amounts of phosphine and disulfide were used, the areas of the disulfide and sulfide peaks in the gas chromatogram were used in the calculation of rate constants:

$$k_2 \quad \frac{f \times (\text{Sulfide Area})}{tR_o(\text{Disulfide Area})}$$

where k_2 = second order rate constant

t = time (seconds)

f = calibration factor (see Appendix I)

R_o = Initial reactant concentration.

All calculations were performed on an IBM 360/50 computer using a least square program (Appendix II). Rate constants were calculated for the initial portion (10-50%) of the reaction for which second order kinetics were seen to be valid.

For those experiments in which non-stoichiometric amounts of reactants were employed, sulfide and/or disulfide concentrations were calculated:

$$(\text{Sulfide Conc.}) = \frac{f*(\text{Sulfide area})(\text{Initial Phosphine Conc.})}{(\text{Phosphine sulfide Area})}$$

This equation is valid if the conversion of phosphine to phosphine sulfide by the sulfur quench is quantitative. This was demonstrated in that 0.247 g (1.00 mmol) of tris(diethylamino) phosphine (1) reacted with excess sulfur to afford 0.275 g (0.99 mmol, 99%) of tris(diethylamino)phosphine sulfide (4). (These concentrations of phosphine and phosphine sulfide were measured by vpc against diphenyl sulfide as a primary standard). From the disulfide concentration thus calculated, the second order rate constant (k_2) was calculated by the method of least squares.

Method B. Ultraviolet Spectrophotometry. A Coleman 124 Spectrophotometer equipped with a Coleman 165 recorder and a Neslab Constant Temperature Regulator ($\pm$ 0.2) was employed at constant wavelength to monitor the disappearance of disulfide with time. The solutions of disulfide and phosphine were equilibrated for 15-30 minutes at a given temperature before each run.

The requisite volumes of disulfide and phosphine stock

solutions were transferred to the uv cell and allowed to further equilibrate in the cell holder for 3-5 minutes prior to measurement of absorbance as a function of time. Pseudo-first order conditions were employed with an excess (at least ten fold stoichiometrically) of phosphine. All runs were performed in duplicate. The value of the pseudo-first order rate constants (k') were calculated from plots of ln $((A_o-A_\infty)/(A_t-A_\infty))$ vs time by the least squares method. All calculations were performed by an IBM 360/50 computer. The rate constants were calculated from the initial portion of the reaction for which first order kinetics were seen to be valid; all reactions were allowed to continue for at least six half-lives before A_∞ was recorded.

In one experiment, 1,2-dithiolane (57) , near stoichiometric concentrations of reactants were employed. The disulfide concentration (and hence the phosphine concentration) was calculated from the reported (131) extinction coefficient for this disulfide. A second order rate plot for this reaction was found to be linear (Fig. 22) and from this plot, the second order rate constant k_2 was calculated by the method of least squares.

APPENDIX I

QUANTITATIVE ANALYSIS BY GAS CHROMATOGRAPHY

APPENDIX I

Quantitative Analysis by Gas Chromatography

In several experiments, it was necessary to perform quantitative analyses by gas chromatography. By using internal standards, the concentration (C_x) of a component x in a mixture may be calculated from the equation:

$$C_x = f_x \frac{C_{STD}}{A_{STD}} A_x$$

$$f_x = \frac{C_x}{C_{STD}} \cdot \frac{A_{STD}}{A_x}$$

where C_x is the concentration of component x, C_{STD} is the concentration of internal standard, A_x and A_{STD} are the gas chromatographic peak areas of unknown x and standard respectively, and f_x is the response (calibration) factor for the particular unknown-standard combination.

The response factor f_x was determined as follows: two to four accurately weighed solutions containing internal standard and compound x were prepared. About 0.5 μl of each solution was injected two or three times into the gas chromatograph and the area of each peak was determined. (The area calculation was performed by a Perkin Elmer Printing Integrator attached to the gas chromatograph.) The concentration ratio (C_x/C_{STD}) was plotted versus the average area ratio (A_x/A_{STD}) for the components in each solution. This plot was linear bisecting the origin and with a slope f_x.

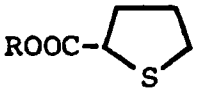
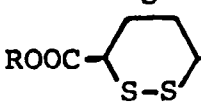
The calibration or response factor f_x was found to be

insensitive to changes in column type or operating parameters (gas flow rates, temperature, etc.). Some variation, however, was observed when the detector characteristics were appreciably altered, for example, on periodic cleaning of the detector. For this reason, the gas chromatograph was recalibrated prior to performing quantitative measurements. Typical response factors used in this work are presented in Table XXII.

All gas chromatographic analyses were performed in duplicate and area ratios were reproducable to ± 1% (average of 10 analyses). Analysis of 5 standard solutions on the precalibrated instrument were found to vary from the theoretical concentration by less than ± 3%.

TABLE XXII

TYPICAL GAS CHROMATOGRAPH RESPONSE FACTORS

Compound	Standard	f
$(Et_2N)_3P$	Ph-S-Ph	1.62
$(Et_2N)_3PS$	Ph-S-Ph	1.27
	Xylene	2.50
	1,2-Dithiane	0.95
Benzyl Sulfide	Benzyl Disulfide	0.88
Benzyl Sulfide	Ph-S-Ph	0.84
Benzyl p-Bromobenzyl sulfide	Ph-S-Ph	0.90
Di-p-bromobenzyl sulfide	Ph-S-Ph	1.00
Benzyl Disulfide	Ph-S-Ph	1.79
 c,t	$(Me_2N)_3P=O$	1.16
 c,t	$(Me_2N)_3P=O$	1.16

APPENDIX II

COMPUTER PROGRAMS (IBM 360/50)

APPENDIX II

Program I. Calculation of Second Order Rate Constants and Activation Parameters by the Method of Least Squares.

Input data for this program is the integrated vpc peak areas of one product and one reactant of a bimolecular reaction. The program is applicable only if both reactants are present in equal concentrations (0.2 M)

Format for input data:

Card #1. Headings (full card).
#2. Gas Chromatographic response factor (f) (col 1,2)
#3. Total number of runs (col 1,2)
#4. Headings for particular run (col 1-12), temperature (C.) (col 13-18), number of points in run (col 19,20).
#5 Data: Product area (col 1-5)
Reactant area (col 6-10)
Time (11-15)
Repeat #5 for each point.

If the initial reactant concentration $\neq$ 0.2 M, the value of A in statement 26 should be changed.

Program:

```
      DIMENSION TEMP(20),TE(20),TA(20),RATE(20),RATE1(20),R(20),R1(20
      DIMENSION X(40), Y(40), T(40), RATIO(40), RT(40)
      DIMENSION HEAD(18)
      DIMENSION ENTX(40), RAT(40)
      DIMENSION S(40)
      DIMENSION TIME(40)
   10 READ(5,15,END=450)(HEAD(M),M=1,18)
   15 FORMAT(18A4)
      READ(5,151)F
  151 FORMAT(F6.4)
      WRITE(6,370)(HEAD(M),M=1,18)
  370 FORMAT(1H1,30X,18A4//55X,18HKINETIC EXPERIMENT///)
      READ(5,45)K
   45 FORMAT(I2)
      SUMR1=0.0
      SUMR=0.0
      SUMTE=0.0
      DO 350 L=1,K
      READ(5,60)TITLE,TITLE1,TITLE2,TEMP(L),NRUN
   60 FORMAT(3A4,F6.1,I2)
      WRITE(6,70)TITLE,TITLE1,TITLE2,TEMP(L)
   70 FORMAT(1H ,3A4,5X,4HTEMP,2X,F6.1/)
      WRITE(6,40)
   40 FORMAT(1H ,21X,4HTIME,6X,12HSULFIDE AREA,3X,14HDISULFIDE AREA,(
     1,5HRATIO, 10X, 24H2 ND ORDER RATE CONSTANT/)
      SUM=0.0
      A=0.20
      DO150 I=1,NRUN
      READ(5,120)X(I),Y(I),T(I)
```

```
120 FORMAT(3F5.1)
    RATIO(I) =(F*X(I))/(A*60*Y(I))
    RT(I)=RATIO(I)/T(I)
    TIME(I)=T(I)
    SUM=SUM+RT(I)
    WRITE(6,140)T(I),X(I),Y(I),RATIO(I),RT(I)
140 FORMAT(1H ,17X,F8.1,7X,F8.1,7X,F8.1,7X,F11.6,10X,E12.6/)
150 CONTINUE
    G=NRUN
    RMEAN=SUM/G
    SUMS=0.0
    DO300I=1,NRUN
    S(I)=(RT(I)-RMEAN)**2
300 SUMS=SUMS+S(I)
    DEV=SQRT(SUMS/(G-1.0))
    STDERR=(DEV*100)/RMEAN
    CALL LINE(NRUN,TIME,RATIO,SLOPE,B,STDDEV)
    WRITE(6,160)RMEAN,SLOPE,B,STDDEV
160 FORMAT(1H ,10X,4HMEAN,3X,E12.6,5X,13HRATE CONSTANT,3X,E12.6,5X,
   29HINTERCEPT,3X,E12.6,3X,6HSTDDEV,3X,E12.6)
    WRITE(6,310)DEV,STDERR
310 FORMAT(1H ,10X,6HSTDDEV,2X,E12.6/10X,6HSTDERR,2X,E12.6/)
    TA(L)=TEMP(L)+273.15
    TE(L)=1.0/TA(L)
    RATE1(L)=SLOPE
    R1(L)=ALOG(RATE1(L)/TA(L)*5.663E+07)
350 CONTINUE
    CALL LINE (K,TE,R1,ACT1,ENT1,STD2)
    H=K
    ENG1=(-ACT1)*1.987
    SUMENT=0.0
    DO360 L=1,K
    RAT(L)=RATE1(L)*1.E03
    ENTX(L)=1.987*((ENG1/(1.987*TA(L)))-ALOG(TA(L))+ALOG(RAT(L))
   1+25.764)
360 SUMENT=SUMENT+ENTX(L)
    ENTR1=SUMENT/H
    WRITE(6,371)(HEAD(M),M=1,18)
371 FORMAT(1H1,30X,18A4//55X,21HACTIVATION PARAMETERS///)
    WRITE(6,380)TITLE,TITLE1,TITLE2
380 FORMAT(1H ,46X,3A4/)
    WRITE(6,390)(TEMP(L),RATE1(L),L=1,K)
    WRITE(6,395)ENG1,ENTR1
390 FORMAT(1H ,56X,F8.1,5X,E12.6)
395 FORMAT(1H0,36X,17HACTIVATION ENERGY,3X,F12.3,5X,8HENTROPHY,3X,
   1F12.1///)
    WRITE(6,400)(ENTX(L),L=1,K)
400 FORMAT(1H ,F12.3)
    ER=STD2*1.987
    WRITE(6,410)ER
410 FORMAT(1H0,F12.3)
    GO TO 10
450 STOP
    END
```

Subroutine:

```
      SUBROUTINE LINE(N,X,Y,SLOPE,B,STDDEV)
      DIMENSION X(40),Y(40)
      DIMENSION R(40)
      SUMX=0.0
      SUMY=0.0
      SUMXY=0.0
      SUMXX=0.0
      SUM=0.0
      DO 10 J=1,N
      SUMX=SUMX+X(J)
      SUMY=SUMY+Y(J)
      SUMXY=SUMXY+X(J)*Y(J)
   10 SUMXX=SUMXX+X(J)**2
      G=N
      DENOM=SUMX**2-G*SUMXX
      SLOPE=(SUMX*SUMY-G*SUMXY)/DENOM
      B=(SUMX*SUMXY-SUMY*SUMXX)/DENOM
      DO 20 I=1,N
      R(I)=(SLOPE*X(I)+B-Y(I))**2
   20 SUM=SUM+R(I)
      STDDEV=SQRT(SUM/(G*SUMXX-SUMX**2))
      RETURN
      END
```

Program II. Program for the Calculation of Pseudo First Order and True Second Order Rate Constants based on UV Absorption Data.

Program: (including data format)

```
C PROGRAM FOR THE CALCULATION OF PSEUDO FIRST ORDER AND TRUE SECOND
C  ORDER RATE CONSTANTS  .......
C DATA CARDS:
C HEADINGS ON CARD ONE...
C CARD TWO:  LIMITING REAGENT CONC. (C1) COL 1-9
C            EXCESS REAGENT (C2) COL 10-19
C            NUMBER OF MEASUREMENTS  COL 20-21
C  MEASUREMENTS  TIME (MIN) COL 1-9 ;  UV ABSORPTION COL 10-19
C  FINAL CARD: FINAL ABSORPTION COL 1-9
      DIMENSION HEAD(20),T(40),A(40),TIME(40),RATIO(40)
   20 READ(5,50)(HEAD(M),M=1,18)
   50 FORMAT(18A4)
      IF(HEAD(1).EQ. END)GO TO 500
      READ(5,100)C1,C2,N
  100 FORMAT(F9.5,F10.5,I2)
      READ(5,200)(T(I),A(I),I=1,N)
  200 FORMAT(2F9.5)
      READ(5,210)AE
  210 FORMAT(F10.5)
      DO35 I=2,N
      TIME(I)=T(I)*60
      IF(A(1).LE.AE)GO TO 30
      RATIO(I)=ALOG((A(1)-AE)/(A(I)-AE))
      GO TO 35
   30 RATIO(I)=ALOG((AE-A(I))/(AE-A(1)))
   35 CONTINUE
      RATIO(1)=0.0
      CALL LINE(N,TIME,RATIO,SLOPE,B,STDDEV)
      RATE=SLOPE/C2
      WRITE(6,300)(HEAD(M),M=1,18)
  300 FORMAT(1H1,53X,25HPSEUDO 1ST ORDER KINETICS//30X,18A4///)
      WRITE(6,350)C1,C2,AE
  350 FORMAT(1H ,21HINITIAL CONCENTRATION//30X,18HLIMITING REACTANT#,
     1 2X, F9.5/30X,16HEXCESS REACTANT#,4X,F10.5//20X,16HFINAL ABSORPTIO
     2N,2X,F10.5//48X,4HTIME, 10X,10HABSORBANCE,13X,5HRATIO//)
      WRITE(6,400)(T(I),A(I),RATIO(I),I=1,N)
  400 FORMAT(1H ,45X, F9.4,10X, F9.5,10X,F10.5)
      WRITE(6,450)SLOPE,B,STDDEV,RATE
  450 FORMAT(1H ,42X,23H1ST ORDER RATE CONSTANT,10X,E12.6/49X,9HINTERCEP
     1T,17X,E12.6/44X,18HSTANDARD DEVIATION,13X,E12.6//41X,
     2 24H2EDN ORDER RATE CONSTANT,10X,E12.6)
      GO TO 20
  500 STOP
      END
```

Subroutine:

```
      SUBROUTINE LINE(N,X,Y,SLOPE,B,STDDEV)
      DIMENSION X(40),Y(40)
      DIMENSION R(40)
      SUMX=0.0
      SUMY=0.0
      X(1)=0.0
      Y(1)=0.0
      SUMXY=0.0
      SUMXX=0.0
      SUM=0.0
      DO10 J=1,N
      SUMX=SUMX+X(J)
      SUMY=SUMY+Y(J)
      SUMXY=SUMXY+X(J)*Y(J)
   10 SUMXX=SUMXX+X(J)**2
      G=N
      DENOM=SUMX**2-G*SUMXX
      SLOPE=(SUMX*SUMY-G*SUMXY)/DENOM
      B=(SUMX*SUMXY-SUMY*SUMXX)/DENOM
      DO20 I=1,N
      R(I)=(SLOPE*X(I)+B-Y(I))**2
   20 SUM=SUM+R(I)
      STDDEV=SQRT(SUM/(G*SUMXX-SUMX**2))
      RETURN
      END
```

Program III. Calculation of Activation Parameters ($\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$) by the Method of Least Squares.

Program: (including data format) --- use subroutine of Program I.

```
C.....PROGRAM FOR THE CALCULATION OF ACTIVATION PARAMETERS
C.....INPUT:  TEMPERATURES AND RATE CONSTANTS
C.....FORMAT:  CARD 1...HEADINGS
C..............CARD 2...NUMBER OF POINTS    COL 1,2
C..............DATA CARDS....TEMPERATURES CENTIGRADE   COL 1-10
C.............................RATE CONSTANT (L/M/SEC)   COL 11-19
C..............CONTROL CARD:  22 IF END OF SERIES,   33 IF END OF DATA
      DIMENSION ENTX(40), RAT(40)
      DIMENSION TEMP(20),TE(20),TA(20),RATE(20),RATE1(20),R(20),R1(20)
      DIMENSION HEAD(18)
   10 READ(5,15)(HEAD(M),M=1,18)
   15 FORMAT(18A4)
      READ(5,45)K
   45 FORMAT(I2)
      READ(5,50)(TEMP(L),RATE1(L),L=1,K)
   50 FORMAT(2F10.5)
      DO 350 L=1,K
      TA(L)=TEMP(L)+273.15
      TE(L)=1.0/TA(L)
      R1(L)=ALOG(RATE1(L)/TA(L)*5.663E+07)
  350 CONTINUE
      CALL LINE (K,TE,R1,ACT1,ENT1,STD2)
      H=K
      ENG1=(-ACT1)*1.987
      SUMENT=0.0
      DO360 L=1,K
      RAT(L)=RATE1(L)*1.E03
      ENTX(L)=1.987*((ENG1/(1.987*TA(L)))-ALOG(TA(L))+ALOG(RAT(L))
     1-25.764)
  360 SUMENT=SUMENT+ENTX(L)
      ENTR1=SUMENT/H
      WRITE(6,371)(HEAD(M),M=1,18)
  371 FORMAT(1H1,30X,18A4//55X,21HACTIVATION PARAMETERS///)
      WRITE(6,390)(TEMP(L),RATE1(L),L=1,K)
      WRITE(6,395)ENG1,ENTR1
  390 FORMAT(1H ,56X,F8.1,5X,E12.6)
  395 FORMAT(1H0,36X,17HACTIVATION ENERGY,3X,F12.3,5X,3HENTROPHY,3X,
     1F12.1///)
      WRITE(6,400)(ENTX(L),L=1,K)
  400 FORMAT(1H ,F12.3)
      ERR=STD2*1.987
      WRITE(6,410)ERR
  410 FORMAT(1H0,F12.6)
      READ(5,320)J
  320 FORMAT(I2)
      IF(J.EQ.33) STOP
      GO TO 10
      END
```

Program IV. Calculation of Second Order Rate Constants.

This program is applicable when the initial concentration of reactants are not equal.

Data format:
Card #1. Number of points in run
#2. Data: Reactant A concentration (col 1-6),
Reactant B concentration (col 7-12)
Time (col 13-18).
Repeat #2 for each point in run.

Program: ---(use subroutine of Program I.)---

```
....CALCULATION OF SECOND ORDER RATE CONSTANTS
      DIMENSION T(20),X(20),P(20),XLG(20),TIME(20)
   10 READ(5,20,END=300)N
   20 FORMAT(I2)
      READ(5,30)(T(I),P(I),X(I),I=1,N)
   30 FORMAT(3F6.5)
      DO 100 I=1,N
      XLG(I)=ALOG((P(I)*X(1))/(X(I)*P(1)))
      TIME(I)=T(I)*60.0
  100 CONTINUE
      CALL LINE (N,TIME,XLG,SLOPE,B,STDDEV)
      RATE=SLOPE/(P(1)-X(1))
      STDEV=STDDEV/(P(1)-X(1))
      WRITE(6,150)
  150 FORMAT(1H1,27HSECOND ORDER RATE CONSTANTS///)
      WRITE(6,180)P(1),X(1)
  180 FORMAT(1H , 5X,21HINITIAL CONCENTRATION//
     15X, 10HREAGENT #1,5X,F10.5,
     2//5X,10HREAGENT #2,5X,F10.5//
     355H     TIME (MIN)                CONC.#1              CONC.#2      )
      WRITE(6,200)(T(I),P(I),X(I),I=1,N)
  200 FORMAT(1H ,5X,F10.5,10X,F10.5,10X,F10.5,/)
      WRITE(6,250)RATE,STDEV
  250 FORMAT(1H ,5X,13HRATE CONSTANT,10X, E12.6//5X,
     118HSTANDARD DEVIATION,5X,E12.6)
      GO TO 10
  300 STOP
      END
```

APPENDIX III

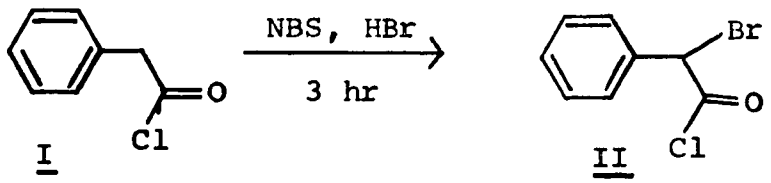
α-BROMINATION OF ACID HALIDES

APPENDIX III

α-BROMINATION OF ACID HALIDES

The α bromination of acids may be accomplished by the Hell-Volhard-Zelinski (HVZ) reaction (240). Although this reaction is believed to proceed by bromination of the acyl bromide which is generated in situ, the direct bromination of an acid chloride, in most cases, proceeds with difficulty (241). Extended reaction times, free radical initiators and high intensity light are often utilized to realize such a bromination. Although N-bromosuccinimide (NBS) is well known as a brominating agent (242), there are no reports of this reagent being employed to directly brominate acid chlorides.

It was found that NBS, in the presence of acid catalysts, effects the bromination of acid halides in relatively short reaction times and in high yield . For example, phenyl acetyl chloride (I) is quantitatively converted (nmr) to the α-bromo



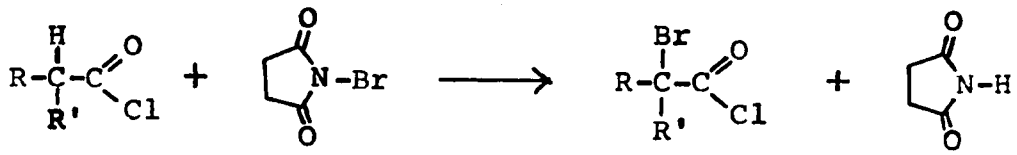
I II

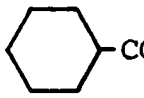
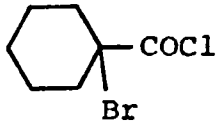
derivative II. This was accomplished by refluxing the acid chloride with a 20% excess of N-bromosuccinimide for 3 hours in carbon tetrachloride solution to which had been added 3-5 drops of HBr/HOAc solution. Filtration of the insoluble succinimide and removal of solvent afforded crude acid chloride II which was shown to be homogeneous by vpc analysis. Distillation provided the α-bromo acid chloride in 75% yield. In a similar manner, a variety of primary and secondary acid chlorides and diacid chlorides were converted to their α-bromo derivatives.

These results are summarized in Table XXIII. Yields in all cases

TABLE XXIII

BROMINATION OF ACID CHLORIDES BY NBS.



Acid Chloride	Reaction time, hr	Product	% Yield[a]
$C_6H_5CH_2COCl$	3	$C_6H_5CH(Br)COCl$	75
$ClCH_2CH_2COCl$	4	$ClCH_2CH(Br)COCl$	70
$CH_2(CH_2COCl)_2$	1	$CH_2(CH(Br)COCl)_2$	75[b]
CH_2CH_2COCl CH_2CH_2COCl	1	$CH_2CH(Br)COCl$ $CH_2CH(Br)COCl$	60[c]
	4.5		58 70[d]

a) Reactions were quantitative (nmr), yields reported are of pure distilled product. b) Isolated as the methyl ester. c) Isolated as the meso diacid. d) Isolated as the amide.

were quantitative as determined by nmr. These compounds could be isolated in high yield and purity. Thus, this bromination reaction would permit the convenient preparation of many α-brominated acyl derivatives such as esters, amides, aldehydes and ketones as well as α-bromo acids.

That the bromination of acid chlorides by NBS does not proceed by a free radical process, but rather by way of an ionic mechanism could be readily demonstrated. Addition of benzoyl

peroxide, a free radical initiator (243), suppressed the rate of bromination to a considerable extent while the addition of a trace of a mineral acid had a strong catalytic effect (Fig. 30).

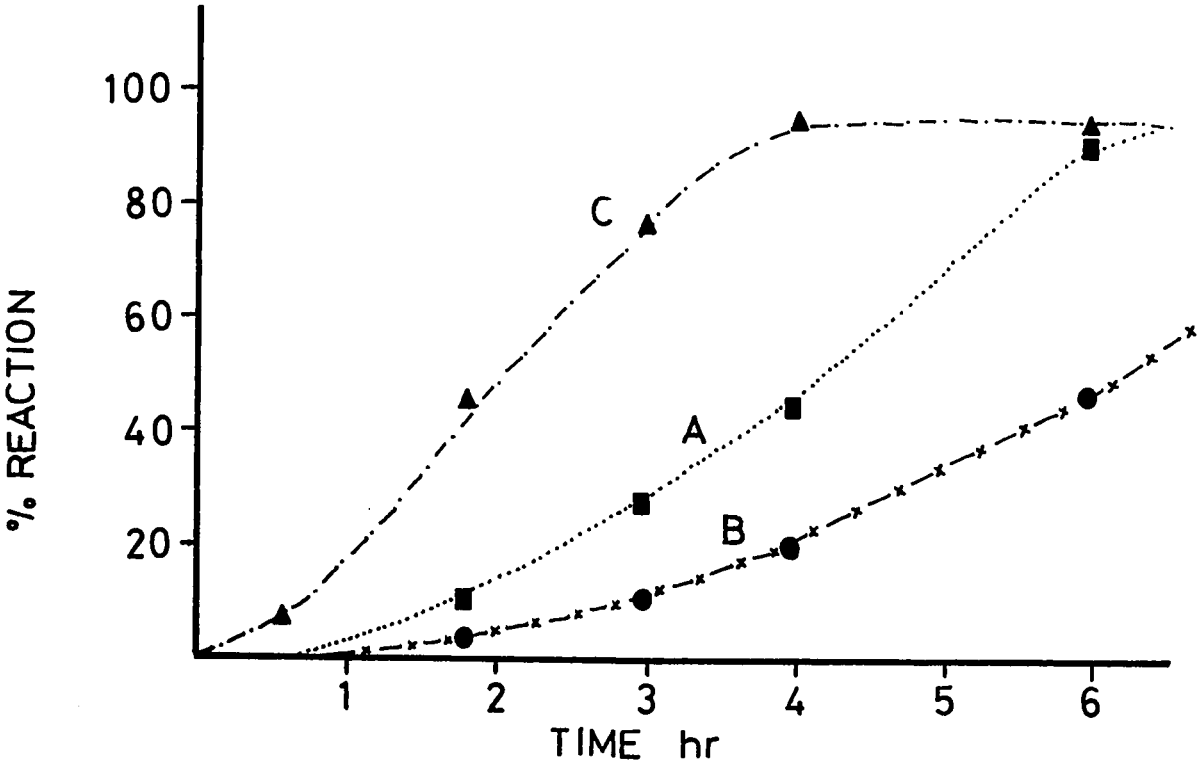
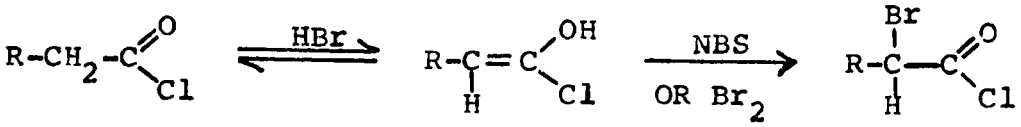


Figure 30. Bromination of Phenyl Acetyl Chloride (I).
A) refluxing carbon tetrachloride (1 M.)
B) as (A), benzoyl peroxide added.
C) as (A), 1 drop HBr/HOAc added.

The function of the acid is presumably to effect enolization of the acid chloride. This enol may then undergo bromination either by reaction with NBS itself, or with bromine generated by



the reaction of NBS with acid. Bromine is generated during the reaction as evidenced by the development of a deep red coloration.

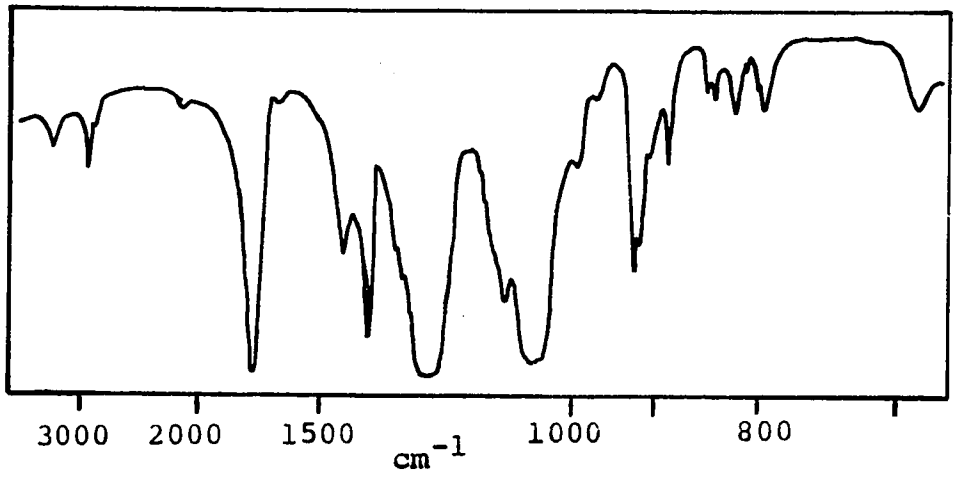
This bromination reaction appears to be both convenient

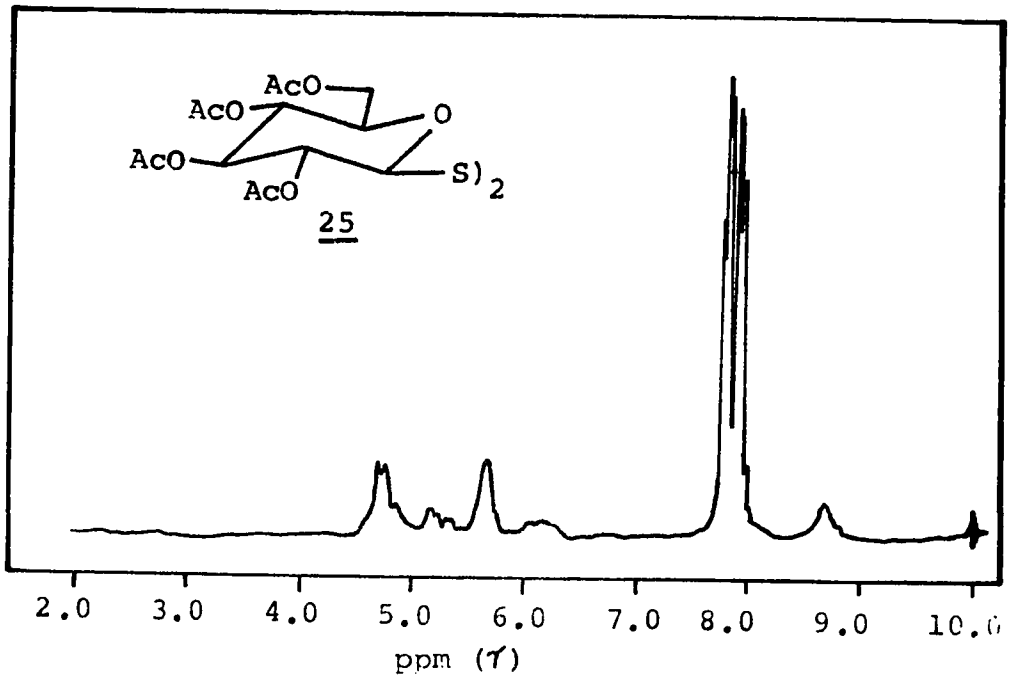
and general; the high yields and short reaction times make it competitive with the HVZ reaction. Since this bromination permits the isolation of the α-bromo acid chloride, from which a wide variety of acyl derivatives may be prepared, the reaction is thus more versatile than the classical HVZ reaction.

APPENDIX IV

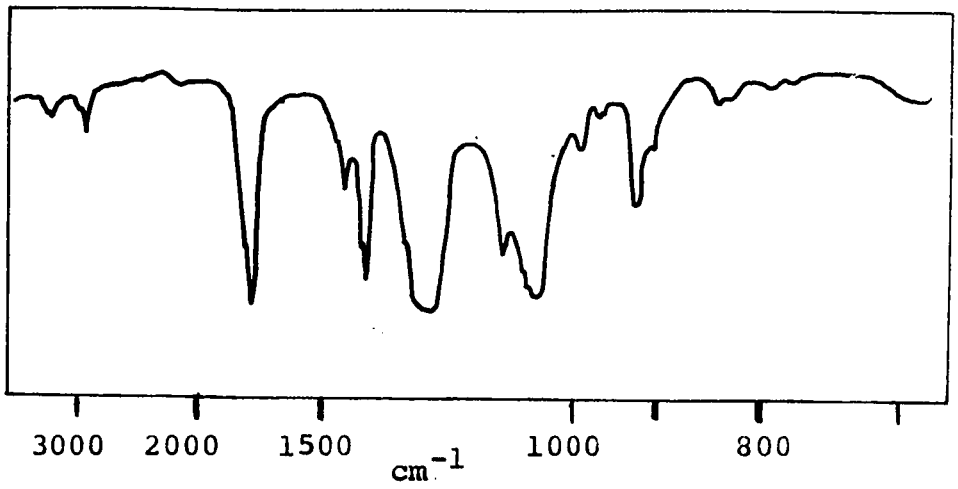
SPECTRA

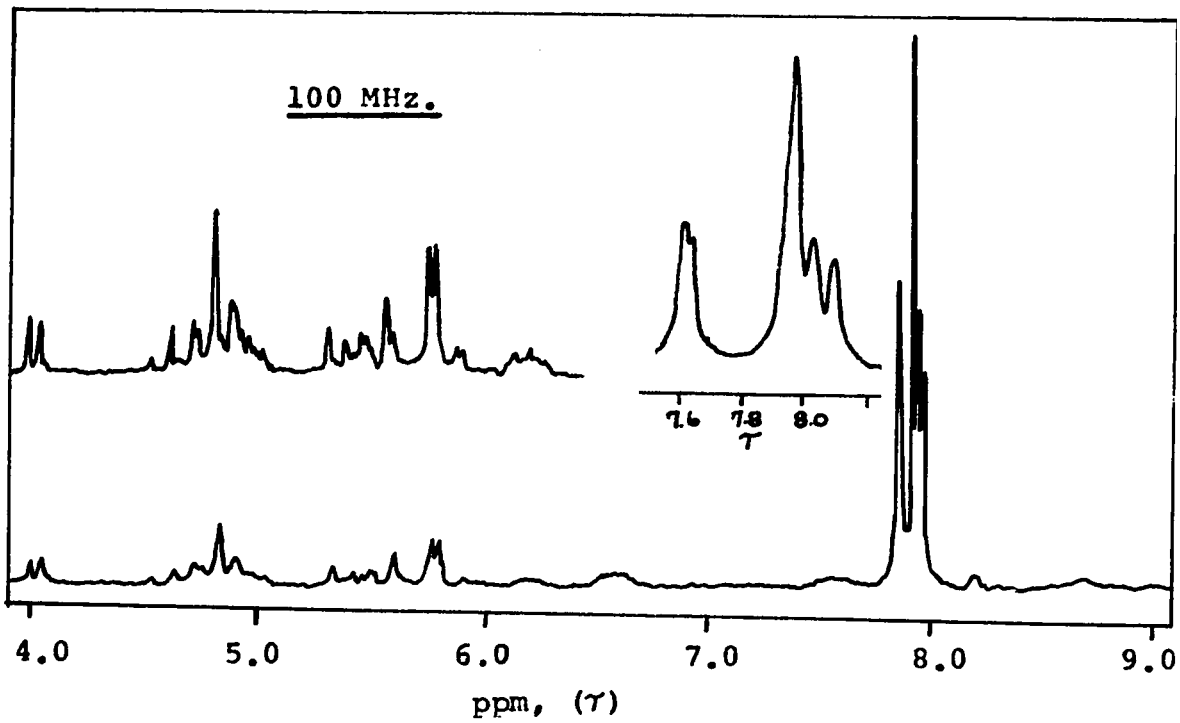
(Solvents and major line positions are recorded in the Experimental Section. Spectra are listed in order of the compound's number.)

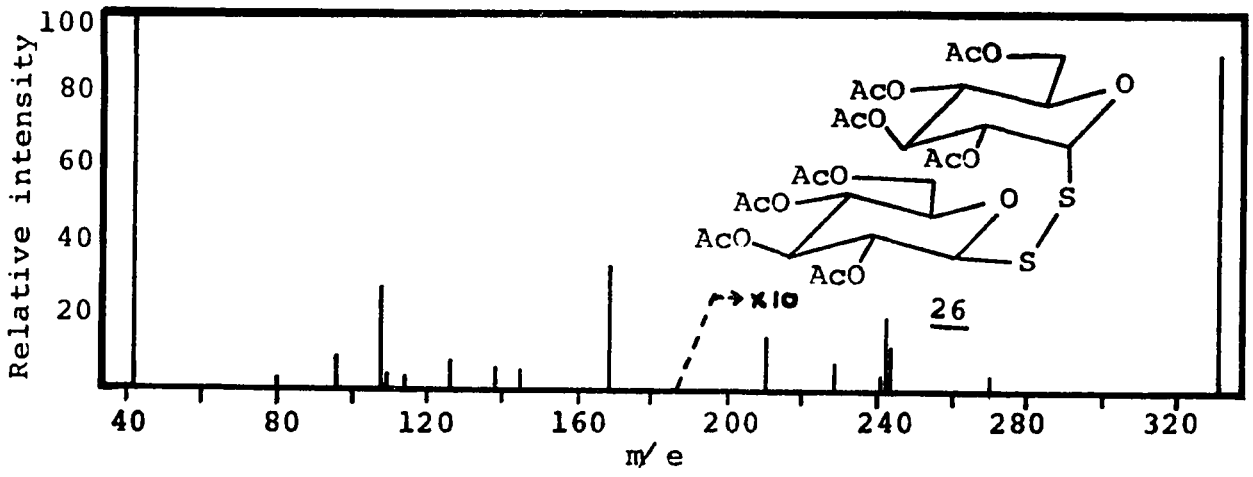




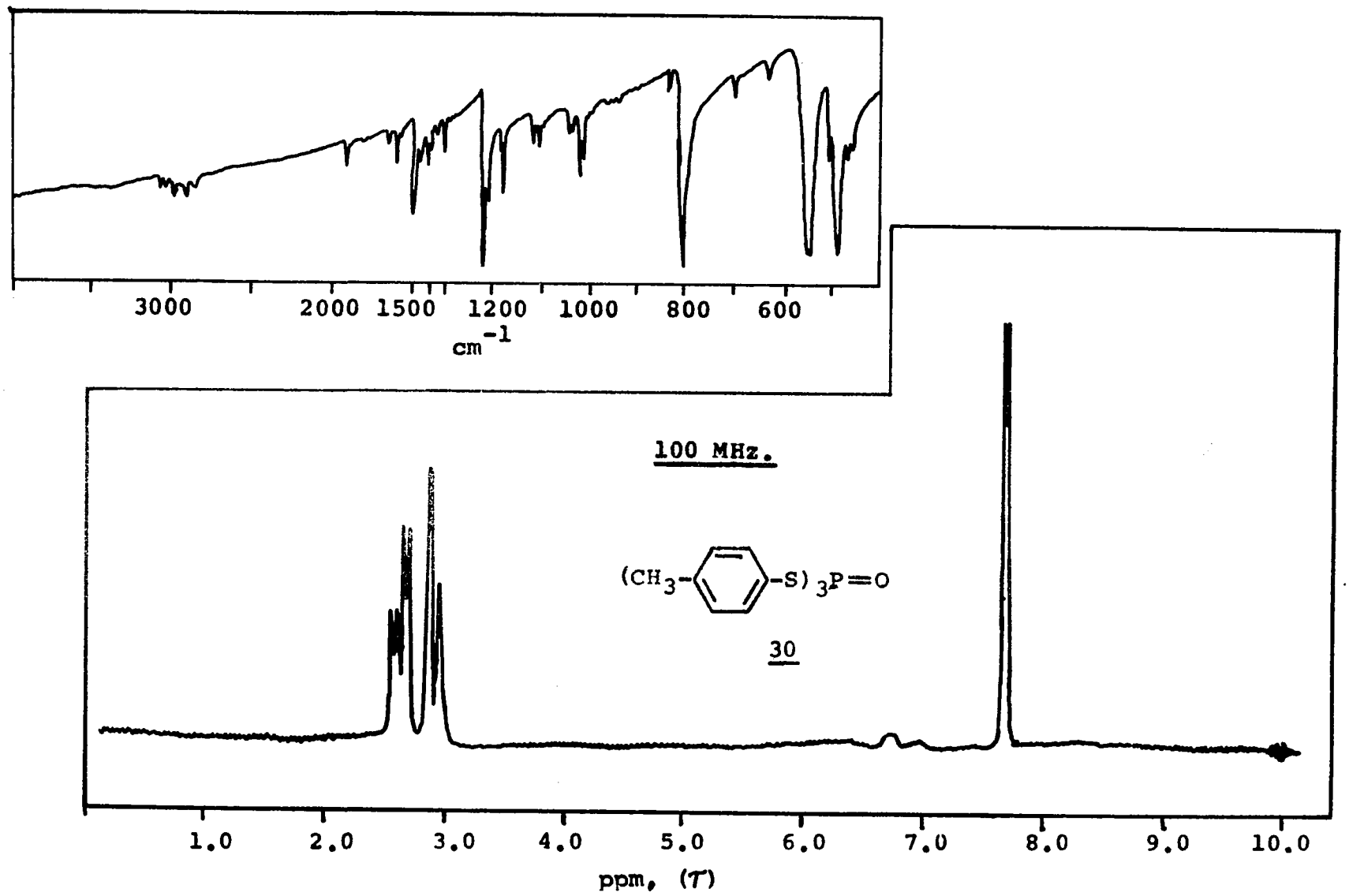
β-D-Glucopyranosyl disulfide octa-O-acetate (25).



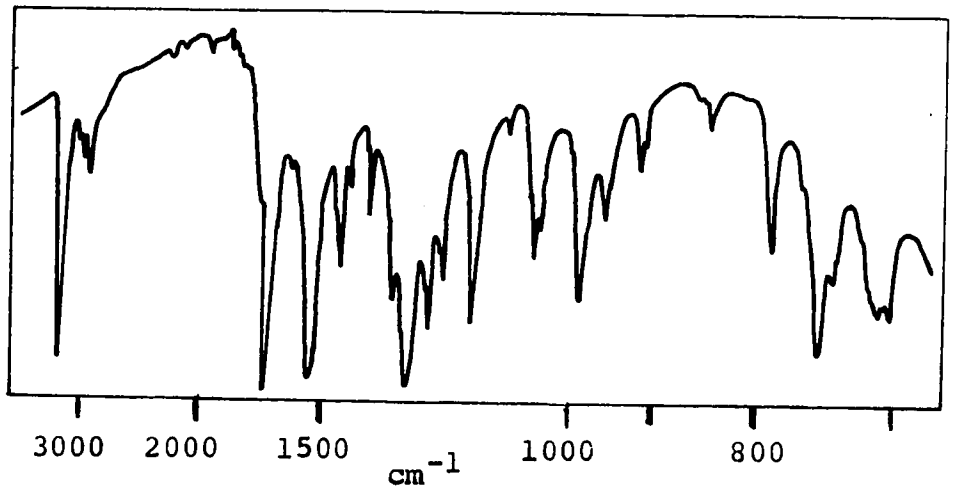


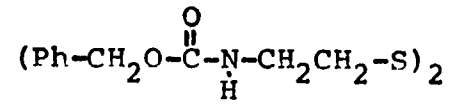


α-D-Glucopyranosyl-1-thio-β-D-glucopyranoside octa-O-acetate (26).

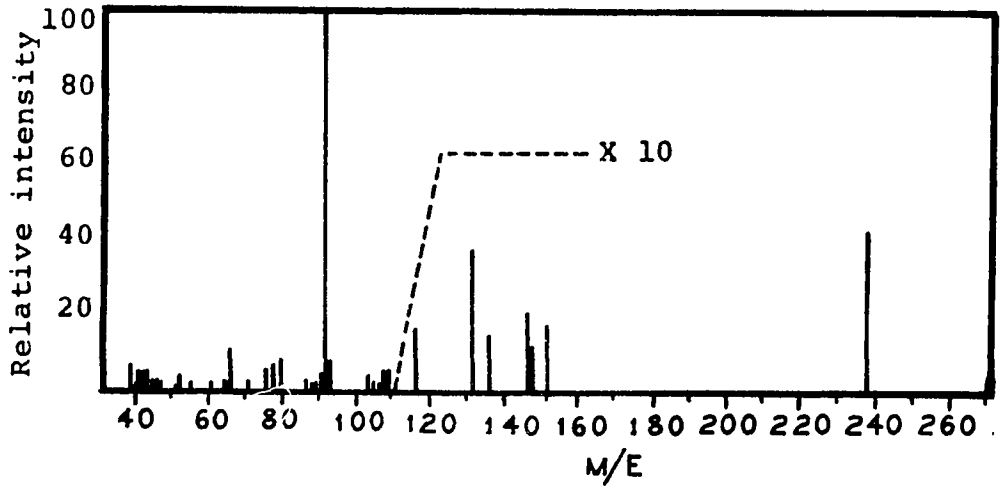


Tri-p-toluene phosphotrithioate (30).

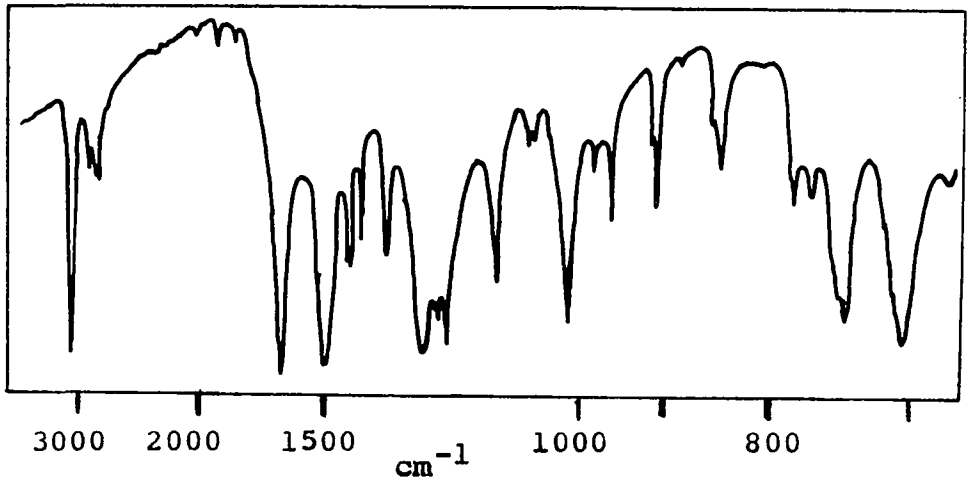


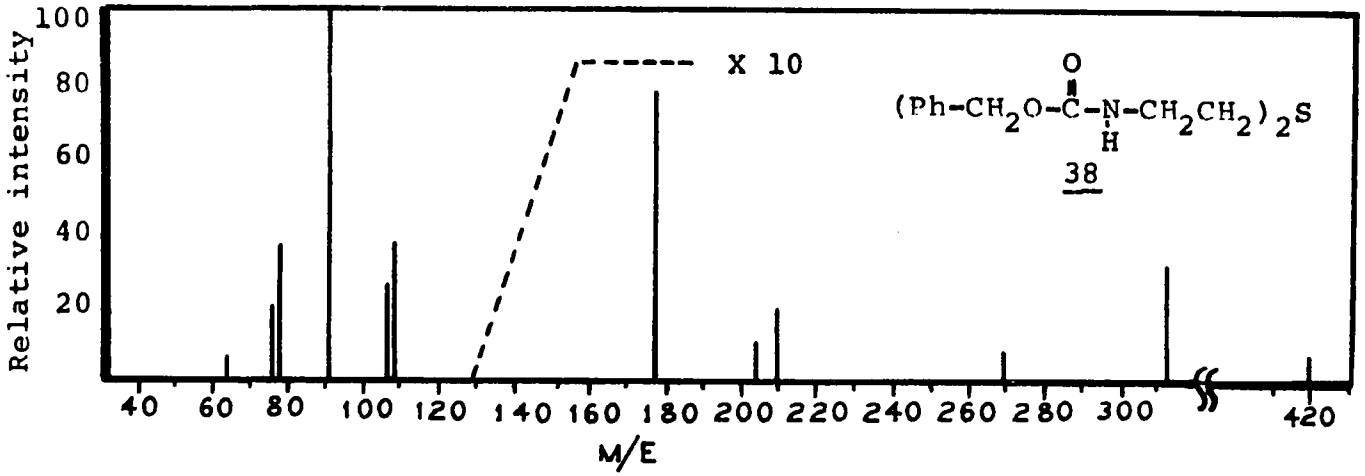


37

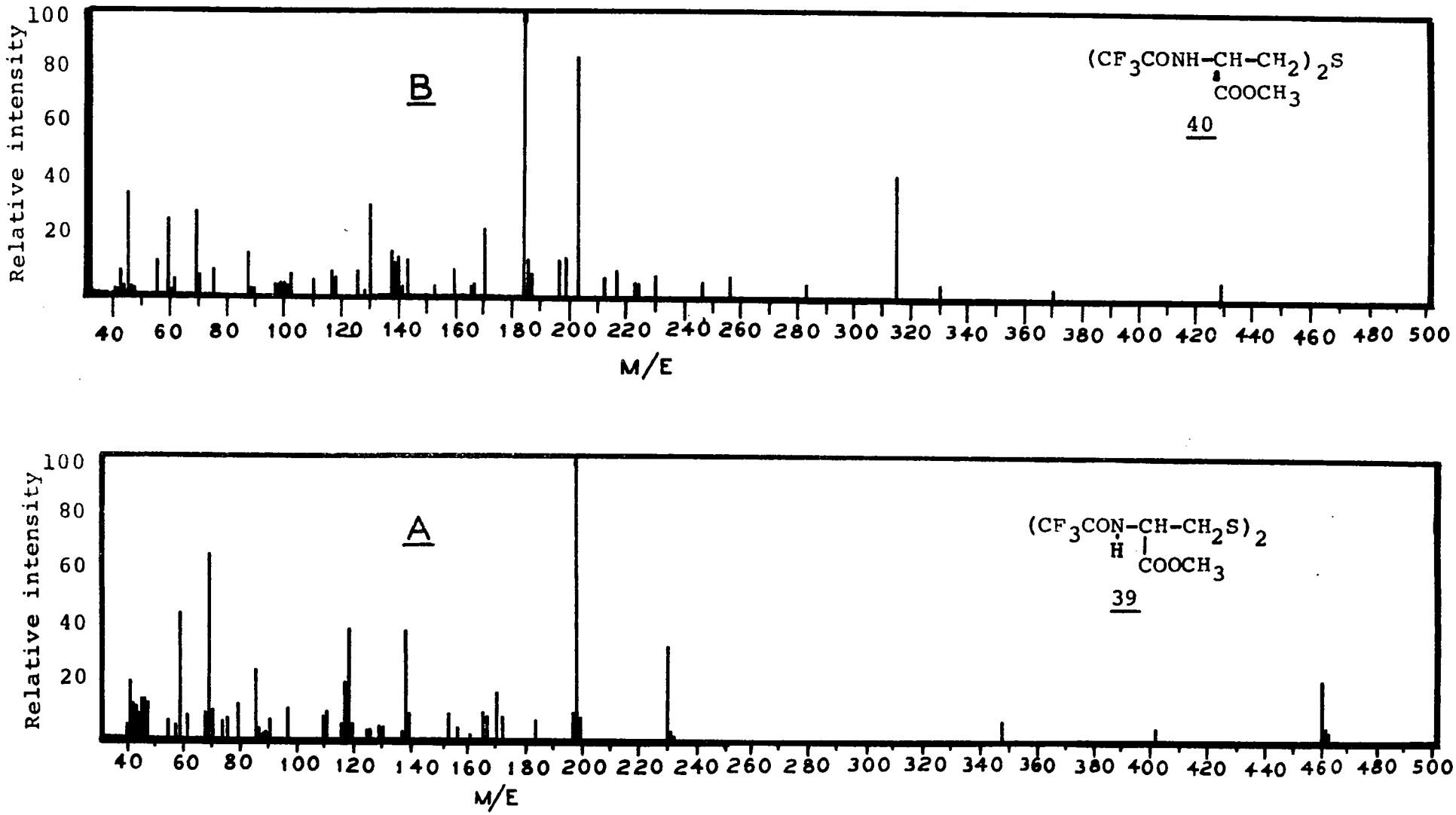


N,N'-Dicarbobenzoxy-2,2'-diamino-diethyl disulfide (37).

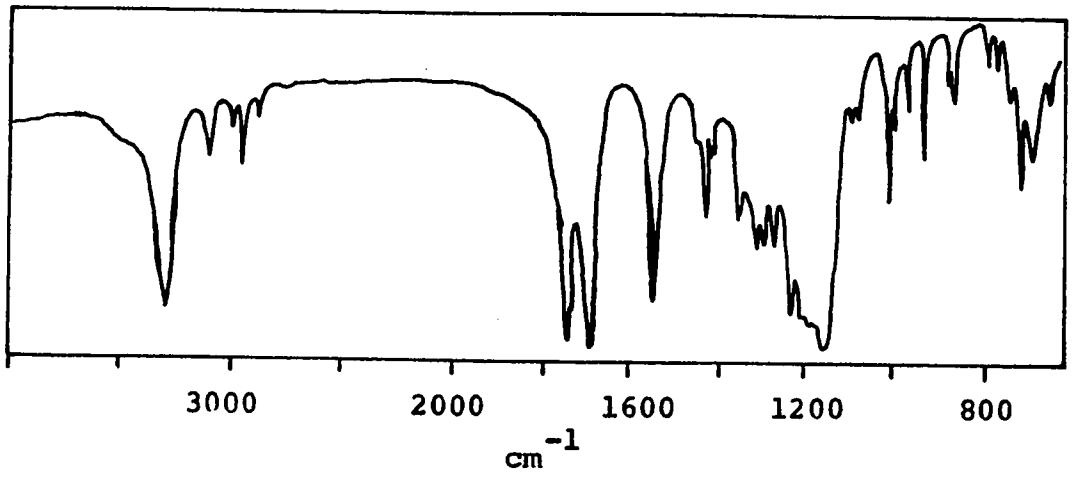


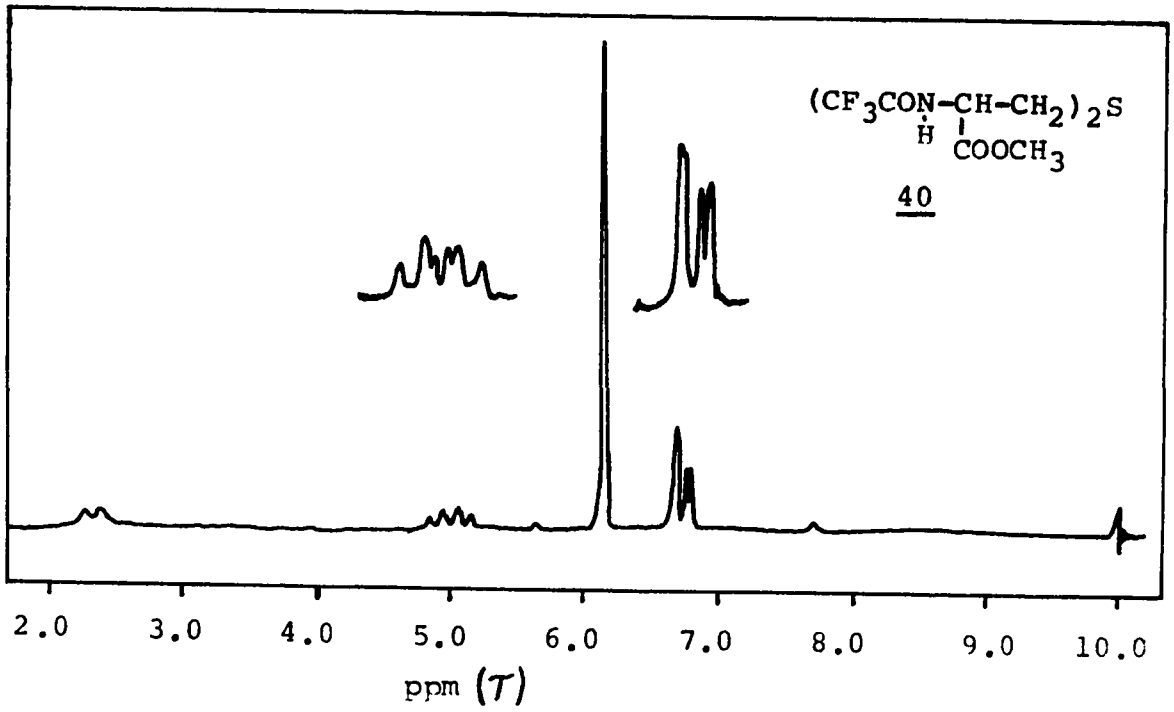


N,N'-Dicarbobenzoxy-2,2'-diamino-diethyl sulfide (38).

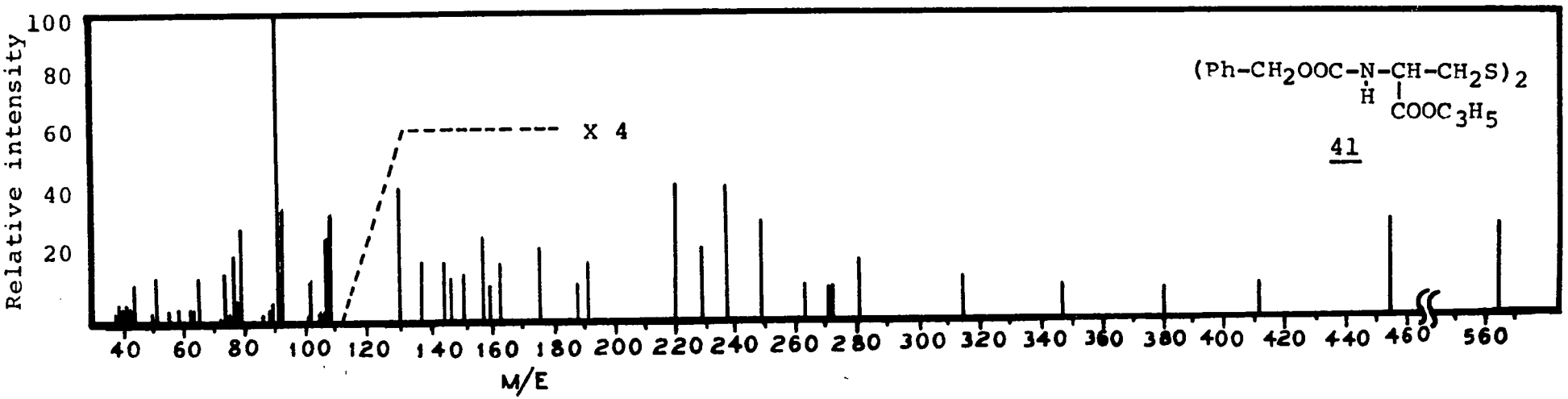


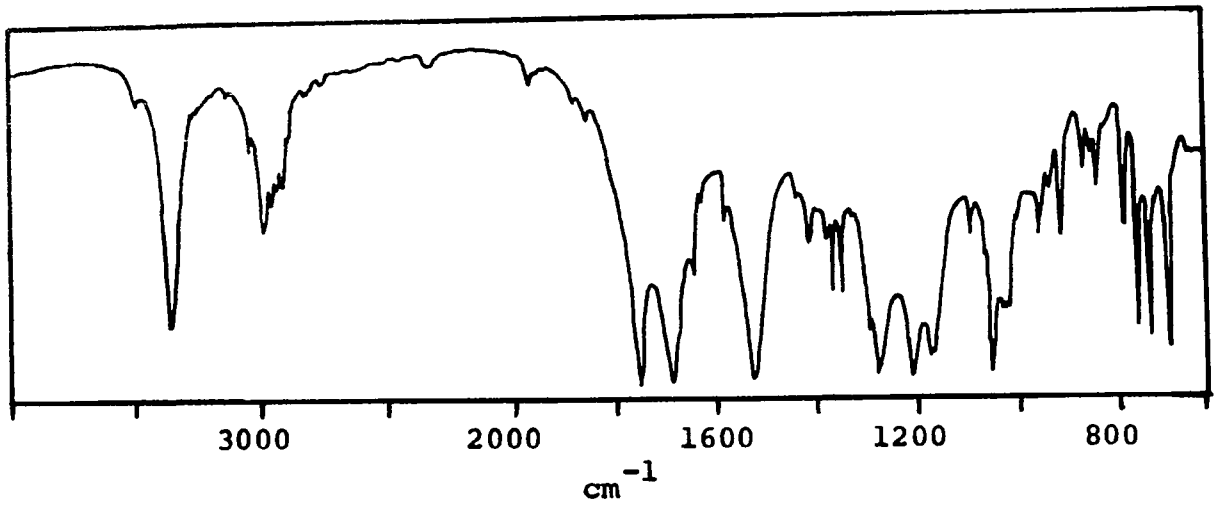
Mass spectra of trifluoroacetyl cystine and lanthionine derivatives. A) N,N'-Bis(trifluoroacetyl)-L-cystine Dimethyl Ester (39). B) N,N'-Bis(trifluoroacetyl)-L-lanthionine Dimethyl Ester (40).



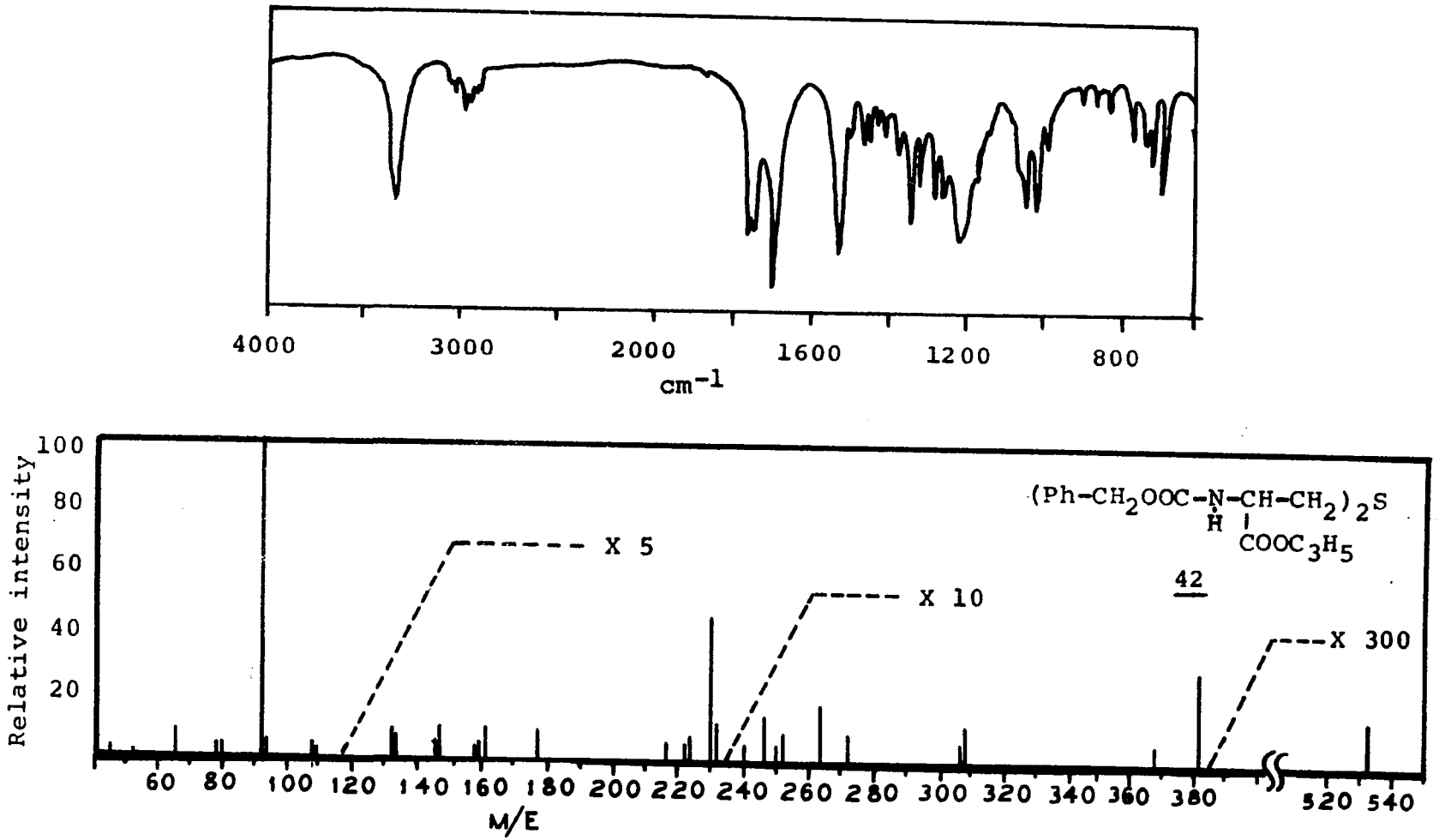


N,N'-Bis(trifluoroacetyl)-l-lanthionine Dimethyl Ester (40)

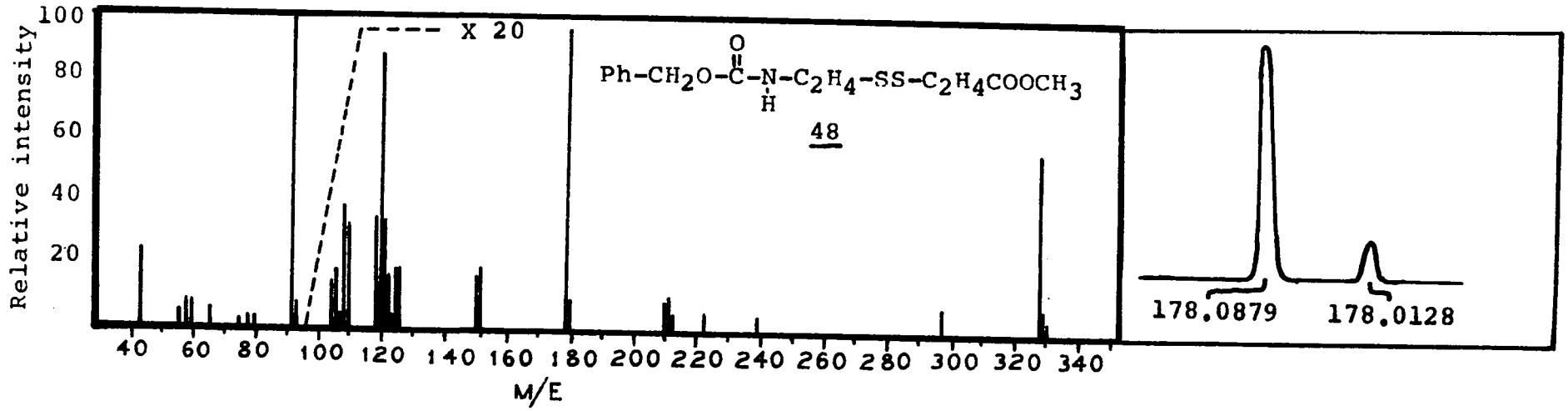


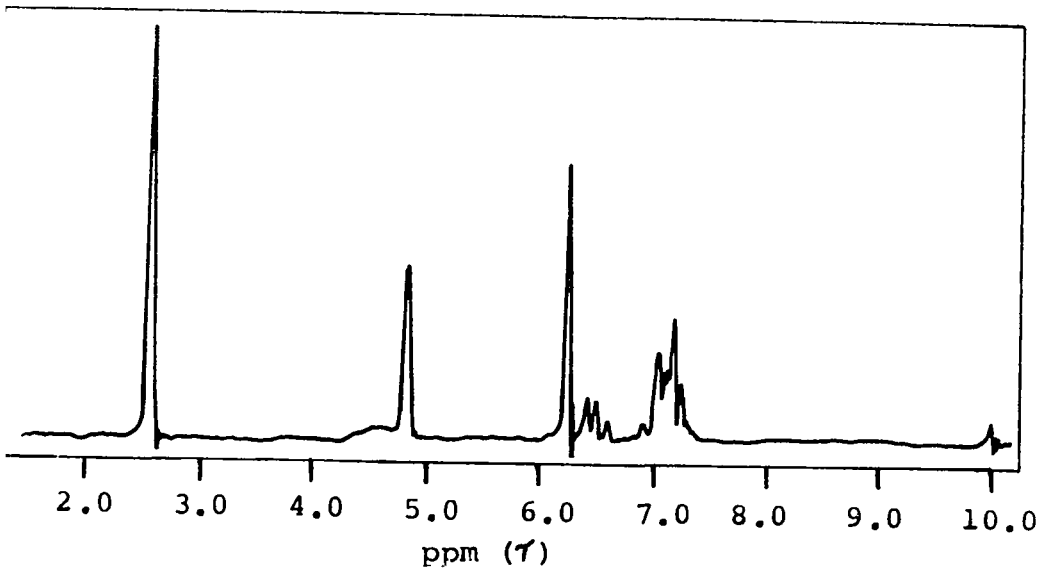


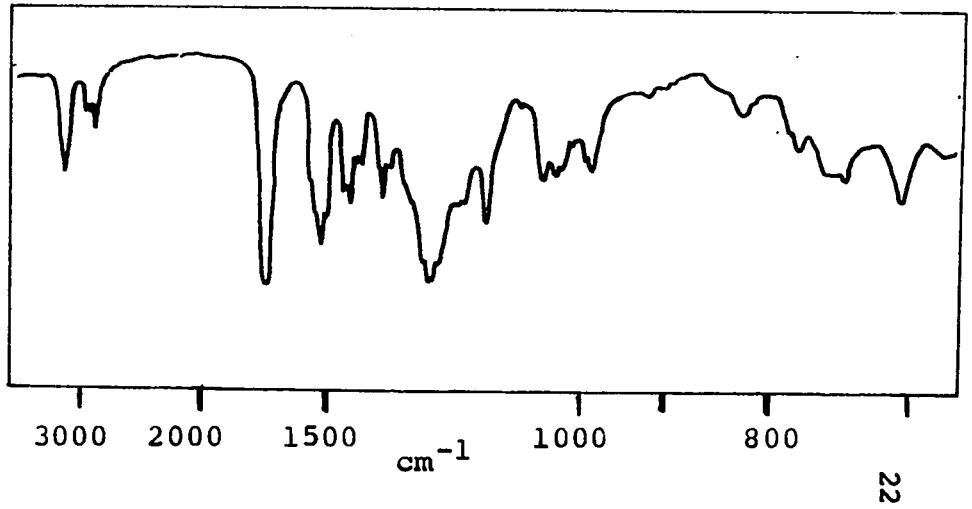
N,N'-Dicarbobenzoxy-L-cystine Diethyl Ester (41)



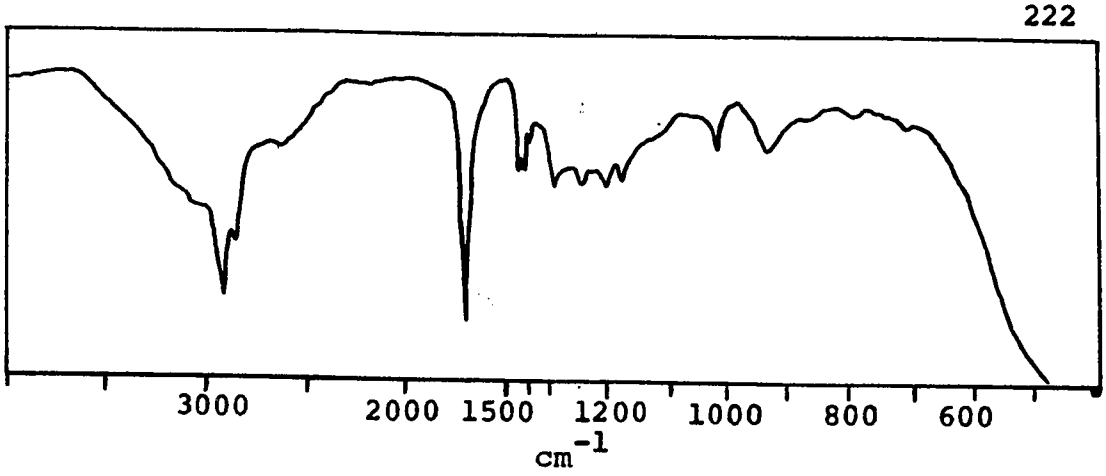
N,N'-Dicarbobenzoxy-L-lanthionine Diethyl Ester (42).

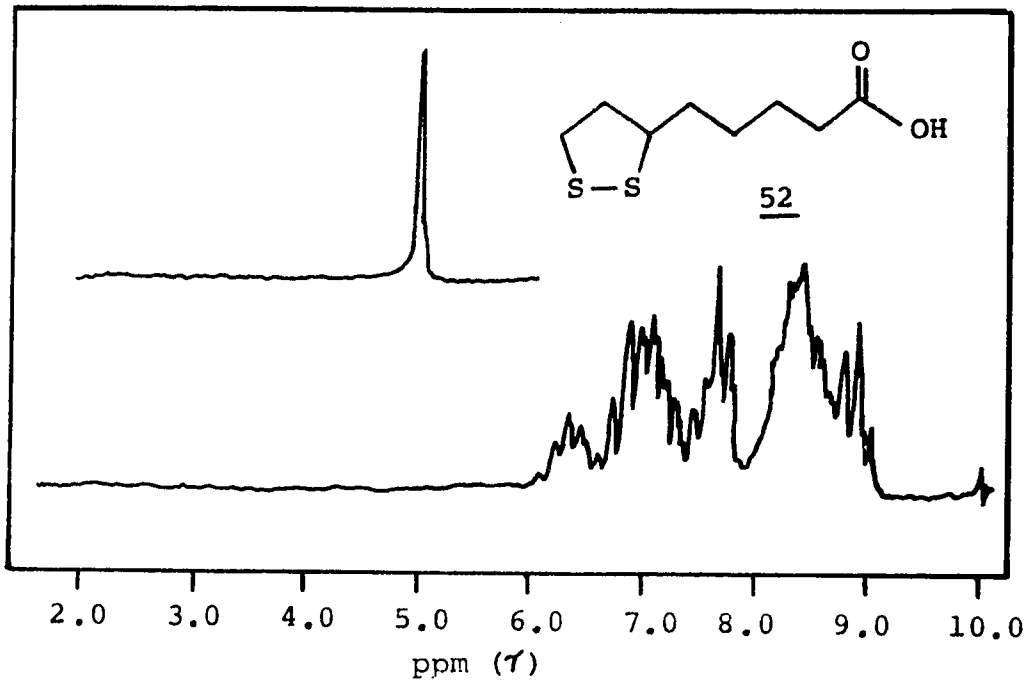


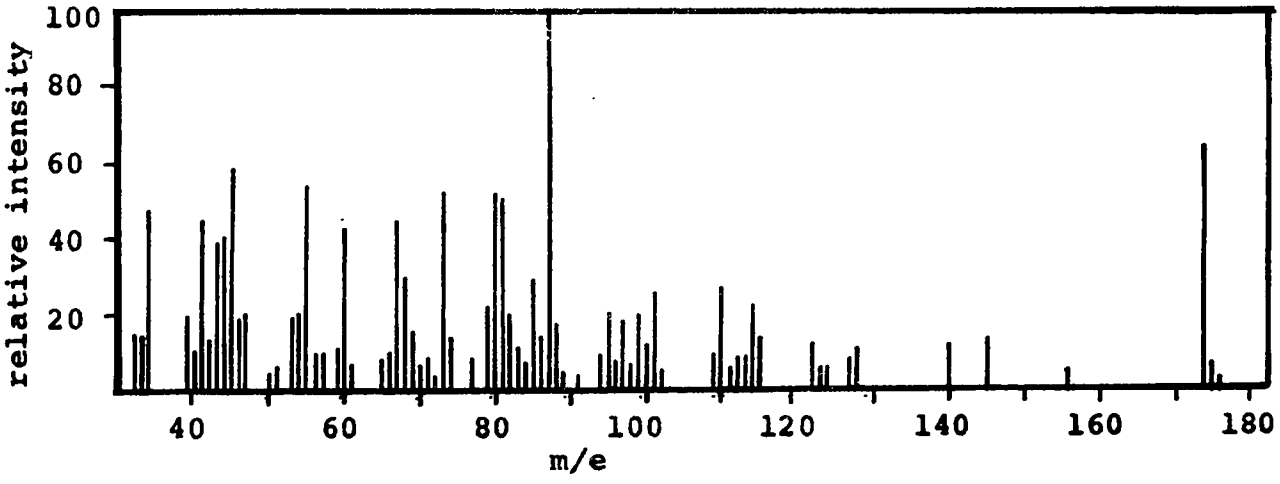




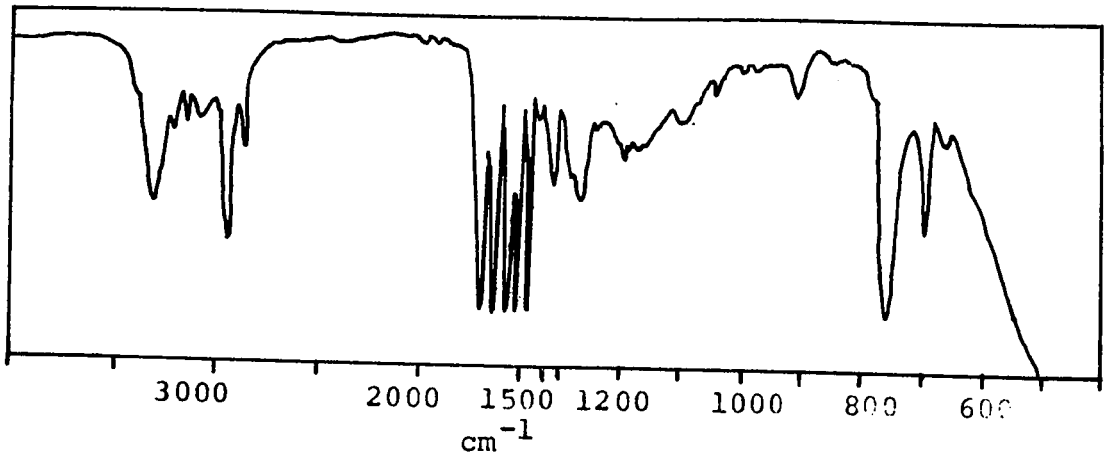
N-Carbobenzoxy-2-amino-2'-carbomethoxy-diethyl Disulfide (48).

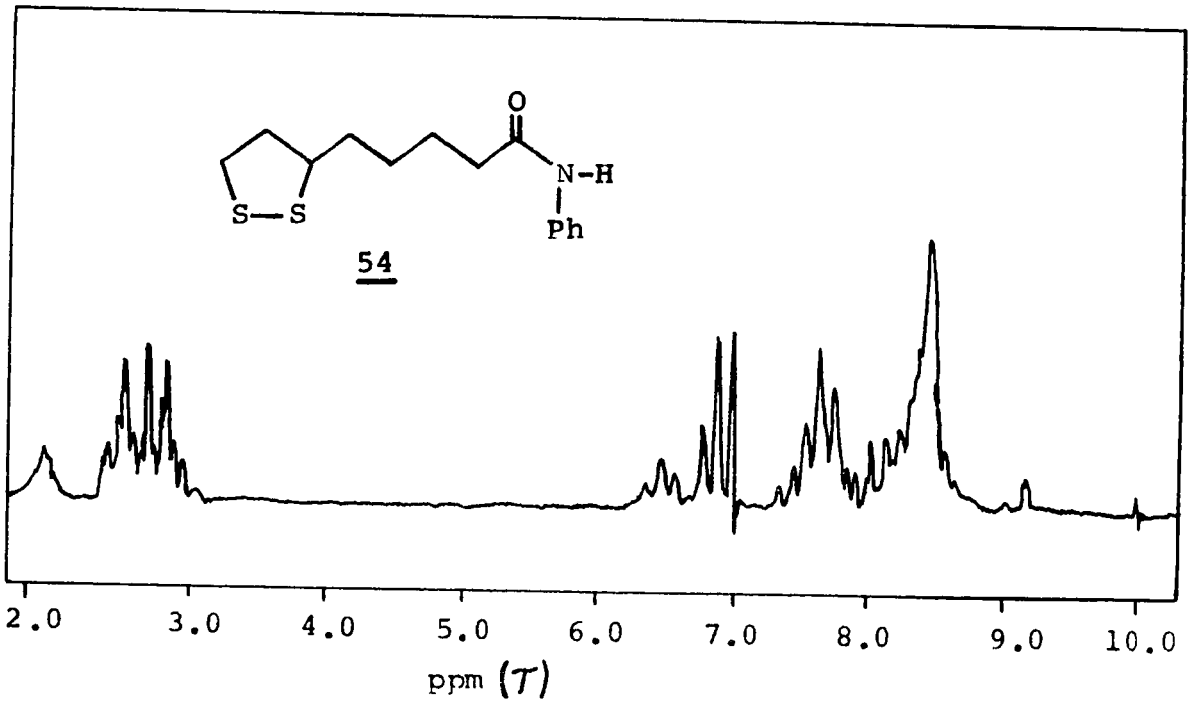


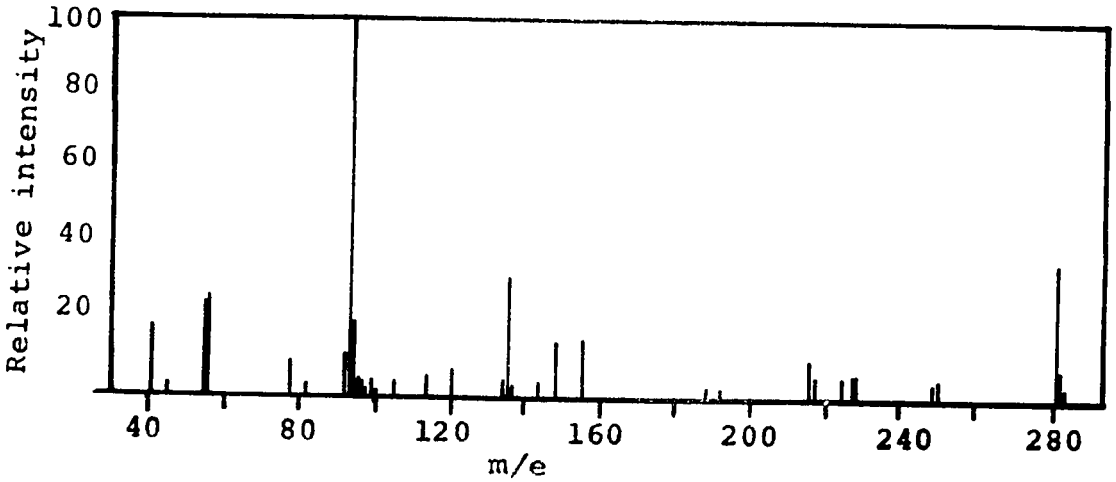




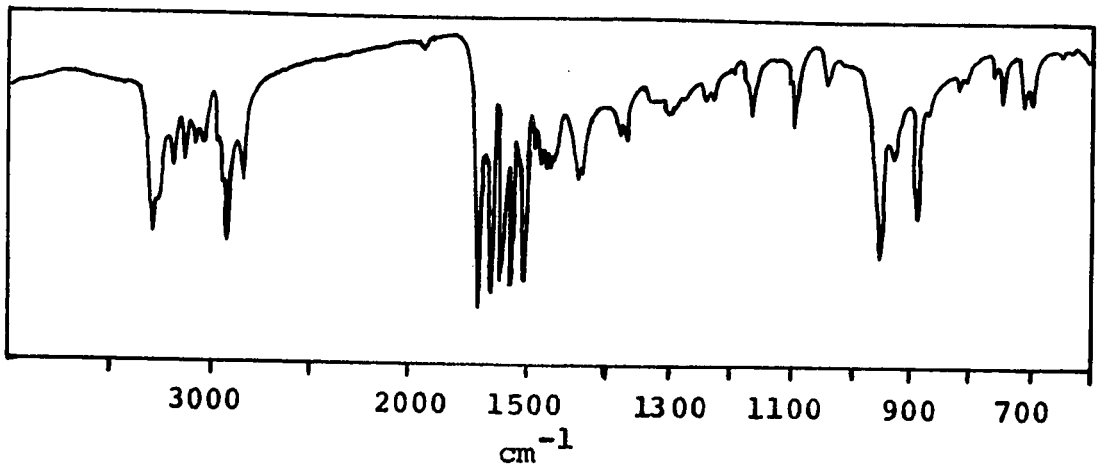
Thietane-2-valeric Acid (52).

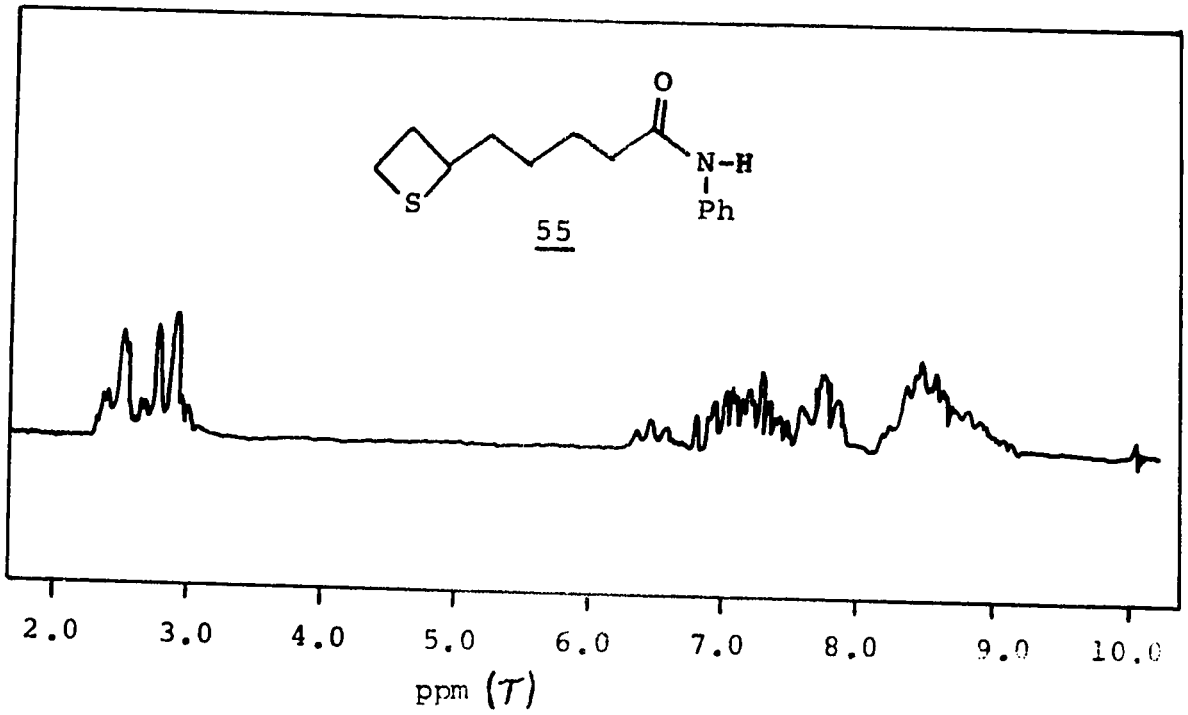


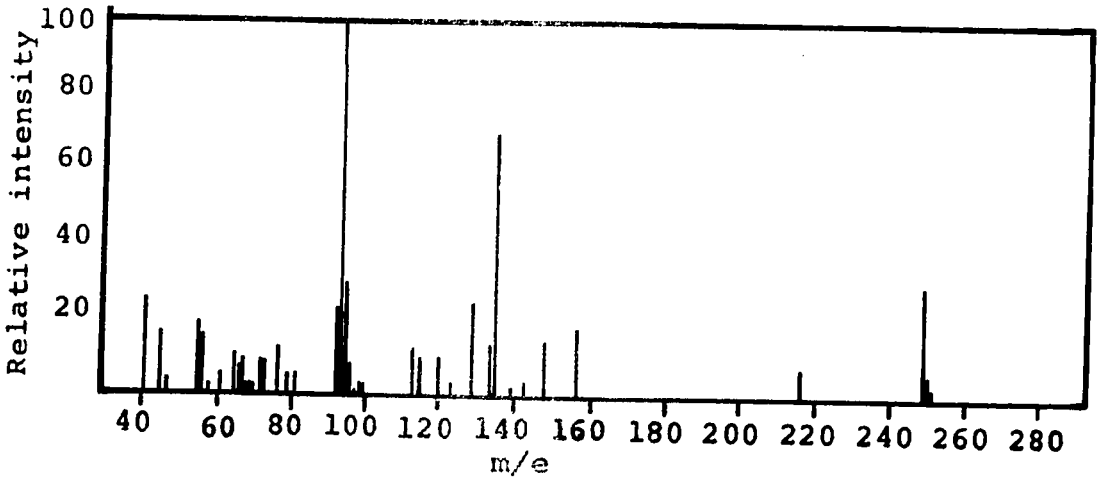




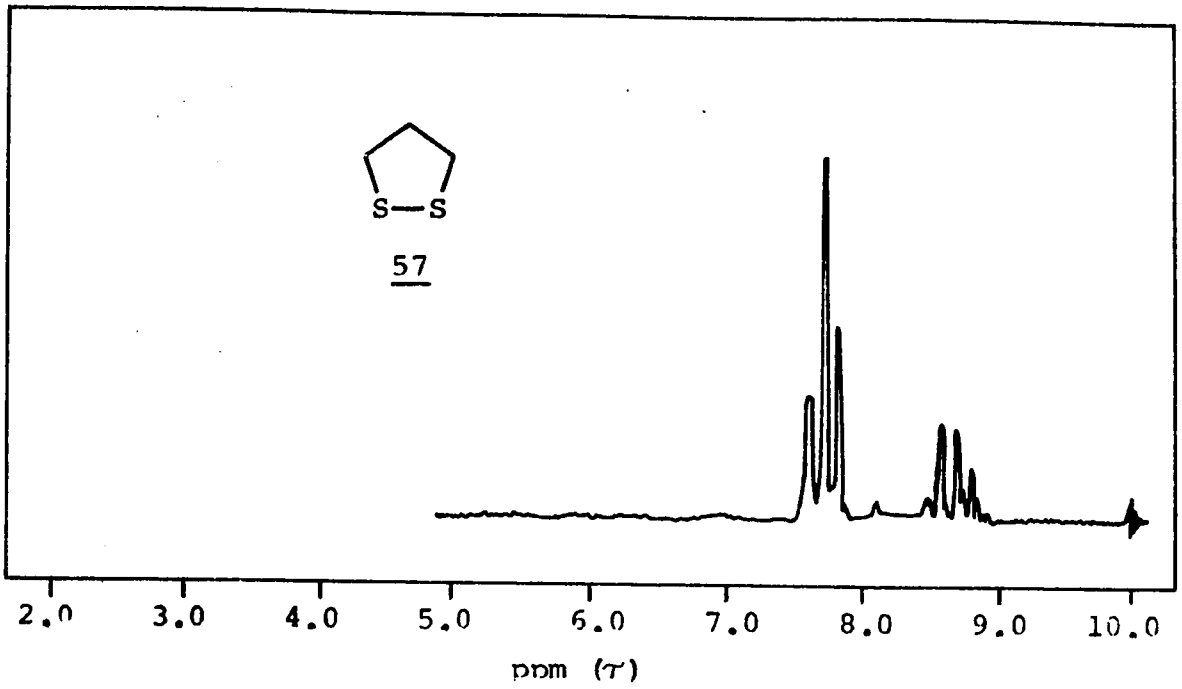
α-Lipoic Acid Anilide (54).



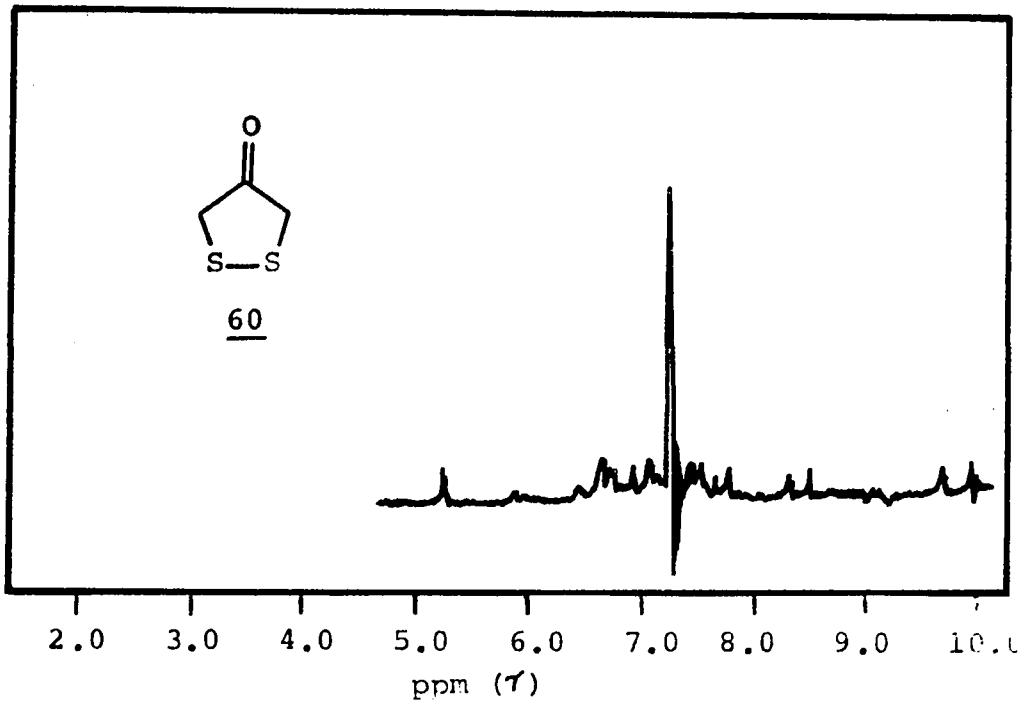




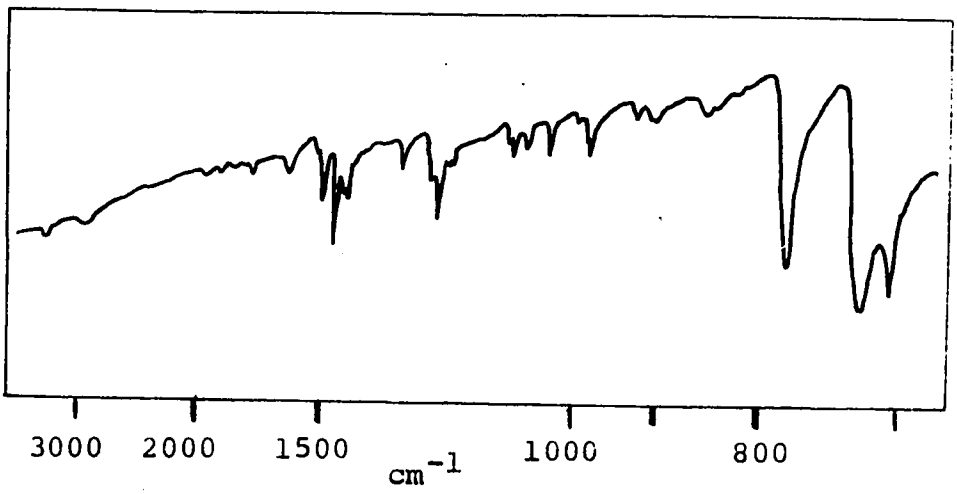
Thietane-2-valeric Acid Anilide (55).

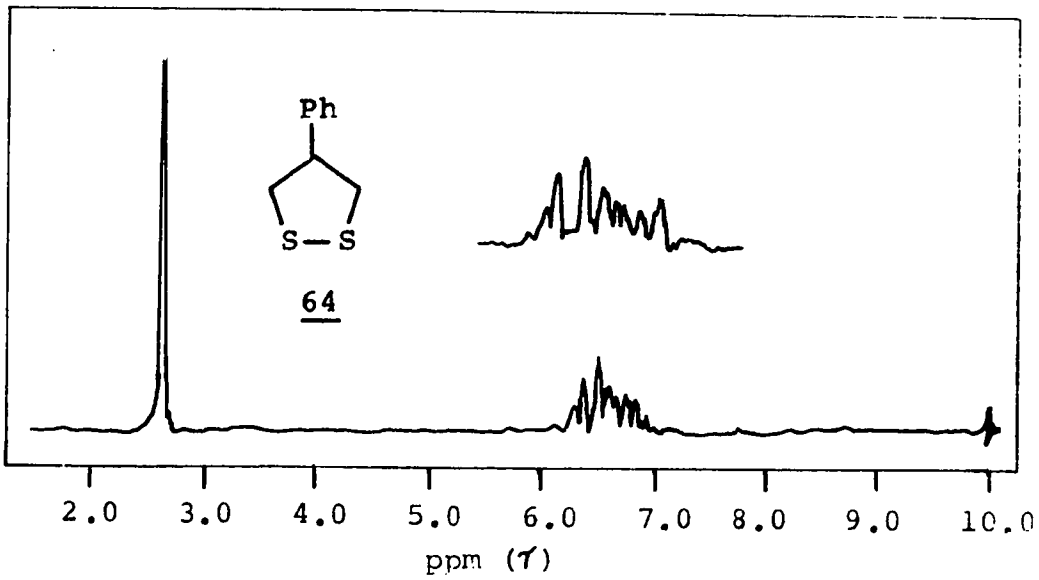


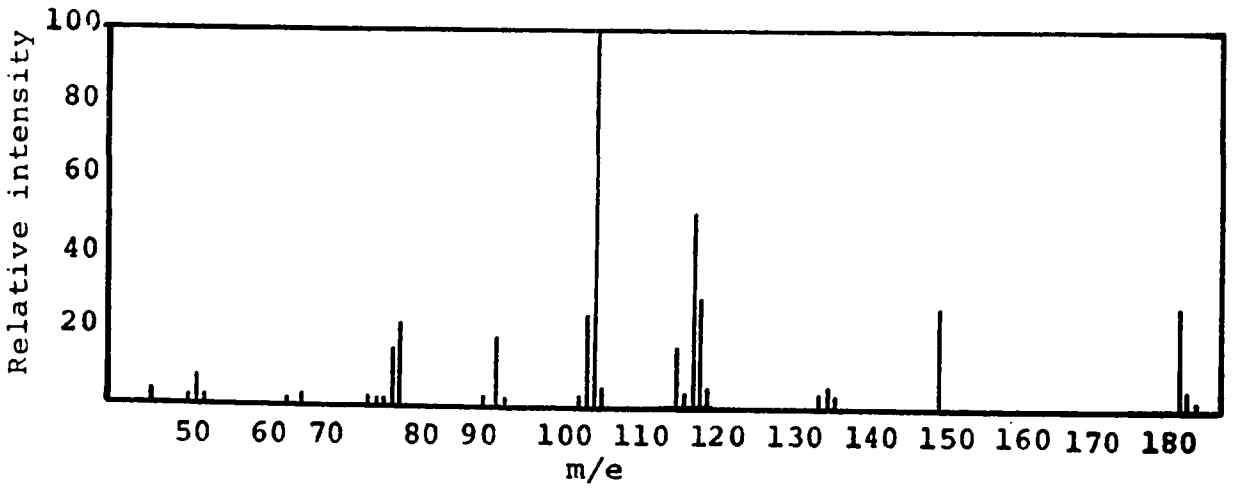
1,2-Dithiolane (57).



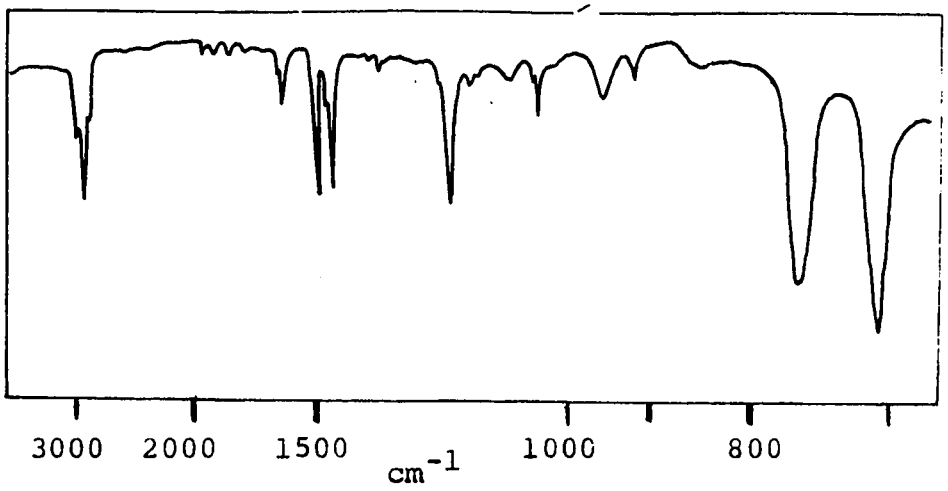
1,2-Dithiolane-4-one (60).

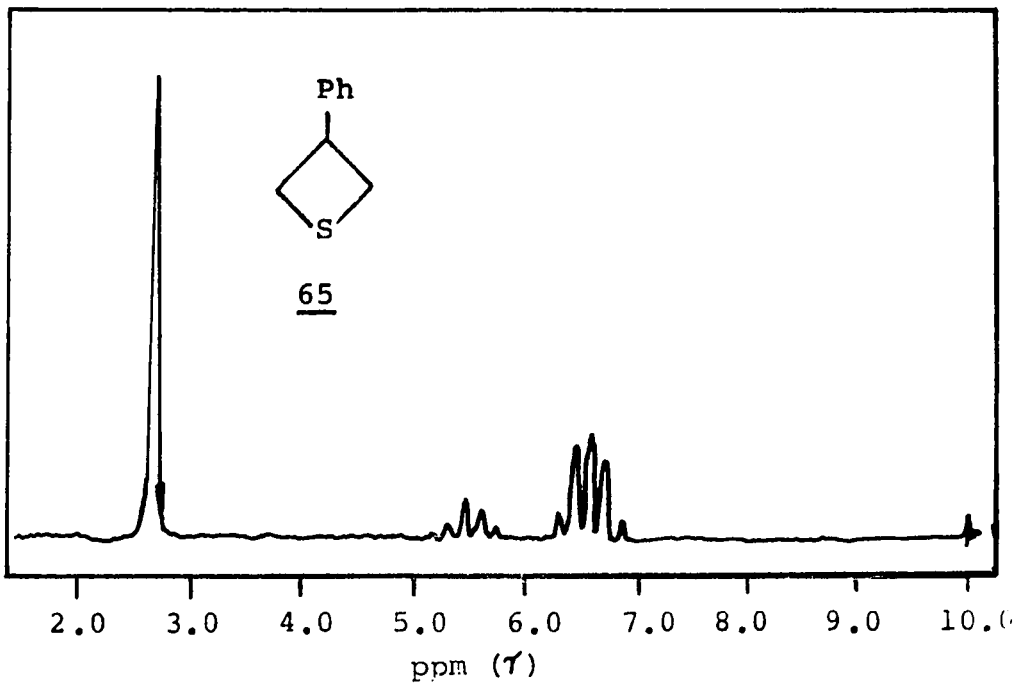


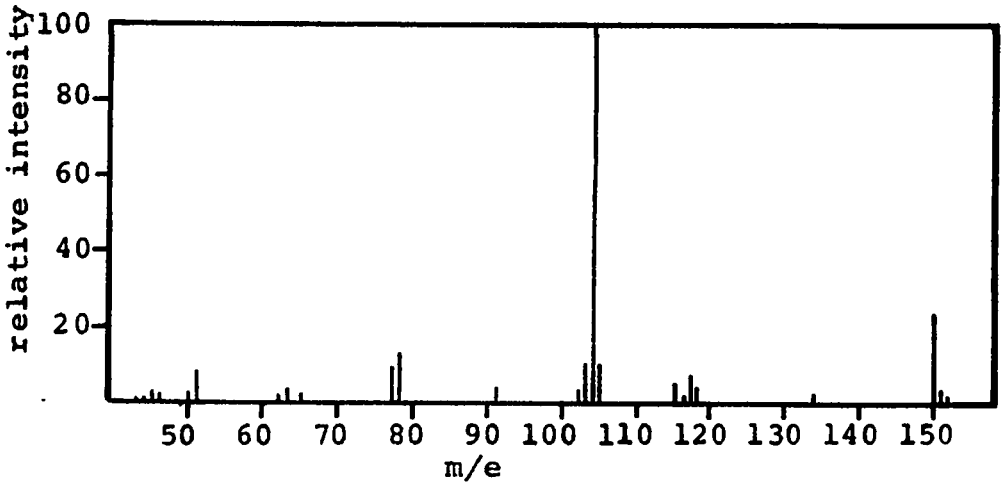




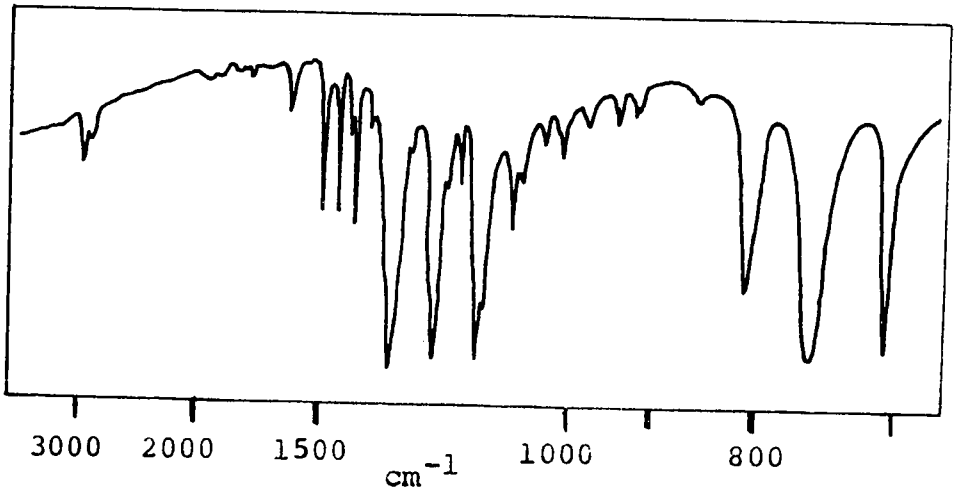
4-Phenyl-1,2-dithiolane (64).

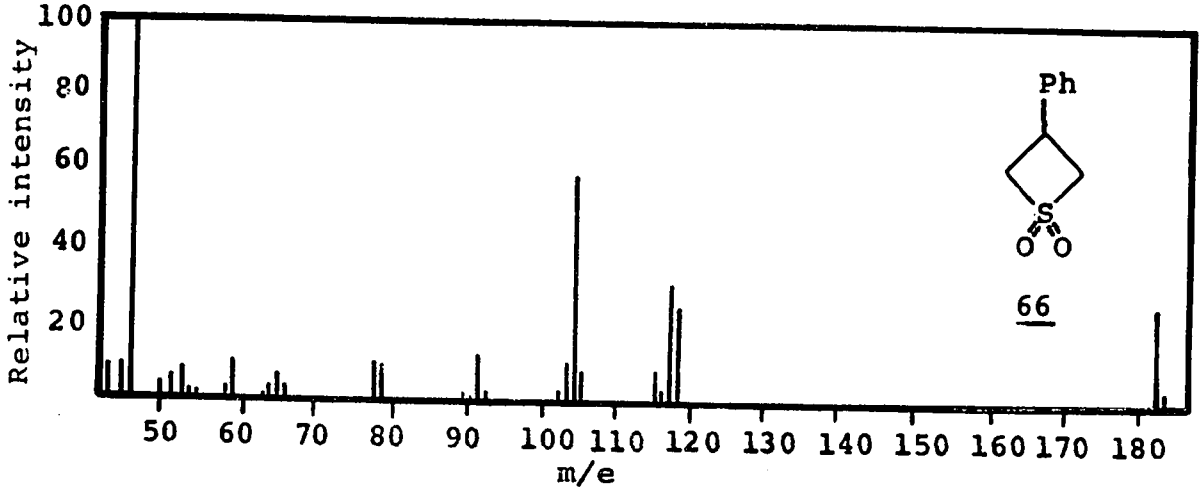




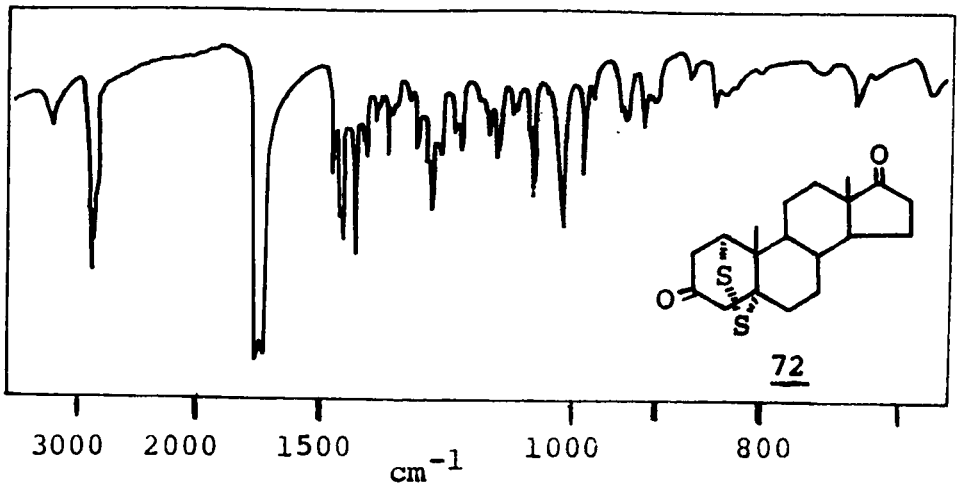


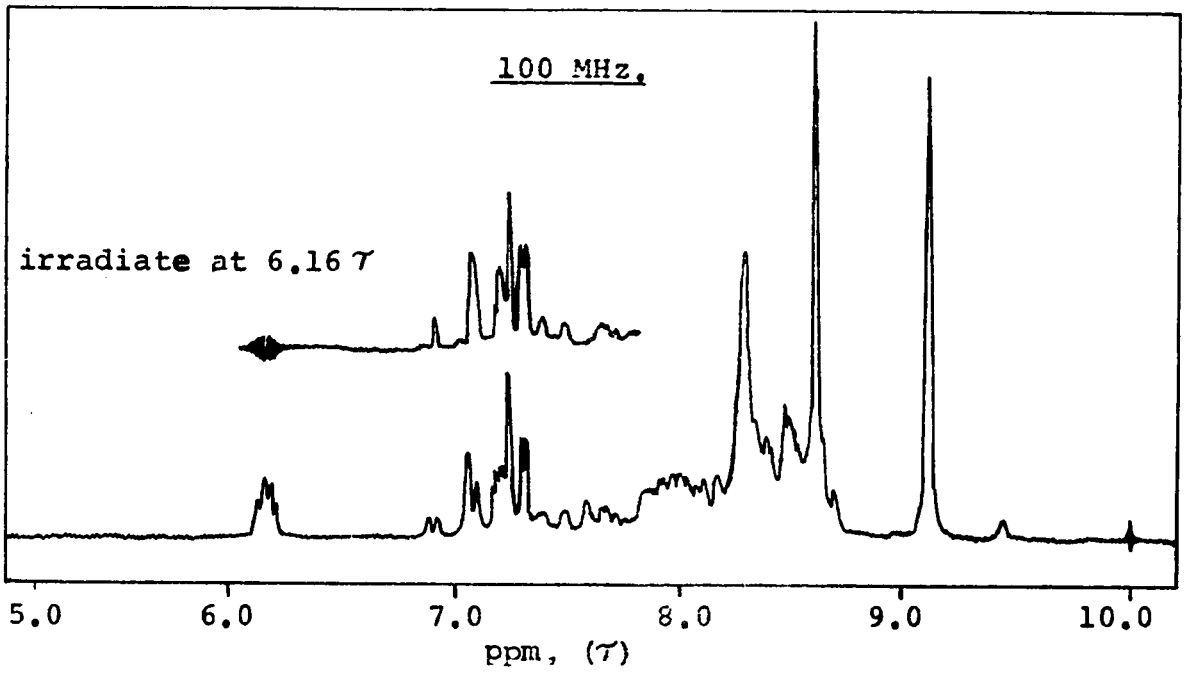
3-Phenylthietane (65).

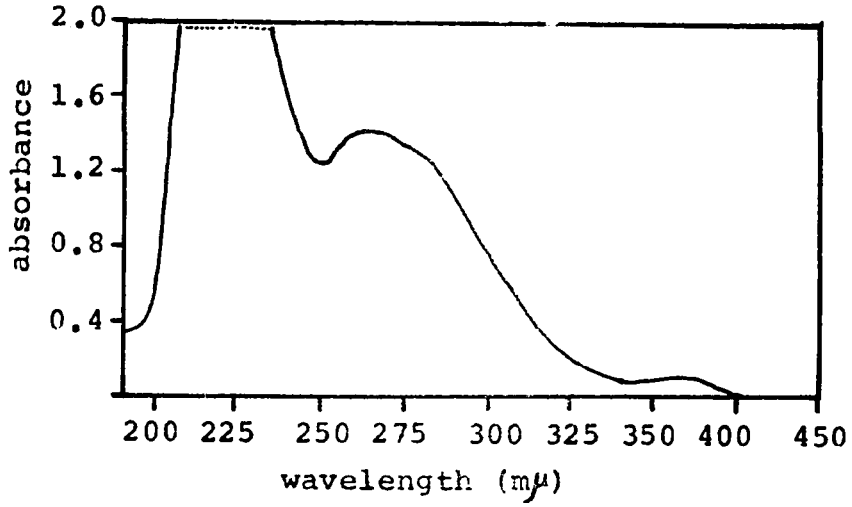




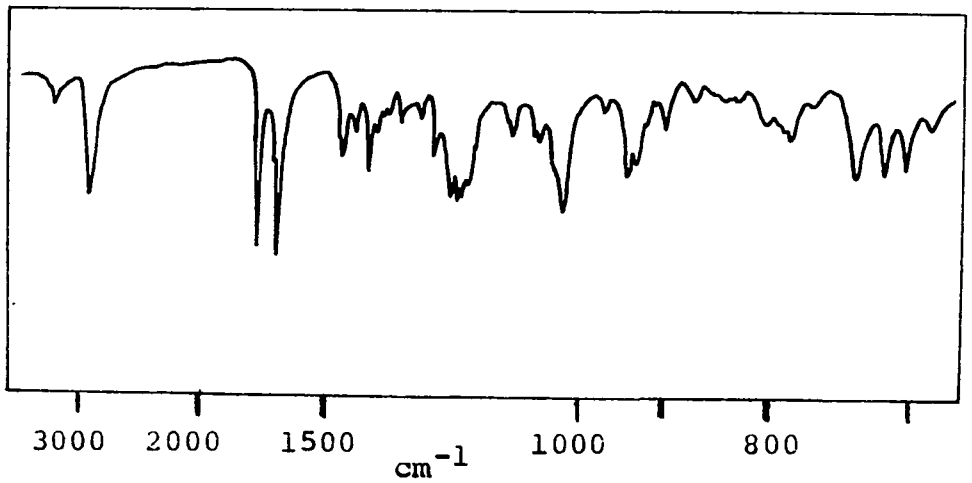
3-Phenylthietane-1,1-dioxide (66).

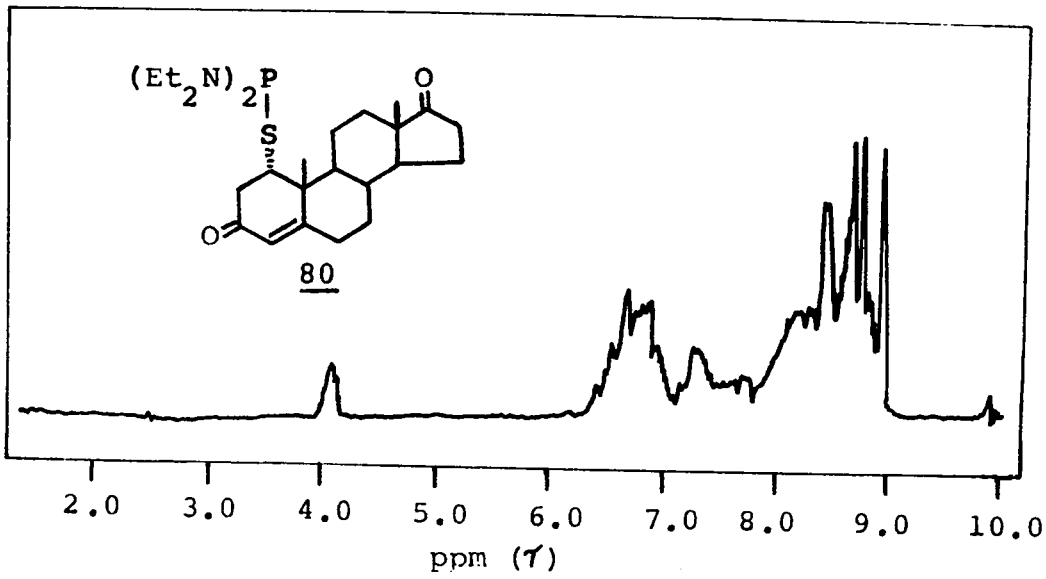


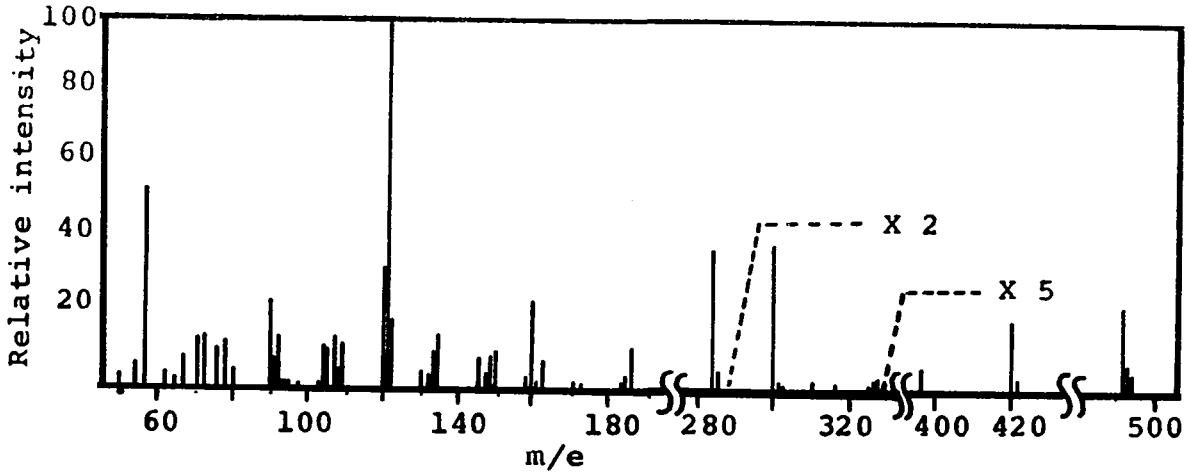


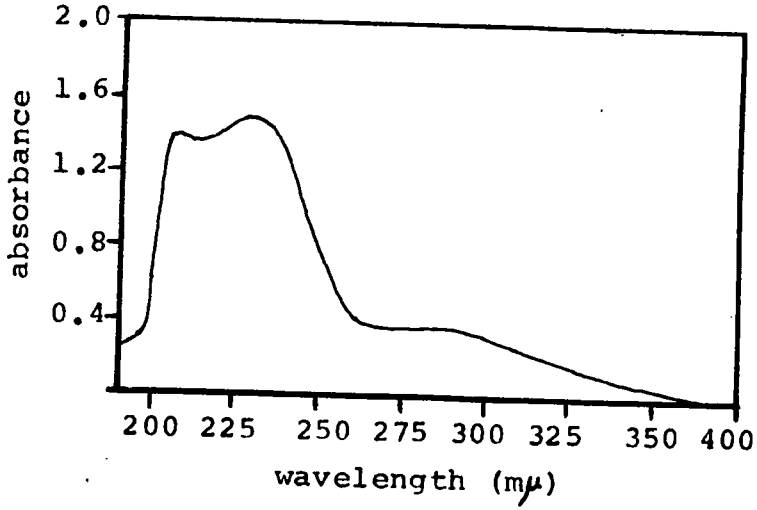


1α,5α-Epidithioandrostane-3,17-dione (72).

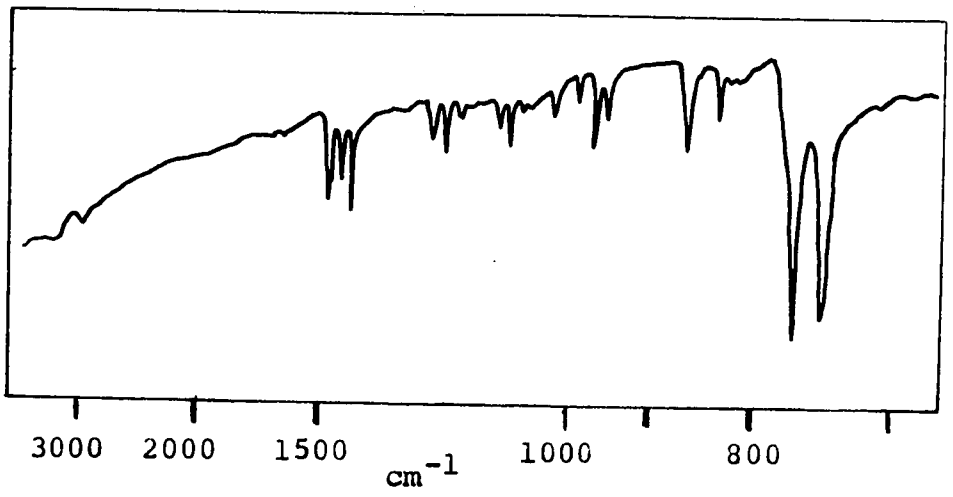


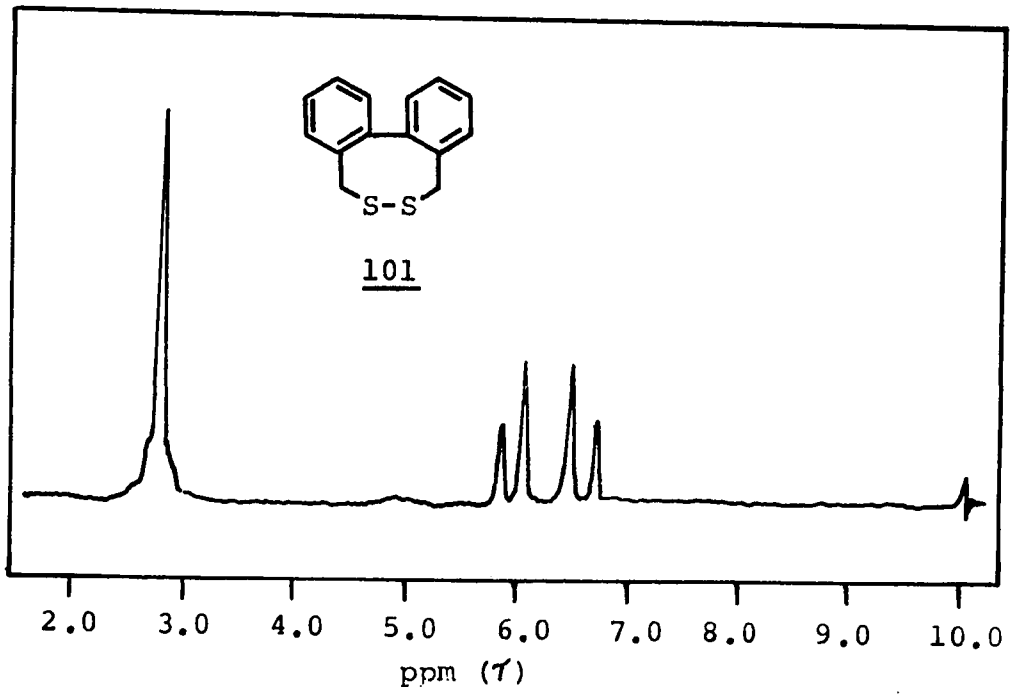




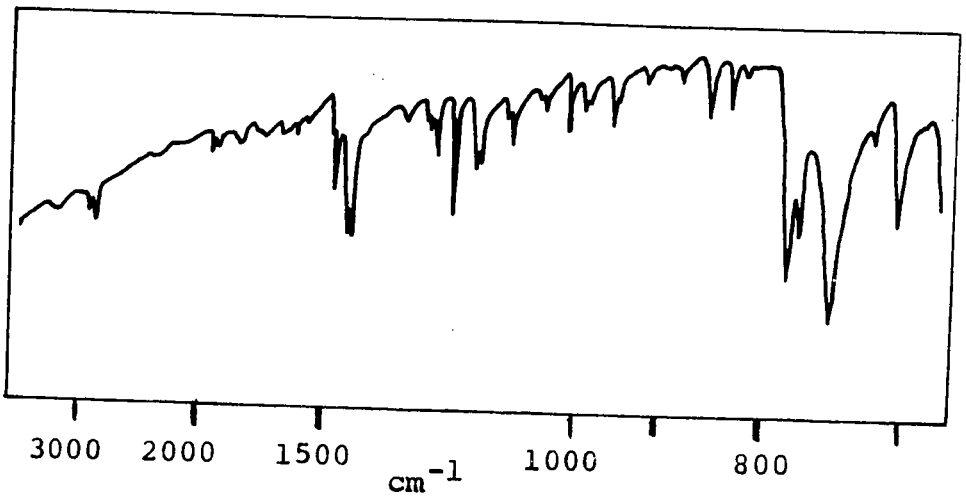


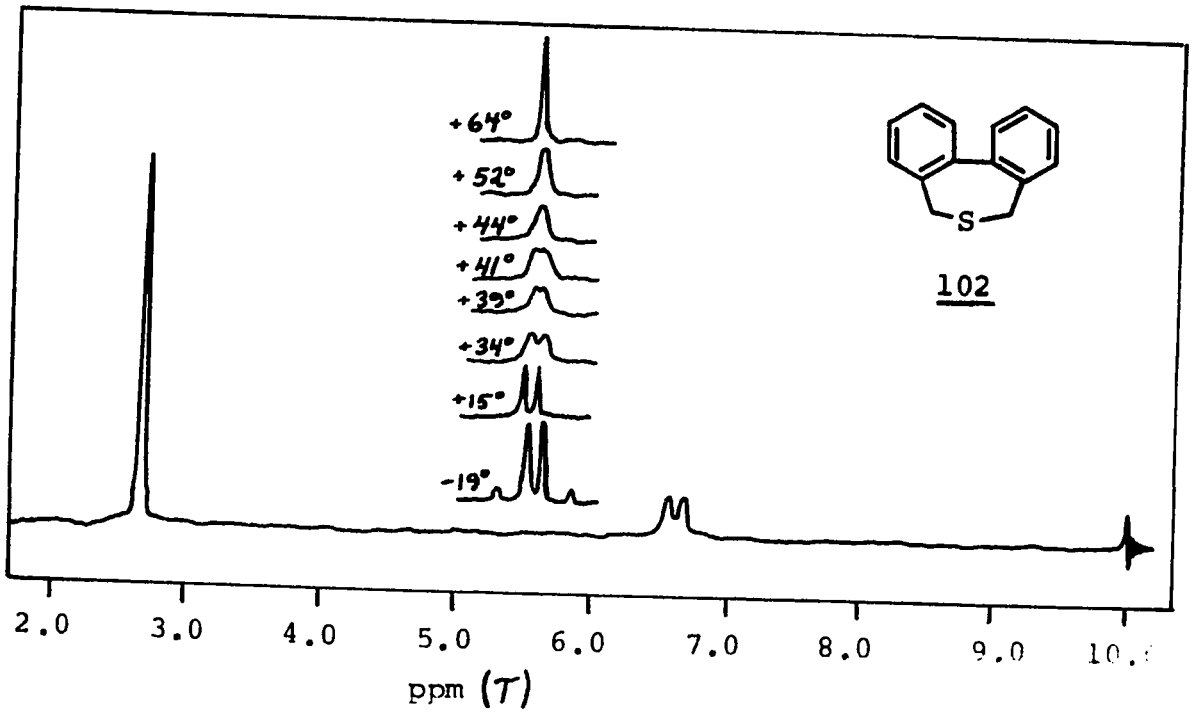
S-Bis(diethylamino)phosphino-1α-thioandrostan-4-ene-3,17-dione (80).



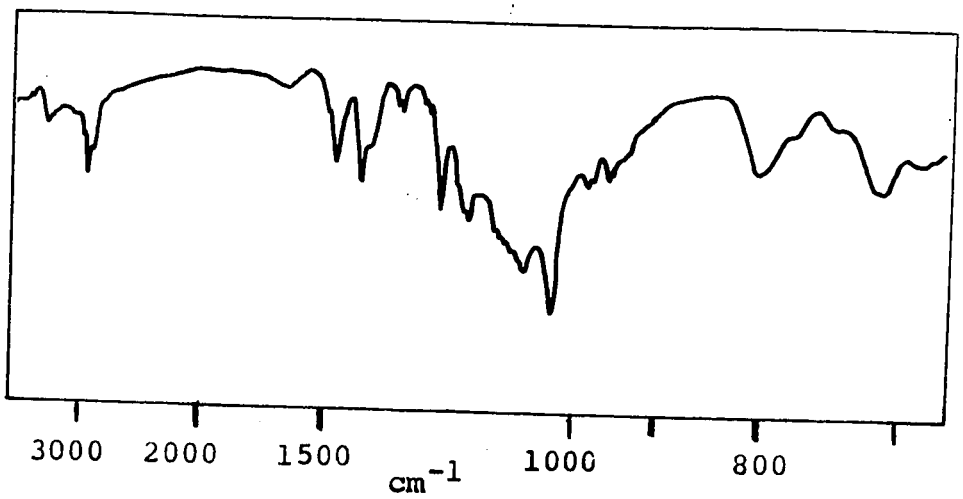


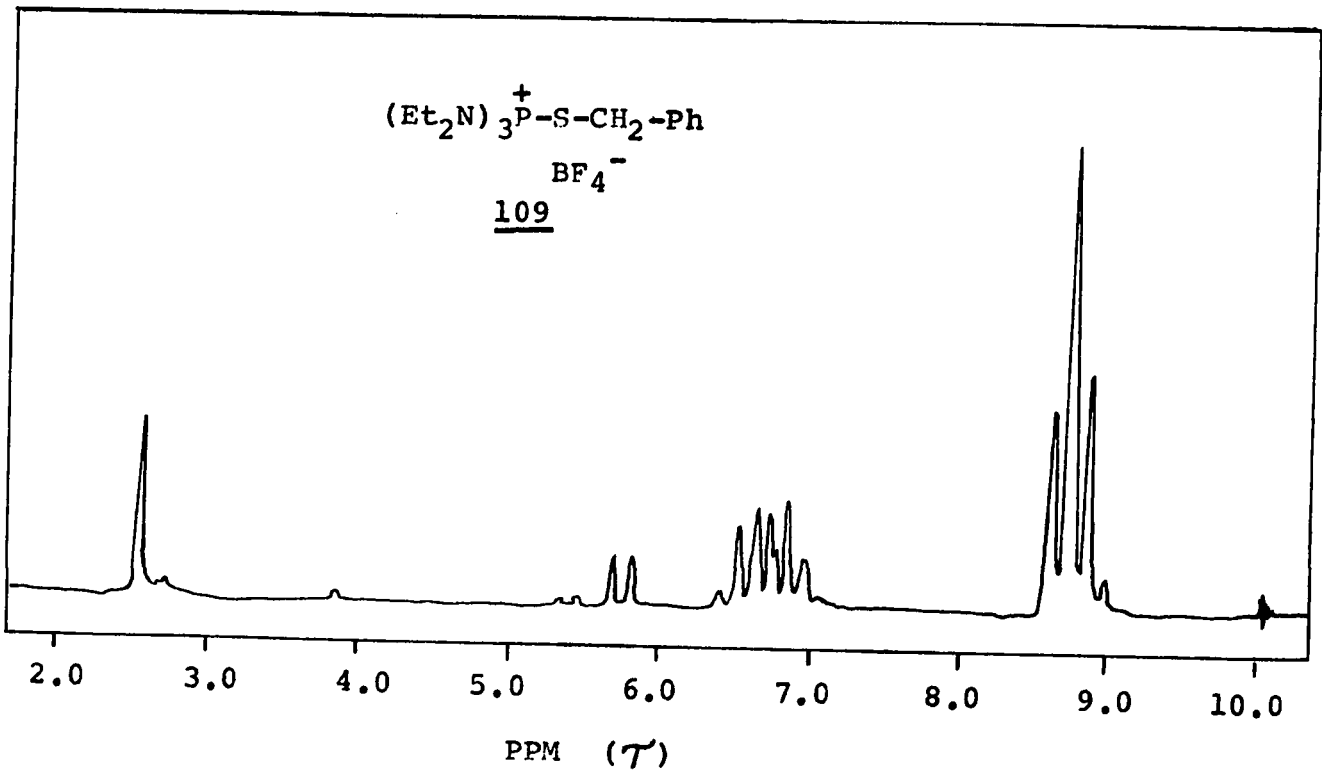
5H,8H-dibenzo [d,f] -1,2-Dithiocin (101).



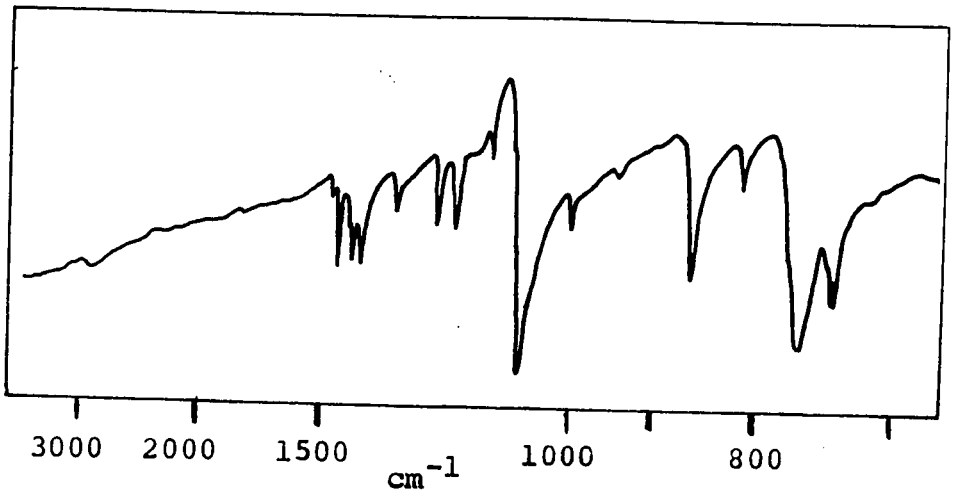


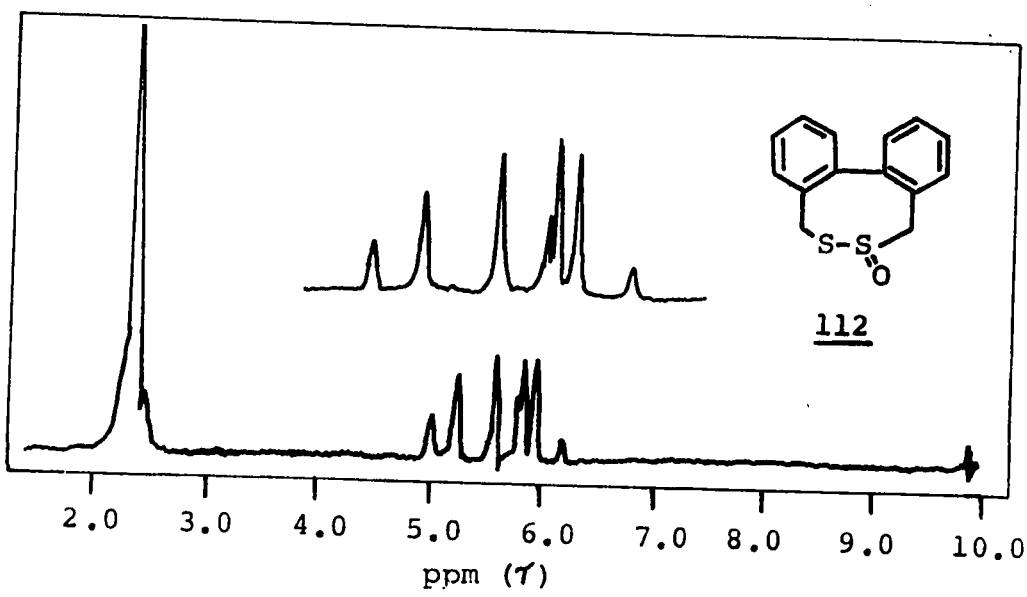
5H,7H-Dibenzo [c,e] thiepin (102).



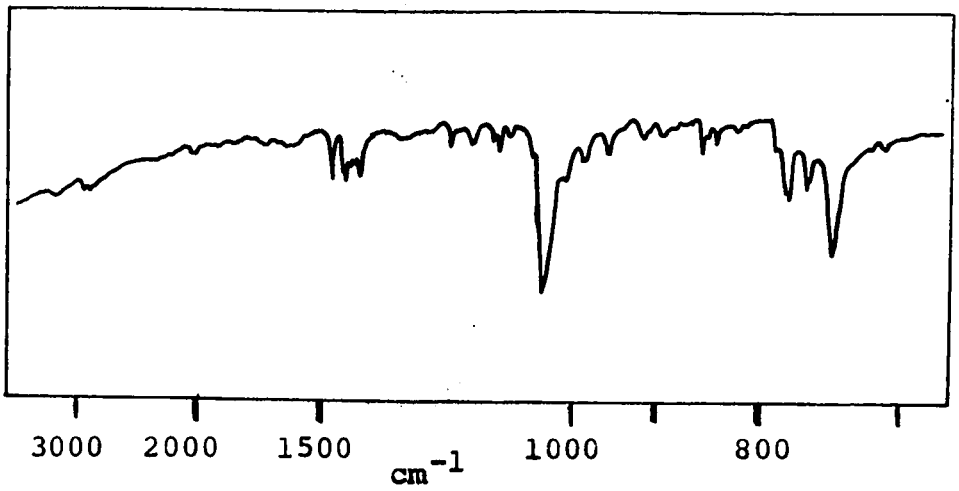


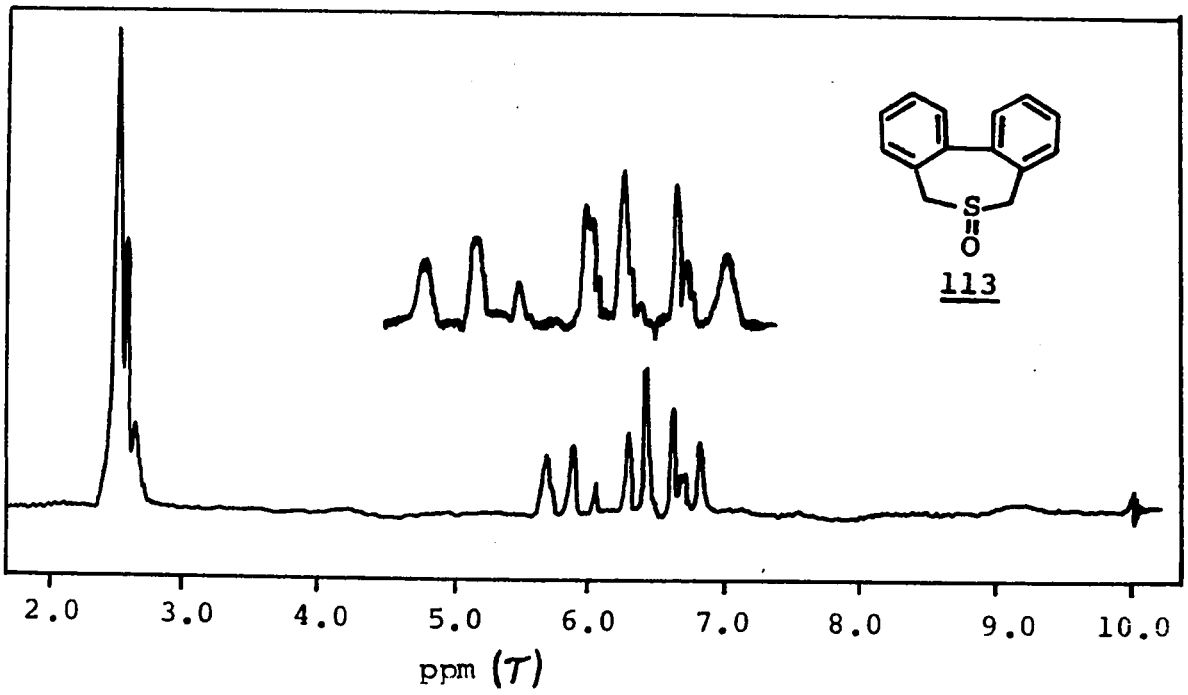
Tris(diethylamino)-benzylthio-phosphonium Tetrafluoroborate (109).



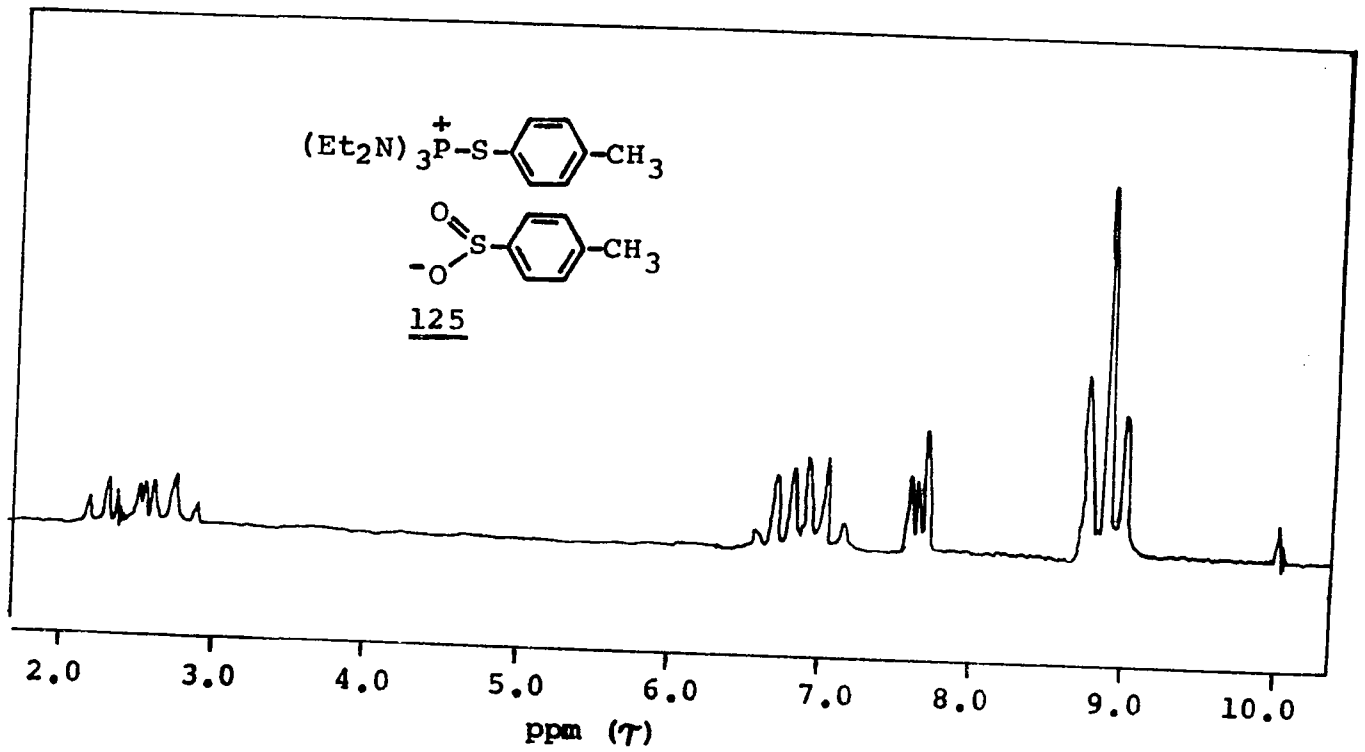


5H,8H-Dibenzo[d,f]-1,2-dithiocin-6-oxide (112).

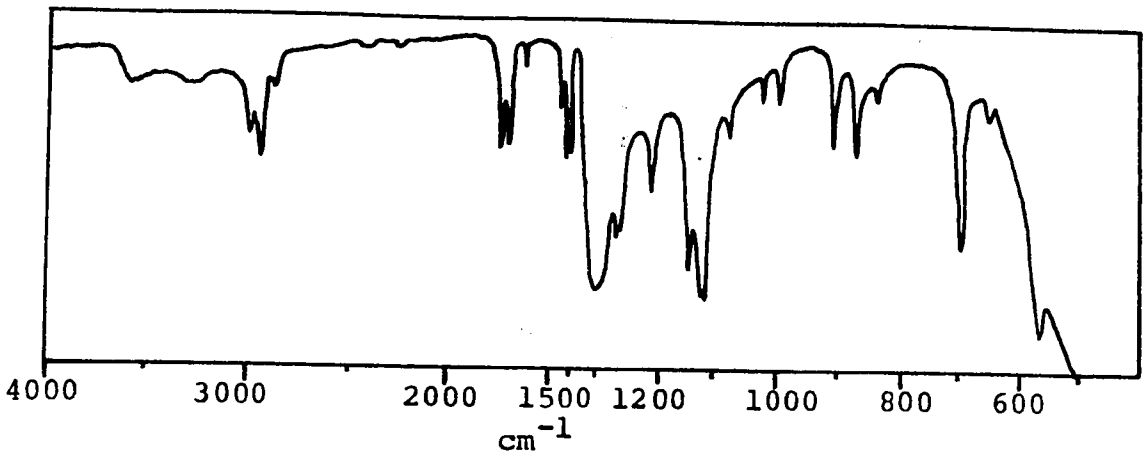


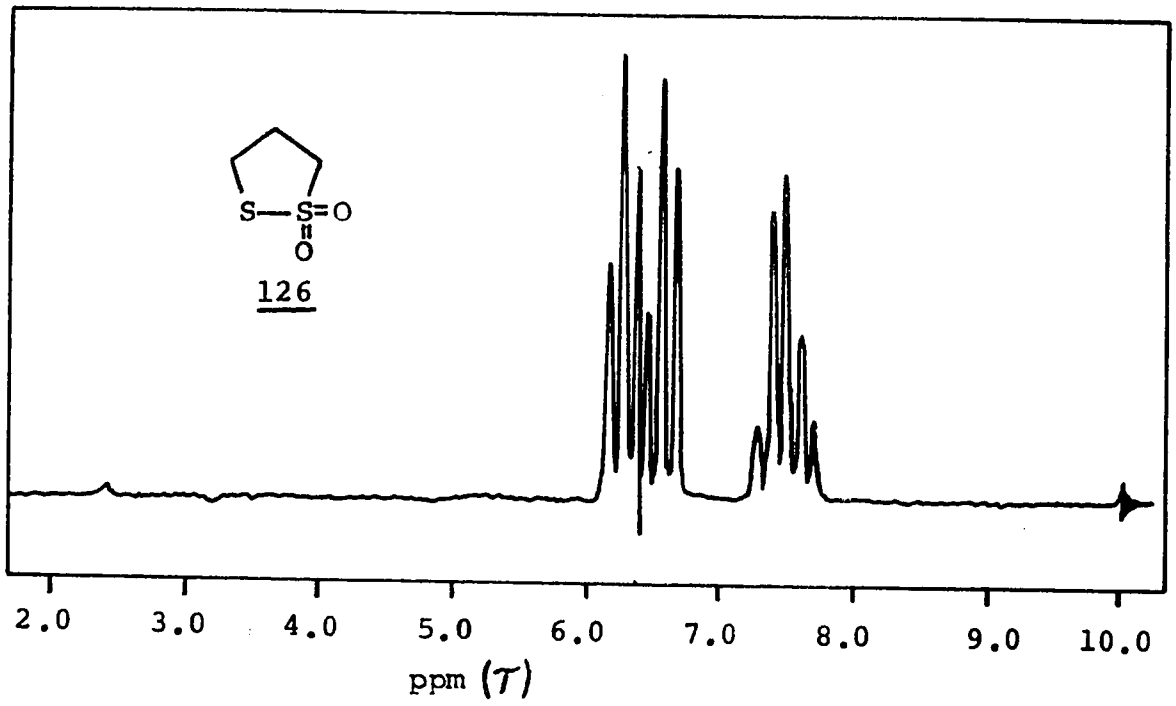


5H,7H-Dibenzo [c,e] thiepin-6-oxide (113).



Tris(diethylamino)-p-tolylthiophosphonium p-Toluenesulfinate (125).





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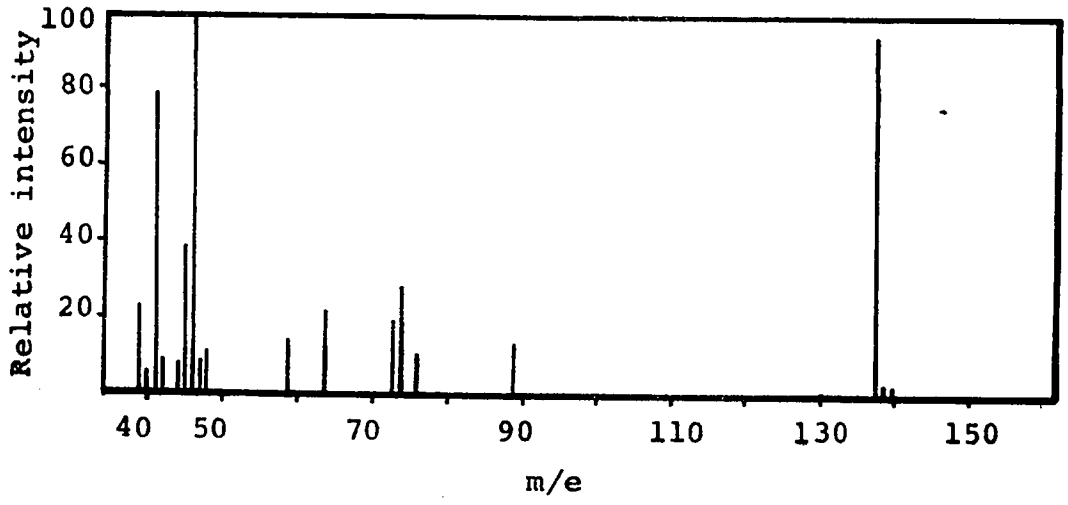
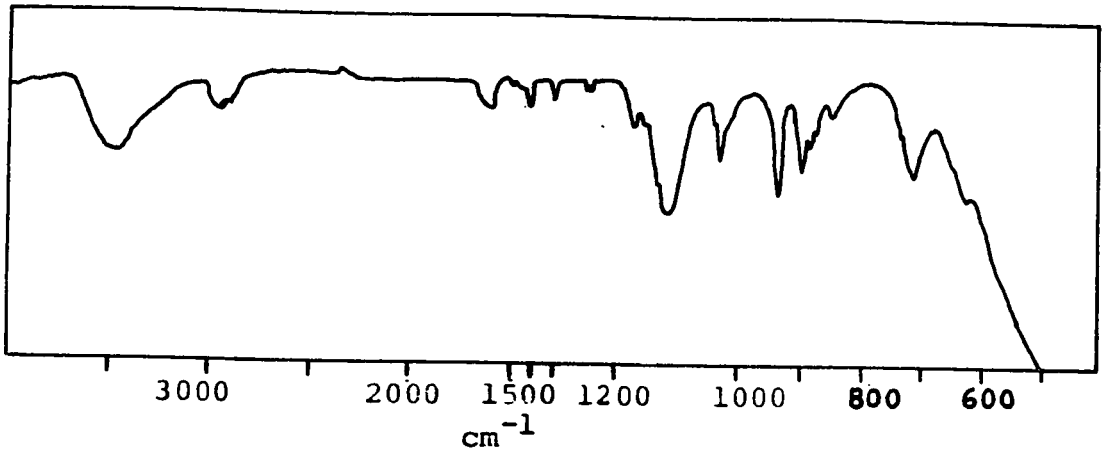
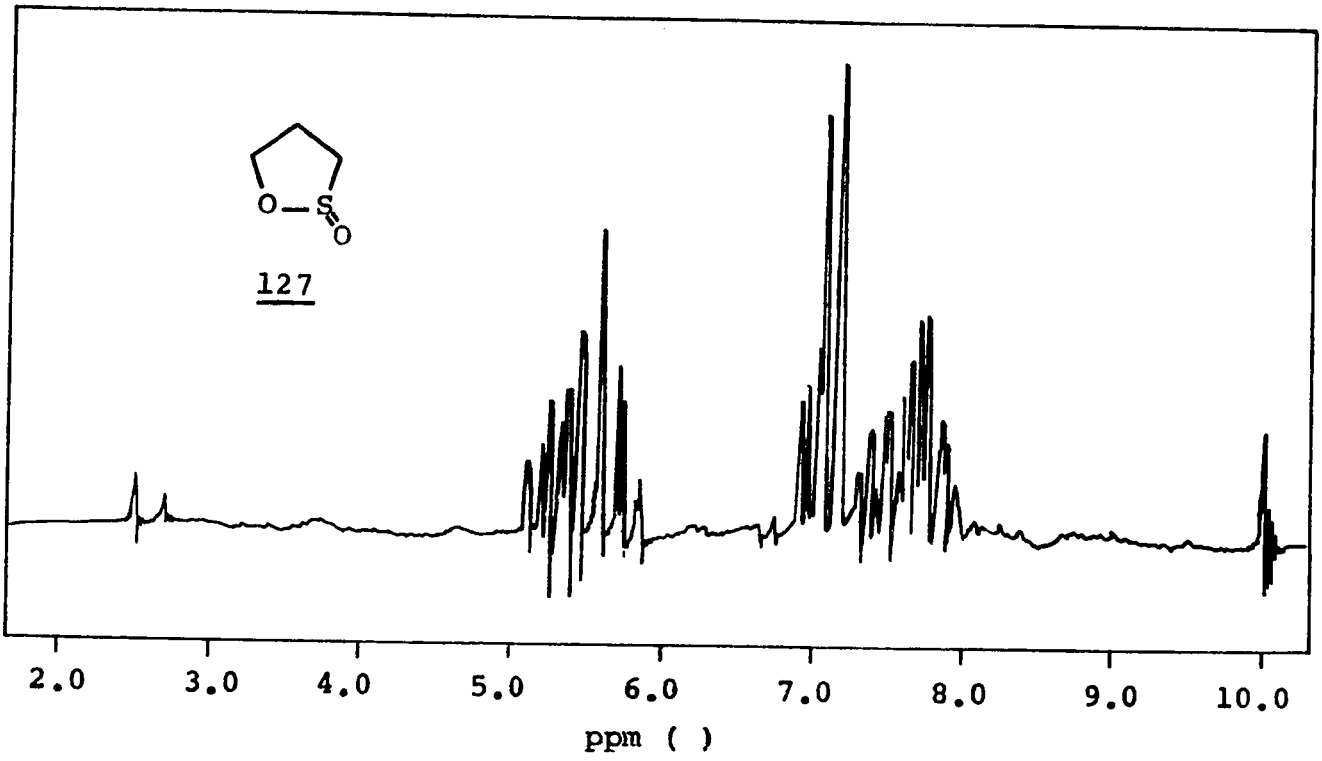
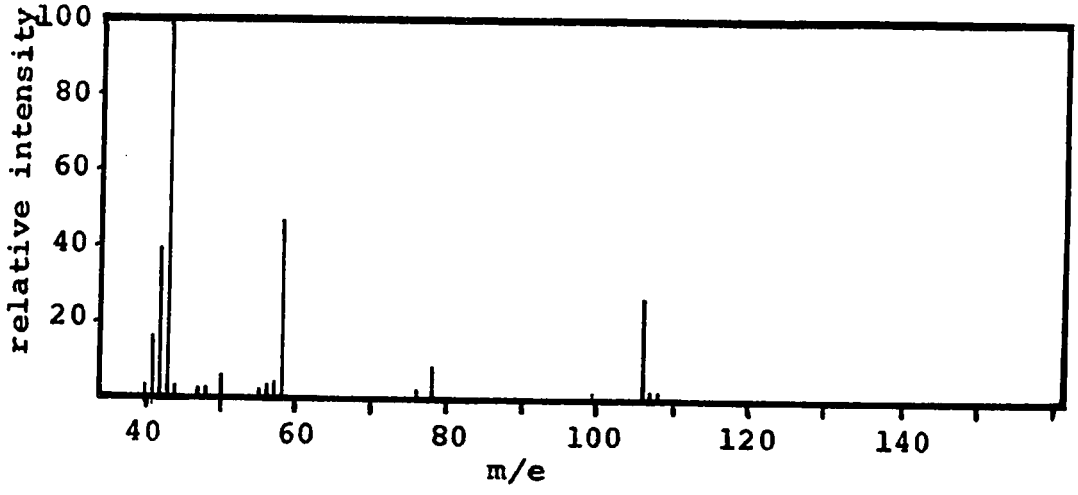


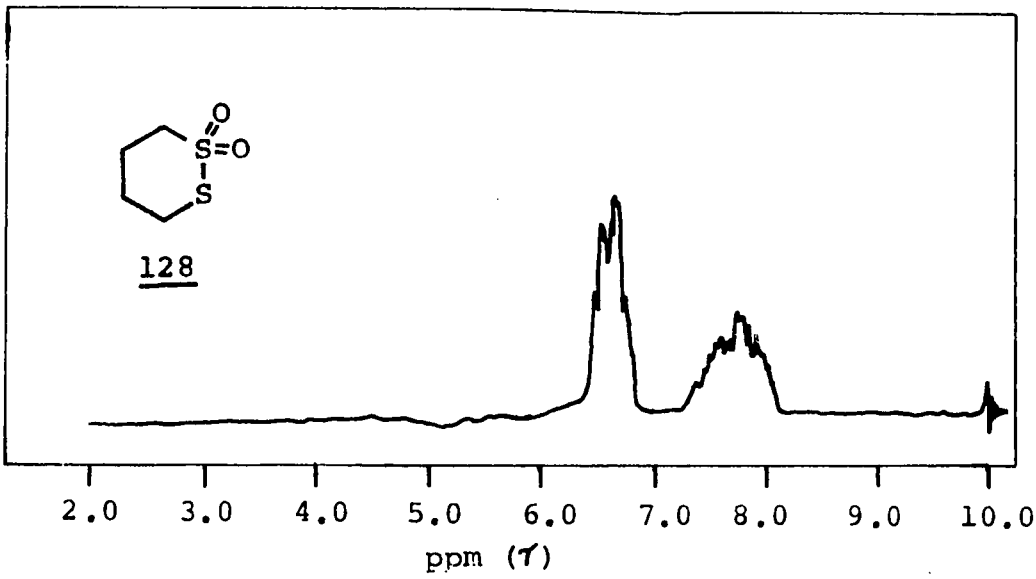
1,2-Dithiolane-1,1-dioxide (126).



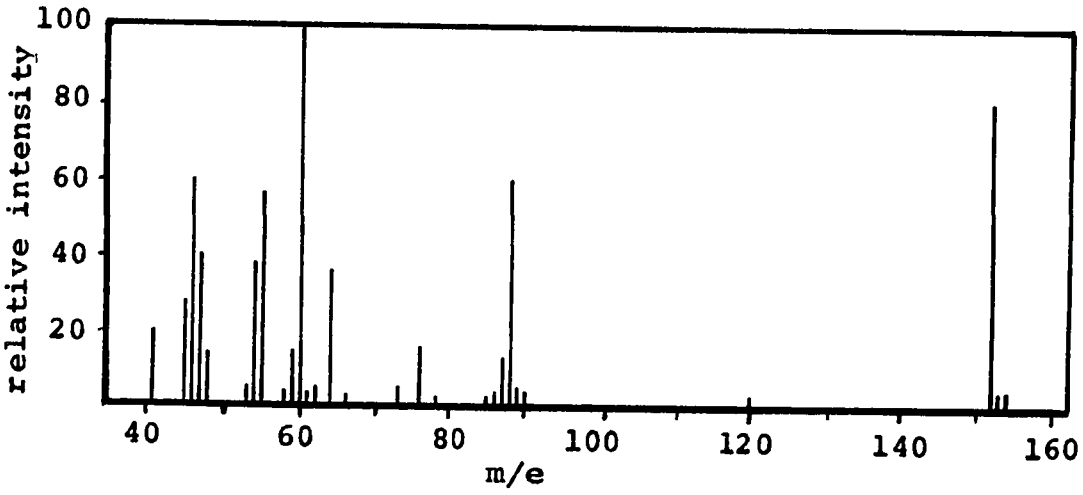




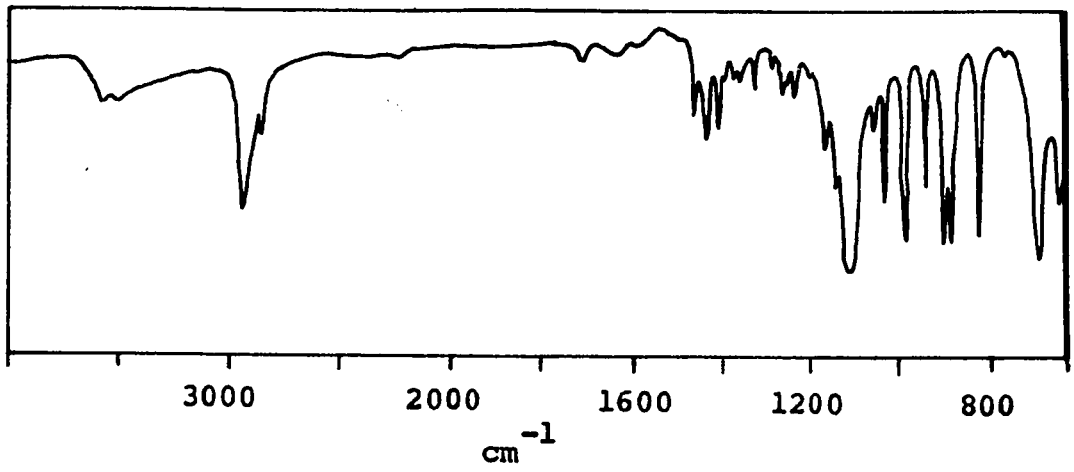
1,2-Oxathiolan-2-oxide (127).

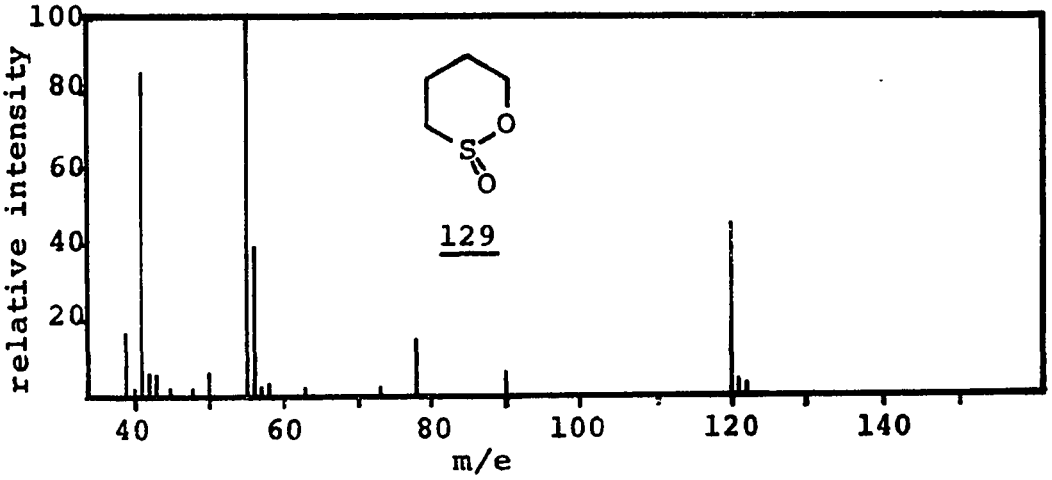


128

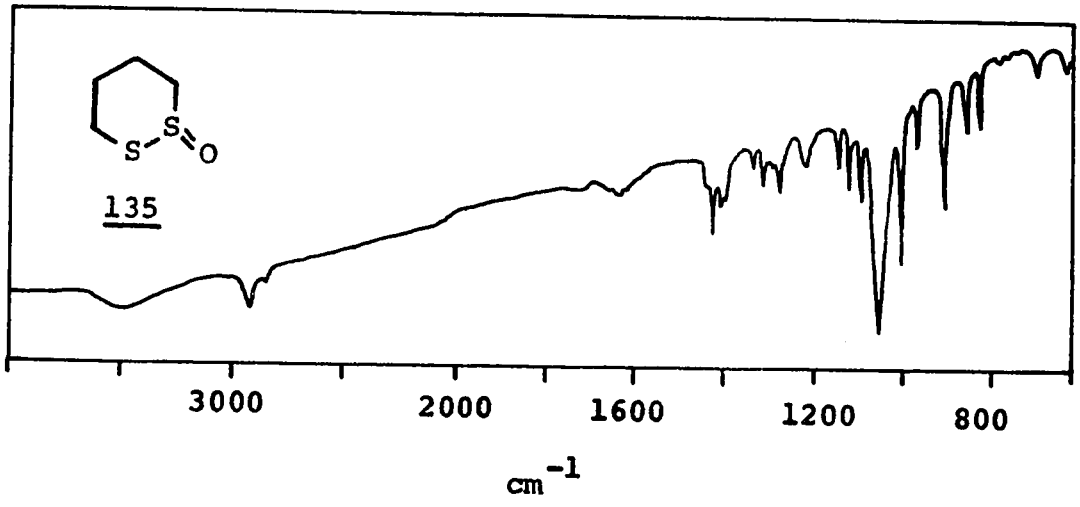


1,2-Dithian-1,1-dioxide (128).





1,2-Oxathian-2-oxide (129).



1,2-Dithian-1-oxide (135).

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