THE CHEMISTRY OF ORGANIC TRISULFIDES

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THE CHEMISTRY OF ORGANIC TRISULFIDES AND RELATED DERIVATIVES

ABSTRACT

Methods of synthesizing unsymmetric trisulfides are investigated. The reaction of thiols with alkyl phthalimido disulfides is a general procedure for this synthesis.

Tris(diethylamino) phosphine desulfurizes alkyl, aryl and cyclic trisulfides to disulfides. A kinetic study reveals that the desulfurization of aromatic trisulfides proceeds by nucleophilic attack of the phosphine on the central sulfur atom to form a phosphonium salt in the rate limiting step. Triphenylphosphine and tris(diethylamino) phosphine exhibit a dichotomy of behaviour towards aliphatic trisulfides as the former attacks and extrudes the central sulfur atom while the latter removes terminal sulfur. Nucleophilic attack of the aminophosphine provides a phosphonium salt which decomposes to products *via* S_N2 attack of hydrodisulfide anion on carbon.

Aminophosphines desulfurize alkyl phthalimido disulfides to N-alkylphthalimides; sulfenic sulfonic thioanhydrides are converted to thiosulfonates. The latter loss of sulfur also proceeds solvolytically. The mass spectral fragmentation of a variety of organo-sulfur compounds is discussed.

Ph.D. David K. Ash Department de Chimie

La Chimie des Trisulfures Organiques et de leurs Derivés

Résumé

Les méthodes de synthèse des trisulfures non symétriques sont étudiées. La réaction des thiols avec les phtalimido-disulfures d'alkyles est un procédé général pour cette synthèse.

La tris (diéthylamino) phosphine désulfure les trisulfures cycliques, ceux d'alkyles et d'aryles pour former les disulfures correspondants. Une étude cinétique montre que la désulfuration des trisulfures aromatiques se fait par une attaque nucléophilique de la phosphine sur l'atome central de soufre, donnant lieu à la formation d'un sel de phosphonium dans l'étape déterminante. La triphényl phosphine et la tris (diéthylamino) phosphine présentent une dichotomie de comportement à l'égard des trisulfures aliphatiques, comme la première attaque et expulse l'atome central de soufre tandis que la dernière enlève le soufre terminal. L'attaque nucléophilique de l'aminophosphine fournit un sel de phosphonium qui se transforme en produits par une attaque S_N2 de l'anion hydrodisulfure sur le carbon.

Les aminophosphines désulfurent les phtalimido disulfures d'alkyles pour former les N-alkylphtalimides. Les thioanhydrides sulfèno-sulfoniques sont convertis en thiosulfonates. La dernière mode d'expulsion du soufre procède aussi par voie solvolytique. La spectrométrie de masse d'une variété de composés organiques du soufre est discutée.

THE CHEMISTRY OF ORGANIC TRISULFIDES AND RELATED DERIVATIVES

by

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D.K. Ash

INTRODUCTION

Sulfur is one of the few elements which is found in the free state. It was known and used by our earliest ancestors who burned it in religious ceremonies as early as 2000 BC. The Egyptians were using sulfur compounds as dyes about 1600 BC. Some of the early references to sulfur in the literature include Homer in "The Odyssey" (850 BC),

> "Bring me fire that I may burn sulfur, the divine curer of ills."

and Pliny in "Historia Naturalis" (23 AD),

> "Burning sulfur will keep out enchantments - yea, and drive away foul fiends."

Interest in sulfur and its compounds has continued over the past four thousand years but many of its reactions still have unexplored mechanisms.[1]

This thesis concerns an investigation of a class of organo-sulfur compounds known as trisulfides. An organic trisulfide consists

R-S-S-S-R

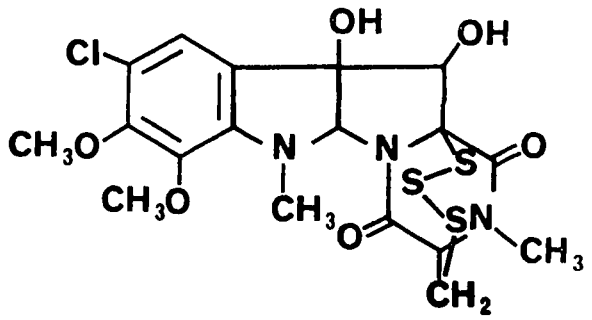
of three consecutive sulfur atoms with an organic grouping bonded to each of the terminal sulfurs.

Naturally Occurring Trisulfides

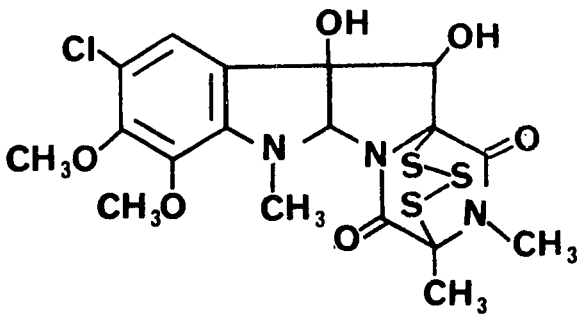
The simplest and the most complex examples of this functional group are found among the trisulfides which exist in nature. Recently dimethyl trisulfide was isolated from the defence glands of the

CH_3-S-S-S-CH_3

ponerine ant, Paltothyreus tarsatus.[2] The fungus Pithomyces chartarum, which occurs in New Zealand pastures, produces a mixture of toxic metabolites responsible for liver damage and facial eczema in sheep. Among the several sulfur-containing metabolites are the trisulfides sporidesmin C[3] and sporidesmin E.[4,5] The latter is the most cytotoxic mould metabolite described so far. Lenthionine, which has been isolated



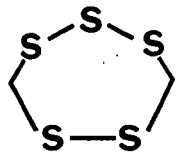
sporidesmin C



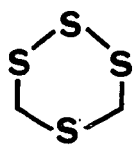
sporidesmin E

from the mushroom Lentinus edodes, is a seven-membered ring containing both a trisulfide and a disulfide linkage. It is used to flavour food

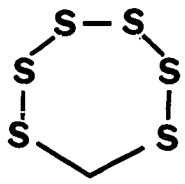
lenthionine



1,2,3,5-tetrathiane



hexathiepin

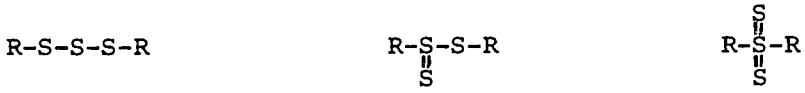


and is also active against some bacteria and fungi. Other polysulfides isolated from this mushroom include 1,2,3,5-tetrathiane and hexathiepin.[6]

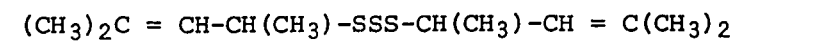
Aliphatic trisulfides are also found in the aroma of various foods. Methyl propyl trisulfide was identified among the constituents of cocoa aroma[7] while dimethyl, methyl propyl and methyl 2-propenyl trisulfides are constituents of garlic aroma.[8]

Structure, Bonding and Stereochemistry of Trisulfides

The synthesis of a series of polysulfides up to the octasulfide derivatives has been reported.[9] The arrangement of sulfur atoms in polysulfides has been the subject of considerable controversy. The issue is whether the sulfur chains are linear or "branch-bonded". The possible arrangements for trisulfides are shown below.[10] The



fact that polysulfides are easily desulfurized to disulfides by the action of alkali , alkali-metal sulfite and cyanide was thought to indicate that the removable sulfur atoms are bonded differently from the others and are not part of unbranched chains.[11] Recently, a branch-bonded trisulfide was proposed as an intermediate to account for the thermal



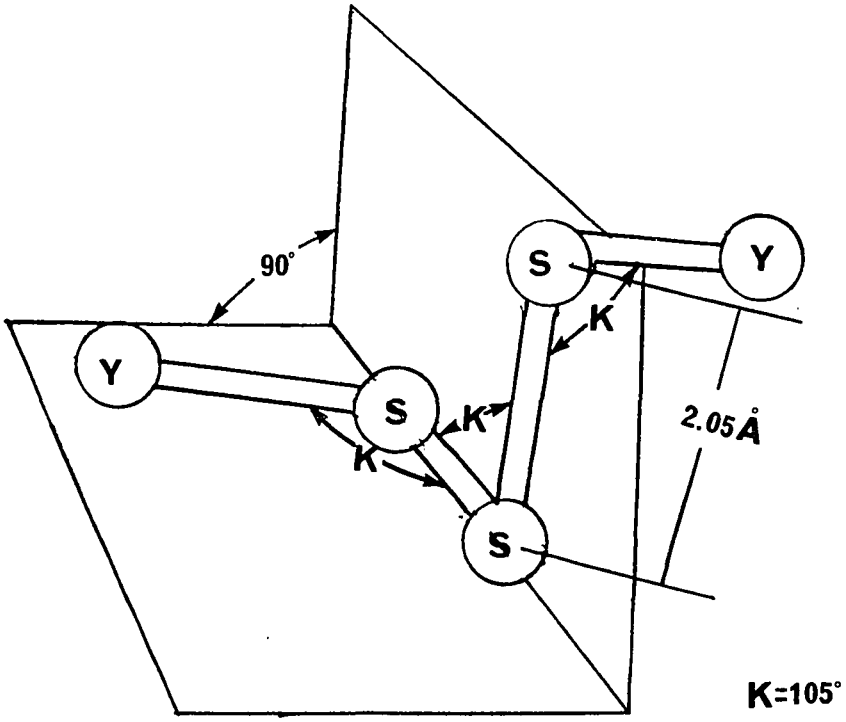
racemization of bis-(1,3-dimethylbut-2-enyl) trisulfide.[12] An equilibrium between the linear and branched trisulfide was advanced to explain the conversion of disulfides to trisulfides by reaction with dihydrogen

disulfide.[13] Despite these proposals, a wide variety of physical techniques have established a straight-chain structure for tri- and higher polysulfides. These include ultraviolet,[9,14] infrared[14(c)] and Raman spectroscopy,[15] dipole moment measurements,[16] diamagnetic susceptibilities,[17] electron diffraction,[18] and X-ray crystal structure determination.[19]

By analogy with the bonding of sulfur atoms in disulfides,[20] it is thought that both the σ bond joining carbon to sulfur and the σ bond uniting the two sulfur atoms in trisulfides have almost entirely p character. In each of the sulfurs of the trisulfide one non-bonded pair of electrons is located in the 3s orbital while the remaining non-bonded pair of electrons occupies a 3p orbital. The repulsion of these filled 3p orbitals on sulfur is minimized when the dihedral angle (YSS-SSS) is 90° (Fig. 1). The length of a bond between two divalent sulfur atoms in organic trisulfides lies in the range 2.04 - 2.065Å. The sulfur valency angle in these compounds varies between 103° and 107°.[21,22]

As a consequence of the geometry outlined above, two rotational-isomeric forms of trisulfides may exist. The atoms or groups attached to the terminal sulfur atoms are rotated about 90° out of the plane of the three sulfur atoms, either to the same side of the plane, cis (Fig.1(b)), or to opposite sides, trans (Fig. 1(a)). There are two enantiomeric trans forms. If the two groups Y (Fig.1) are alike, the cis-form has a mirror plane of symmetry while the trans-form possesses a two-fold axis of molecular symmetry.[22,23] An X-ray study of di-2-iodoethyl trisulfide shows that the configuration of this molecule is trans in the crystalline state.[19]

(a)



(b)

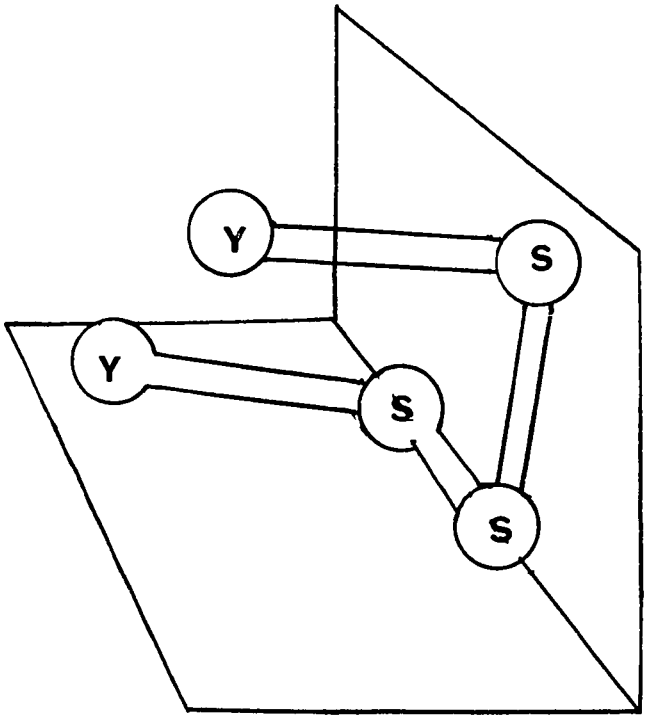
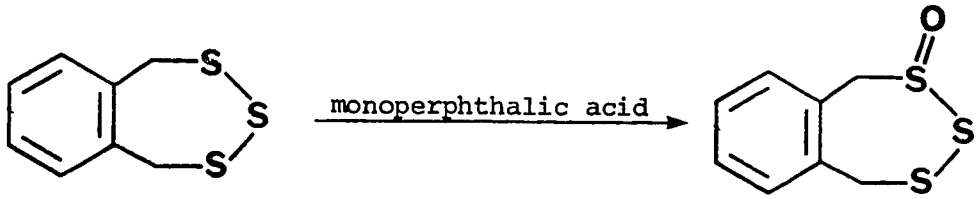


Fig. 1 Dihedral angle of trisulfides:
(a) <u>trans</u> (b) <u>cis</u>

Reactions of Trisulfides

Organic trisulfides are known to undergo both oxidation and reduction reactions. Examples of the former include the reaction of 2,3,4-benzotrithiepin with monoperphthalic acid to yield the 2-oxide.[24]



Nmr spectroscopy was used to elucidate the location of the oxygen atom in the product as the formation of 2,3,4-benzotrithiepin-3-oxide was also possible. The spectrum showed a pair of AB quartets whose central points were 9 Hz apart. This small difference in the chemical shifts of the two sets of benzylic protons, (CH_2-S-S-) and (CH_2-S(O)-S-), is in accord with the difference in the shifts observed for the benzylic protons of dibenzylthiosulfinate. The fact that each methylene group

$$C_6H_5CH_2\text{-}S(O)\text{-}S\text{-}CH_2C_6H_5$$

appears as a quartet was ascribed to a degree of conformational rigidity of the cyclic seven-membered ring system.[24] The oxidation of dialkyl trisulfides with an excess of peroxide produced new compounds whose

$$R\text{-}S\text{-}S\text{-}S\text{-}R \xrightarrow{H_2O_2} R\text{-}\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}\text{-}S\text{-}\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}\text{-}R$$

elemental analysis indicated the presence of four oxygen atoms per molecule. These products were shown to be symmetrical, through the use of infrared and Raman spectroscopy, and were assigned the dialkanesulfonic thioanhydride structure.[25]

A wide variety of reducing agents such as lithium aluminum hydride,[26] sodium borohydride[13] and sodium-liquid ammonia,[27] are capable

$$R\text{-}S\text{-}S\text{-}S\text{-}R \longrightarrow 2\ RSH + H_2S$$

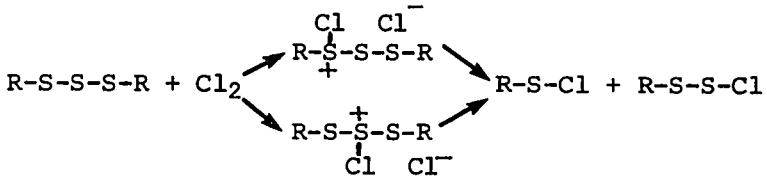
of converting trisulfides to hydrogen sulfide plus thiols.

The sulfur-sulfur bond of trisulfides may be cleaved both homolytically and heterolytically. Homolytic cleavage of dialkyl trisulfides may be induced photochemically to produce di- and tetrasulfides.[28]

$$R\text{-}S\text{-}S\text{-}S\text{-}R \xrightarrow{h\nu} R\text{-}S\text{-}S\cdot + R\text{-}S\cdot \longrightarrow RSSR + RSSSSR$$

Free radicals may also be produced by the thermolysis of trisulfides. On heating, organic trisulfides undergo both end group exchange and disproportionation to sulfides of higher and lower rank.[29]

Scission of the sulfur-sulfur bond of trisulfides may occur heterolytically in the presence of electrophilic reagents. For instance, the chlorinolysis of dimethyl and diethyl trisulfides produces the corresponding alkanesulfenyl chloride and alkyl chlorodisulfide.[30] This reaction appears to proceed <u>via</u> a chloro-sulfonium intermediate similar



to that exhibited in the reaction of disulfides with chlorine.[31] The cleavage of di-o-nitrophenyl trisulfide by bromine[32] is another example of electrophilic rupture of the sulfur-sulfur bond.

The scission of the sulfur-sulfur bonds of trisulfides by nucleophiles occurs readily. This may be due to the large polarizable sulfur atom which may accommodate the negative charge of a mercaptide or a hydrodisulfide ion thus making these ions good leaving groups in

$R\text{-}S^-$ $\qquad\qquad$ $R\text{-}S\text{-}S^-$

mercaptide ion $\qquad\qquad$ hydrodisulfide ion

such reactions. All three sulfur atoms in an organic trisulfide are sterically accessible as the sulfur-sulfur bond length averages 2.05Å while the carbon-sulfur bond distance is of the order of 1.8Å.[21,33]

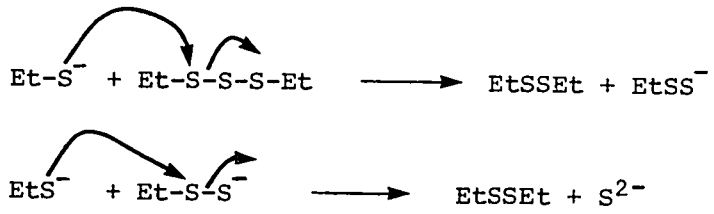
Foss[34] has proposed that trisulfides may undergo isotopic exchanges with their own thio anions as shown below. However,

$$R\text{-}S\text{-}S\text{-}S\text{-}R + R\text{-}{}^{35}S^- \rightleftharpoons R\text{-}S\text{-}S\text{-}{}^{35}S\text{-}R + R\text{-}S^-$$

Evans and Saville[35] have suggested that displacement on a terminal sulfur atom is a likely alternative as a hydrodisulfide anion would be released. Since the hydrodisulfide anion could presumably be resonance stabilized, it should be better than RS^- as a leaving group from sulfur. Evidence for their proposal came from the reaction of diethyl trisulfide with ethanethiol in the presence of piperidine. According to Foss[34] no net

$$Et\text{-}S\text{-}S\text{-}S\text{-}Et + 2\ EtSH \xrightarrow{\text{base}} 2\ EtSSEt + H_2S$$

change would be observed but instead two moles of diethyl disulfide per mole of trisulfide were rapidly obtained. This reaction is rationalized as follows.



In the absence of base, no detectable decomposition of the trisulfide could be observed over several hours.

Species capable of adding sulfur, like sulfite and cyanide ion, may desulfurize trisulfides to disulfides via nucleophilic scission of a sulfur-sulfur bond. For example, diphenyl,[36] di-p-tolyl[36,37] and dibenzyl[37,38] trisulfides are desulfurized by cyanide ion while sulfite ion extrudes sulfur from dibenzyl, dimethyl[39] and di-p-tolyl trisulfides.[37] It seems reasonable to assume that these reactions are ionic displacements, the first step being a displacement of mercaptide by cyanide or sulfite, and the last step the displacement of thiocyanate or thiosulfate by the mercaptide.[40]

$$R\text{-}S\text{-}S\text{-}S\text{-}R + {}^{-}X \longrightarrow R\text{-}S\text{-}S\text{-}X + RS^{-} \longrightarrow RSSR + {}^{-}SX$$

$$X = CN, NaSO_3$$

Alternatively, at least in the case of the aliphatic trisulfides, the nucleophile may attack a terminal sulfur atom displacing the hydrodisulfide anion.

$$R\text{-}S\text{-}S\text{-}S\text{-}R + {}^{-}CN \longrightarrow R\text{-}SCN + RSS^{-} \longrightarrow RSSR + {}^{-}SCN$$

Nucleophilic attack of the displaced anion on carbon would give the

observed products, disulfide plus thiocyanate ion. Thus, there are two possible mechanisms for the desulfurization of trisulfides by nucleophiles but few mechanistic studies have been advanced to differentiate them.

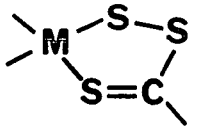
Some trisulfides are desulfurized to the corresponding disulfides plus hydrogen sulfide by alkali.[32] However, the most general reagents for the desulfurization of trisulfides are trivalent phosphorous compounds and their use is discussed in the next section.

Desulfurization with Trivalent Phosphorous Compounds

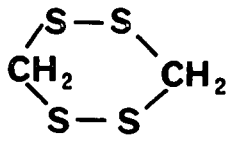
There are several reviews of the desulfurization of a variety of organo-sulfur compounds by trivalent phosphorous compounds.[41,42,43,44] The sulfur compounds (Fig. 2) include disulfides, trisulfides, tetrasulfides, metal dithiolate complexes, 1,2,4,5-tetrathiins, 1,2-trithiocarbonates, episulfides, dithioanhydrides, sulfenate esters, sulfenyl chlorides, thiosulfonate esters, thiosulfinate esters,[45] phthalic thioanhydride,[46] thiepins,[47] sulfenimides,[48] β-ketosulfides[49] and elemental sulfur. The phosphorous reagents in use comprise trialkyl phosphites, triaryl phosphites, triaryl phosphines, trialkyl phosphines, phosphorous trichloride[50] and tris(dialkylamino) phosphines. In view of the extensive literature covered by the references above only the reaction of trisulfides with trivalent phosphorous compounds will be reviewed here.

Phosphines and phosphites act as selective desulfurizing agents because of their ability to undergo valence expansion from trivalent to pentacovalent phosphorous. Furthermore, these trivalent

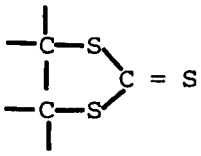
n = 2, disulfides
n = 3 trisulfides
n = 4 tetrasulfides



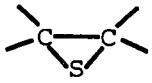
metal dithiolate



1,2,4,5-tetrathiin

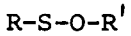


1,2-trithiocarbonate

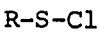


episulfide

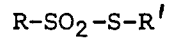
dithioanhydride



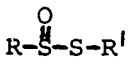
sulfenate ester



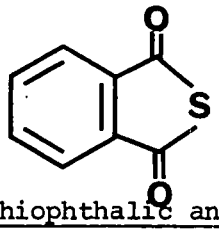
sulfenyl chloride



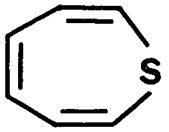
thiosulfonate ester



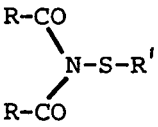
thiosulfinate ester



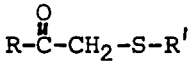
thiophthalic anhydride



thiepin



sulfenimides



β-ketosulfides

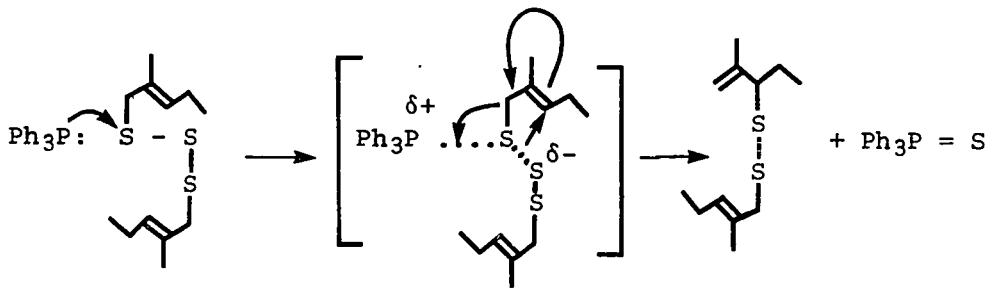
Fig. 2 Structures of compounds which have been desulfurized by phosphines

phosphorous compounds are more powerful nucleophiles than the corresponding amines despite their weak basicity.[51] The high bond energy of the phosphorous-sulfur bond which is formed provides a driving force for these desulfurization reactions.

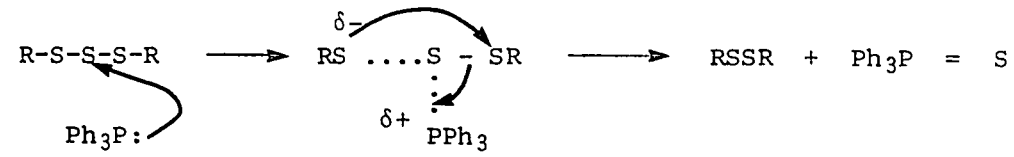
There are several reports in the chemical literature which refer to the desulfurization of organic trisulfides with triphenylphosphine. Moore and Trego[26] studied the reaction of symmetric dialkenyl trisulfides with this phosphine. The product composition of the desulfurization of di-(2-methylpent-2-enyl) trisulfide indicated that disulfides had been

$$CH_3CH_2CH = C(CH_3)CH_2SSSCH_2C(CH_3) = CHCH_2CH_3$$

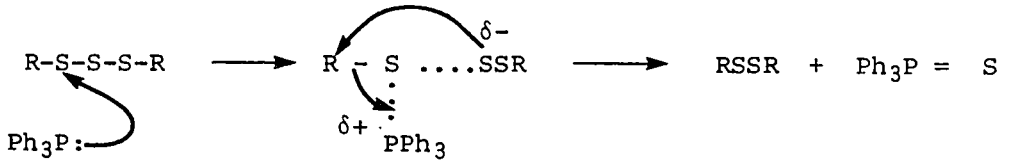
formed by two alternate routes, one involving allylic rearrangement of the alkenyl moiety and the other not involving the alkenyl group. The former reaction was believed to proceed by an SN_i'[52] mechanism analagous to that observed in the reaction of triphenylphosphine with dialkenyl disulfides.[53] The straightforward desulfurization was proposed to



occur <u>via</u> one or both of the following pathways. Either the phosphine would attack and extrude the central sulfur atom as in equation 1, or the terminal sulfur as in equation 2.



eq.1



eq.2

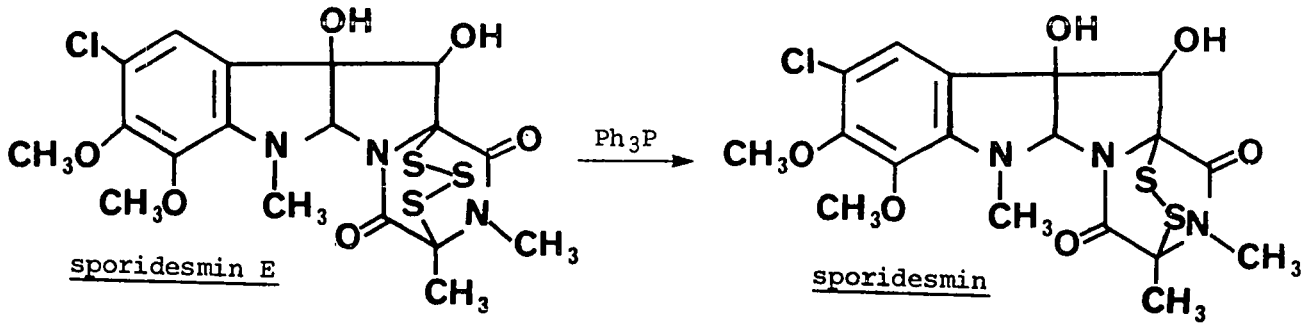
$R = - CH_2C(CH_3) = CHCH_2CH_3$

One of the findings of this study was that the desulfurizations of the disulfides are faster in all cases than the desulfurizations of their precursor trisulfides.

The desulfurization of several trisulfides to disulfides by triphenylphosphine has been reported.[54] The authors' only comment on a possible mechanism for this reaction was, "These reactions were considered to initiate by the nucleophilic attack of phosphine to the sulfur of trisulfides". They did not state which sulfur atom, central or terminal, was attacked. It should be noted that some of the results in this publication are in conflict with the literature.[55]

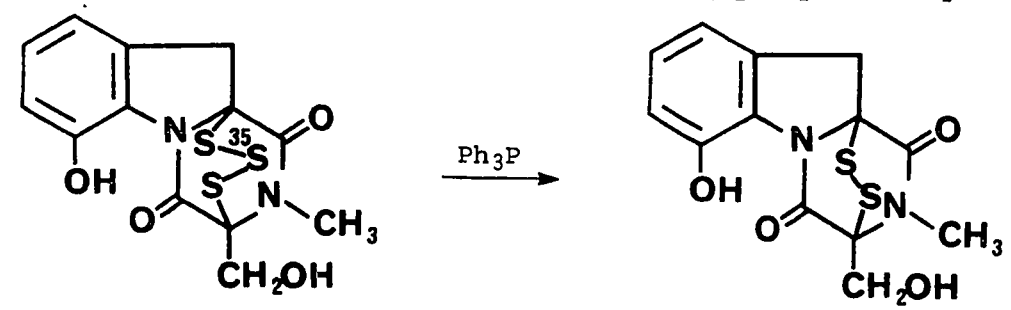
Fehér and Kurz[56] have studied the effects of para substituents on the desulfurization of diaryl trisulfides by triphenylphosphine and found that electron withdrawing groups accelerate the rate of reaction. A rho value[57] of + 0.98 was obtained. The activation energy ranged between 6-20 k cal $mole^{-1}$ while the entropy of activation varied between -47 and -15 entropy units. The authors did not propose a mechanism for this reaction.

Triphenylphosphine is known to desulfurize sporidesmin E to sporidesmin.[4,5] A recent communication[58] has reported on the



sporidesmin E sporidesmin

use of natural products of known configuration to study the stereochemistry of the desulfurization of trisulfides with triphenylphosphine. Thiodehydrogliotoxin reacted with triphenylphosphine to yield



thiodehydrogliotoxin dehydrogliotoxin

dehydrogliotoxin having identical circular dichroism to the natural product. Furthermore, ^{35}S-labelled thiodehydrogliotoxin gave labelled triphenylphosphine sulfide and unlabelled dehydrogliotoxin. The authors conclude that "a decision may be made concerning the mode of desulfurization of trisulfides. It is clear that the reaction proceeds preferentially at sulfur bonded to sulfur atoms rather than at sulfur atoms which are substituents of carbon". However, thiodehydrogliotoxin might constitute a special case and it would be misleading to use it as a model to generalize on the mechanism of the reaction. It is difficult to imagine

the terminal sulfur atom being extruded as this would appear to necessitate front side displacement of triphenylphosphine sulfide by hydrodisulfide anion. This requirement for front side displacement is a consequence of the geometry of the ring system.

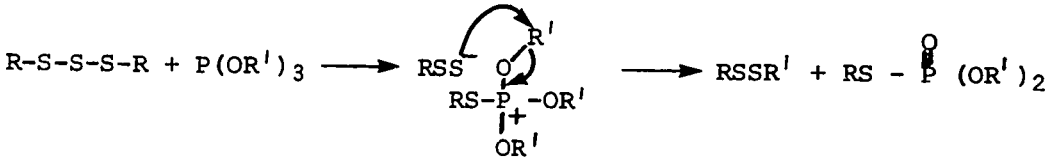
The present study was undertaken in order to obtain further insight into the mechanistic details of the reaction of trivalent phosphorous compounds with organic trisulfides.

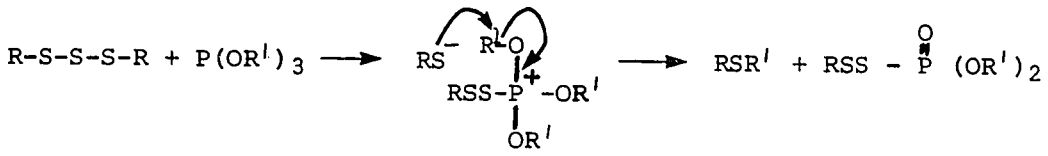
Trivalent Phosphorous Compounds

The foregoing has indicated that only triarylphosphines have been used to desulfurize trisulfides to disulfides. Although phosphites are less nucleophilic than phosphines, due to the presence of electronegative oxygen atoms adjacent to phosphorous, they may act as desulfurizing reagents. This is believed to be due to a stabilization of

R_3P	$(RO)_3P$	$(R_2N)_3P$
phosphines	phosphites	aminophosphines

the intermediate phosphonium salt by electromeric release from oxygen as well as the formation of a strong phosphorous-oxygen bond. Despite this, phosphites are not likely to be of use in the selective desulfurization of trisulfides as the reaction would likely be complicated by an Arbuzov-like rearrangement.[42,51,59] In this case the disulfide or





sulfide produced would have exchanged one of its alkyl or aryl groups with the phosphite.

A class of trivalent phosphorous compounds which might be suitable for the desulfurization of organic trisulfides are the nucleophilic aminophosphines. The lower electronegativity of nitrogen relative to oxygen would make aminophosphines more nucleophilic than phosphites as the lone-pair of electrons on phosphorous would be more available for reaction. Also, electromeric release by the nitrogen atoms would stabilize a tetravalent intermediate or transition-state complex. In addition, aminophosphines are not likely to undergo Arbuzov-type rearrangements.[43] Since tris(dialkylamino) phosphines have been used to desulfurize disulfides which were inert towards triphenylphosphine, they should be suitable reagents for the selective desulfurization of trisulfides.[43]

Synthesis of Trisulfides - symmetric

Alkyl and aryl mono and disulfides are relatively easy to prepare and are generally stable, easily characterized compounds. In the synthesis of trisulfides, polysulfides are often obtained and the isolation, purification and characterization of individual trisulfides is difficult. In some cases clean cut separations appear impossible due to the similar properties of a series of sulfides. Early chemists

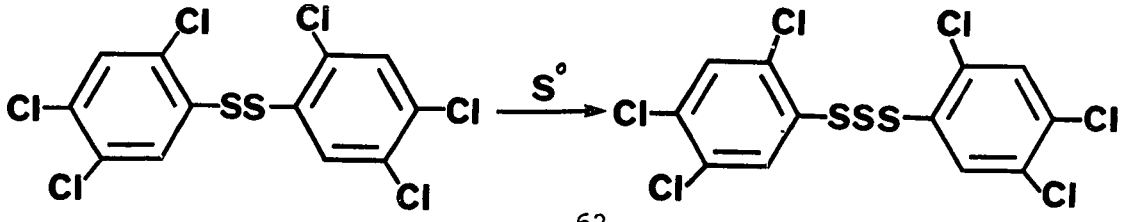
attempted the reaction of alkyl halides with sodium trisulfide,

$$2\ R\text{-}Br + Na_2S_3 \longrightarrow RSSSR + 2\ NaBr$$

however, as sodium trisulfide is an equilibrium mixture of several sulfides, di-, tri-, and tetrasulfides were obtained as products.[60] The reaction of thiols with sulfur in the presence of a catalytic amount

$$2\ RSH + S^0 \xrightarrow{R'NH_2} RSSSR + H_2S$$

of an amine produces a mixture of polysulfides which, in some cases, contains about 90 percent of the trisulfide.[61] The preparation of certain substituted diaryl trisulfides via addition of sulfur to



diaryl disulfides has been reported.[62]

Mixtures of polysulfides are obtained when sodium or potassium sulfide react with two molar equivalents of an alkanesulfenyl chloride. For example, with 2-methyl-2-propanesulfenyl chloride, 8% of disulfide, 58% of trisulfide and 34% of tetrasulfide was produced. These compounds

$$2\ (CH_3)_3C\text{-}S\text{-}Cl + Na_2S \longrightarrow (CH_3)_3C\text{-}S_n\text{-}C(CH_3)_3 + 2\ NaCl$$

n	%
2	8
3	58
4	34

could not be separated from one another by repeated fractional distillation and gas-liquid chromatography was required.[63] This is consistent with the observation that aliphatic sulfenyl chlorides produce mixtures of di-, tri-, and tetrasulfides on treatment with hydrogen sulfide.[64] In contrast to this, aromatic sulfenyl chlorides,[65]

$$2\ \text{Ar-S-X} + \text{H}_2\text{S} \longrightarrow \text{ArSSSAr} + 2\ \text{HX}$$

sulfenyl thiocyanates[65] and sulfenyl bromides[32] react with hydrogen sulfide or heavy metal sulfides (PbS, HgS, Ag_2S or Tl_2S) with the formation of trisulfides in relatively pure form. Recently, the amine catalyzed reaction of hydrogen sulfide with α-chloromethyl acrylate has been reported[66] to produce di(β-carbomethoxyethyl) trisulfide along with the corresponding disulfide and other products. Attempts to separate the trisulfide from the disulfide by high vacuum fractional distillation were unsuccessful.

The reaction of diphenyl disulfide with dihydrogen disulfide results in the formation of diphenyl tri- and tetrasulfides. Higher

$$\text{C}_6\text{H}_5\text{SSC}_6\text{H}_5 + \text{H}_2\text{S}_2 \longrightarrow \text{C}_6\text{H}_5\text{S}_n\text{C}_6\text{H}_5 + \text{H}_2\text{S} \qquad n = 3,4,5,6$$

sulfides may also have been produced. However, dibenzyl disulfide and cystine are unaffected by this sulfurating reagent. Benzenethiol and α-toluenethiol readily gave mixtures of polysulfides on treatment with dihydrogen disulfide. The nmr spectrum of the latter indicated

that the ratio of di-, tri-, tetra- and pentasulfides was 2:10:7:4.[13]

The reaction of sulfonyl chlorides with potassium

$$R\text{-}SO_2\text{-}Cl + R'\text{-}SO_2S^-K^+ \longrightarrow R\text{-}SO_2\text{-}S\text{-}SO_2\text{-}R' \xrightarrow{4\ Ph_3P} RSSSR$$

thiosulfonates gives dialkanesulfonic thioanhydrides which are reported[54] to undergo deoxygenation with triphenylphosphine to produce trisulfides. Symmetric trisulfides may be obtained by the thioalkylation of sulfide ion by two molar equivalents of thiosulfonate but this method is not

$$R\text{-}SO_2\text{-}S\text{-}R' + Na_2S \longrightarrow R'SS^-Na^+ \xrightarrow{RSO_2SR'} R'SSSR' + RSO_2^-Na^+$$

applicable to the preparation of unsymmetric trisulfides.[63] The decomposition of alkyl and aryl dithiosulfites gives equimolar amounts of dialkyl trisulfides and dialkyl disulfides according to the following

$$2\ R\text{-}S\text{-}\overset{\overset{O}{\|}}{S}\text{-}S\text{-}R \longrightarrow RSSSR + RSSR + SO_2$$

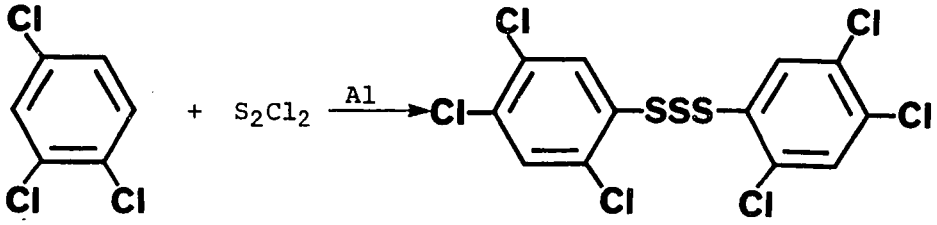
stoichiometry.[67] The application of Bunte salts (salts of S-alkyl or S-aryl hydrogen thiosulfates) to the synthesis of trisulfides has been reported.[24,39,68,69] Interaction with 0.5 molar equivalents of

$$2\ R\text{-}S\text{-}SO_3^-Na^+ + Na_2S \longrightarrow RSSSR + 2\ Na_2SO_3$$

sodium sulfide effects the desired transformation. This method is not

always successful as disulfides rather than trisulfides are sometimes obtained.[68] Other limitations include the formation of mixtures of di-, tri- and tetrasulfides[39] as well as the difficulties in preparing some Bunte salts.[24]

Treatment of 1,2,4-trichlorobenzene with sulfur monochloride and aluminum gives the 5,5'-trisulfide.[62,70] Perhaps the most



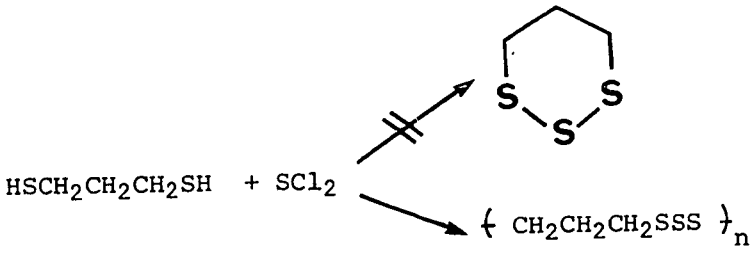
general method for the synthesis of symmetric organic trisulfides is the interaction of sulfur dichloride with two molar equivalents of a thiol.[71] One limiting feature of this synthetic scheme would be the reaction of sulfur dichloride with olefinic or hydroxylic functions in the mercaptan.[72] It should be noted that some authors have found

$$2\ RSH + SCl_2 \longrightarrow RSSSR + 2\ HCl$$

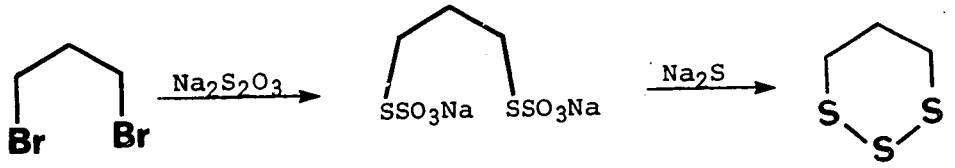
difficulty executing this reaction.[63]

Synthesis of Trisulfides - cyclic

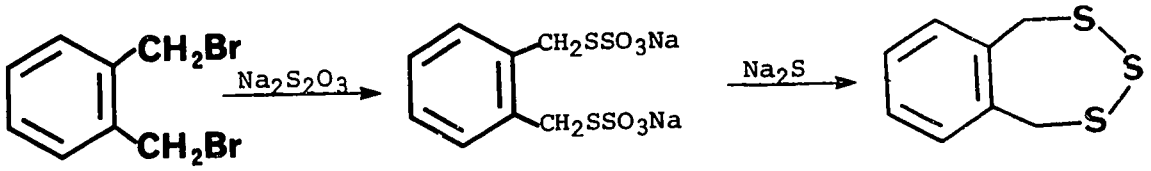
Many of the methods used for the preparation of symmetric trisulfides are not applicable to the synthesis of cyclic trisulfides. For example, the attempted synthesis of 1,2,3-trithiane by reacting 1,3-propanedithiol with sulfur dichloride was unsuccessful, only polymer being obtained.[24] However, the trithiane and 2,3,4-benzotrithiepin



were prepared by the action of sodium sulfide on the precursor bifunctional Bunte salts.[24]



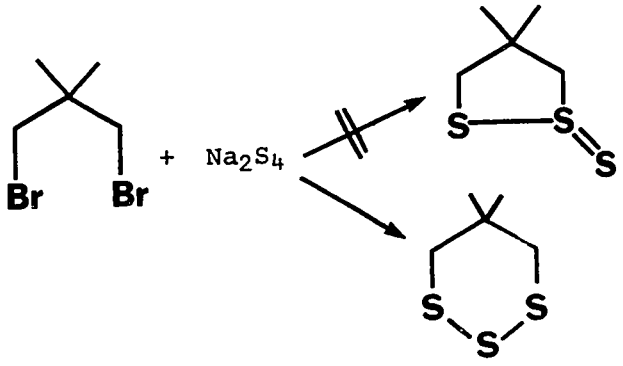
trithiane



2,3,4-benzotrithiepin

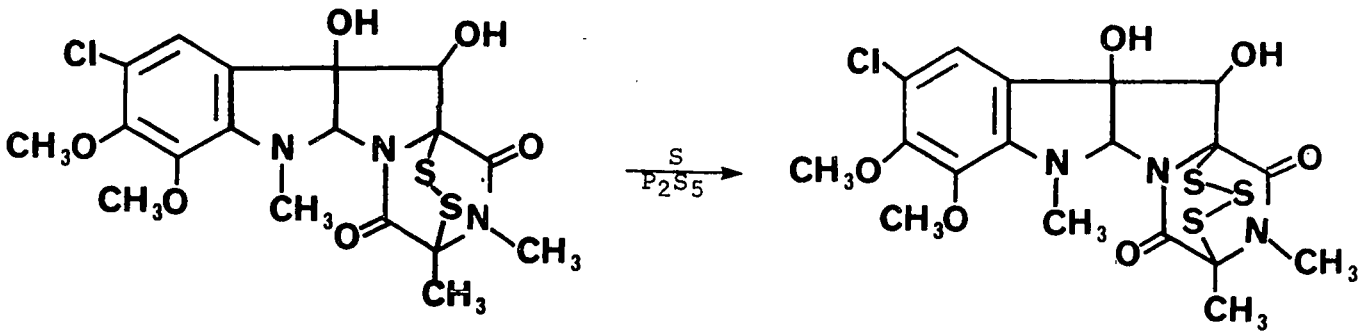
Other cyclic trisulfides have been synthesized by this method.[73]

Backer and his co-workers[74] devised a synthesis of cyclic trisulfides based on the reaction of sodium tetrasulfide with substituted 1,3-dibromides. For example, the interaction of 2,2-dimethyl-1,3-dibromopropane with sodium tetrasulfide gave a trisulfide which was assigned a branch-bonded structure. It was subsequently shown[75] that these



compounds were actually linearly bonded trisulfides. Despite this evidence, a later worker incorrectly assigned the branch-bonded structure to the product of a similar reaction.[76]

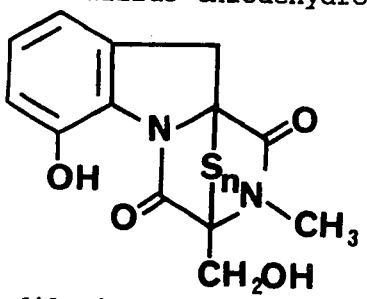
Sporidesmin, a naturally occurring polycyclic disulfide, was converted to the corresponding trisulfide, sporidesmin E, with a



sporidesmin

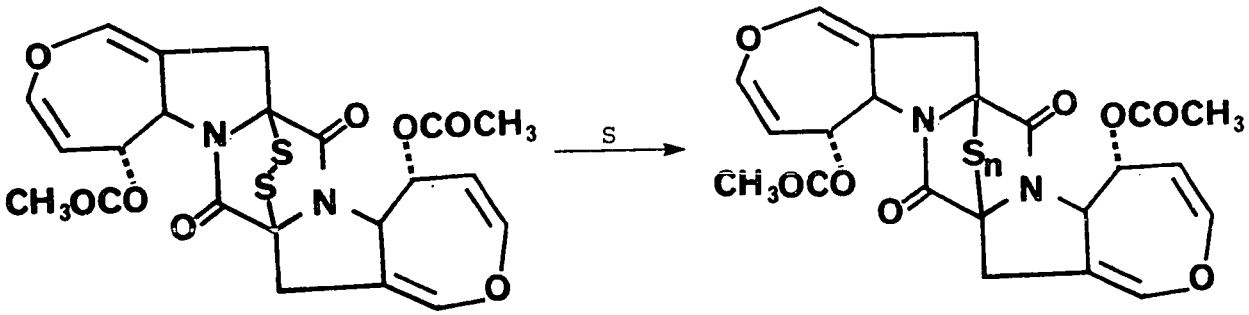
sporidesmin E

combination of sulfur and phosphorous pentasulfide.[4,5] This transformation was also effected by dihydrogen disulfide.[13] This reagent was also used to convert dehydrogliotoxin (n=2) to higher sulfides including the trisulfide thiodehydrogliotoxin (n=3).[13] Elemental



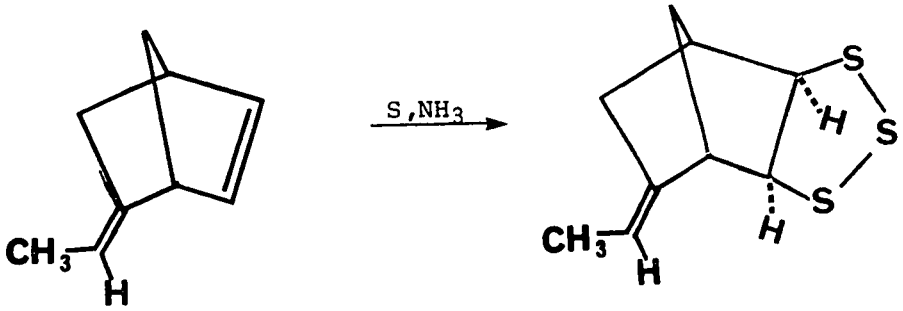
n=2,dehydrogliotoxin
n=3, thiodehydrogliotoxin

sulfur was readily inserted into the disulfide linkage of acetylaranotin, a naturally occurring antiviral antibiotic, without requiring any added thiol or other catalyst. A mixture of tri- and tetrasulfides resulted.[77]



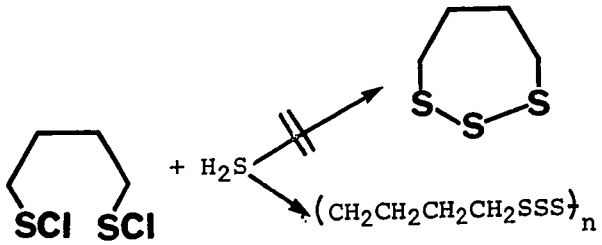
n = 3,4

A recent communication has disclosed a selective and stereospecific sulfurization of certain olefins. The reaction proceeds



when elemental sulfur is activated by ammonia in the presence of an amide.[27]

The interaction of hydrogen sulfide with tetramethylene disulfenyl chloride did not yield 1,2,3-trithepane but rather polymeric material was obtained.[78]



Synthesis of Trisulfides - unsymmetric

The problem of devising a synthesis for unsymmetric organic trisulfides is more complex than that of symmetric trisulfides. Differentiating between a pure trisulfide and a fortuitous mixture of equimolar amounts of the two symmetric trisulfides is difficult as the

$$R\text{-}S\text{-}S\text{-}S\text{-}R' \qquad \text{or} \qquad RSSSR + R'SSSR'$$

infrared and nuclear magnetic resonance spectra would be very similar. Elemental analysis would not distinguish the two but mass spectroscopy could be utilized. Many of the methods of preparing symmetric trisulfides are unsuitable to obtain the unsymmetric derivatives. For example, if two different thiols are allowed to react with elemental sulfur in the presence of a catalytic amount of an amine (cf. ref. 61)

$$RSH + R'SH + S \xrightarrow{R''NH_2} RSSSR + RSSSR' + R'SSSR'$$

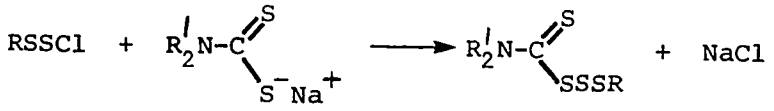
the product formed would be a mixture of each of the symmetric trisulfides as well as the unsymmetric trisulfide. Separation of pure unsymmetric trisulfide would likely prove difficult. There are some examples of the synthesis of unsymmetric trisulfides in the chemical literature.

The reaction of mercaptans with alkyl chlorodisulfides,[30,81] acyl chlorodisulfides[79] and aryl chlorodisulfides[80,81] is reported to give unsymmetric trisulfides which may be isolated in pure form. Also,

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

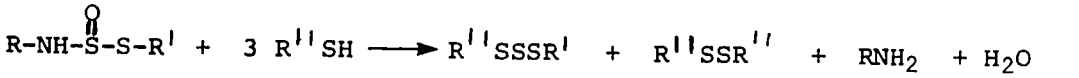
R = alkyl, acyl, aryl

chlorodisulfides interact with sodium dialkylaminecarbodithioate to produce a type of trisulfide.[82] This approach has been found

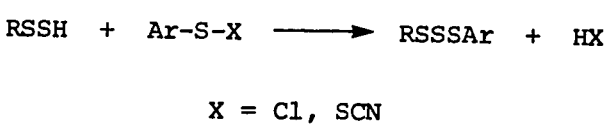


inconvenient due to the relative unavailability and instability of chlorodisulfides.[63] Another author has reported that few chlorodisulfides are sufficiently stable for investigation.[86]

Another method of synthesizing unsymmetric trisulfides is the interaction of an N-arylamidothiosulfite with a thiol.[83] Objections which have been raised against this preparation are that the multiplicity



of products,[63] especially the symmetric disulfide,[14(a)] make isolation difficult. There is some justification for these qualifications as the elemental analyses, on trisulfides prepared by this route, deviate from the calculated values by an average of 0.56%, 0.83% and 0.78% for carbon, hydrogen and sulfur respectively.[83] A third method for synthesizing unsymmetric trisulfides is the reaction of an arenesulfenyl chloride or



thiocyanate with alkyl hydrodisulfides.[14(a)] The unavailability and

instability of hydrodisulfides has limited the possible generality of this method.[63] Some unsymmetric trisulfides have been prepared via the deoxygenation of dialkanesulfonic thioanhydrides by triphenylphosphine.[54]

In view of the lack of a general method for the synthesis of unsymmetric trisulfides a study of several routes which might achieve this goal was undertaken.

DISCUSSION

Synthesis of Trisulfides - symmetric

The deoxygenation of organo-sulfur compounds by trivalent phosphorous reagents is well documented. Triarylphosphines[84] and triarylphosphites[85] readily abstract oxygen from thionyl chloride.

$$Ph_3P + SOCl_2 \longrightarrow SCl_2 + Ph_3P=O$$

$$(PhO)_3P + SOCl_2 \longrightarrow SCl_2 + (PhO)_3P=O$$

The reaction of thiosulfinate esters with triphenylphosphine results in the formation of disulfides.[86] Disulfides are also produced by the

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

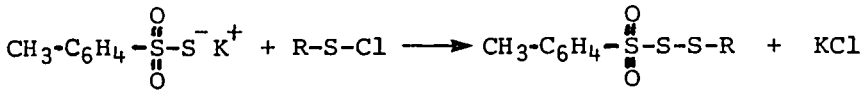
$$R\text{-}\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}\text{-}S\text{-}R + 2\ Ph_3P \longrightarrow RSSR + 2\ Ph_3P=O$$

deoxygenation of thiosulfonate esters.[87] On this basis it seemed probable that trisulfides could be synthesized via the interaction of trivalent phosphines with an oxidized derivative of a trisulfide. The reduction of dialkanesulfonic thioanhydrides with triphenylphosphine[51] is an example where this approach has been successful.

Sulfenic sulfonic thioanhydrides (sulfenyl thiosulfonates),

$$R\text{-}S\text{-}S\text{-}\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}\text{-}R$$

a class of compounds which may function as precursors to organic trisulfides, are readily available.[88] Accordingly, a series of alkanesulfenic p-toluenesulfonic thioanhydrides were prepared



1, R = p-$CH_3C_6H_4$-

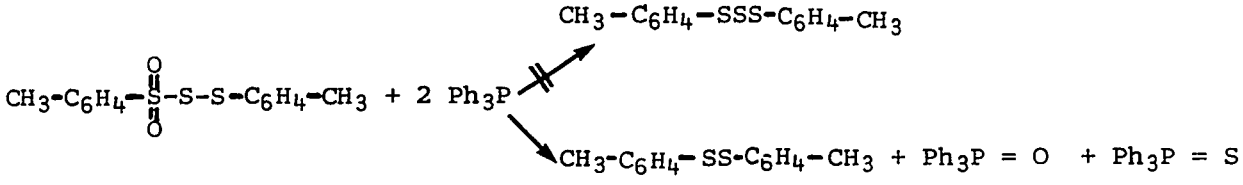
2, R = 2,4-di-$NO_2C_6H_3$-

3, R = o-$NO_2C_6H_4$-

4, R = C_6H_5-

5, R = C_2H_5-

via the reaction of an alkane- or arenesulfenyl chloride with potassium p-toluenethiosulfonate. The attempted deoxygenation of p-toluenesulfenic p-toluenesulfonic thioanhydride (1) with two molar equivalents of triphenylphosphine (6) did not yield the expected di-p-tolyl trisulfide. The products of this reaction were di-p-tolyl disulfide (7) along with



1 6 7 8 9

triphenylphosphine oxide (8) and triphenylphosphine sulfide (9). Thus desulfurization accompanied the desired deoxygenation. The full details

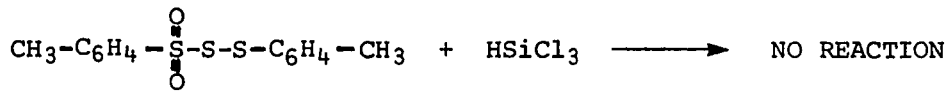
of the reaction of 1 with triphenylphosphine will be discussed subsequently but these results show that this approach to the synthesis of trisulfides was unsuccessful.

Another class of powerful deoxygenating agents is the silicon hydrides. For example, trichlorosilane has been shown to convert phosphine oxides to phosphines[89] and diaryl sulfoxides to diaryl sulfides.[90]

$$R_3P{=}O + HSiCl_3 \longrightarrow R_3P + H_2 + Cl_3SiOSiCl_3$$

$$Ar_2S{=}O + HSiCl_3 \longrightarrow Ar_2S + HOSiCl_3$$

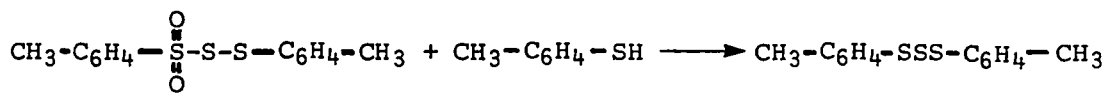
However, p-toluenesulfenic p-toluenesulfonic thioanhydride (1) was inert towards trichlorosilane when refluxed in benzene for 22 hours.



1

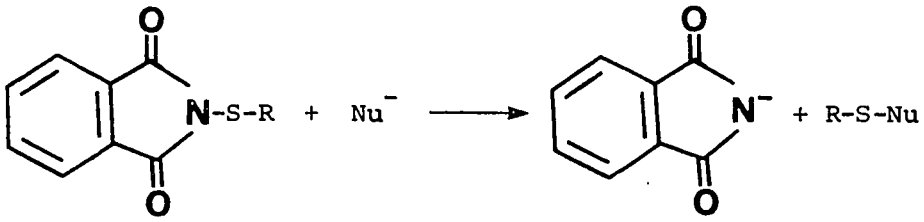
It has been shown[91] that organic disulfides may be prepared

by thioalkylating thiols with thiosulfonates. By analogy, it was expected that thiols could be dithioalkylated with sulfenic sulfonic thioanhydrides. Confirmation for this came from the reaction of

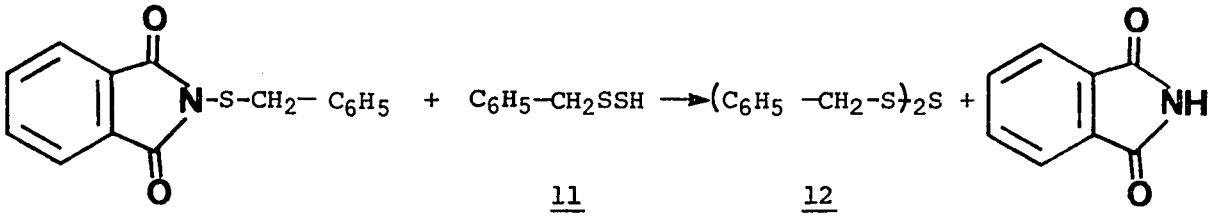


1 10

p-toluenesulfenic p-toluenesulfonic thioanhydride (1) with p-toluenethiol which produced di-p-tolyl trisulfide (10) in 44% yield. Symmetric organic trisulfides were also synthesized by a variation of the known reaction of arenesulfenyl chlorides with alkyl hydrodisulfides.[14(a)] The finding that the phthalimido grouping of sulfenimides was displaced by the attack of nucleophiles[48] prompted the replacement

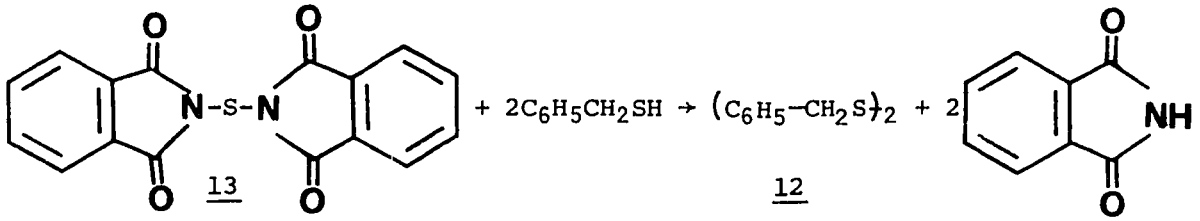


of arenesulfenyl chlorides by sulfenimides. It should be noted that the latter are stable crystalline compounds while the former are unstable liquids. Thus, the reaction of N-(benzylthio) phthalimide with benzyl



11 12

hydrodisulfide (11) produced a 98% yield of dibenzyl trisulfide (12).[1] Also, the interaction of N,N'-thiobisphthalimide (13) with two molar



13 12

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[1] D.N. Harpp, D.K. Ash, T.G. Back, J.G. Gleason, B.A. Orwig, W.F. Van Horn and J.P. Snyder, Tetrahedron Letters, 3551 (1970).

equivalents of α-toluenethiol results in the formation of dibenzyl trisulfide (12).

Perhaps the most straightforward method of synthesizing symmetric trisulfides is via the reaction of sulfur dichloride (14) with two molar equivalents of thiol. This process has presented difficulty to some chemists.[63] This is likely due to the fact that SCl_2 may contain free chlorine along with some sulfur monochloride (S_2Cl_2) so that the product may contain di- and tetrasulfides along with the desired trisulfide. The impurities in sulfur dichloride (14) arise as the chlorides of sulfur are equilibrium mixtures.[60] However, pure

$$2\ SCl_2 \rightleftharpoons S_2Cl_2 + Cl_2$$

14

sulfur dichloride (14) may be obtained by fractional distillation and may be stabilized with phosphorous pentachloride to prevent disproportionation.[92] Refrigeration is also recommended. Reaction of pure sulfur dichloride

$$2\ RSH + SCl_2 \longrightarrow RSSSR + 2\ HCl$$

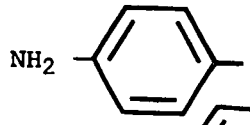
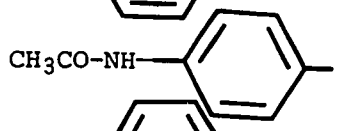
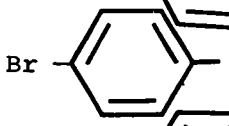
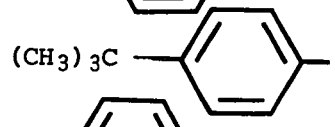
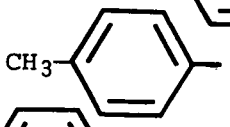
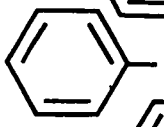
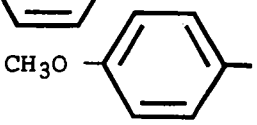
14

with thiols is an effective method of obtaining pure symmetric trisulfides in good to excellent yield. A summary of the trisulfides synthesized via this route is shown in Table 1. Primary, secondary and tertiary aliphatic as well as aromatic trisulfides were prepared.

TABLE 1

SYNTHESIS OF SYMMETRIC TRISULFIDES

$$2\ RSH + SCl_2 \xrightarrow{14} RSSSR + 2\ HCl$$

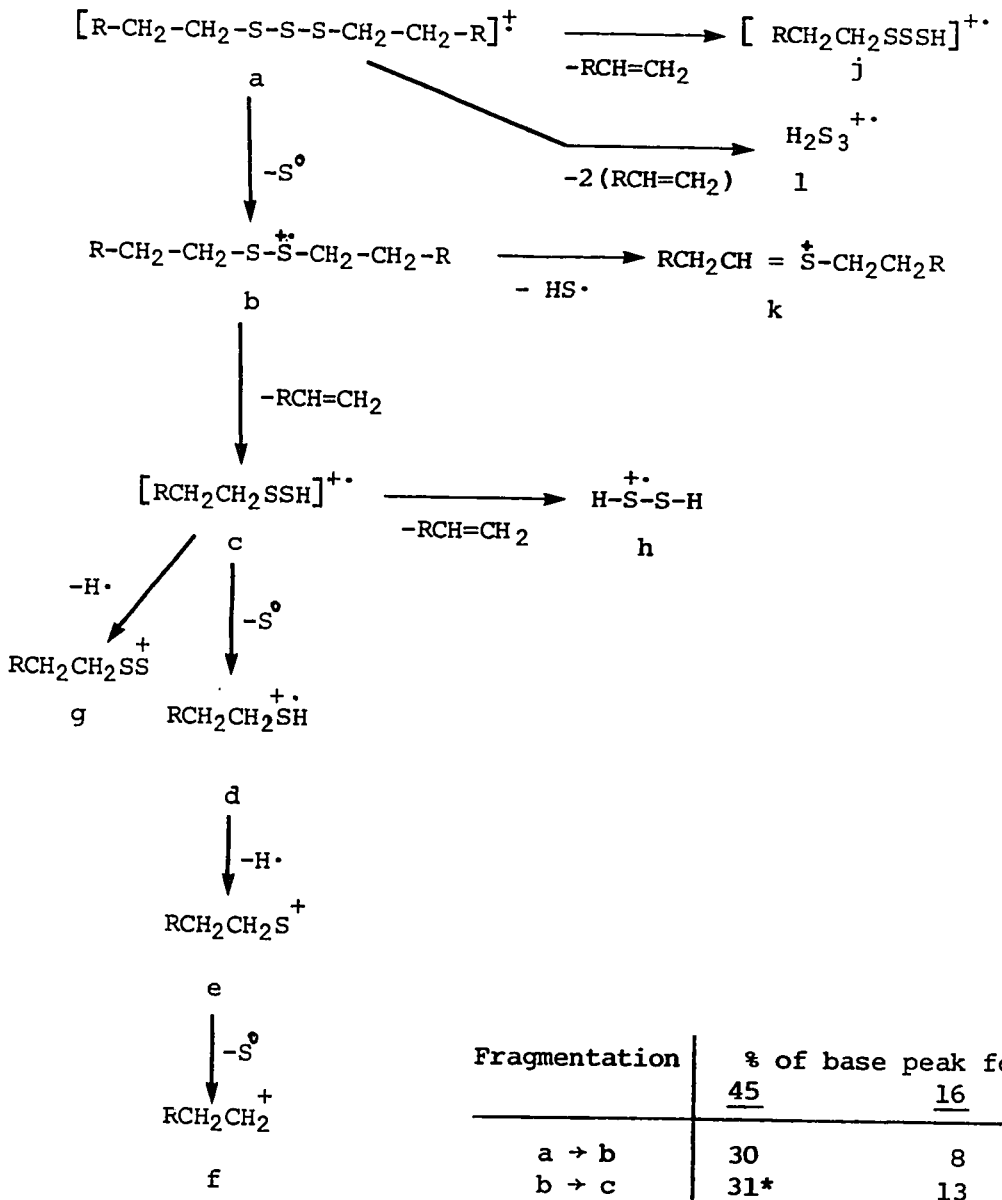
Compound	R	% RSSSR
15	$CH_3(CH_2)_4-$	61
16	$CH_3CH_2CH_2-$	53
17	$CH_3O-CO-CH_2-$	78
12	$C_6H_5CH_2-$	82
18	$(CH_3)_2CH-$	67
19	$(CH_3)_3C-$	66
20		78[a]
21		74
22		78
23		79
10		86
24		84
25		85

(a) Isolated as the dihydrochloride

The mass spectral fragmentation pattern of symmetric trisulfides is worthy of note. As seen in Fig. 3, all three n-alkyl trisulfides investigated lose a sulfur atom from the molecular ion a to form the radical ion b which ejects an olefinic fragment to give an alkyl hydrodisulfide ion c. Other ions in the mass spectra may be accounted for by loss of sulfur, olefin or hydrogen atom. These fragmentation patterns are in accord with those proposed for the spectra of organic disulfides.[93] The mass spectra of di-isopropyl trisulfide (18) and di-tert-butyl trisulfide (19) may be explained by the pattern shown in Figs. 4(a) and 4(b) respectively. Both 18 and 19 lose an olefin fragment to form the alkyl hydrotrisulfide radical ions o and s. This fragmentation is confirmed by the observation of the appropriate metastable peak in the spectrum. The mass spectral fragmentation of diphenyl (24), di-p-tolyl (10) and dibenzyl trisulfides (12) exhibits loss of a sulfur atom and the subsequent decompositions are the same as those of the corresponding disulfides.[93] One generalization which may be made concerning the behaviour of organic trisulfides on electron impact is the tendency for the extrusion of a sulfur atom to form the radical ion of

$$R\text{-}S\text{-}S\text{-}S\text{-}R + e \longrightarrow [\, R\text{-}S\text{-}S\text{-}S\text{-}R \,]^{+\cdot} \longrightarrow RS\overset{+\cdot}{S}R + S^{\circ}$$

the corresponding disulfide.



Fragmentation	% of base peak for ion formed		
	45	16	17
a → b	30	8	52
b → c	31*	13	52*
c → d	29	-	40
d → e	57	-	52
c → g	22	-	-
c → h	33*	-	-
a → 1	-	10	-
c → e	-	100	-
e → f	-	100	100
b → k	-	4	2
a → j	-	-	8*

* metastable peak observed for this fragmentation

Fig. 3 Mass spectral fragmentation patterns of di-n-alkyl trisulfides 45 (R=H), 16 (R=CH_3) and 17 (R=$CH_3CH_2CH_2$)

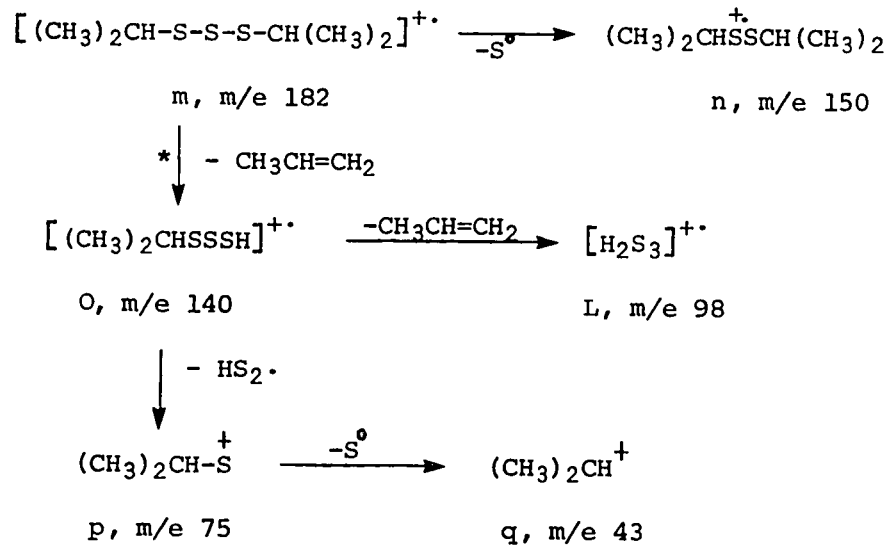


Fig. 4(a) Mass spectral fragmentation of di-i-propyl trisulfide (18)

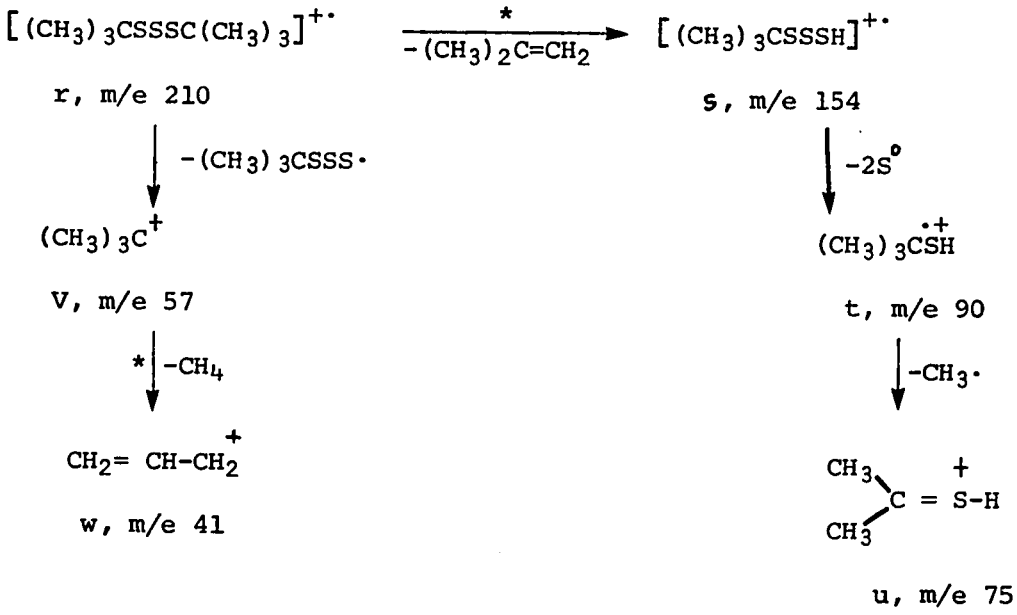
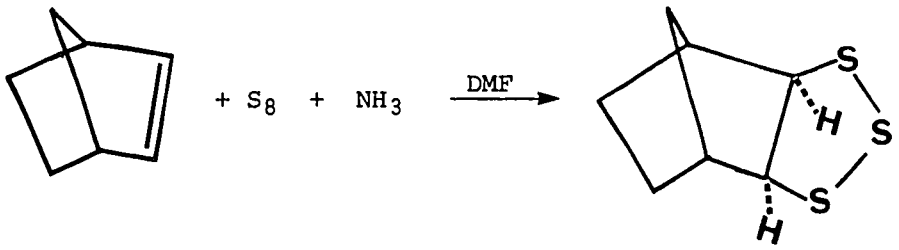


Fig. 4(b) Mass spectral fragmentation of di-t-butyl trisulfide (19)

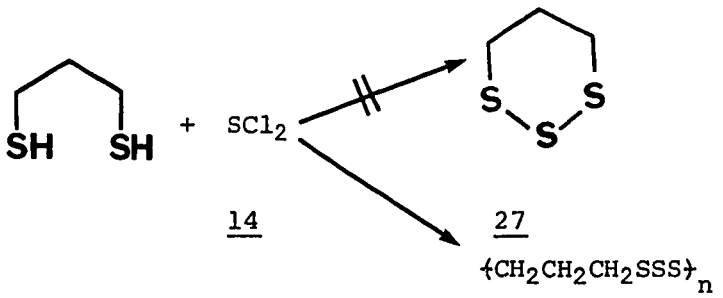
Synthesis of Trisulfides - cyclic

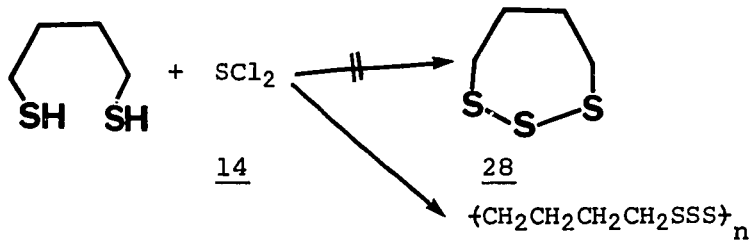
Exo-3,4,5-trithiatricyclo[5.2.1.$0^{2.6}$] decane (26) was obtained via the sulfuration of bicyclo [2.2.1]hept-2-ene with sulfur and ammonia in dimethylformamide as described by Shields and Kurtz.[27]



26

Attempts were made to apply the reaction between thiols and sulfur dichloride to the synthesis of cyclic trisulfides. However, both 1,3-propanedithiol and 1,4-butanedithiol reacted with sulfur dichloride(14)

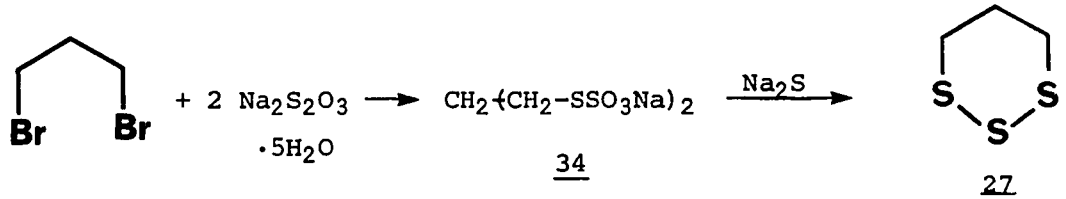




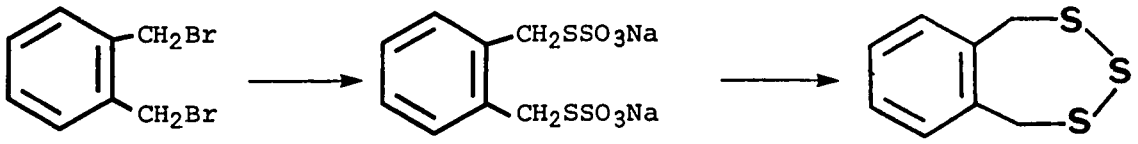
to yield intractable polymeric material rather than the desired 1,2,3-trithiane (27) and 1,2,3-trithepane (28). Cyclic trisulfides of known stereochemistry were required for an investigation of some

desulfurization reactions which are discussed subsequently. Accordingly, the synthetic sequence outlined below was investigated (Fig. 5). The reaction of meso-α,α'-dibromoadipic acid (29), prepared from adipic acid and N-bromosuccinimide, with potassium ethyl xanthate and subsequent treatment with ammonium hydroxide afforded meso-α,α'-dimercaptoadipic acid (30). However, the attempted cyclization of the dithiol 30 with sulfur dichloride (14) did not yield a cyclic trisulfide. Apparently, polymerization occurred and cis-4,7-dicarboxy-1,2,3-trithiepane (31) was not obtained. Possibly the presence of a carboxylic acid functionality interfered with the desired reaction and so the diacid 30 was esterified with methanolic hydrochloric acid to produce the diester 32. The interaction of sulfur dichloride (14) with meso-α,α'-dimercapto dimethyl adipate (32) again failed to produce a cyclic trisulfide and so alternative routes to 31 and 33 were explored.

The method of Milligan and Swan[24] of synthesizing cyclic trisulfides via bifunctional Bunte salts was used to prepare 1,2,3-trithiane (27) and 2,3,4-benzotrithiepin (37) in yields of 56 and 72% respectively. For example, the reaction of 1,3-dibromopropane with two equivalents of sodium thiosulfate pentahydrate gave disodium trimethylene dithiosulfate (34)



34 27



36 37

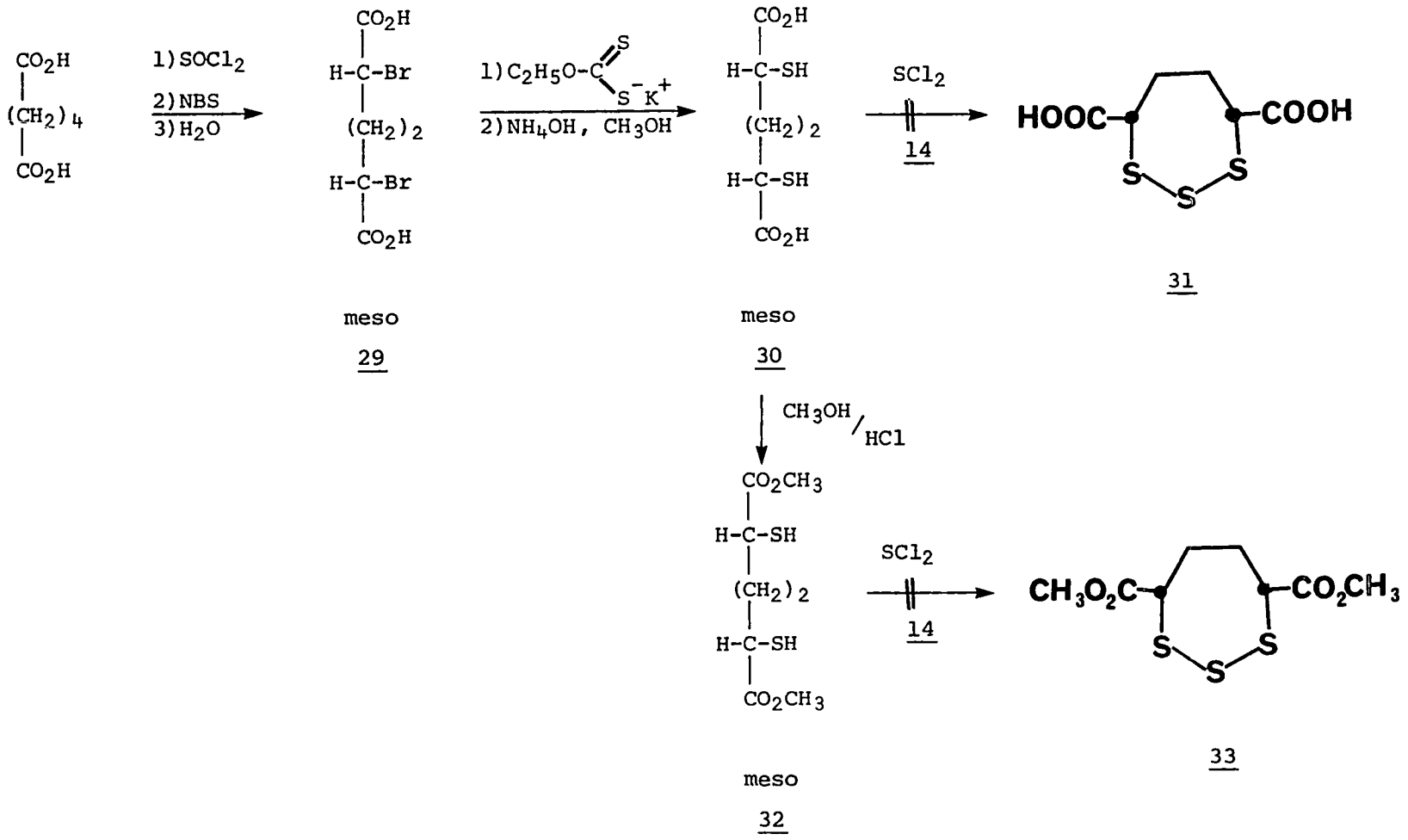


Fig. 5 Attempted synthesis of cis-4,7-dicarboxy-1,2,3-trithiepane (31) and cis-4,7-dimethoxycarbonyl-1,2,3-trithiepane (33)

which was converted to 27 with sodium sulfide in the presence of formaldehyde and phosphate buffer. Analogously, α,α'-dibromo-o-xylene was converted to 36 and 37. Based on the success of the Bunte salt method an attempt at the synthesis of trisulfides 31 and 33 was made. The route followed is shown in Fig. 6. The reaction of meso-α,α'-dibromoadipic acid (29) with sodium thiosulfate did not result in the formation of the desired disodium dithiosulfate 40. The presence of the carboxylic acid functionality was undoubtedly a complicating factor as it is known that Bunte salts decompose under acidic conditions.[24] Conversion of the diacid 29 to its disodium salt followed by treatment with sodium thiosulfate pentahydrate was also unsuccessful for the preparation of 40 as, here too, the reaction mixture became acidic. It is not apparent why or how this reaction turned acidic. In view of the synthesis of the Bunte salts of the esters of bromomalonic and bromosuccinic acids,[94] it was decided to convert the dibromoadipic acid 29 to its diester 39. Fischer esterification of meso-α,α'-dibromoadipic acid (29) produced the desired meso-α,α'-dibromo dimethyl adipate (39) but in very low yield. An improved preparation was achieved *via* the reaction of adipic acid with thionyl chloride, N-bromosuccinimide and finally methanol. Interaction of 39 with sodium thiosulfate did not result in the isolation of the required Bunte salt 41. Furthermore, the action of sodium sulfide nonahydrate on material which might contain some of the disodium dithiosulfate 41 did not yield cis-4,7-dicarbomethoxycarbonyl-1,2,3-trithiepane(33).

Milligan and Swan[24] have also encountered difficulty in the preparation of certain Bunte salts as decomposition occurs under acidic

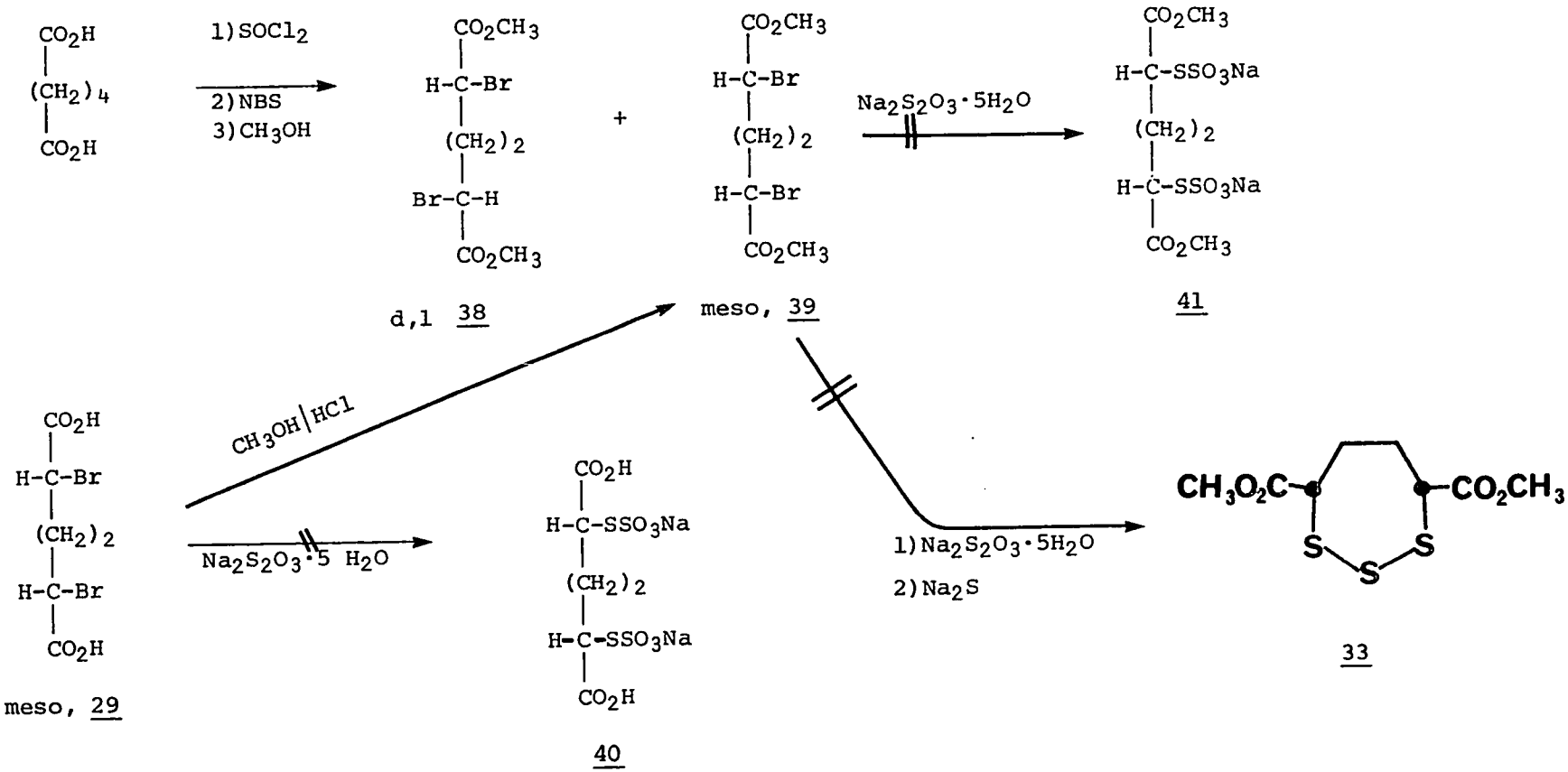
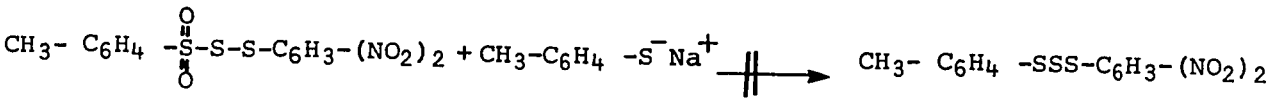


Fig. 6 Attempted synthesis of cis-4,7-dicarboxy-1,2,3-trithiepane (31) and cis-4,7-dimethoxycarbonyl-1,2,3-trithiepane (33) via Bunte salts.

conditions. The same authors reported that the attempted synthesis of cyclic trisulfides, via bifunctional Bunte salts, has led to mixtures of cyclic di-, tri- and tetrasulfides in some cases and to polymeric materials in most other cases.[24] Undoubtedly, the difficulties encountered in the attempted preparation of cis-4,7-dicarbomethoxycarbonyl-1,2,3-trithiepane (33) and cis-4,7-dicarboxy-1,2,3-trithiepane (31) reflect these tendencies discussed above.

Synthesis of Trisulfides - unsymmetric

It was shown earlier that symmetric organic trisulfides could be prepared via the dithioalkylation of thiols with sulfenic sulfonic thioanhydrides. In order to extend this method to the synthesis of unsymmetric trisulfides, the reaction of 2,4-dinitrobenzenesulfenic p-toluenesulfonic thioanhydride (2) with sodium p-toluenethiolate (42) was investigated. The expected p-tolyl 2-4-dinitrophenyl trisulfide,



2 42

which would arise from nucleophilic displacement of the p-toluenesulfinate anion, was not obtained. Instead, a 40% yield of di-p-tolyl disulfide (7) was isolated. A rationalization for its formation is shown in Figure 7. Attack of mercaptide 42 on the central sulfur atom of 2 results in displacement of the most stable anion.[1]

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[1] An alternate pathway shown in the dotted lines in figure 7 has not been excluded. The relative stability of the p-toluenethiosulfonate ion in comparison to the 2, 4 - dinitrobenzenethiolate is not known.

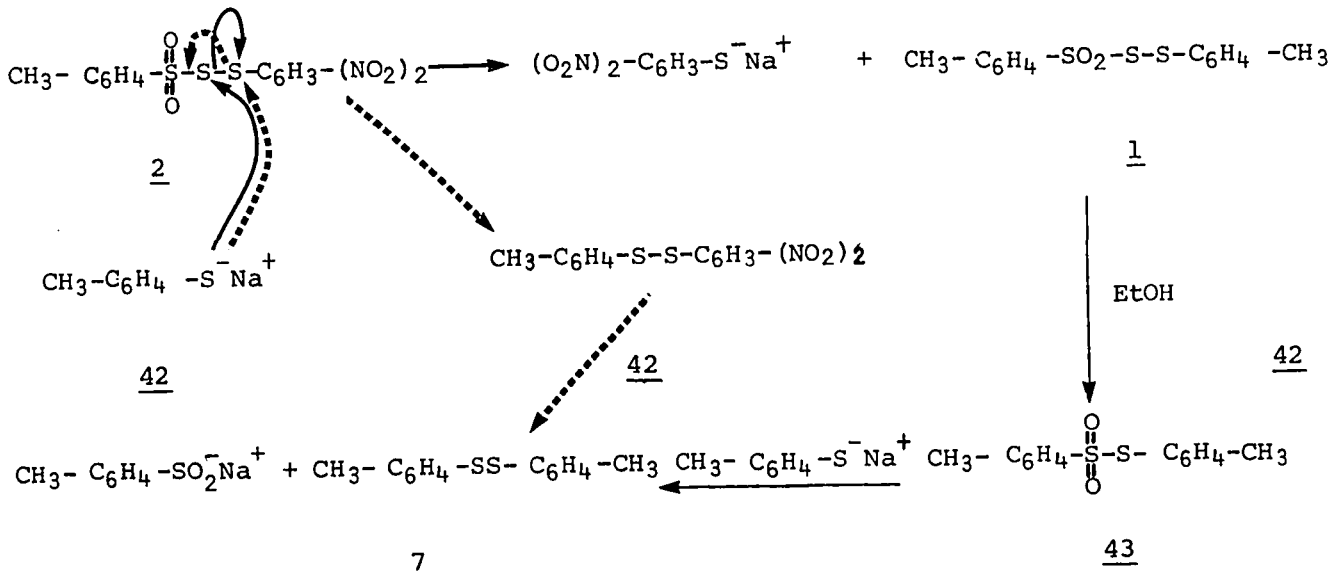
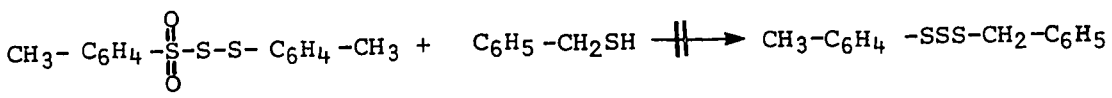


Fig. 7 Pathway for the formation of di-p-tolyl disulfide (7)

The 2,4-dinitrobenzenethiolate ion is probably a better leaving group than the p-toluenesulfinate ion.[95] The p-toluenesulfenic p-toluenesulfonic thioanhydride (1) loses sulfur in the reaction solvent ethanol to form p-tolyl p-toluenethiosulfonate (43). This loss of sulfur by 1 in ethanol has been investigated and will be discussed subsequently. The reaction of thiosulfonates with thiols and thiolates is known to result in the formation of disulfides.[91] Treatment of p-toluenesulfenic



1

p-toluenesulfonic thioanhydride (1) with α-toluenethiol did not result in the synthesis of p-tolyl benzyl trisulfide but gave an uncharacterized oil.

The preparation of unsymmetric trisulfides by the sequential addition of two different thiols to sulfur dichloride was investigated but this method produced mixtures of the two symmetric trisulfides as well as the desired product. For example, the reaction of one molar equivalent of ethanethiol (44) with sulfur dichloride (14) was allowed to proceed to completion before the second mercaptan, α-toluenethiol was added. The products subsequently isolated from the reaction

$$\underset{\underline{14}}{SCl_2} \xrightarrow[2)\ C_6H_5CH_2SH]{1)\ CH_3CH_2SH\ (\underline{44})} \underset{\underline{45}}{(CH_3CH_2S)_2S} + \underset{\underline{12}}{(C_6H_5CH_2S)_2S}$$

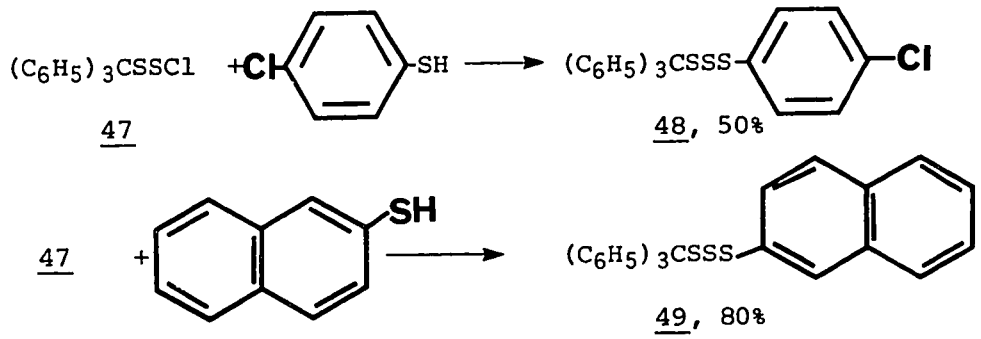
mixture were diethyl trisulfide (45) and dibenzyl trisulfide (12). Other combinations attempted involved p-toluenethiol plus α-toluenethiol p-toluenethiol plus ethanethiol (44); both reactions produced di-p-tolyl trisulfide (10) as the only isolable material.

It was felt that the addition of a thiol to sulfur dichloride at low temperature might lead to the isolation of the chlorodisulfide which should be formed. This aim was realized as the addition of triphenylmethanethiol (46) to sulfur dichloride (14) at -78°C produced a precipitate of triphenylmethyl chlorodisulfide (47). This compound

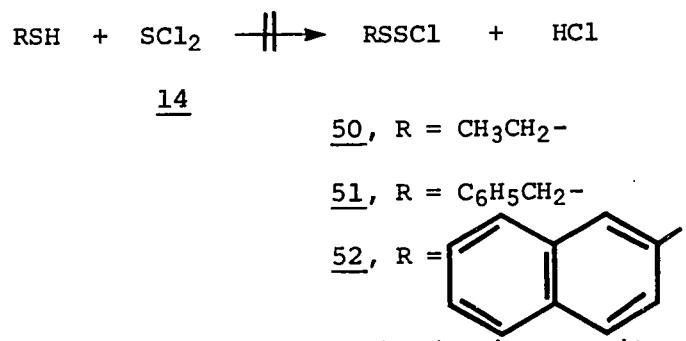
$$\underset{\underline{46}}{(C_6H_5)_3CSH} + \underset{\underline{14}}{SCl_2} \longrightarrow \underset{\underline{47}}{(C_6H_5)_3C\text{-}S\text{-}S\text{-}Cl} + HCl$$

could be isolated in yields of 70% and is stable enough to be recrystallized.

The mass spectrum of 47 did not exhibit a molecular ion but the peak of highest mass could be assigned to the triphenylmethyl carbonium ion m/e 243. Several new unsymmetric trisulfides were formed by the interaction of thiols with 47. For example, the reaction of 47 with



p-chlorobenzenethiol and 2-naphthalenethiol produced triphenylmethyl p-chlorophenyl trisulfide (48) and triphenylmethyl 2-naphthyl trisulfide (49) in yields of 50% and 80% respectively.[1] However, this reaction did not prove to be a general one for the synthesis of unsymmetric trisulfides as pure ethyl (50), benzyl (51) and 2-naphthyl chlorodisulfides (52) could not be isolated despite several attempts at each. The reaction

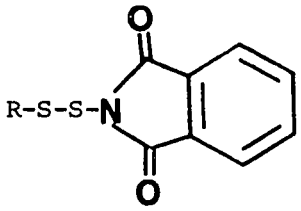


of ethyl chlorodisulfide (50), (maximum purity obtained ca. 90%) with benzenethiol, 1-propanethiol, 2-methyl-2-propanethiol and α-toluenethiol

[1] This work has been published; D.N. Harpp and D.K. Ash, Intl. J. Sulfur Chem., A, 1, 211 (1971).

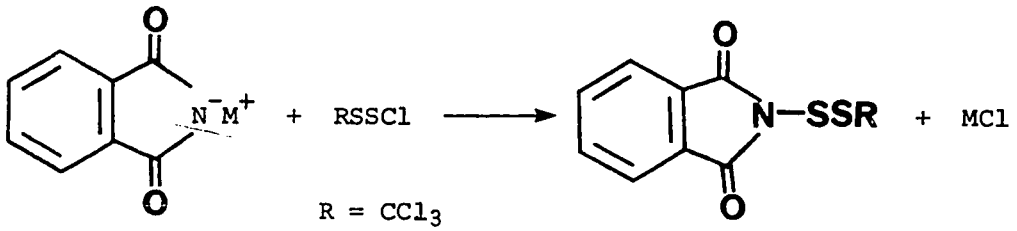
was investigated. In all cases examined, no pure unsymmetric trisulfides could be obtained by fractional distillation, column chromatography on silica gel or preparative vapour phase chromatography.

If the chlorine of an alkyl chlorodisulfide could be replaced by some other good leaving group, which would also lend stability, isolation might be possible. The phthalimido grouping seemed a likely candidate as its high molecular weight might provide stability and evidence for its propensity to act as a leaving group was obtained from the reaction of benzyl hydrodisulfide (11) with N-(benzylthio) phthalimide which produced dibenzyl trisulfide (12) in 98% yield. Therefore a compound containing two sulfur atoms between the hydrocarbon



and phthalimido groups was required. Reaction of these compounds with thiols should give the desired unsymmetric trisulfides.

To date only three closely related examples of alkyl phthalimido disulfides have been reported.[96] These were prepared by the reaction of an alkali metal derivative of phthalimide with a chlorodisulfide.

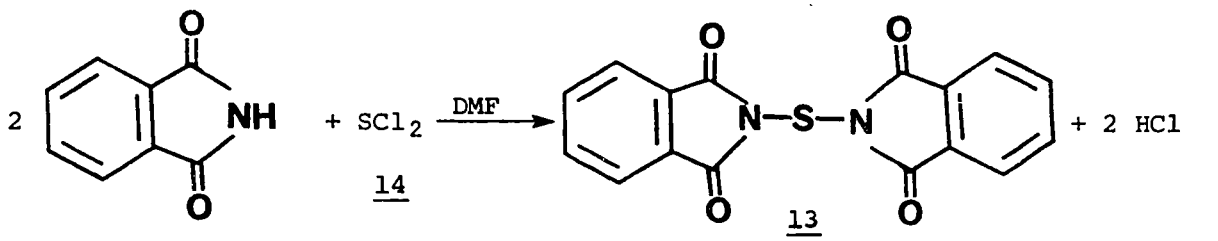


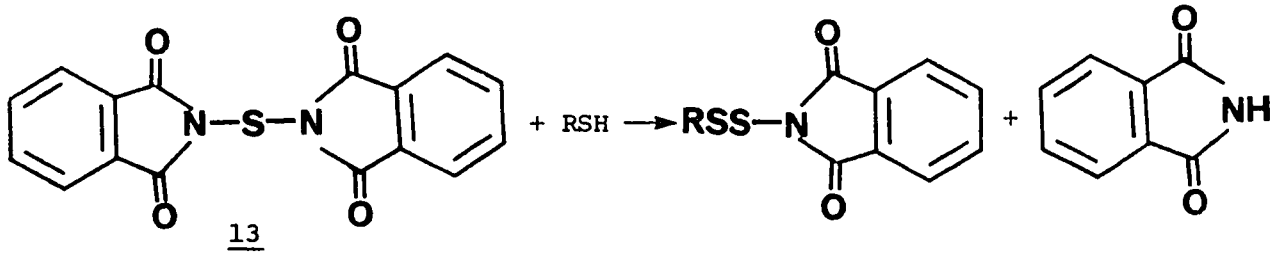
R = CCl_3

= $CBrCl_2$

= CCl_2CCl_3

Due to the unavailability and instability of chlorodisulfides, a general method for the preparation of alkyl phthalimido disulfides from readily available, stable starting materials was sought. Displacement of the imide from N-(alkylthio) imides [97] by thiols, hydrodisulfides, alkoxides and phosphines has resulted in the preparation of disulfides,[98] trisulfides,[98(b)] sulfenate esters[99] and N-alkylimides[48] respectively. These reactions are believed to occur by attack of the nucleophiles at the sulfur atom of the N-(alkylthio) imides. By analogy with these reactions, it was expected that the treatment of N,N'-thiobisphthalimide (13),





prepared from sulfur dichloride (14) and phthalimide, with one molar equivalent of thiol should produce the desired alkyl phthalimido disulfides. As shown in Table II this reaction proceeds in good to excellent yield and is applicable to primary, secondary and tertiary aliphatic as well as aromatic mercaptans. The products are all stable, white crystalline compounds.[1]

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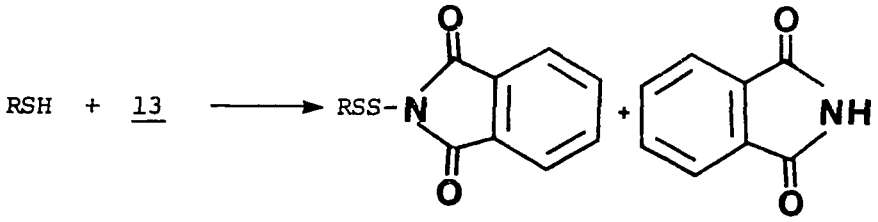
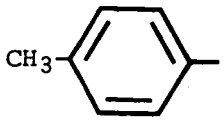
[1] This work has been published: D.N. Harpp and D.K. Ash, Int. J. Sulfur Chem., A, 1, 57 (1971).

TABLE II

SYNTHESIS OF ALKYL PHTHALIMIDO DISULFIDES



Compound	R	% Yield
54	$CH_3CH_2CH_2$-	75
55	CH_3O-CO-CH_2-	77
56	$(CH_3)_2CH$-	74
57	$(CH_3)_3C$-	74
58	$C_6H_5CH_2$-	90
59		81

The mass spectral fragmentation patterns of these phthalimido disulfides was investigated in some detail. The important fragmentation modes for disulfides 54, 56 and 57 (Figure 8, Figure 9) involve loss of the alkenyl portion by cleavage of the β C-H bond; in addition, alkyl cations are formed by rupture of the C-S bond. The former process was confirmed by the appropriate metastable peaks. A characteristic of the mass spectrum of each of the phthalimido disulfides is an ion bb at m/e 179 (Fig. 8). The breakdown of this ion via loss of sulfur to give x, m/e 147 and subsequent losses of .OH, .CN, and CO to ultimately yield aa, is observed for each of compounds 54 - 59. On electron impact, carbomethoxymethyl phthalimido disulfide (Fig. 10) (55) displays cleavages expected from a methyl ester.[100] The proposed fragmentation patterns for 58 and 59 are seen in Figures 11 and 12 respectively.

The reactions of alkyl phthalimido disulfides with thiols was investigated as a possible route to the synthesis of unsymmetric trisulfides. The interaction of p-tolyl phthalimido disulfide (59) with α-toluenethiol produced a mixture containing di-p-tolyl trisulfide (10), dibenzyl trisulfide (12) and the unsymmetric p-tolyl benzyl trisulfide. A rationalization for the formation of the symmetric trisulfides by thiol disproportionation is shown in Figure 13.

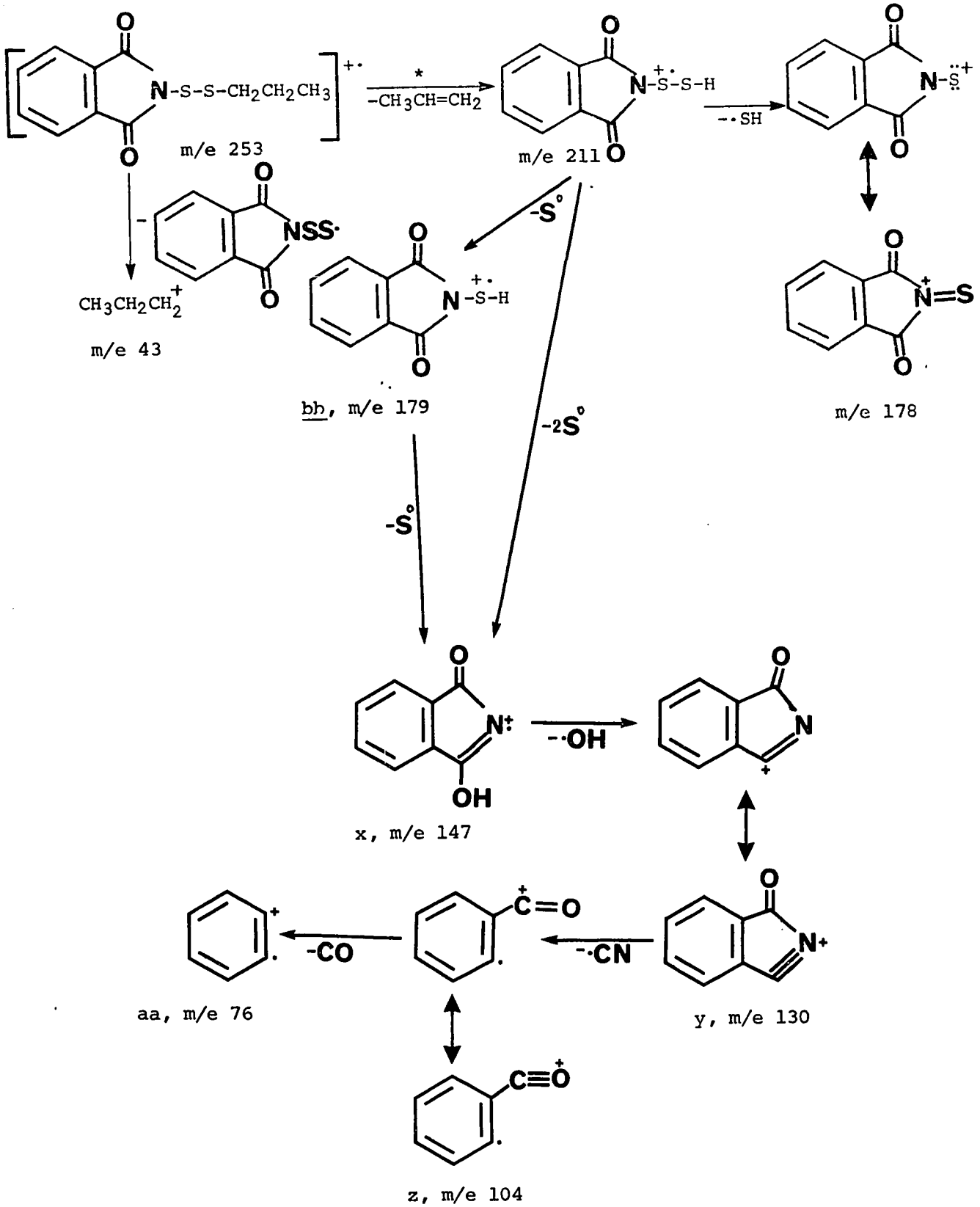
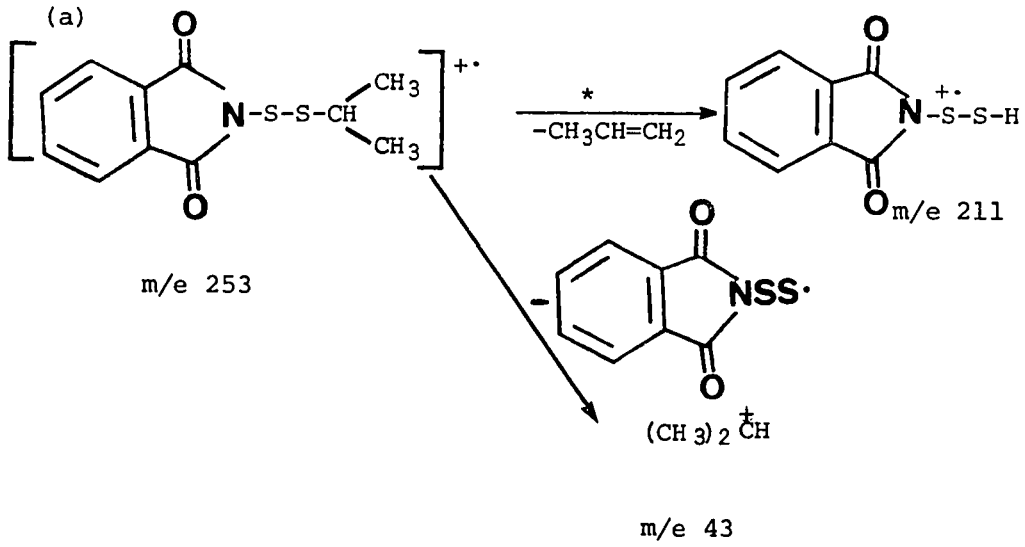
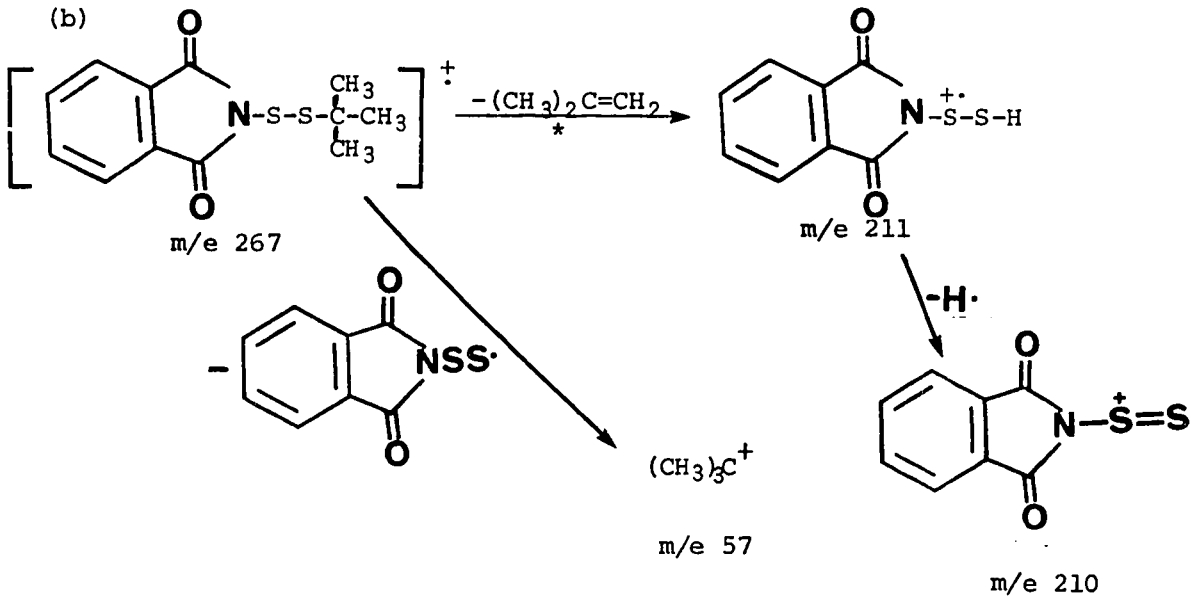


Figure 8 Mass spectral fragmentation of n-propyl phthalimido disulfide (54)



peaks at 179, 178, 147, 130, 104, 76 as in Fig. 8



peaks at 179, 178, 147, 130, 104, 76 as in Fig. 8

Figure 9 Mass spectral fragmentations of isopropyl (56) and t-butyl phthalimido disulfides (57)

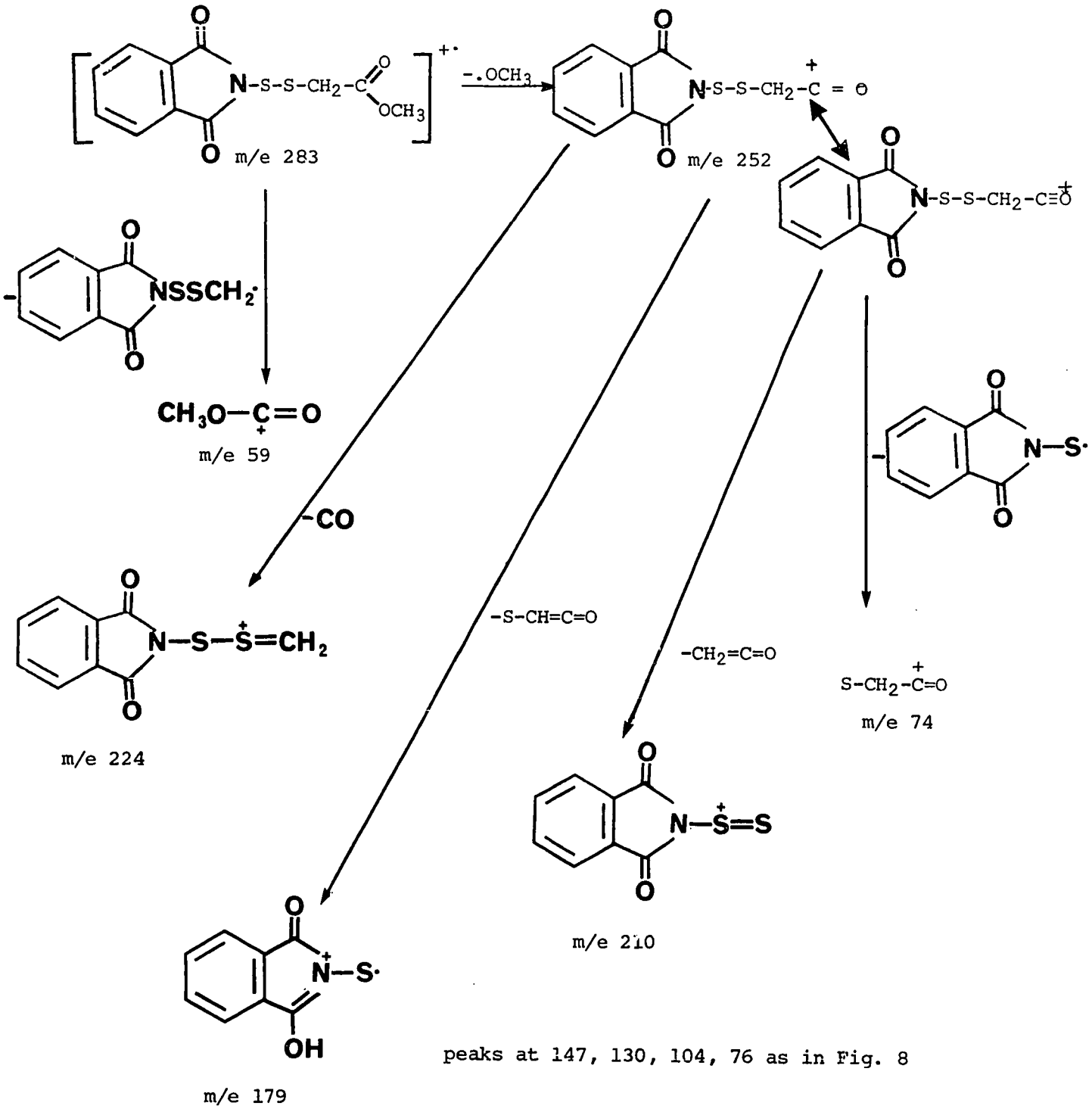
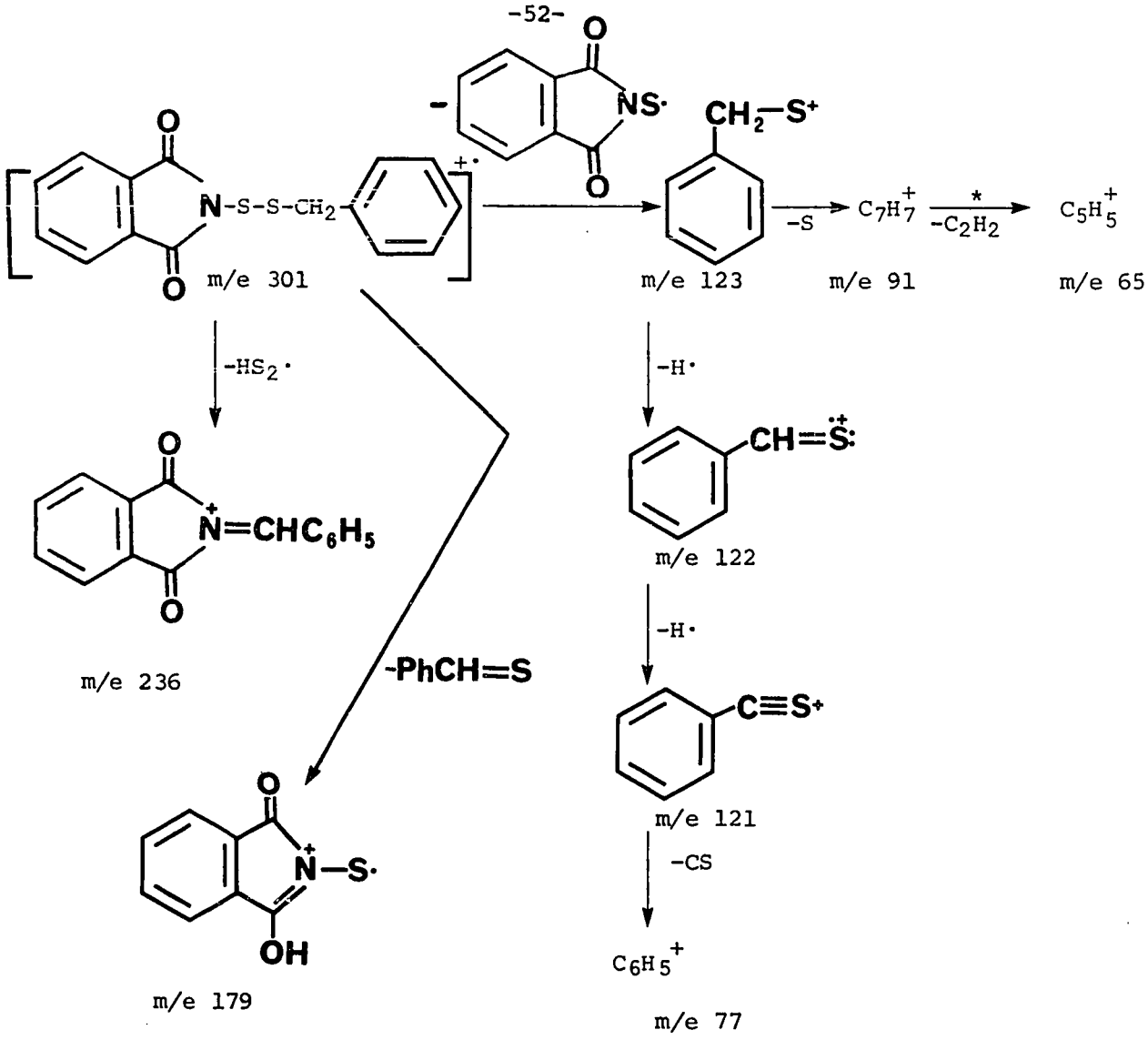
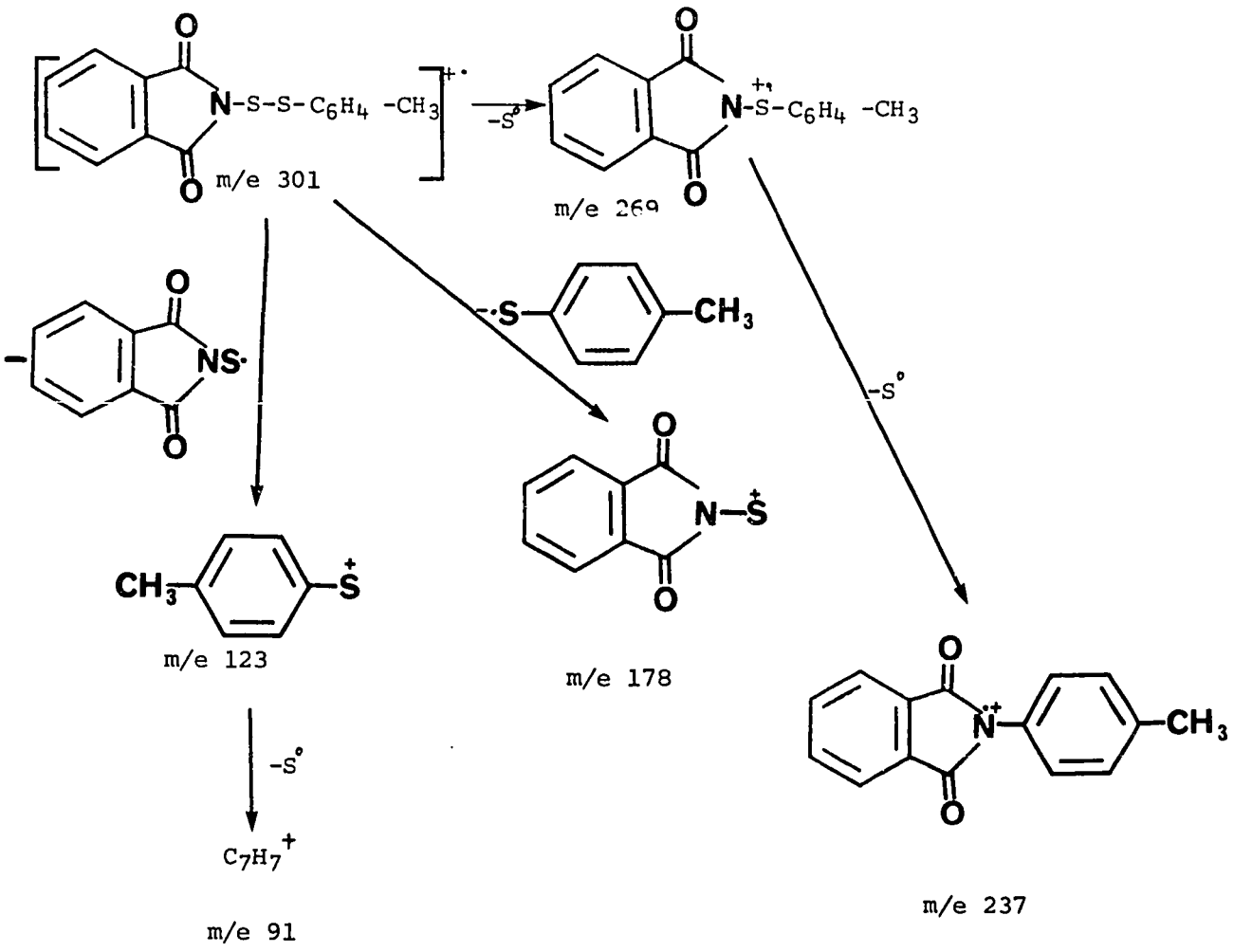


Figure 10 Mass spectral fragmentation of carbomethoxymethyl phthalimido disulfide (55)



peaks at 147, 130, 104, 76 as in Fig. 8

Figure 11 Mass spectral fragmentation of benzyl phthalimido disulfide (58)



peaks at 147, 130, 104, 76 as in Fig.8

Figure 12 Mass spectral fragmentation of p-tolyl phthalimido disulfide (59)

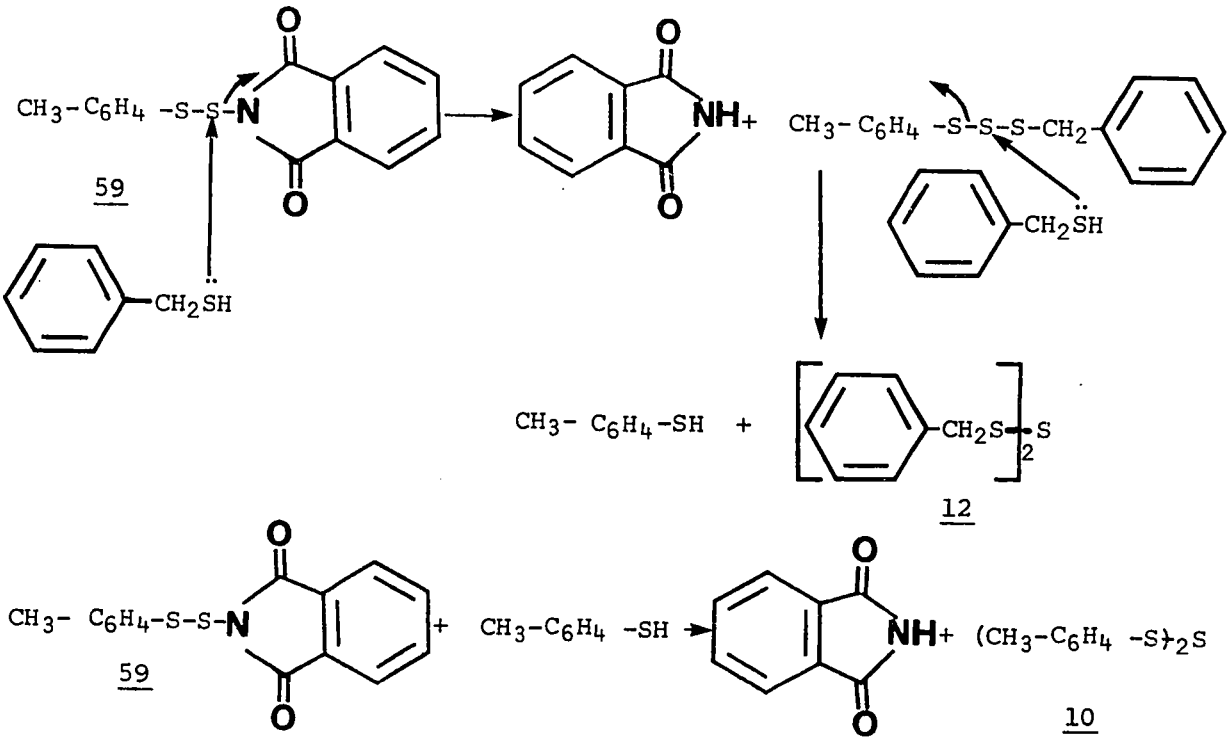
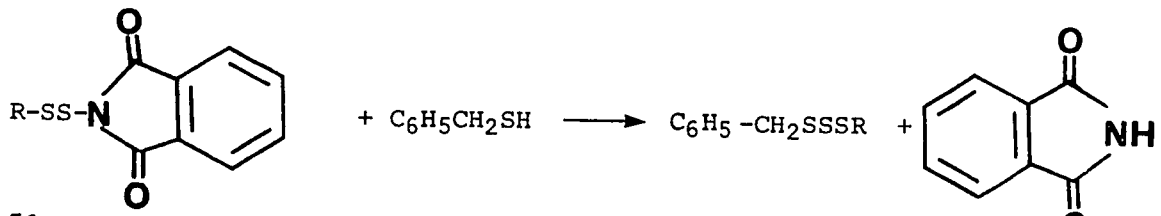


Figure 13 Pathway for the formation of symmetric trisulfides 10 and 12 from the reaction of α-toluenethiol with p-tolyl phthalimido disulfide (59)

The analogous thiol induced disproportionation of disulfides is well documented.[101] Similarly, the reaction of p-toluenethiol and p-bromophenylmethanethiol (53) with 58 did not result in the isolation of unsymmetric trisulfides. However, the addition of α-toluenethiol to n-propyl phthalimido disulfide (56) and isopropyl phthalimido disulfide (57) produced the unsymmetric trisulfides, n-propyl benzyl trisulfide (60) and isopropyl benzyl trisulfide (61).[1] These were isolated in yields of



56 R = $CH_3CH_2CH_2$-

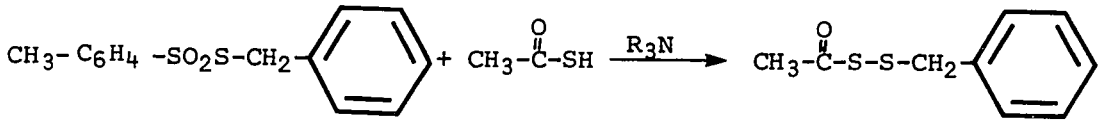
57 R = $(CH_3)_2CH$-

60 R = $CH_3CH_2CH_2$-

61 R = $(CH_3)_2CH$-

30% and 67% respectively and were of approximately 95% purity as determined by vapour phase chromatography. Small traces of the two symmetric trisulfides were also detected in both cases probably as a result of some thiol induced disproportionation during the long reaction time (4.5 to 6.5 days). Improvement in this synthesis of unsymmetric trisulfides can likely be achieved by changing the reaction conditions, since the faster the reaction, the less chance for thiol induced exchange to occur.

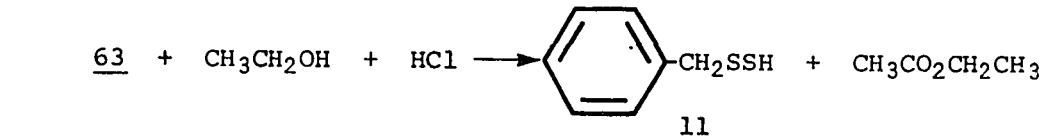
Isopropyl benzyl trisulfide (61) was also synthesized by an alternate method. The reaction of thioacetic S-acid (64) with benzyl p-toluenethiosulfonate (62) in the presence of triethylamine produces acetic α-toluenesulfenic thioanhydride (63). Hydrolysis of 63



62 64 63

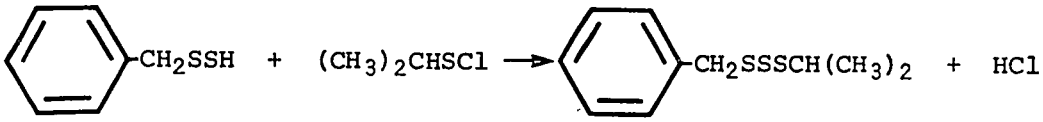
[1] This work has been published; D.N. Harpp and D.K. Ash, Intl. J. Sulfur Chem., A, 1, 211 (1971).

with ethanolic hydrochloric acid gave benzyl hydrodisulfide (11).[102] The interaction of 2-propanesulfenyl chloride (65), prepared from the chlorinolysis of di-isopropyl disulfide with chlorine, with benzyl



63 + CH_3CH_2OH + HCl → CH_2SSH + $CH_3CO_2CH_2CH_3$

11



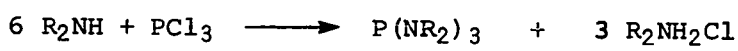
CH_2SSH + $(CH_3)_2CHSCl$ → $CH_2SSSCH(CH_3)_2$ + HCl

11 65 61

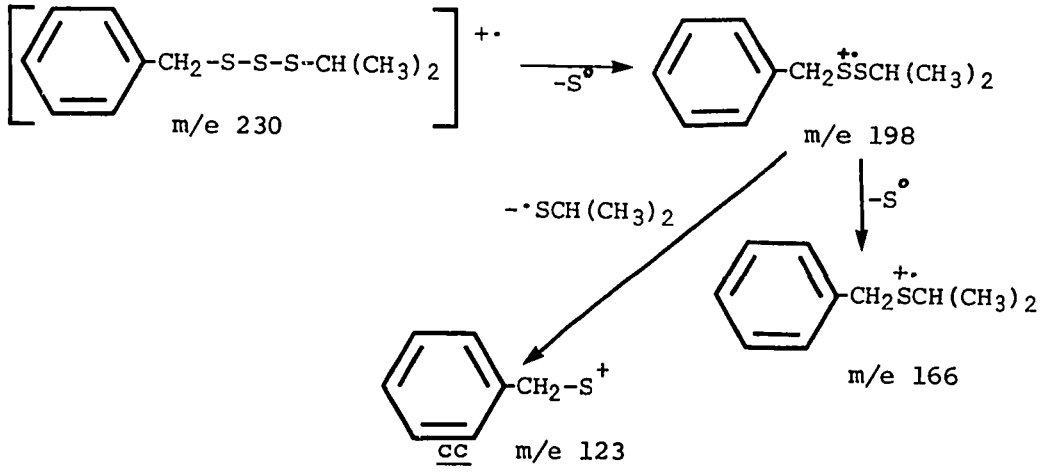
hydrodisulfide resulted in the formation and isolation of isopropyl benzyl trisulfide (61). The mass spectral fragmentation pattern of isopropyl benzyl trisulfide (61), illustrated in Figure 14(a), indicates that sequential loss of sulfur atoms results in the formation of ions corresponding to unsymmetrical di- and monosulfides. Fragment cc formed by cleavage of the disulfide undergoes the same decomposition mode as was evident in Figure 11.

Synthesis of Phosphines

Aminophosphines may be prepared via the reaction of dialkylamines with phosphorous trichloride.[103,104,105,106] These aminophosphines are highly reactive and care must be taken in the choice of solvents used for their preparation and reactions since they react violently with alcohols[104]

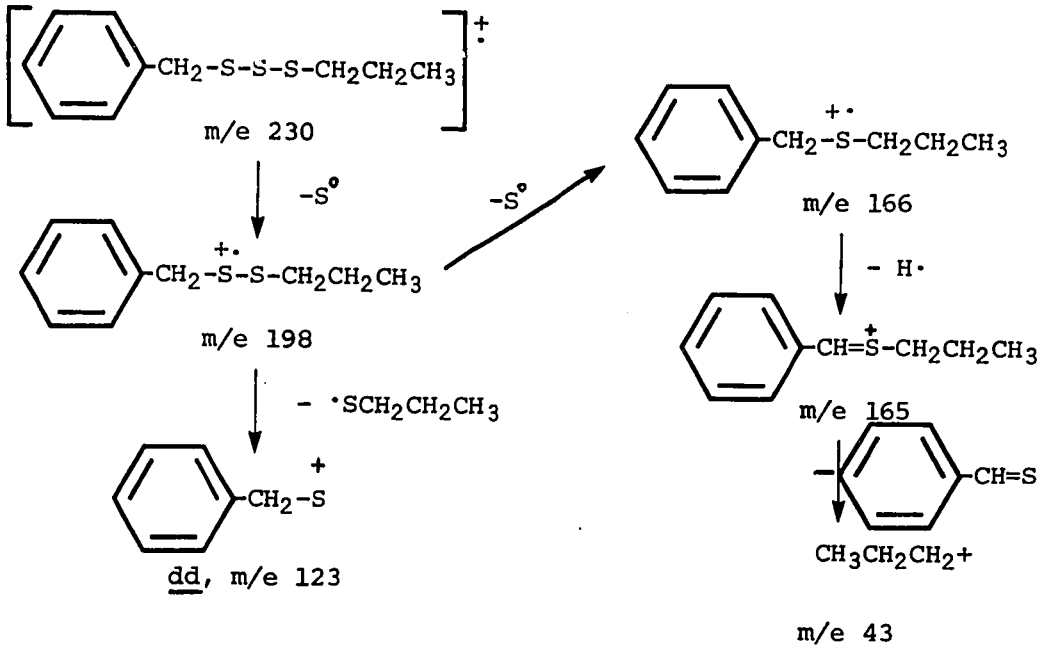


$6\ R_2NH + PCl_3 \longrightarrow P(NR_2)_3 + 3\ R_2NH_2Cl$



cc fragments to produce peaks at 123, 121, 91, 77, 65 as in Fig. 11

Figure 14(a) Mass spectral fragmentation of isopropyl benzyl trisulfide (61)



dd fragments to produce peaks at 122, 121, 91 and 65 as in Fig. 11

Figure 14(b) Mass spectral fragmentation of n-propyl benzyl trisulfide (60)

and carbon tetrachloride.[105,107] Reaction with ketones may also occur.[104,108] Solvents towards which the aminophosphines are inert include ether, benzene, hexane and ethyl acetate.

Several tris(dialkylamino) phosphines have become commercially available recently. Large quantities (100 g.) of these aminophosphines may be prepared conveniently in the laboratory by a modification of reported procedures.[103,105] In this manner, tris(diethylamino) phosphine (66) was prepared from the reaction of diethylamine with phosphorous trichloride.

$$[(CH_3CH_2)_2N]_3P$$

66

Desulfurization of Trisulfides by Phosphines

A review of the existing literature on the desulfurization of trisulfides by phosphines was presented on page 10. As mechanistic details of the interaction between phosphines and trisulfides are not available a more detailed examination of this reaction was warranted. Since tris(diethylamino) phosphine (66) exhibits a high degree of reactivity

$$[(CH_3CH_2)_2N]_3P$$

66

in desulfurization reactions, (as exemplified by its ability to desulfurize disulfides which were inert towards triphenylphosphine[109]), an investigation of its reaction with organic trisulfides was of interest.

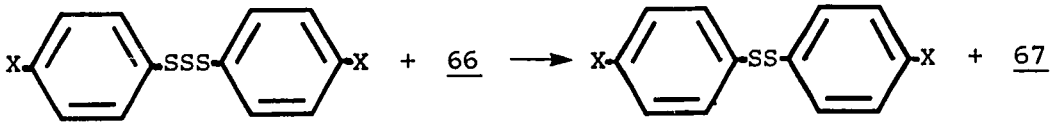
The reaction of diaryl trisulfides was attempted first as it was known[109] that the diaryl disulfides, which might be formed, would not

undergo desulfurization with the aminophosphine 66. The reaction of di-p-tolyl trisulfide (10) with one molar equivalent of tris(diethylamino) phosphine (66), in anhydrous diethyl ether at room temperature, was very rapid, as vapour phase chromatographic analysis of the reaction mixture, after 3 minutes, indicated that all of 66 had been converted to tris(diethylamino) phosphine sulfide (67). Subsequent chromatographic

$$CH_3\text{-}C_6H_4\text{-}SSS\text{-}C_6H_4\text{-}CH_3 + [(CH_3CH_2)_2N]_3P \rightarrow CH_3\text{-}C_6H_4\text{-}SS\text{-}C_6H_4\text{-}CH_3 + [(CH_3CH_2)_2N]_3P=S$$

10 66 7 67

work-up resulted in the isolation of the desulfurized product, di-p-tolyl disulfide (7) in 81% yield. Other diaryl trisulfides underwent this facile desulfurization reaction on treatment with the aminophosphine 66. For example, di-p-methoxyphenyl trisulfide (25) and diphenyl trisulfide (24) gave the corresponding disulfides in yields of 62% and 92% respectively.



25, X = CH_3O

24, X = H

68, X = CH_3O

69, X = H

The desulfurization of dialkyl trisulfides with the aminophosphine 66 was also expected to proceed rapidly but the isolation of pure dialkyl disulfides might be complicated by the fact that a number of dialkyl

disulfides are known[109] to undergo rapid reaction with the same phosphine.

$$RSSSR + \underline{66} \longrightarrow RSSR + \underline{67}$$

$$RSSR \xrightarrow[\underline{66}]{} RSR + 67$$

If disulfides proved competitive with trisulfides in the reaction with tris(diethylamino) phosphine (66) dialkyl sulfides would be produced along with the desired dialkyl disulfides. As a test for this possibility, the reaction of dibenzyl trisulfide (12) with one molar equivalent of tris(diethylamino) phosphine (66) was investigated. The reaction was performed in anhydrous diethyl ether at room temperature.

$$\underset{\underline{12}}{C_6H_5CH_2SSSCH_2C_6H_5} + \underline{66} \longrightarrow \underset{\underline{70}}{C_6H_5CH_2SSCH_2C_6H_5} + \underline{67}$$

After column chromatography on silica gel a 94% yield of dibenzyl disulfide (70) was obtained. No trace of dibenzyl sulfide was observed. Similarly, the desulfurization of di-n-pentyl (15), di-n-propyl (16) and di-carbomethoxymethyl (17) trisulfides produced the corresponding disulfides (71, 72, 73) in yields of 71 - 91%; no indication of mono-sulfides was detected by vpc. The fact that no di-carbomethoxymethyl sulfide was detected in the desulfurization of trisulfide 17 is worthy of

$$\underset{\underline{17}}{CH_3O\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_2\text{-}SSS\text{-}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}OCH_3} + \underline{66} \longrightarrow \underset{\underline{73}}{(CH_3O\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_2\text{-}S\rightarrow_2} + \underline{67}$$

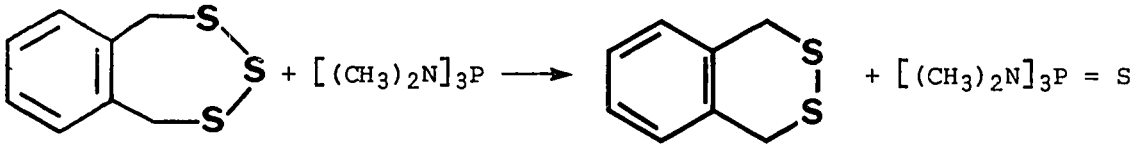
comment. The kinetics of the desulfurization of disulfide 73 by the aminophosphine 66 to produce monosulfide have been studied and the second order rate constant for this reaction was found to be 1.03×10^{-1} $\ell M^{-1} sec^{-1}$ in benzene at 30°C.[110(a)] Despite this very fast rate for the conversion of 73 to monosulfide, none of the latter was detected. This implies that the desulfurization of 17 proceeds much more rapidly than the desulfurization of 73. In summary, the rate of desulfurization

$$\underset{}{RSSSR} \xrightarrow[\underline{66}]{k_1} \underset{k_1 >> k_2}{RSSR} \xrightarrow[\underline{66}]{k_2} RSR$$

of aliphatic trisulfides by tris(diethylamino) phosphine (66) is much faster than the rate of desulfurization of the corresponding aliphatic disulfides. This is in direct contrast with the work of Moore and Trego[53] who found, in the case of dialkenyl trisulfides, that the desulfurizations of the disulfides are, in all cases, faster than the desulfurizations of their precursor trisulfides. They used triphenylphosphine (6) as the desulfurizing agent. The reaction of phosphine 6 with dibenzyl trisulfide (12) resulted in the formation of dibenzyl disulfide (70) along with triphenylphosphine sulfide (9).

$$\underset{\underline{12}}{C_6H_5CH_2SSSCH_2C_6H_5} + \underset{\underline{6}}{(C_6H_5)_3P} \rightarrow \underset{\underline{70}}{C_6H_5CH_2SSCH_2C_6H_5} + \underset{\underline{9}}{(C_6H_5)_3P=S}$$

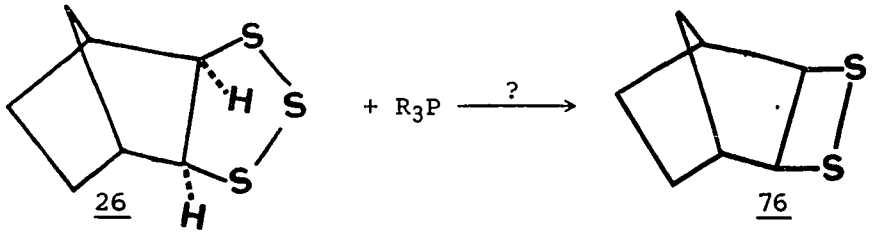
The desulfurization of cyclic trisulfides was also of interest. The reaction of 2,3,4-benzotrithiepin (37) with tris (dimethylamino) phosphine (74), in benzene at room temperature,



37 74 75

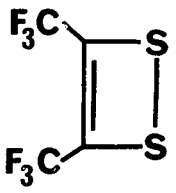
followed by column chromatography over silica gel, resulted in the isolation of 2,3-benzodithiin (75) in 77% yield. It may be noted that the reactivity of the methylaminophosphine 74 is comparable to that of the ethylaminophosphine 66 in desulfurization reactions.[110(b)]

The interaction of exo-3,4,5-trithiatricyclo [5.2.1.$0^{2,6}$] decane (26) with phosphines was investigated as a possible route to the unknown heterocycle 3,4-dithiatricyclo [4.2.1.$0^{2,5}$] nonane (76).

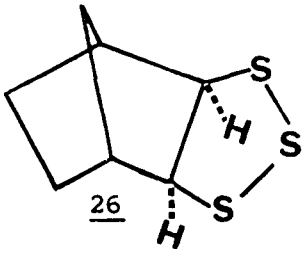


26 76

This compound, if formed, would be the second example of the disulfide system in a four-membered ring and first in a saturated four-membered ring. Krespan[111] has reported the preparation of bis-(trifluoromethyl)-1,2-dithiete. Reaction of the cyclic trisulfide 26 with one molar



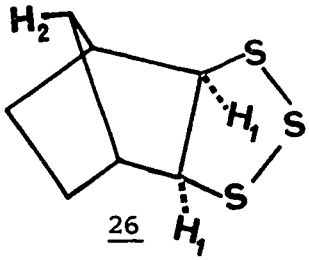
equivalent of tris(dimethylamino) phosphine (74) produced tris (dimethylamino) phosphine sulfide, an oil 77 and unreacted starting material 26. Column chromatography of the reaction mixture did not



26 + 74 ⟶ 26 + $(Me_2N)_3P = S$ + 77

separate pure 77 from the trisulfide 26.

The interaction of triphenylphosphine (6) with trisulfide 26 produced a white solid 78 and triphenylphosphine sulfide (9) (78 - 82%). Isolation of the solid by column chromatography provided a material with a broad melting point range. The infrared spectrum of this substance was very similar to that of starting trisulfide 26 with only slight differences in the 1300-600 cm^{-1} region. The nmr spectrum of 26



+ 6 ⟶ 78 + 9

(Figure 15) shows a doublet (J_{12} ~ 2 Hz) at 6.4 τ(d, 2H) which may be assigned to the sulfur geminal protons (H_1) which are coupled to the bridge anti proton (H_2), a multiplet 7.55 τ(2H), due to the resonances of the bridgehead protons, and multiplets at 7.9 - 9.1τ for the remaining 6 hydrogen atoms.[27] In the nmr spectrum of the product, 78, (Figure 16) the resonance at 6.4τ was absent but a new signal at 6.6τ was evident.

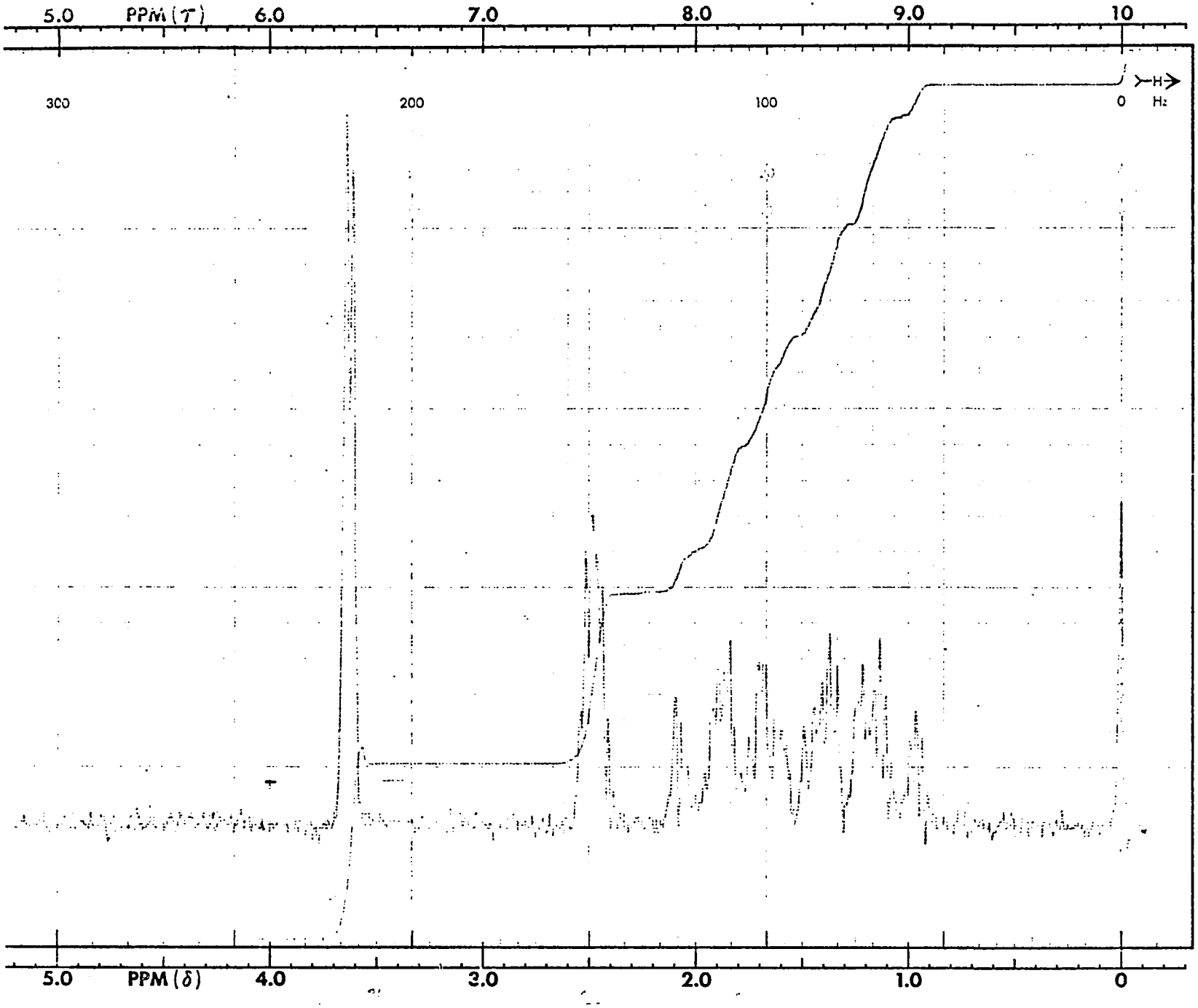


Figure 15. Nmr spectrum of exo - 3, 4, 5 - trithiatricyclo [5.2.1.$0^{2,6}$] decane (26).

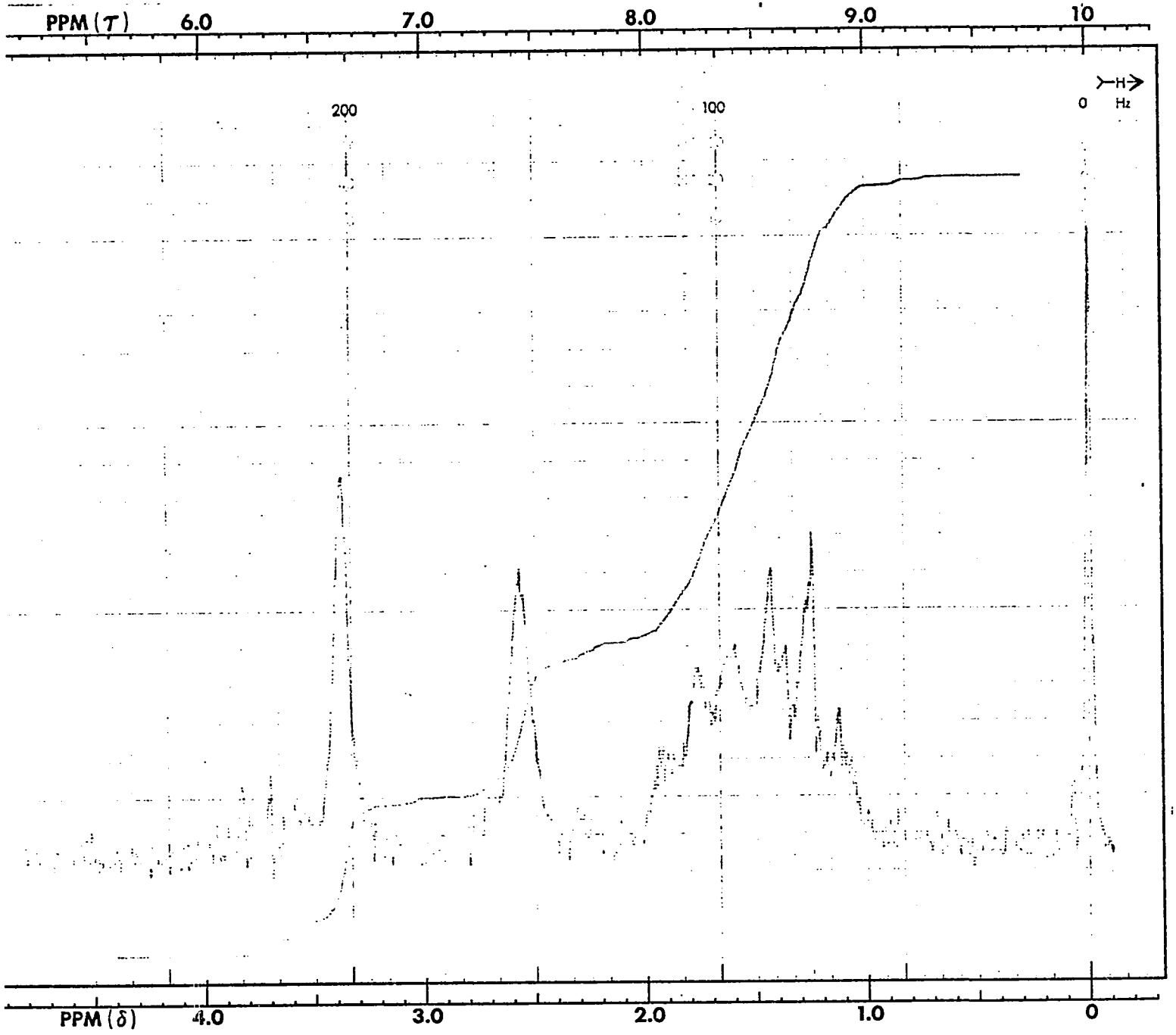
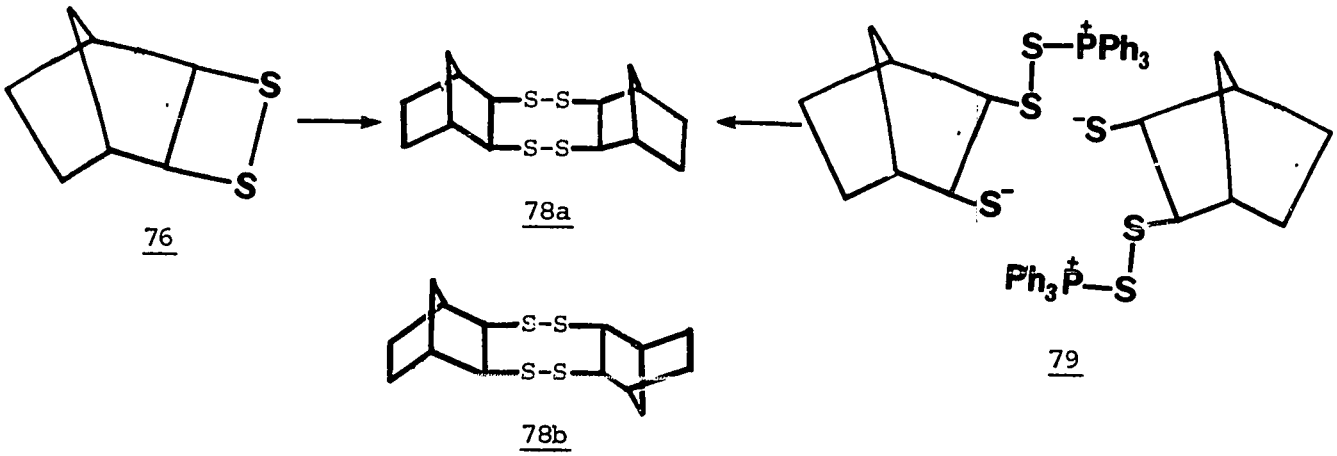


Figure 16. Nmr spectrum of desulfurization product 78.

This signal (a broad singlet or, more likely, an unresolved multiplet) at 6.6τ may be attributed to protons geminal to a sulfur atom of a disulfide linkage. This is supported by the data of van Wazer and Grant[112] who found that protons on carbon adjacent to sulfur of a polysulfide absorb further downfield as the number of sulfur atoms in the chain is increased. The mass spectrum of 78 exhibits a parent peak at m/e 316. This is indicative of the dimer of 76 which may be formed during or after the desulfurization of 26. Thus 78 may arise from the dimerization of 3,4-dithiatricyclo [4.2.1.$0^{2,5}$] nonane (76) or the phosphonium salt 79. From the broad melting range and other

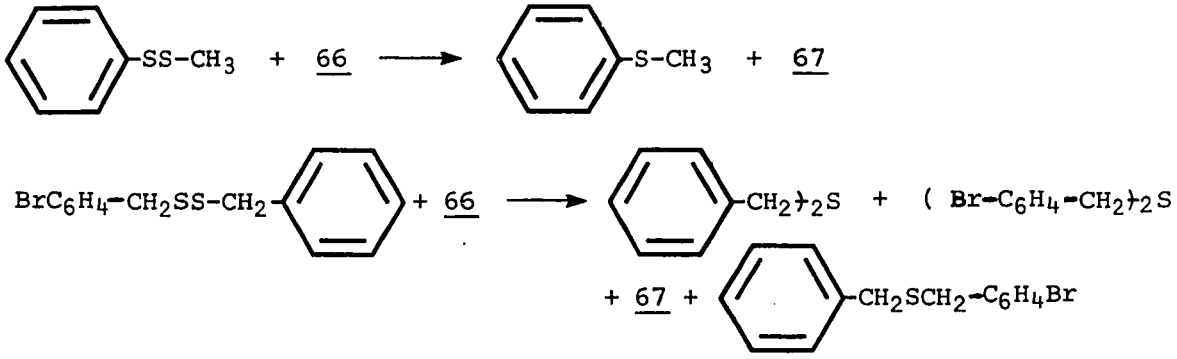


76 78a 79

78b

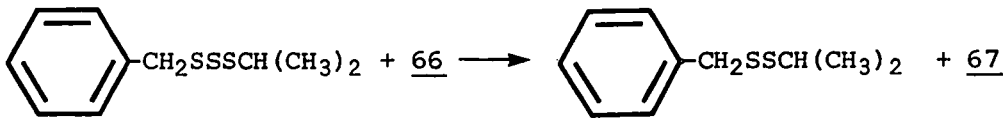
evidence presented it is likely that 78 is a mixture of two dimers 78a and 78b. There is precedent for assuming retention of configuration at the carbon atom α to sulfur as it was shown (vide infra) that triphenylphosphine (6) attacks and extrudes the central sulfur atom of trisulfides. Separation of 78a from 78b was not achieved.

The reaction of unsymmetric trisulfides with phosphines was of interest in view of the fact that some unsymmetric disulfides give only unsymmetric monosulfide on desulfurization while others give the two symmetric monosulfides along with the unsymmetric monosulfide. The former pathway is followed with disulfides in which the



two mercaptide halves have significantly different pKa values.[109]

Accordingly, the reaction of isopropyl benzyl trisulfide (61) with tris(diethylamino) phosphine (66) was studied. An analysis of the reaction mixture by vapour phase chromatography indicated that tris (diethylamino) phosphine sulfide (67) and one other compound had been formed. Chromatographic work up resulted in the isolation of isopropyl



61 80, 96%

benzyl disulfide (80) in 96% yield. The structure of the unsymmetric disulfide 80 was confirmed by nmr and mass spectrometry. The benzylic and methine protons in disulfide 80 were at approximately 4 Hz upfield

from the resonances of these protons in trisulfide 61 (Figure 17). The mass spectrum of isopropyl benzyl disulfide (80) revealed a parent peak at m/e 198 (27% of base peak) and a base peak at m/e 91 assignable to the tropylium ion. The only other peak of greater than 10% relative abundance was at m/e 65 which results from the loss of C_2H_2 from the tropylium ion.[113] The desulfurization of n-propyl benzyl trisulfide (60) also gave the unsymmetric disulfide 81. Traces of the two symmetric disulfides were detected by vpc. In the nmr of n-propyl benzyl disulfide (81), the benzylic and methylene (α to sulfur) protons resonate 16 and 30 Hz respectively upfield from the signal of these protons in the trisulfide 60 (Figure 18).

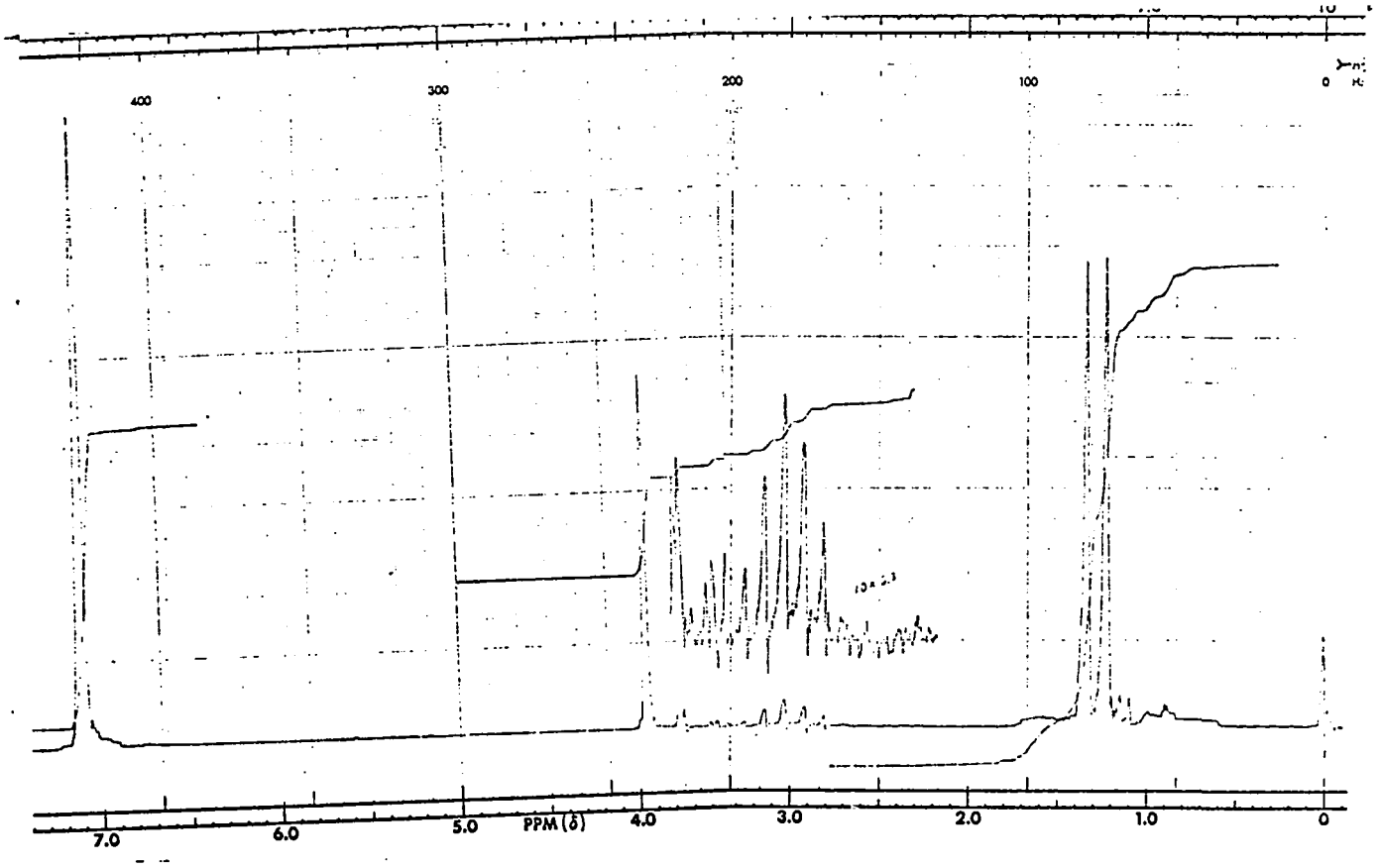


Figure 17(a). Nmr spectrum of isopropyl benzyl trisulfide (61).

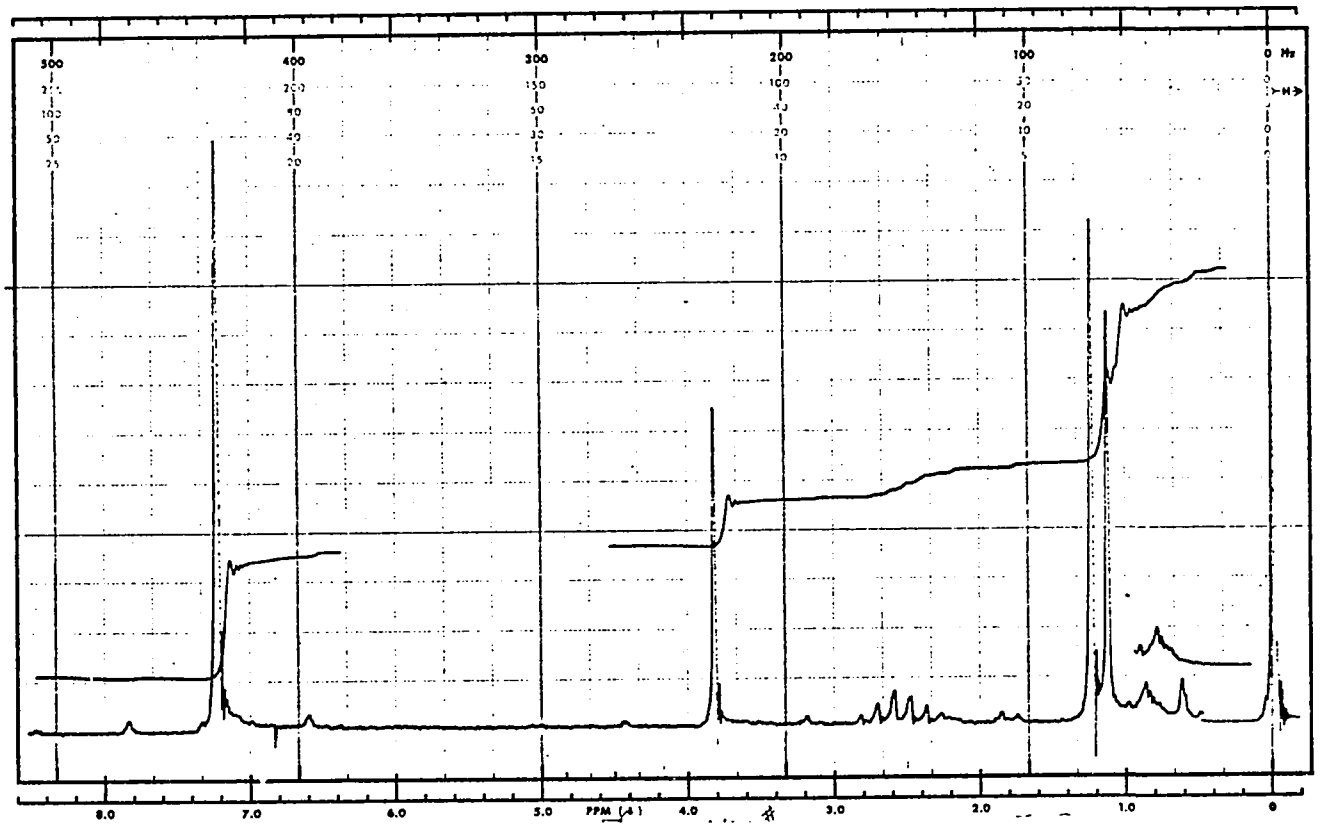


Figure 17(b). Nmr spectrum of isopropyl benzyl disulfide (80).

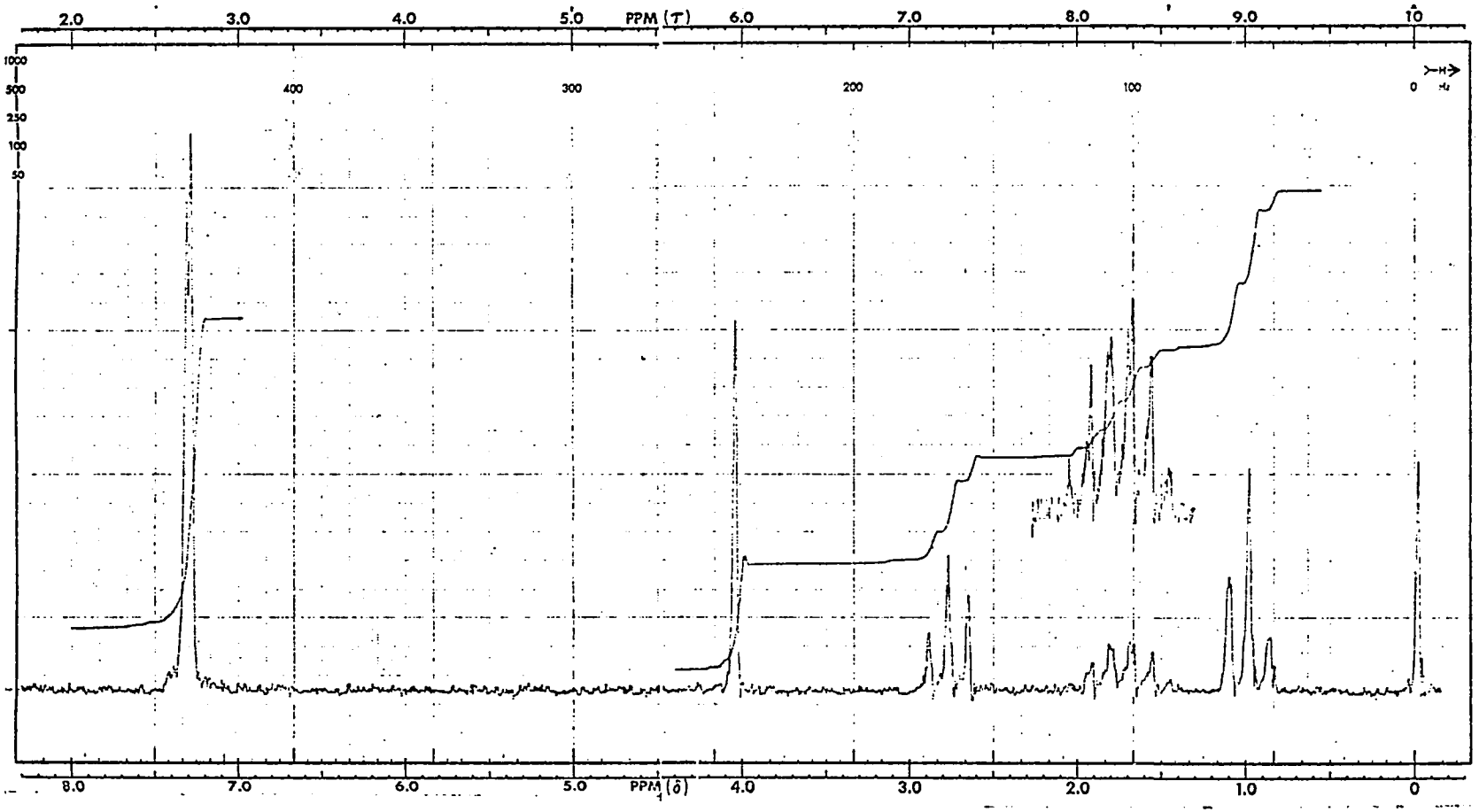


Figure 18(a). Nmr spectrum of n-propyl benzyl trisulfide (60).

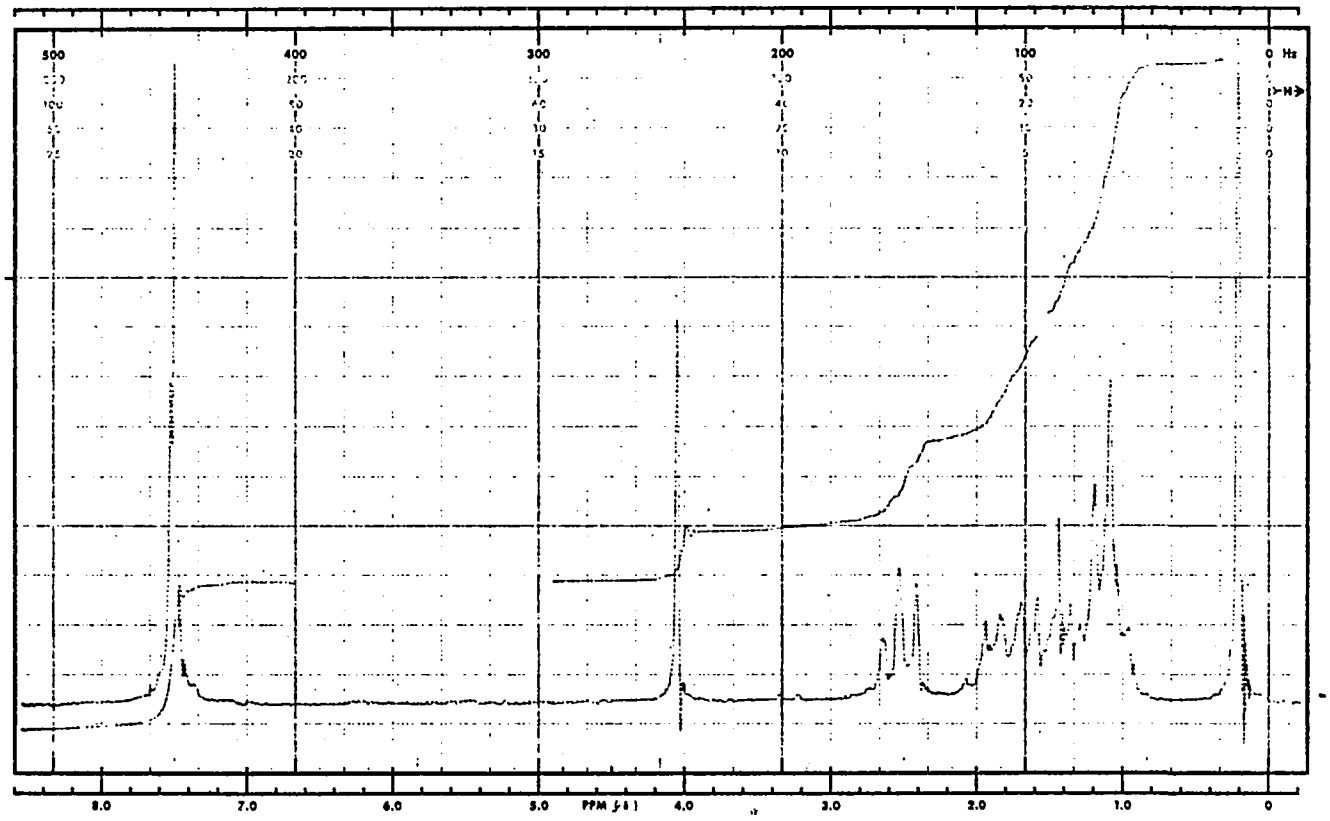
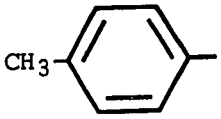
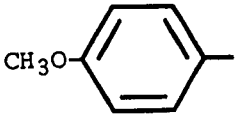
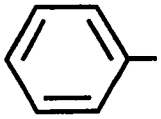
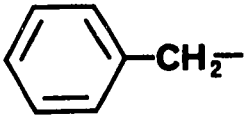
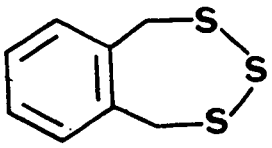


Figure 18(b). Nmr spectrum of n-propyl benzyl disulfide (81).

TABLE III

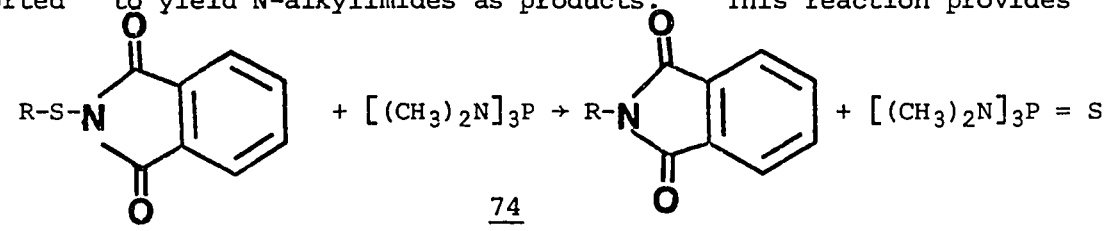
DESULFURIZATION OF SYMMETRIC TRISULFIDES

$$RSSSR + [(CH_3CH_2)_2N]_3P \longrightarrow RSSR + [(CH_3CH_2)_2N]_3P = S$$

Trisulfide		Disulfide	
Compound	R	% Yield	Compound
10		81	7
25		62	68
24		92	69
12		94	70
15	$CH_3(CH_2)_4-$	71	71
16	$CH_3(CH_2)_2-$	80	72
17	$CH_3O-CO-CH_2-$	91	73
37		77	75

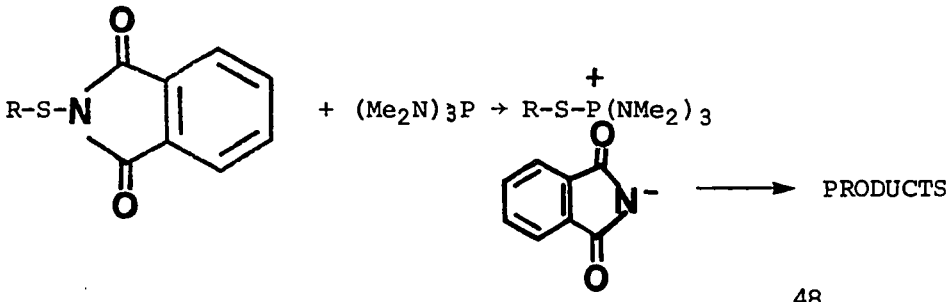
Desulfurization of Alkyl and Aryl Phthalimido Disulfides

Displacement of the imide group from N-(alkylthio)-imides[97] by thiols, hydrodisulfides and alkoxides has resulted in the formation of disulfides[98], trisulfides[98(b)], and sulfenate esters[99] respectively. These reactions are believed to occur by attack of the nucleophiles at the sulfur atom of the N-(alkylthio) imides. Recently, the desulfurization of thioimides by tris(dimethylamino) phosphine (74) has been reported[48] to yield N-alkylimides as products. This reaction provides



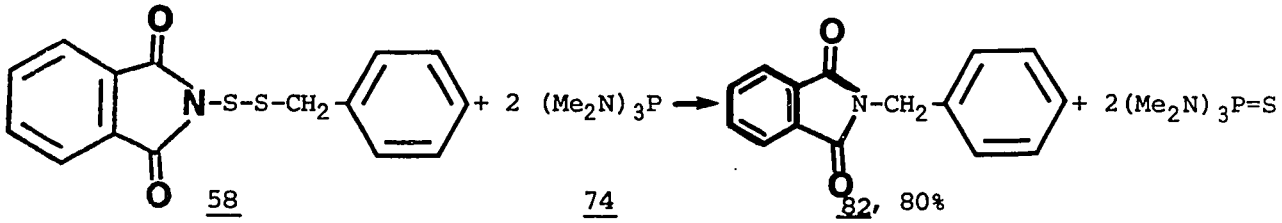
74

an alternate route to N-alkylphthalimides, important intermediates in the Gabriel synthesis of primary amines. The probable mechanism for



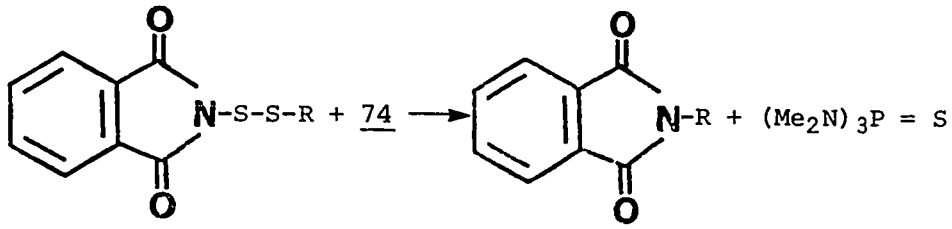
this transformation, as shown above, has been discussed[48].

Based on these precedents, it was felt that the alkyl phthalimido disulfides, synthesized earlier, were likely to undergo desulfurization on treatment with the aminophosphine 74. Confirmation came from the reaction of benzyl phthalimido disulfide (58) with two molar equivalents



58 74 82, 80%

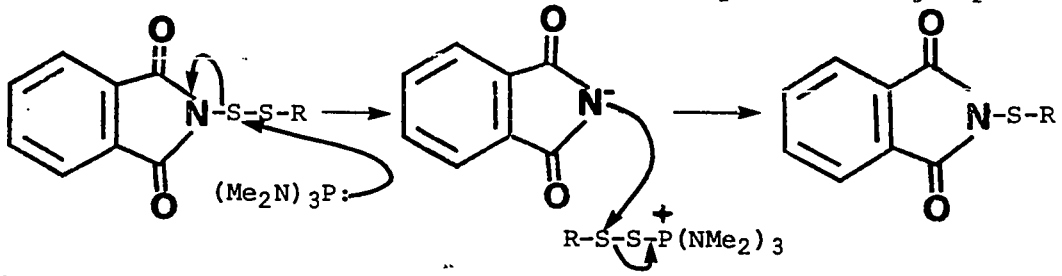
of 74 which resulted in the isolation of N-benzylphthalimide (82) in 80% yield. Both n-propyl (54) and i-propyl phthalimido disulfides (56) underwent this desulfurization to provide the corresponding N-alkyl-phthalimides (83) and (84) in yields of 62% and 21% respectively. The



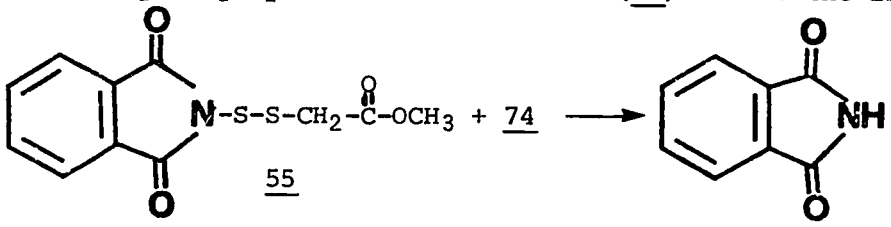
54, R = $CH_3CH_2CH_2$- 83, R = $CH_3CH_2CH_2$-, 62%

56, R = $(CH_3)_2CH$- 84, R = $(CH_3)_2CH$- , 21%

low yield in the latter reaction is more likely a reflection of the difficulty in isolating the product than an indication of the fact that S_N2 reactions are less facile at secondary carbon in comparison to a primary carbon center [52]. These reactions likely occur via attack of the phosphine at the sulfur atom bonded to the phthalimido group with



subsequent attack of the anion formed on sulfur to give an N-(alkylthio)-phthalimide. The latter is known to undergo further desulfurization with 74 as outlined above[48]. The attempted desulfurization of carbomethoxymethyl phthalimido disulfide (55) led to the isolation of an

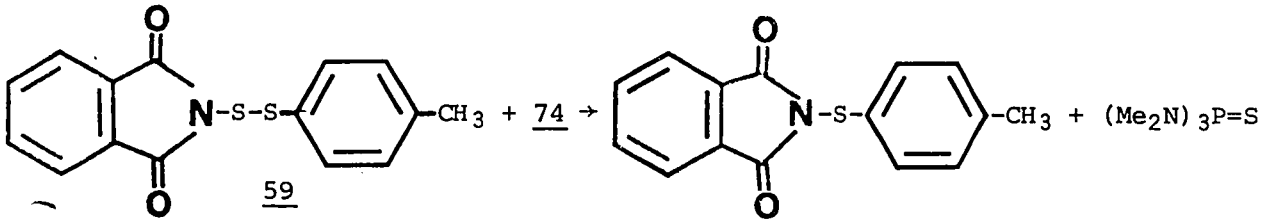


55

uncharacterized brown oil and phthalimide. Phthalimide was also

isolated from the unsuccessful attempted desulfurization of N-(carbomethoxymethylthio)phthalimide[48] and probably arises via abstraction of one of the acidic protons of the methylene group by the phthalimido anion.

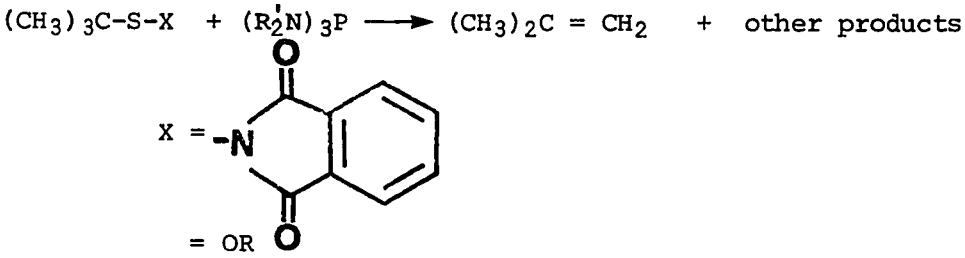
Since it was known that N-(arylthio)phthalimides were inert towards aminophosphine 74, it was expected that the treatment of an aryl phthalimido disulfide with this desulfurizing reagent would give an N-(arylthio)phthalimide. This aim was realized as the reaction of



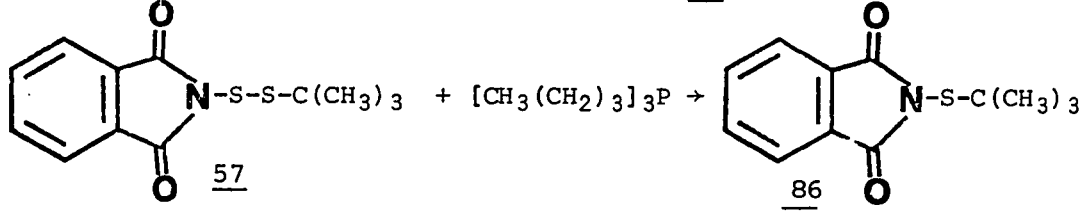
59 85

p-tolyl phthalimido disulfide (59) with tris(dimethylamino)phosphine (74) provided N-(p-tolylthio)phthalimide (85).

In view of the observations that aminophosphines cause fragmentation of N-(t-butylthio)phthalimide[48] (86) and o-alkyl-t-butylsulfenate esters[99] to isobutene, but that tri-n-butylphosphine effects the smooth desulfurization of the latter[99], the reaction of t-butyl phthalimido



disulfide (57) with tri-n-butylphosphine was investigated. This interaction provided N-(t-butylthio)phthalimide (86) in 73% yield.



57 86

Mechanism of Desulfurization

The reactions of phosphines with organo-sulfur and organo-oxygen compounds have been subjected to mechanistic scrutiny in a few instances.[109,114,115] Generally, these interactions proceed via either a phosphonium salt or a pentacovalent intermediate. In some cases, the presence of both has been postulated as occurring along the reaction coordinate. In their investigation of the reaction between elemental sulfur and triphenylphosphine, Bartlett and Meguerian[116] suggested a pathway involving a series of ionic intermediates. There

$$Ph_3P + S_8 \longrightarrow Ph_3\overset{+}{P}\text{-S-S-(S)}_5\text{-}S^{-} \xrightarrow{Ph_3P} Ph_3P = S + Ph_3\overset{+}{P}\text{-S-S-(S)}_4\text{-}S^{-} \longrightarrow \text{etc....}$$

is ample evidence[59,117] for the existence of a phosphonium salt intermediate in the extensively studied Arbuzov reaction. The experimental work on the reaction of disulfides with tris(diethylamino) phosphine (66)

$$(RO)_3P + R'I \longrightarrow RO\text{-}\overset{OR}{\overset{|}{\underset{OR}{\underset{|}{P}}}}\overset{+}{-}R'\ I^{-} \longrightarrow RI + (RO)_2\overset{O}{\overset{\|}{P}}R'$$

has led to the proposal that this interaction involves the intermediacy of a phosphonium salt.[109] In some cases, this ionic intermediate was

isolated and identified by ^{31}P magnetic resonance spectroscopy. Other

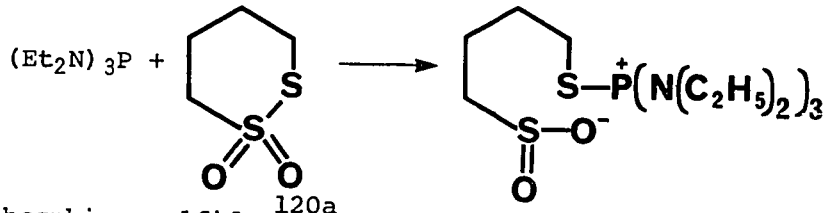
$$RSSR + (Et_2N)_3P \rightarrow RS^- \; R\text{-}S\text{-}\overset{+}{P}\text{-}(Et_2N)_3 \rightarrow RSR + (Et_2N)_3P=S$$

examples of the isolation of stable phosphonium salts include the reaction of alkyl halides with phosphines,[118] the alkylation of phosphine oxides[119]

$$Ph_3P + RCH_2Br \longrightarrow Ph_3\overset{+}{P}\text{-}CH_2R \; \overset{-}{Br}$$

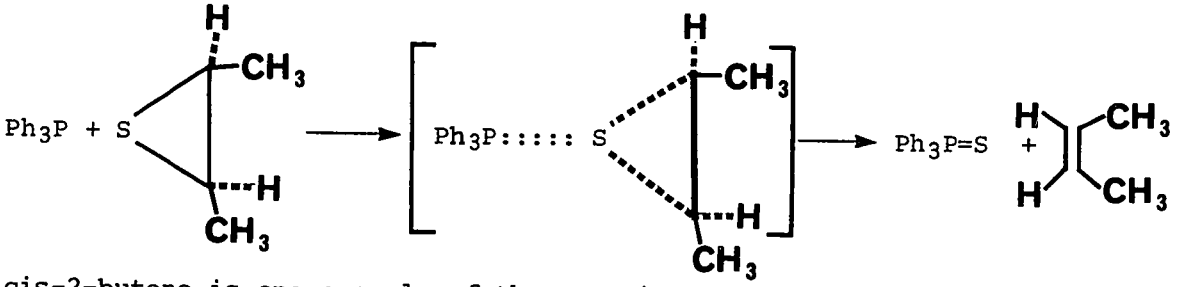
$$Ph_3P{=}O + Et_3\overset{+-}{O}BF_4 \longrightarrow Ph_3\overset{+}{P}\text{-}OEt \; \overset{-}{BF_4} + (Et)_2O$$

$$Ph_3P{=}S + Et_3\overset{+-}{O}BF_4 \longrightarrow Ph_3\overset{+}{P}\text{-}S\text{-}Et \; \overset{-}{BF_4} + (Et)_2O$$



and phosphine sulfides[120a] and the desulfurization of 1,2-dithiane-1, 1-dioxide.[120b]

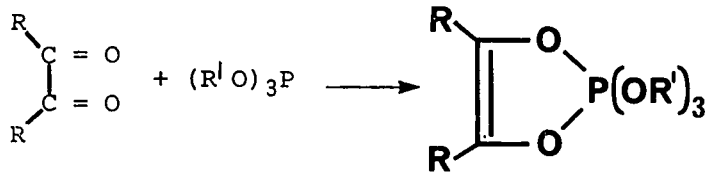
The desulfurization of cis-2-butene episulfide to yield



cis-2-butene is one example of the reactions of phosphorous nucleophiles not involving an ionic intermediate.[121] Since minimal solvent effects were noted in a kinetic study of this reaction a non-polar transition state was suggested.[122] Intermediates containing a pentavalent phosphorous

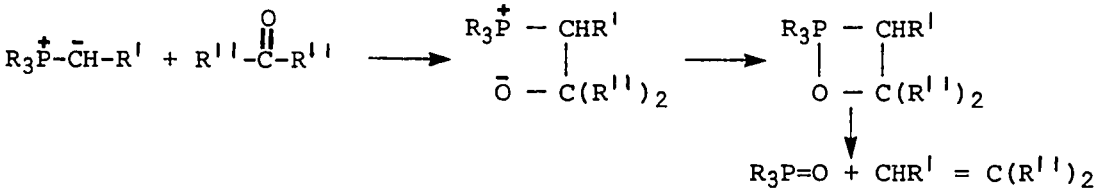
atom have been implicated in the deoxygenation of peroxides with

$$EtOOEt + (EtO)_3P \longrightarrow (EtO)_5P \longrightarrow (EtO)_3P{=}O + EtOEt$$

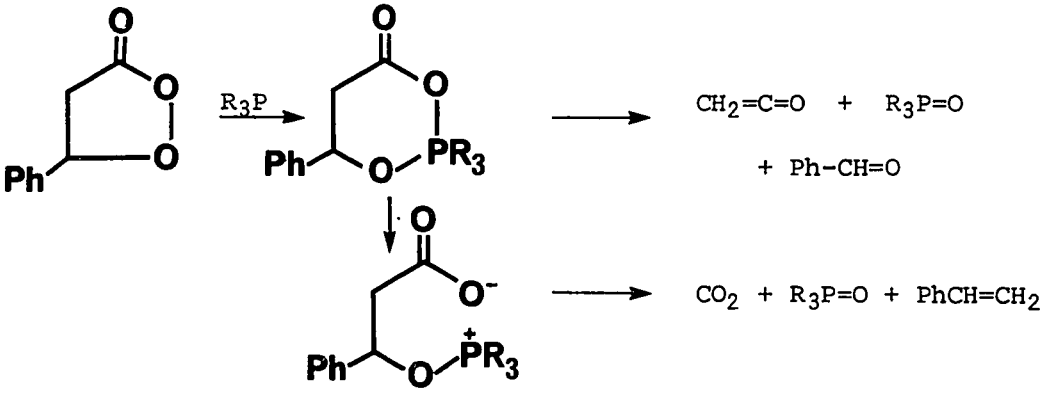


triethyl phosphite[123] and the reaction of α-diketones with phosphites.[124]

The Wittig reaction is thought to involve both ionic and pentacovalent intermediates.[125] The interaction of a phosphonium ylide with a carbonyl compound produces a dipolar species which cyclizes to a



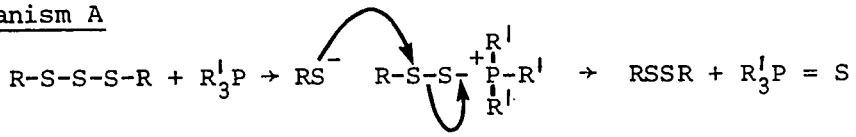
pentavalent intermediate. Decomposition of the latter gives an olefin plus phosphine oxide. The deoxygenation of cis-2-butene epoxide has been postulated as proceeding through a similar intermediate.[126] There are also examples in the literature involving ionization of a pentavalent intermediate to a phosphonium salt. Adam[127] has invoked this process



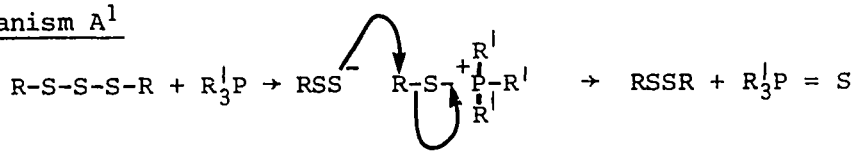
in his investigation of the deoxygenation of cyclic peroxyesters.

In view of the studies outlined above, several mechanistic pathways appear possible for the desulfurization of organic trisulfides by phosphines. These are outlined in Figure 19. Mechanism A involves nucleophilic attack of the phosphine to the central sulfur atom of the trisulfide with displacement of a mercaptide ion. The phosphonium salt then breaks down to give products as indicated. An ionic species is also involved in Mechanism A^1 but in this case phosphine attack occurs on a terminal sulfur atom so that a hydrodisulfide ion is displaced. Mechanisms B and B^1 invoke the intermediacy of a pentavalent phosphorous species which arises via insertion of the phosphine into the sulfur-sulfur bond of the trisulfide. A direct abstraction process in which one of the sulfur atoms is removed through a non-polar transition state is exemplified in Mechanisms C and C^1. It should be noted that Mechanisms A, B and C all involve loss of the central sulfur atom of the trisulfide while Mechanisms A^1, B^1 and C^1 invoke extrusion of one of the terminal sulfur atoms. Thus a knowledge of which sulfur, central or terminal, is removed by the phosphine would reduce the number of mechanistic pathways by one half. Accordingly an investigation of the desulfurization of radioactively labelled trisulfides was undertaken.

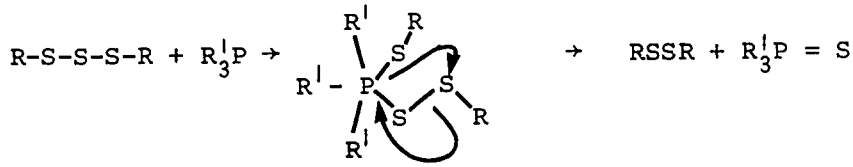
Mechanism A



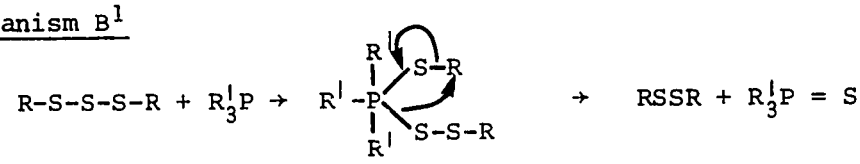
Mechanism A[1]



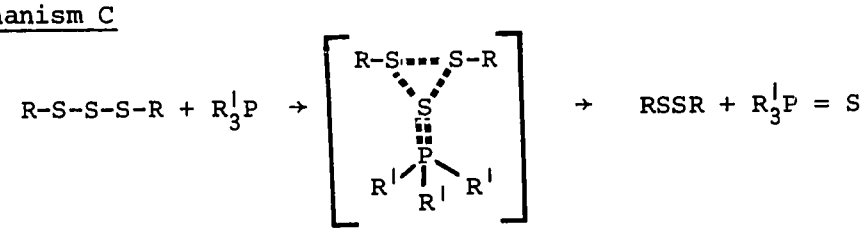
Mechanism B



Mechanism B[1]



Mechanism C



Mechanism C[1]

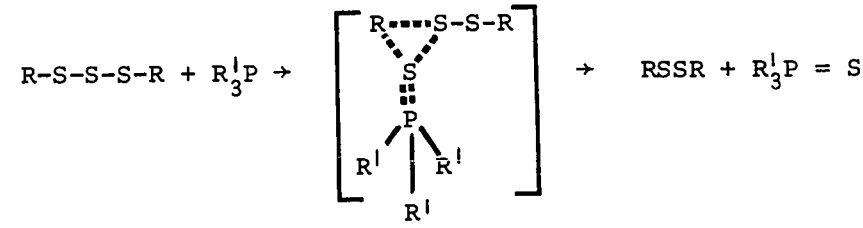
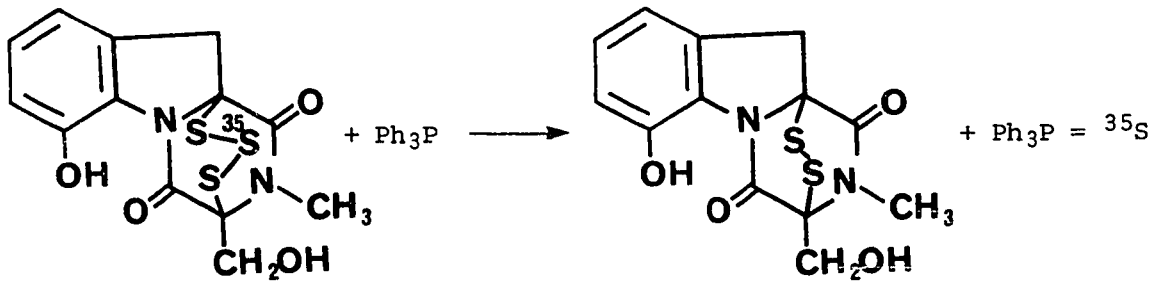


Figure 19 Possible mechanistic pathways for the desulfurization of organic disulfides by phosphines.

Radiochemical Studies

As discussed earlier, a recent publication has shown by ^{35}S radioactive tracer work that the central sulfur atom of thiodehydrogliotoxin is removed by triphenylphosphine.[58] The authors



concluded that "a decision may be made concerning the mode of desulfurization of trisulfides. It is clear that the reaction proceeds preferentially at sulfur bonded to sulfur atoms rather than at sulfur atoms which are substituents of carbon". Thiodehydrogliotoxin may constitute a special case and it would be misleading to use it as a model to generalize on the mechanism of the reaction. It is difficult to imagine the terminal sulfur atom being extruded as this would appear to necessitate front side displacement of triphenylphosphine sulfide by hydrodisulfide anion. The requirement for front side displacement is a consequence of the geometry of the ring system. (Figure 20). A substrate which could mechanistically accommodate removal of both sulfur atom types was required.[2] Accordingly, ^{35}S-labelled dibenzyl trisulfide (12*) was prepared from α-toluenethiol plus radioactive sulfur dichloride (14*).

$$2\ C_6H_5CH_2SH + {}^{35}SCl_2 \longrightarrow C_6H_5CH_2\text{-}S\text{-}{}^{35}S\text{-}S\text{-}CH_2C_6H_5$$

14* 12*

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[2] The radiochemical experiments described here have been published: D.N. Harpp and D.K. Ash, Chem. Comm., 811 (1970).

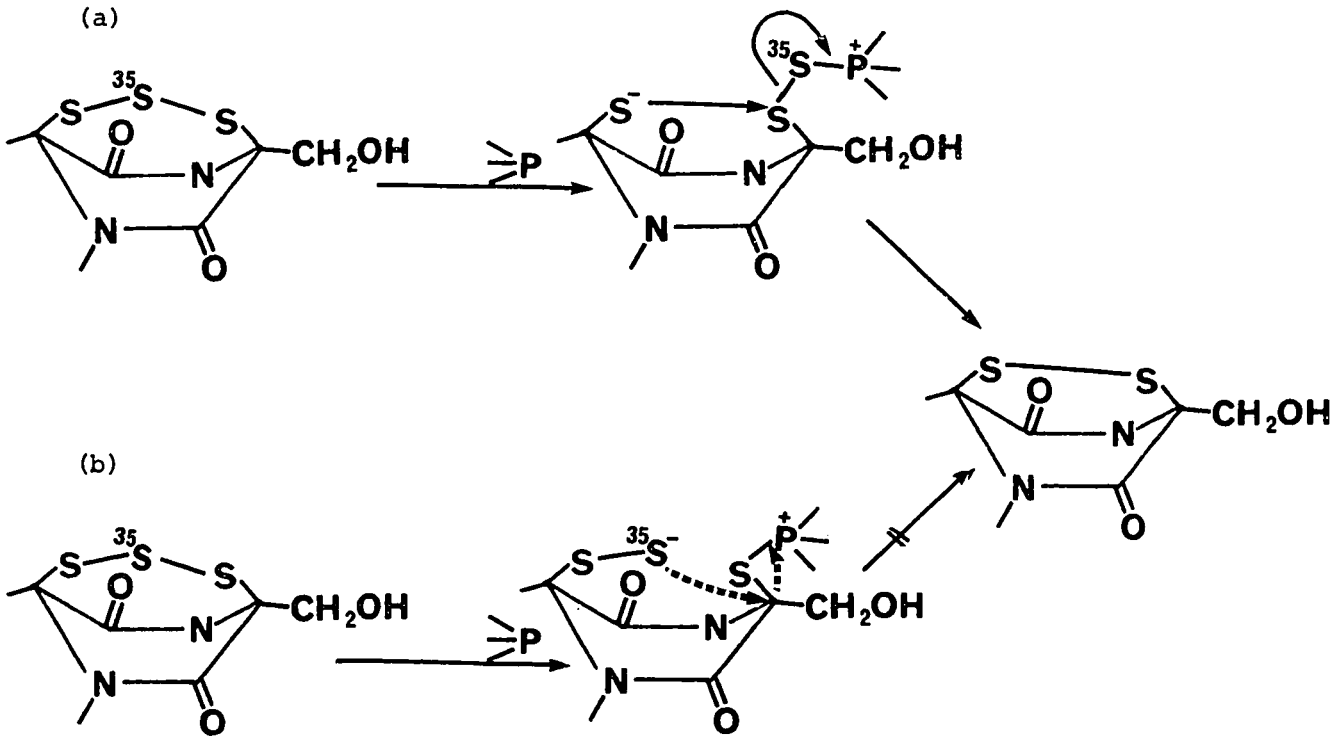
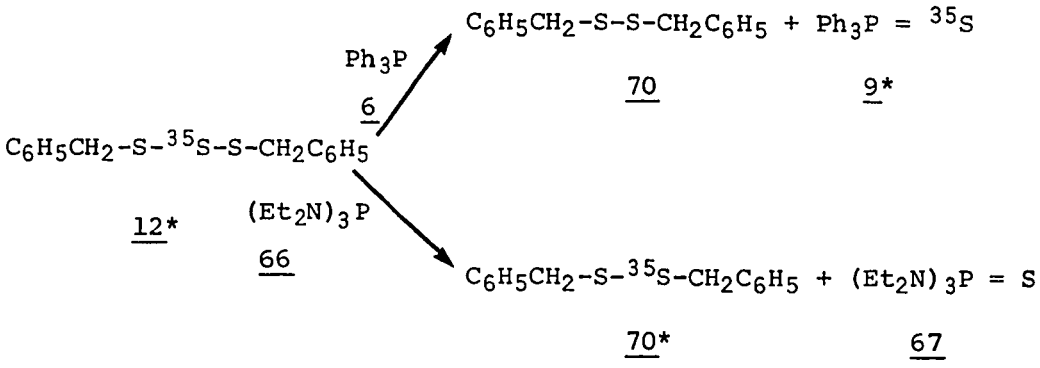


Figure 20 (a) Attack and extrusion of central sulfur of thiodehydrogliotoxin;

(b) Illustration of front side displacement which would be required for loss of terminal sulfur.

The radioactively labelled trisulfide 12* was desulfurized with triphenylphosphine (6). In this case, as in the gliotoxin derivative, predominantly the central sulfur atom (90%) is extruded by the phosphine.[3] In contrast with these results, a complete reversal of reaction pathway was noted with the same trisulfide 12* and tris (diethylamino) phosphine (66). This phosphine removes mainly the terminal sulfur atom (96%). Interestingly, tri-n-butylphosphine



exhibited intermediate behaviour in that it removed significant amounts of both sulfur atom types (terminal, 25%; central, 75%). Thus the mode of desulfurization of dialkyl trisulfides is highly dependent on the type of phosphine used. The radiochemical results are summarized in Table IV. As shown in the table, both triphenylphosphine (6) and tris(diethylamino) phosphine (66) remove only the central sulfur atom of diaryl trisulfides. On the basis of these radiochemical experiments it may be concluded that the desulfurization of diaryl trisulfides by

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[3] The fact that triphenylphosphine (6) attacks and extrudes the central sulfur atom has been used to rationalize the reaction of 6 with the cyclic trisulfide 26 (vide supra).

TABLE IV

RADIOCHEMICAL EXPERIMENTS

$$R_3P + R^1\text{-}S\text{-}^{35}S\text{-}S\text{-}R^1 \rightarrow R^1\text{-}S\text{-}S\text{-}R^1 + R_3P = S$$

R	R^1	Activity (m Ci $mole^{-1}$) R^1SSSR^1	R^1SSR^1	$R_3P = S$
C_6H_5	$C_6H_5CH_2$	0.138	0.014	0.122
Et_2N	$C_6H_5CH_2$	0.138	0.137	0.006
n-Bu	$C_6H_5CH_2$	0.098	0.024	0.071
C_6H_5	p $CH_3C_6H_4$	0.046	< 0.001	0.046
Et_2N	p $CH_3C_6H_4$	0.057	0.002	0.056

$$CH_3-C_6H_4-S-{}^{35}S-S-C_6H_4-CH_3 + R_3P \rightarrow CH_3-C_6H_4-SS-C_6H_4-CH_3 + R_3P={}^{35}S$$

10* 7

6, R = C_6H_5 9*, R = C_6H_5

66, R = NEt_2 67*, R = NEt_2

tris(diethylamino) phosphine (66) and triphenylphosphine (6) proceeds via either of mechanisms A, B or C. The same pathways are possible for the reaction of dialkyl trisulfides with triphenylphosphine. However, since the terminal sulfur atom is extruded, the desulfurization of dialkyl trisulfides with the aminophosphine 66 occurs by one of mechanisms A^1, B^1 or C^1 (Figure 19).

Kinetics of Desulfurization

Information concerning the mechanism of the desulfurization of aromatic and aliphatic trisulfides by tris (diethylamino) phosphine (66) was obtained from a study of the kinetics and energetics of the reaction.

For a mono - or bimolecular reaction (equation 1) the rate of reaction at any given time t is given by

$$wA + xB \longrightarrow yC + zD \qquad \text{eq. 1}$$

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

the expression in equation 2 where k is the kinetic rate constant. The overall reaction order, n, is defined by equation 3.[128]

$$n = w + x \qquad \text{eq. 3}$$

The desulfurization of trisulfides by phosphine 66 was found to be a very rapid reaction whose kinetics were best studied by means of ultraviolet spectroscopy. The uv spectra of most trisulfides exhibit a broad absorption at ca. 255-260 mμ which extends beyond 325 mμ. The ultraviolet maxima could not be used to follow the desulfurization since aminophosphines show a strong end absorption at 270-280 mμ. However, it was possible to monitor the reaction using that part of the trisulfide absorption which extended beyond the cut-off wavelength of the phosphine.

The desulfurization of four aromatic and two aliphatic trisulfides was carried out under pseudo-first order conditions with the aminophosphine 66 as the excess (20-330 fold) reagent. The decrease in absorption at 320 mμ was monitored as a function of time and this data permitted the calculation of the pseudo-first order rate constant (k') by the application of the method of least squares to a plot of ln $\frac{(Ao - A\infty)}{(Ao - At)}$ versus time, t. (eq. 4). The initial concentration of the excess reagent

$$k' = \frac{1}{t} \ln \frac{(Ao - A\infty)}{(At - A\infty)} \qquad \text{eq. 4}$$

$$k_2 = \frac{1}{tCo} \ln \frac{(Ao - A\infty)}{(At - A\infty)} \qquad \text{eq. 5}$$

(Co) was used to determine the true second order rate constant (k_2) via equation 5. Ao, A_t and $A\infty$ are the optical densities at t = 0, t = t and t = ∞ respectively. The actual calculations were done by computer using the program in Appendix I.

The data shown in Table V and plotted in Figure 21 is typical for the desulfurization of trisulfides by aminophosphine 66. The linear plot is indicative of a reaction proceeding under first order conditions. It is deduced that the desulfurization of trisulfides by 66 is first order in trisulfide. By varying the concentrations of tris (diethylamino) phosphine (66) and using the expression in equation 6 the first

$$k = \frac{k'}{(\text{PHOSPHINE})} \qquad \text{eq. 6}$$

order dependence of rate on phosphine concentration was also established. This is illustrated in Table VI. Thus the desulfurization of trisulfides by the aminophosphine 66 is a second order reaction, first order in trisulfide and first order in phosphine.

A summary of the kinetic results obtained in this study may be found in Table VII which includes rate constants at three different temperatures, enthalapy of activation ($\Delta H^{\ddagger}$) and entropy of activation ($\Delta S^{\ddagger}$). The activation parameters were calculated from the rate constants using the computer program in Appendix I. A typical Arrhenius plot is shown in Figure 22 to illustrate the close fit of experimental data to theoretical expressions.

TABLE V

DESULFURIZATION OF DI-N-PROPYL TRISULFIDE (16) BY TRIS(DIETHYLAMINO)PHOSPHINE (66) IN BENZENE AT 40.0°C

TIME (MIN)	$\ln \frac{(Ao - A\infty)}{(At - A\infty)}$
0.0	0.0
2.0	0.1161
4.0	0.2253
6.0	0.3418
8.0	0.4457
10.0	0.5618
12.0	0.6758
14.0	0.7850
16.0	0.9076
18.0	1.0226
20.0	1.1253

TABLE VI

DESULFURIZATION OF DI-N-PROPYL TRISULFIDE (16) BY TRIS(DIETHYLAMINO) PHOSPHINE (66) IN BENZENE AT 40.0°C.

TRISULFIDE	k' (sec^{-1})[a]	[PHOSPHINE] (M)	k ($l\ mole^{-1}\ sec^{-1}$)
$CH_3CH_2CH_2$- (16)	0.93×10^{-3}	0.100	0.93×10^{-2}
	1.27×10^{-3}	0.125	1.01×10^{-2}
	1.55×10^{-3}	0.150	1.03×10^{-2}

[a] Average of two runs; reproducibility ± 5%.

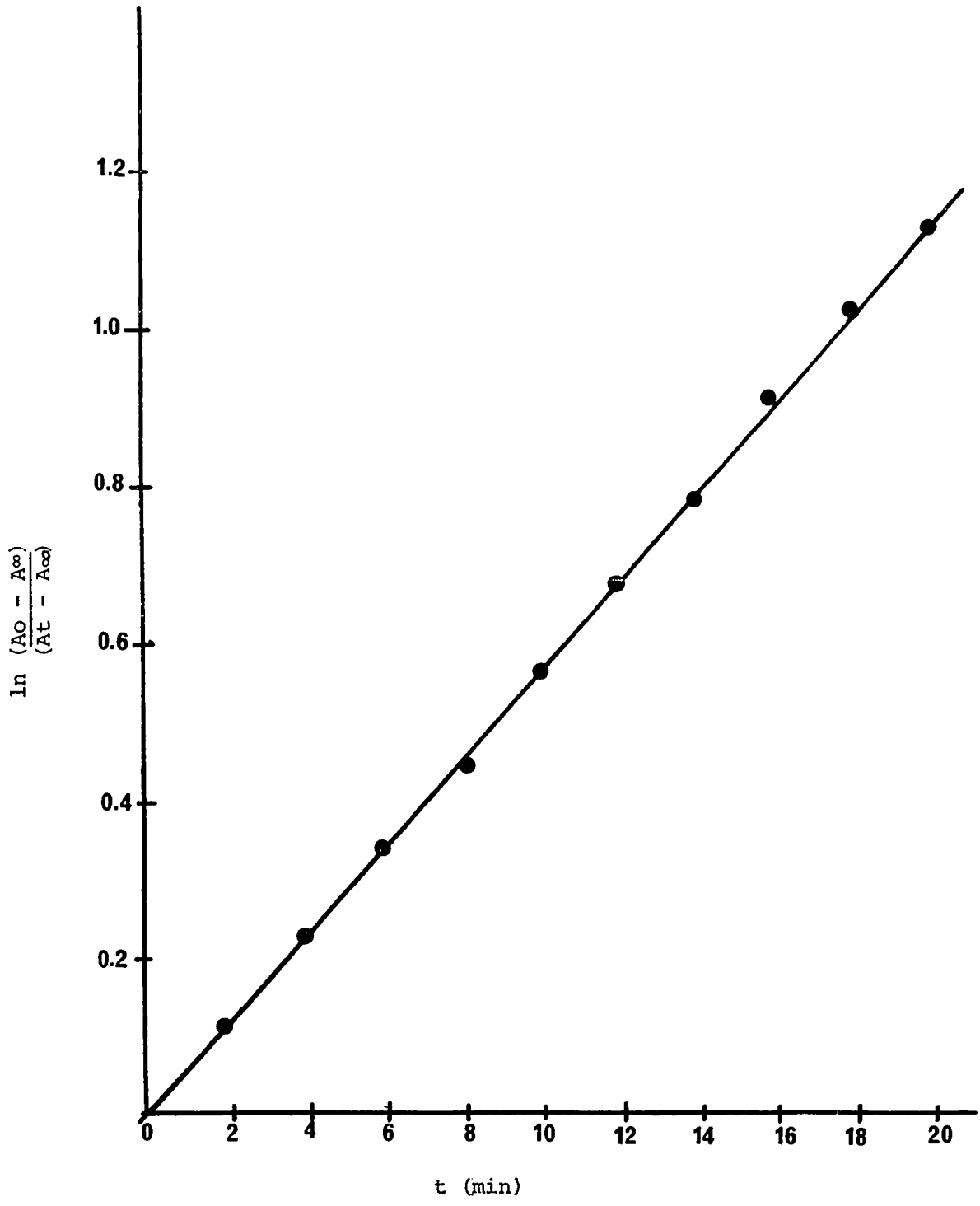


Figure 21. Pseudo first order plot for the desulfurization of di-n-propyl trisulfide (16) by tris (diethylamino) phosphine (66) in benzene at 40.0°C.

TABLE VII

SUMMARY OF KINETIC RESULTS

Tri-sulfide	R	k_2[a] (1 mole^{-1} sec^{-1}) in benzene at 21.0°C	30.0°C	40.0°C	50.0°C	$\Delta H^{\ddagger}$ (k cal mole^{-1})	$\Delta S^{\ddagger}$[b] (eu)
22	$pBrC_6H_4$-	-	$3.2\pm0.01\times10^{-2}$	$4.5\pm0.02\times10^{-2}$	$9.1\pm0.03\times10^{-2}$	9.7±0.9	-24
23	$p(CH_3)_3CC_6H_4$-	-	$4.4\pm0.03\times10^{-3}$	$6.0\pm0.03\times10^{-3}$	$7.4\pm0.04\times10^{-3}$	4.5±0.4	-45
10	$pCH_3C_6H_4$-	-	$5.4\pm0.04\times10^{-3}$	$6.6\pm0.04\times10^{-3}$	$9.6\pm0.04\times10^{-3}$	5.0±0.4	-43
25	$pCH_3OC_6H_4$-	-	$6.4\pm0.04\times10^{-3}$	$6.9\pm0.04\times10^{-3}$	$1.1\pm0.01\times10^{-2}$	4.4±0.9	-44
12	$C_6H_5CH_2$-	$6.8\pm0.03\times10^{-1}$	$7.9\pm0.04\times10^{-1}$	$9.8\pm0.05\times10^{-1}$	-	2.9±0.2	-40
16	$CH_3CH_2CH_2$-	-	$5.9\pm0.05\times10^{-3}$	$9.3\pm0.03\times10^{-3}$	$1.5\pm0.02\times10^{-2}$	8.3±0.1	-32

[a] Average of two runs; errors are standard deviations; reproducibility ± 5%.

[b] Error ± 10%.

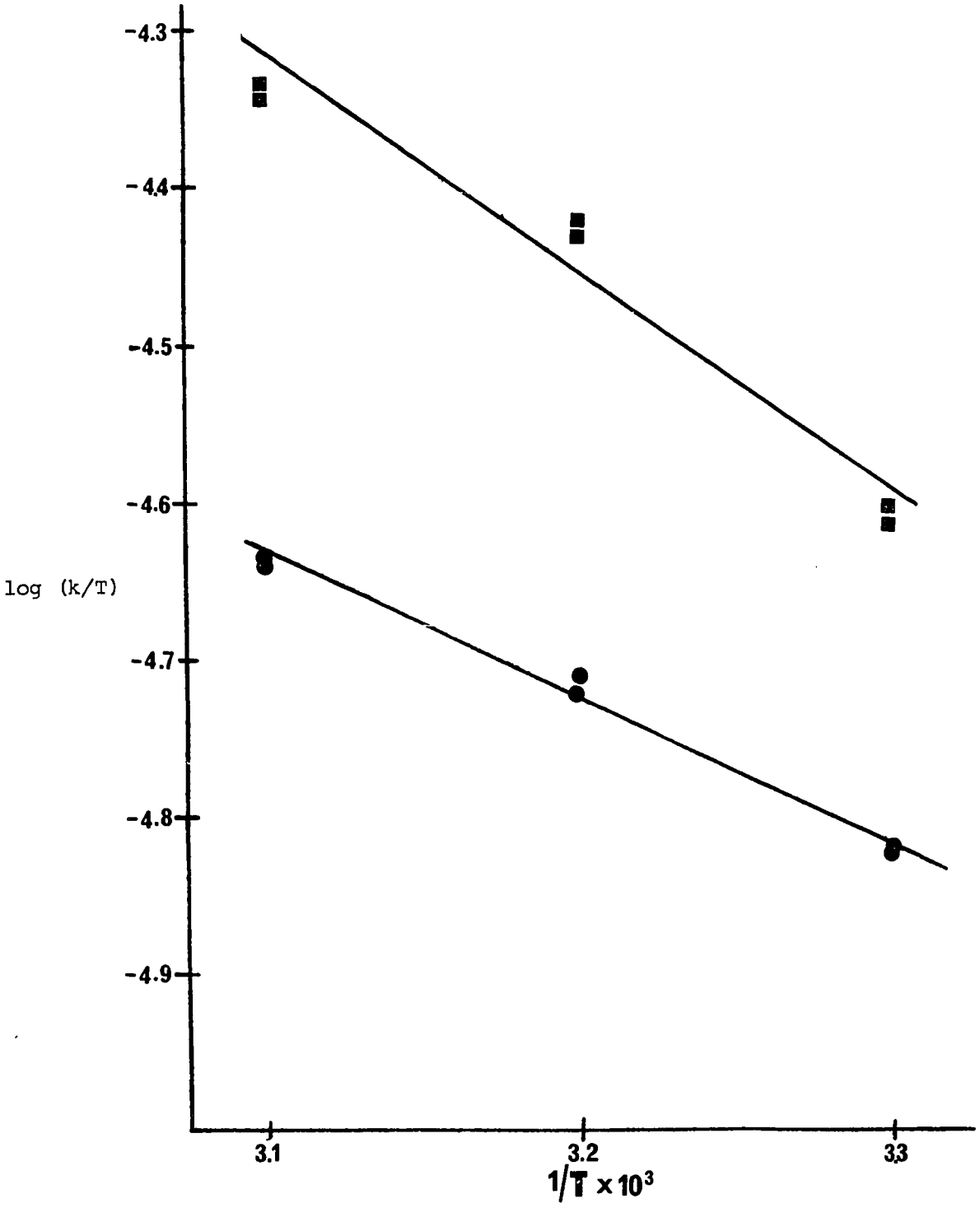


Figure 22. Arrhenius plot for the desulfurizations of di-n-propyl trisulfide (16) (■) and di-t-butyl phenyl trisulfide (23) (●).

The kinetics of the reaction of di-n-propyl trisulfide (16) and di-p-tolyl trisulfide (10) with tris(diethylamino) phosphine (66) were measured in three solvents, cyclohexane, benzene and ethyl acetate to determine if any solvent effect existed. The data is summarized in Table VIII. A plot of the logarithm of the second order rate constant versus

TABLE VIII

SOLVENT EFFECT

Trisulfide	k_2^a ($l\ mole^{-1}\ sec^{-1}$) Solvent at 50.0°C Cyclohexane	Benzene	Ethyl acetate	Relative Ratio
$CH_3CH_2CH_2$- 16	$5.6\pm0.06\times10^{-4}$	$1.5\pm0.02\times10^{-2}$	$3.8\pm0.03\times10^{-2}$	1:27:68
$pCH_3C_6H_4$- 10	$1.3\pm0.03\times10^{-3}$	$9.6\pm0.04\times10^{-3}$	$1.5\pm0.07\times10^{-2}$	1:8:12
ε[b]	2.02	2.24	6.02	
$E_t(30)$[c]	30.9	34.5	38.1	

[a] Average of two runs; errors are standard deviations.

[b] Data from refernece 130.

[c] Data from reference 133.

$E_t(30)$ a solvent polarity parameter[133] is shown in figure 23 for the desulfurization of trisulfides 16 and 10. The shape of this curve is similar to that observed in the desulfurization of aliphatic disulfides by phosphine 66.[44(a)]

Four symmetrically para substituted aromatic trisulfides were desulfurized with phosphine 66 and the rate constants plotted against Hammett's σ values in Figure 24. Since both phenyl rings are equally and equivalently substituted the following expression[129a] (equation 7) may be used where n equals the number of

$$\log \frac{k}{k_o} = n\sigma\rho \qquad \text{eq. 7}$$

substituted rings. A positive rho value of 1.04 was obtained indicating that electron withdrawing groups accelerate the rate of reaction. The correlation coefficient for this relationship between log k and σ was 0.975. The probability of finding a correlation as great as this by chance is less than 3 percent[129b].

Discussion of Kinetic Results

The rationalization of the kinetic and radiochemical results and the discussion of the mechanism of desulfurization will be separated into two parts, aliphatic trisulfides and aromatic trisulfides. As noted earlier, radiochemical experiments have shown that triphenylphosphine (6) removes mostly the central sulfur atom from dibenzyl trisulfide (12) while tris(diethylamino) phosphine (66) extrudes primarily the terminal sulfur.

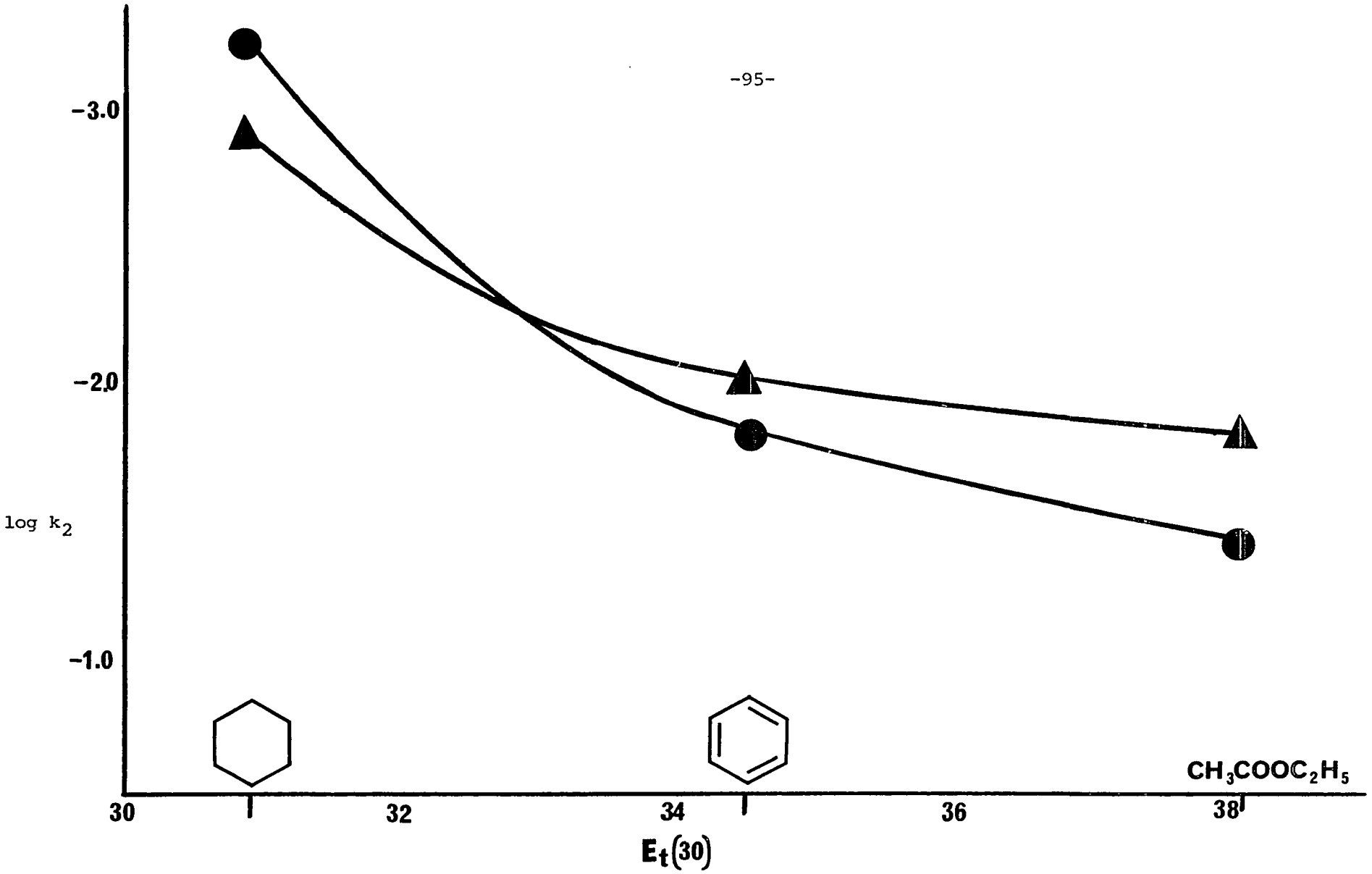


Figure 23. Solvent effect in the desulfurization of di-n-propyl (●) trisulfide (16) and di-p-tolyl (▲) trisulfide (10).

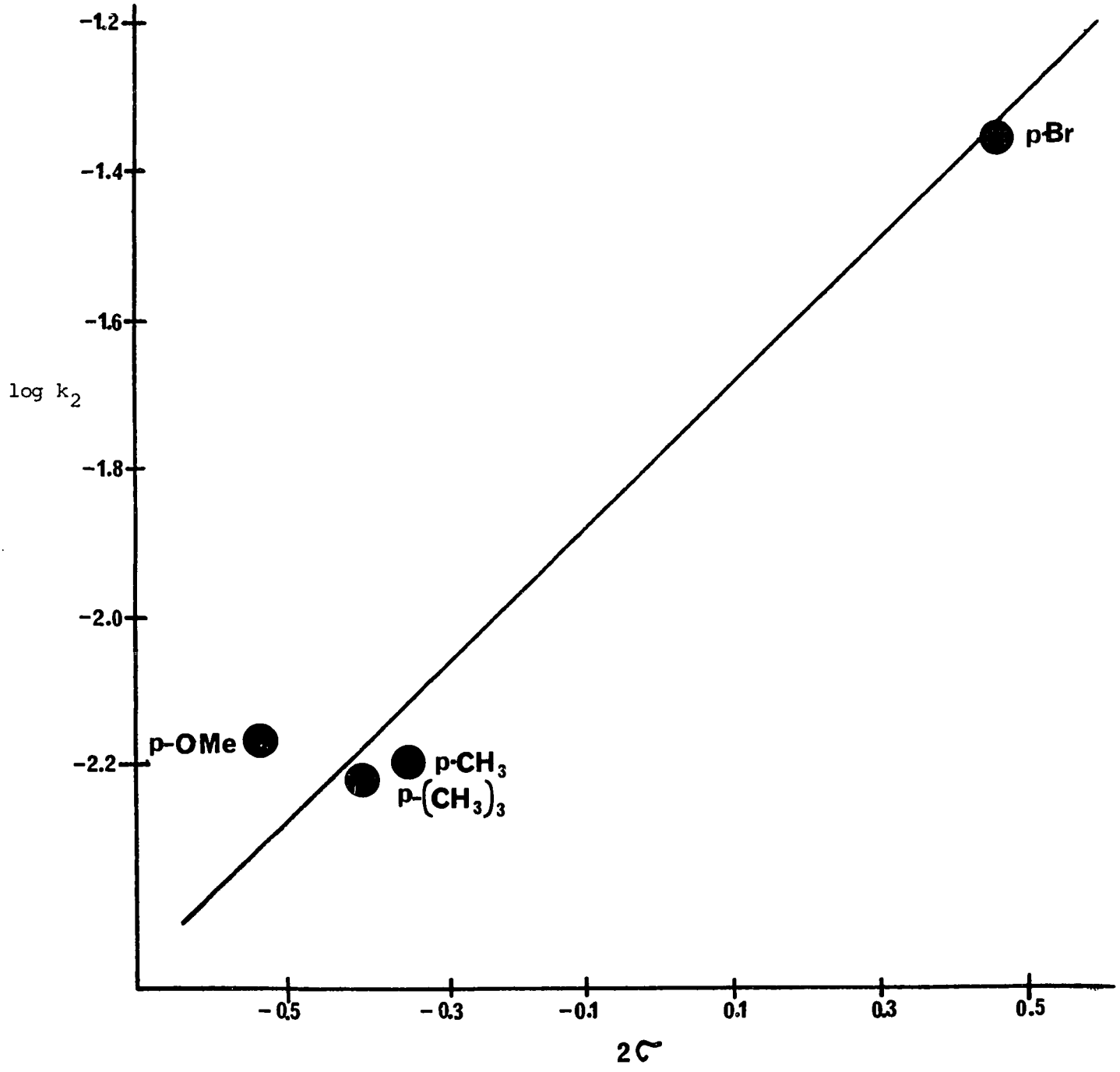


Figure 24. Hammett plot for the desulfurization of aromatic trisulfides by tris (diethylamino) phosphine (66) in benzene at 40.0°C.

Kinetic data have indicated that the desulfurization of aliphatic trisulfides is a second order reaction, first order in trisulfide and aminophosphine 66.

The rate of reaction exhibits a marked dependence on the polarity of the reaction medium. The solvent effect for the desulfurization of di-n-propyl trisulfide (16) is compared with that observed in a number of ionic reactions (Table IX). This comparison illustrates that the solvent effect is of the same order of magnitude as that observed in the reaction of

TABLE IX

COMPARISON OF SOLVENT EFFECTS IN VARIOUS REACTIONS

SOLVENT	ε	Relative rate of reaction: Di-p-tolyl trisulfide (10) +(66)	Di-n-propyl trisulfide (16) +(66)	S_8+Ph_3P (6)[a]	Menschutkin Reaction[b]	Benzyl disulfide (70) +(66)[c]
Hexane	1.89	-	-	-	0.01	-
Cyclohexane	2.02	0.13	0.04	0.01	-	0.03
Benzene	2.28	1.0	1.0	1.0	1.0	1.0
Chlorobenzene	5.62	-	-	2.6	3.5	-
Ethyl acetate	6.02	1.6	2.5	-	-	2.6

[a] Data from reference 116.

[b] Data from reference 131.

[c] Data from reference 132.

an alkyl halide with a tertiary amine (Menschutkin reaction)[131] where nearly 50% ionization has occurred in the transition state[116]. A similar solvent dependence of the reaction rate was noted in the reaction of triphenylphosphine (6) with elemental sulfur and most importantly, the desulfurization of benzyl disulfide (70) with tris(diethylamino) phosphine (66)[132]. The observed solvent effect in the desulfurization of aliphatic trisulfides would suggest that a charged intermediate is being formed before or during the transition state.

The activation parameters for the desulfurization of di-n-propyl (16) and dibenzyl trisulfide (12) by aminophosphine 66 are shown in Table X. The corresponding data for some disulfides is included for comparison. The low values for the enthalpy of activation reflect the facility and the velocity of the reaction of aliphatic trisulfides with tris(diethylamino) phosphine (66). The large negative entropy term suggests the existence of a highly ordered

TABLE X

ACTIVATION PARAMETERS IN BENZENE

COMPOUND	$\Delta H^{\ddagger}$ (kcal mole^{-1})	$\Delta S^{\ddagger}$ (eu)
$C_6H_5CH_2SSSCH_2C_6H_5$ (12)	2.9 ± 0.2	-40
$CH_3CH_2CH_2SSSCH_2CH_2CH_3$ (16)	8.3 ± 0.1	-32
$C_6H_5CH_2SSCH_2C_6H_5$ [a] (70)	13.5	-24
$C_6H_5CH_2SSC_6H_4pCH_3$ [a]	5.4	~35

[a] Data from reference 132.

transition state. It may be noted that the desulfurization of trisulfide 12 exhibits a significantly lower enthalpy and larger negative entropy than the desulfurization of the corresponding disulfide 70.

The following mechanism, consistent with the facts outlined above, is proposed for the desulfurization of aliphatic trisulfides with aminophosphines. This mechanism

$$R\text{-}S\text{-}S\text{-}S\text{-}R + R'_3P \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R\text{-}S\text{-}S^- \quad \begin{matrix} R\text{-}S \\ \\ \end{matrix} \overset{+}{P}\begin{matrix} R' \\ -R' \\ R' \end{matrix} \xrightarrow{k_2} RSSR + R'_3P = S$$

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

$$R' = (CH_3CH_2)_2N\text{-}$$

accounts for the removal of a terminal sulfur atom by the phosphine 66 and the rate expression is in accord with the kinetic results which show the reaction to be first order in each reactant. The rate expression is based on the steady state approximation which is justified on the grounds that no intermediates were detected[128]. The formation of a phosphonium salt intermediate would be a highly ordered process which is consistent with the large negative entropy of activation. The observed solvent effect would require that k_1 be rate limiting. However if k_2 is not very much greater than k_{-1} it should not be neglected in considering the overall rate of the reaction. This is reflected in the observation that the relative rates of reaction are consistent with an S_N2 process as exemplified by the second step in the above mechanism.

As seen in Table XI, the desulfurization of dibenzyl trisulfide (12) proceeds 134 times faster than the desulfurization of di-n-propyl trisulfide (16). For comparison, the relative rates of reaction of

TABLE XI

RELATIVE RATES OF REACTION

ALKYL GROUP	Reaction of trisulfide + (66)[a]	S_N2 reaction of iodide ion with alkyl chloride[b]
CH_3CH_2-	-	2.5
$CH_3CH_2CH_2-$	1.0	-
$CH_3CH_2CH_2CH_2-$	-	1.0
$C_6H_5CH_2-$	134.0	200

[a] in benzene at 30°C.

[b] Data from reference 133.

an alkyl chloride with iodide ion are also tabulated. Since the latter is known to be a bimolecular substitution reaction[133] and the relative rates of reaction are very similar, this data implies that the overall rate for the desulfurization of aliphatic trisulfides by tris (diethylamino) phosphine (66) may well include a substantial contribution from k_2. (i.e. k_1 and k_2 may be comparable in magnitude). The formation of the phosphonium salt is written as a reversible process in accord with the corresponding reaction of disulfides with aminophosphines[134].

The second order rate constants for the desulfurization of several disulfides and trisulfides are shown in Table XII. From these figures it may

TABLE XII

RATES OF DESULFURIZATION OF DISULFIDES AND TRISULFIDES

COMPOUND	k_2 (1 mole^{-1} sec)[a]	RELATIVE RATES RS_3R/RS_2R
$C_6H_5CH_2SSSCH_2C_6H_5$ (12)	$7.9 \pm 0.04 \times 10^{-1}$	1.7×10^4
$C_6H_5CH_2SSCH_2C_6H_5$ (70)[b]	$4.7 \pm 0.2 \times 10^{-5}$	
$CH_3CH_2CH_2SSSCH_2CH_2CH_3$ (16)	$5.9 \pm 0.05 \times 10^{-3}$	3.7×10^6
$(CH_3CH_2CH_2CH_2CH_2S)_2$	$1.6 \pm 1.0 \times 10^{-9}$	

[a] In benzene at 30°.

[b] Data from reference 132.

be seen that the desulfurization of aliphatic trisulfides by tris(diethylamino) phosphine (66) proceeds at a rate 10^4 to 10^6 times that of the corresponding disulfides. This contrasts with the findings of Moore and Trego[26] who reported that triphenylphosphine (6) desulfurizes dialkenyl disulfides at a faster rate than the corresponding trisulfides.

This large difference in reaction velocity may be explained by the fact that there are factors in the trisulfide desulfurization which tend to increase both k_1 and k_2 relative to their values in the disulfide desulfurization. The hydrodisulfide ion (RSS^-) is expected to be a better leaving group than the mercaptide ion (RS^-) as it could presumably be resonance stabilized[35]. This would make k_1 larger. The enhanced nucleophilicity of the hydrodisulfide ion due to the α - effect[135, 136]. would show up as a larger value of k_2. Hudson[135] has stated that "a positive α - effect is produced by a decrease in the overlap integral of orbitals containing lone pairs of electrons in the course of a chemical reaction. Enhanced reactivities should be observed in the reaction of nucleophiles such as ROO^-, ClO^- and RSS^- with all types of electrophiles."

An estimate of the pKa of benzyl and propyl hydrodisulfide may be made by consideration of the following data. Gleason and Harpp[44(a)] found a linear relationship (figure 25) between the pKa of the displaced mercaptide and the logarithm of the second order rate constant for the reaction of disulfides with tris(diethylamino) phosphine. From this plot and the second order rate constants for the desulfurization of dibenzyl (12) and di-n-propyl trisulfides (16) at 30°C the pKa of benzyl hydrodisulfide is estimated to be 8.7 while that of the propyl derivative is 10.3. Thus the hydrodisulfides appear to differ from the corresponding mercaptans[44(a)] by approximately 2-3 pKa units.

One possible explanation for the dichotomy of behaviour exhibited by triphenylphosphine (6) and tris(diethylamino) phosphine (66) towards aliphatic trisulfides involves the hard soft acid base theory of Pearson[134(b)].

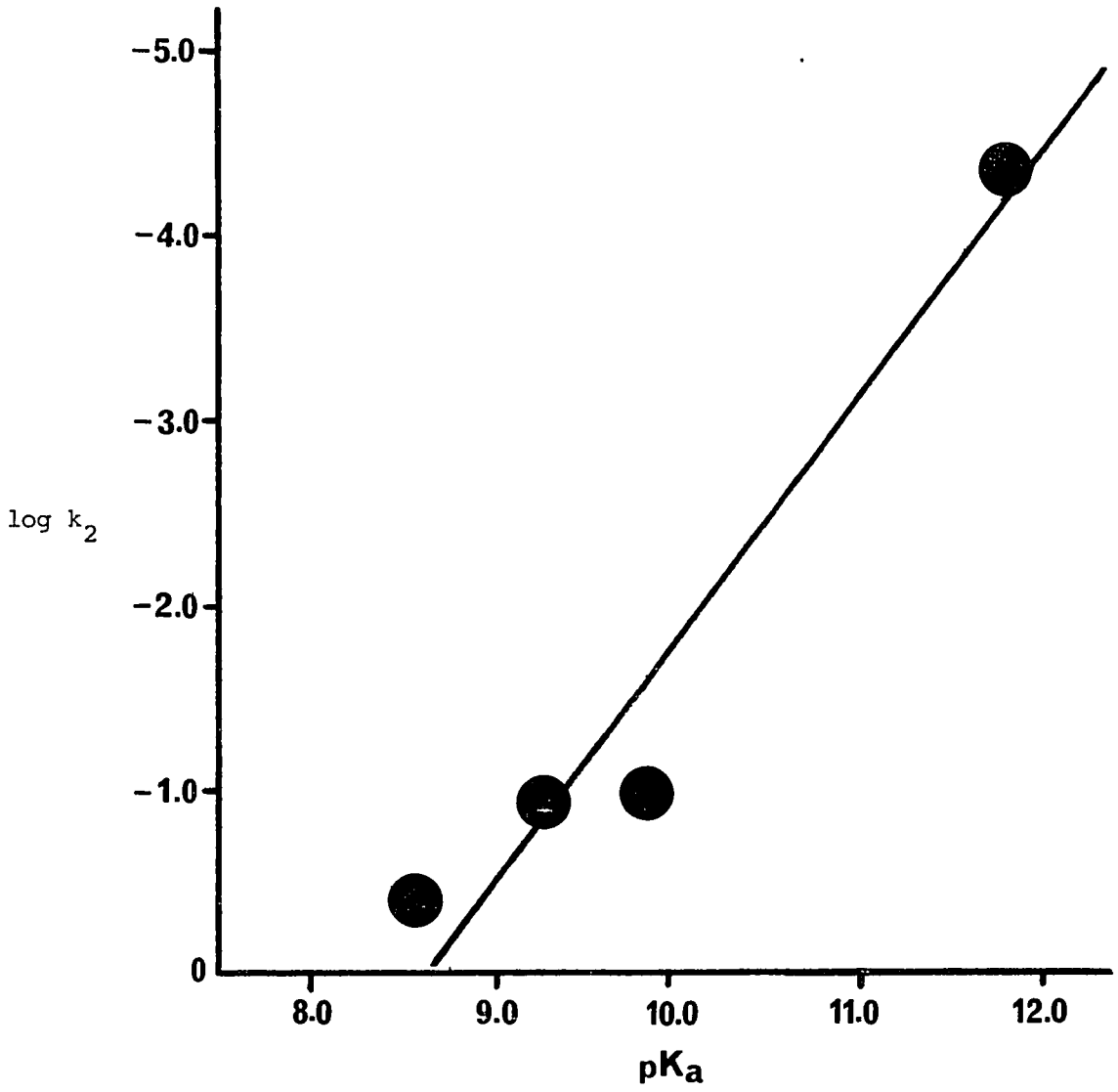
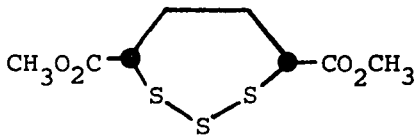


Figure 25. A plot of pKa of the displaced mercaptide versus the logarithm of the second order rate constant for the desulfurization of disulfides by (66).

Simply stated, the HSAB theory proposes that hard acids interact better with hard bases than with soft bases. The same is true for the affinity of soft acids for soft bases. Pearson[134(b)] found that triphenylphosphine (6) reacted ca. 25,000 times as fast as aminophosphine 66 in a nucleophilic substitution on a Pt (II) center, a soft substrate. From this data[1] it is deduced that phosphine 6 is a softer base than phosphine 66. Since, in the desulfurization reaction, the softer phosphine attacks the central sulfur atom preferentially it is reasonable to extrapolate that sulfur bonded to other sulfur atoms is softer than sulfur which has one carbon substituent.

In order to obtain a substrate with which to probe the propensity of a series of phosphines to attack the central or terminal sulfur of a trisulfide, efforts were directed towards a synthesis of trisulfide 33 (vide supra). The reaction of a phosphine with



33

cis - 4, 7 - dimethoxycarbonyl - 1, 2, 3 - trithiepane (33) would yield the corresponding disulfide.

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[1] From the large summary of rate data compiled by Pearson[134(b)] the relative degree of softness of triphenylphosphine (6) and tris (diethylamino) phosphine (66) may be in question. The experiments outlined here may clarify this point.

Attack on the central sulfur atom would not involve any change in stereochemistry at the carbon center. However, attack and extrusion of a terminal sulfur by the phosphine would result in inversion at one of the α carbon atoms[44(a)]. Thus the ratio of cis/trans disulfide would reflect the ratio of attack on central versus terminal sulfur. With a range of phosphines the product distribution might be correlated with phosphine softness. This is an area which may be of interest for future work.

Aromatic Trisulfides

Fehér and Kurz[56] have studied the kinetics of the desulfurization of a series of para substituted aromatic trisulfides by triphenylphosphine (6). The reaction was found to be irreversible and quantitative. The solvent used as the reaction medium had to be dry to avoid the formation of thiol. Although not mentioned by the authors, this indicated the presence of mercaptide ion. The progress of the reaction was followed by monitoring the dielectric constant of the solution. Fehér and Kurz found that the reaction was second order, first order in trisulfide and triphenylphosphine (6), at least until it was 60 percent complete. Their results are summarized in Table XIII. The authors stated that the reaction was accelerated by electron withdrawing groups and that electron donating groups stabilize the trisulfide against attack by the phosphine. The desulfurization is characterized by relatively low enthalpies of activation and large negative entropies of activation. From a

TABLE XIII[a]

DESULFURIZATION OF AROMATIC TRISULFIDES WITH TRIPHENYLPHOSPHINE

p-substituent	k (l mole^{-1} sec^{-1})[b]	$\Delta H^{\ddagger}$ (kcal mole^{-1})	$\Delta S^{\ddagger}$ (eu)
NO_2-	4.39×10^{-2}	6.2	-47
C_2H_5-O-CO-	2.33×10^{-2}	8.1	-42
CH_3-CO-	1.91×10^{-2}	8.4	-42
Br-	6.95×10^{-3}	11.4	-34
t-Butyl-	1.84×10^{-3}	11.1	-38
CH_3-S-	1.78×10^{-3}	10.6	-39
H-	1.83×10^{-3}	10.3	-40
CH_3-	1.25×10^{-3}	11.7	-38
CH_3O-	6.56×10^{-4}	11.4	-38
NH_2-	7.28×10^{-5}	20.3	-15

[a] Data from reference 56.

[b] In toluene at 40°C.

plot of log k versus twice the Hammett substituent constant σ, a value for rho of + 0.98 was obtained. Fehér and Kurz did not comment on a possible mechanism for this desulfurization process.

As our radiochemical experiments (vide supra) had shown that triphenylphosphine (6) and tris(diethylamino) phosphine (66) exhibit a dichotomy of behaviour towards aliphatic trisulfides it was felt that

this difference might possibly extend to their reaction with aromatic trisulfides. As discussed earlier it was found that both phosphines remove the central sulfur atom from aromatic trisulfides. Kinetic studies of the desulfurization of aromatic trisulfides (vide supra) with tris(diethylamino) phosphine (66) have shown the reaction to be second order overall, first order in each reactant. As noted in Table IX the desulfurization of di-p-tolyl trisulfide (10) exhibits a positive solvent effect which is somewhat smaller than that shown by aliphatic trisulfides. The activation parameters for the reaction of phosphine 66 with aromatic trisulfides are summarized in Table XIV. The low values for the enthalpy of activation reflect the facility and velocity of the reaction while the large negative entropies suggest the existence of a highly ordered transition state. The plot of reaction rate versus 2σ yields a rho value of + 1.04 (Figure 24).

TABLE XIV

DESULFURIZATION OF AROMATIC TRISULFIDES WITH (66)

p-substituent		k^a (1 mole^{-1} sec^{-1})	$\Delta H^{\ddagger}$ (kcal mole^{-1})	$\Delta S^{\ddagger}$ (eu)
Br-	(22)	4.5×10^{-2}	9.7	-24
CH_3-	(10)	6.6×10^{-3}	5.0	-43
$(CH_3)_3C$-	(23)	6.0×10^{-3}	4.5	-45
CH_3O-	(25)	6.9×10^{-3}	4.4	-44

[a] In benzene at 40°C.

The following mechanism, consistent with the facts outlined above, is proposed for the desulfurization of aromatic trisulfides with tris(diethylamino) phosphine (66).

$$R\text{-}S\text{-}S\text{-}S\text{-}R + R'_3P \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R\text{-}S^- \quad R\text{-}S\text{-}S\text{-}\overset{+}{P}(R')_3 \xrightarrow{k_2} RSSR + R'_3P = S$$

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

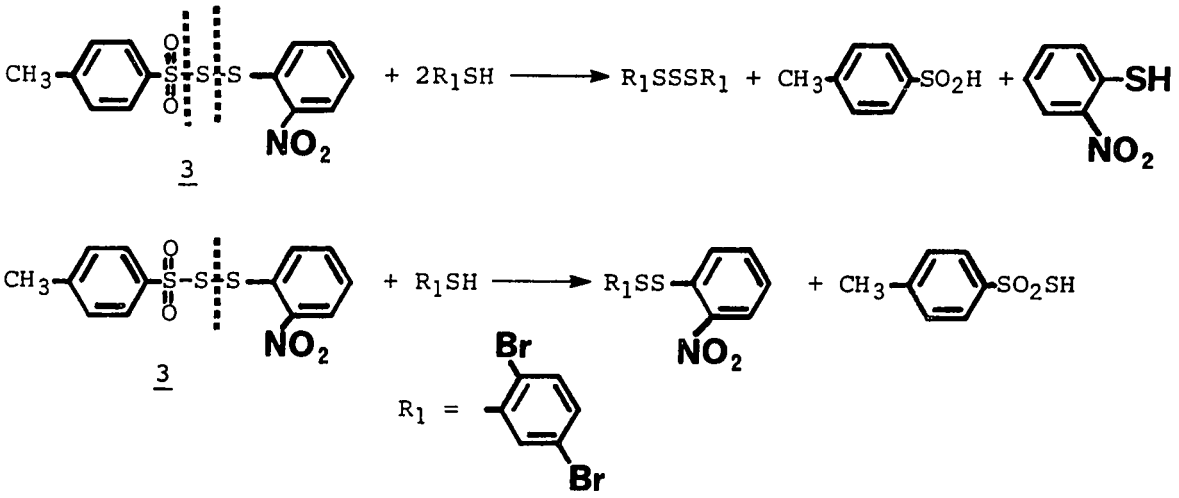
$$R' = (CH_3CH_2)_2N-$$

This mechanism accounts for the extrusion of the central sulfur atom by the phosphine 66 and the rate expression is in accord with the kinetic results which show the reaction to be first order in trisulfide and first order in phosphine. The rate expression is based on the steady state approximation which is justified as no intermediates were detected[128]. The formation of a phosphonium salt as the highly ordered transition state explains the large negative entropy of activation. Salt formation is written as a reversible step as this has been shown to be the case in the analogous disulfide reaction[134]. The solvent effect requires that k_1 be rate limiting. This is confirmed by an examination of how the para substituents affect the rate of reaction. Electron withdrawing groups would stabilize the displaced mercaptide and so increase k_1 while decreasing k_{-1} and k_2. Experimentally, electron withdrawing substituents accelerate the rate of reaction so k_1 must be rate limiting.

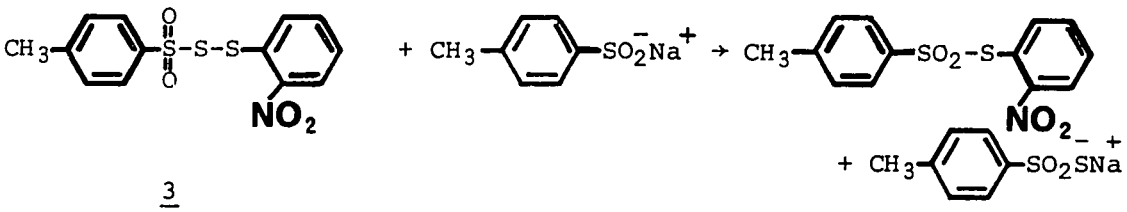
From a comparison of the rates of reaction in Table XIII and Table XIV it may be seen that tris(diethylamino) phosphine (66) desulfurizes aromatic trisulfides at 5-10 times the rate found for triphenylphosphine (6).

The Chemistry of Sulfenic Sulfonic Thioanhydrides

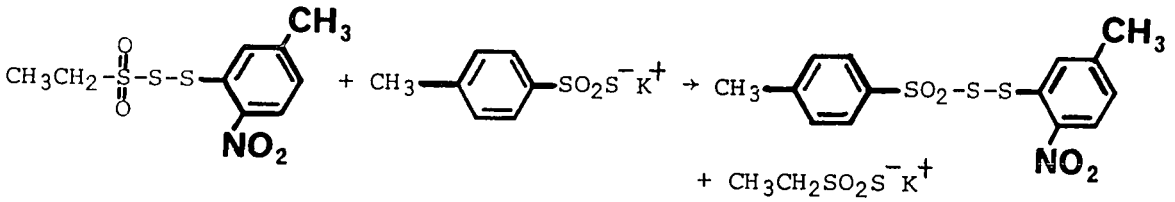
Although sulfenic sulfonic thioanhydrides (sulfenyl thiosulfonates) have been known since 1927[88], the chemistry of this class of compound has received little study. Smiles and co-workers[88(a)] investigated the cleavage of sulfenic sulfonic thioanhydrides with thiols and alkoxides. An example of the former is the reaction of 2-nitrobenzenesulfenic p-toluenesulfonic thioanhydride (3) with 2,5-dibromobenzenethiol to produce di-2,5-dibromophenyl trisulfide and 2,5-dibromophenyl 2-nitrophenyl disulfide.



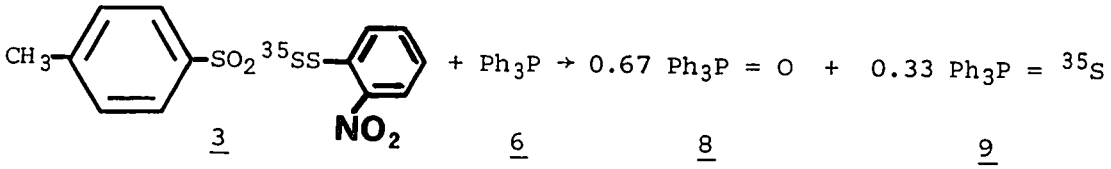
The modes of fission were postulated as occurring as illustrated above but the authors did not state the yields of products obtained and the predominant pathway remains undetermined. Loudon and Livingston[137] reported that the p-toluenethiosulfonate group of 3 was displaced by p-toluenesulfinate



ion and Foss[88(b)] has noted that potassium p-toluenethiosulfonate is capable of displacing the ethanethiosulfonate moiety from 2-nitro-5-methylbenzenesulfenic ethanesulfonic thioanhydride.



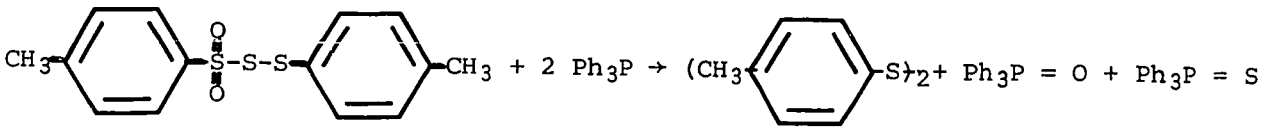
Tsurugi and co-workers[88(d)] have observed that the interaction of 2-nitrobenzenesulfenic p-toluenesulfonic thioanhydride (3) with equimolar triphenylphosphine (6) produces 0.67 equivalents of triphenylphosphine



3 6 8 9

oxide (8) and 0.33 equivalents of triphenylphosphine sulfide (9). A radiochemical experiment determined that the central sulfur atom of 3 was desulfurized by the phosphine 6. The fate of the thioanhydride 3 was not determined.

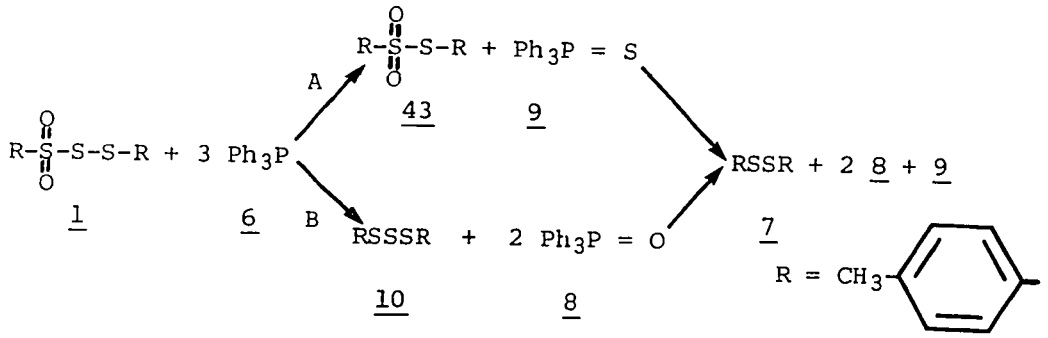
As discussed earlier (p. 28) the reaction of p-toluenesulfenic p-toluenesulfonic thioanhydride (1) with two molar equivalents of



1 6 7 8 9

triphenylphosphine (6) produced di-p-tolyl disulfide (7). To clarify why

this interaction produced disulfide, rather than the expected trisulfide, an investigation of the effect of various stoichiometric ratios of triphenylphosphine (6) on thioanhydride 1 was undertaken.[4] The reaction of three molar equivalents of 6 with 1 gave a 68% yield of di-p-tolyl



disulfide (7) along with phosphine oxide 8 and phosphine sulfide 9. The formation of disulfide may be rationalized in terms of two alternate pathways. Deoxygenation (path B) of 1 would afford the trisulfide 10 which is known[56] to undergo rapid desulfurization to the disulfide 7. Alternately, desulfurization of the sulfenic sulfonic thioanhydride 1 prior to deoxygenation (path A) would also yield 7. When the reaction was performed with one molar equivalent of triphenylphosphine (6), an 81% yield of p-tolyl p-toluenethiosulfonate (43) was realized. No trisulfide was observed. Thus, the reaction of p-toluenesulfenic p-toluenesulfonic thioanhydride (1) with triphenylphosphine (6) proceeds via thiosulfonate 43 as outlined in path A.

The behavior of thioanhydrides towards tris(diethylamino)phosphine (66) was also examined. The reaction of p-toluenesulfenic p-toluenesulfonic thioanhydride (1) with aminophosphine 66 afforded three products;

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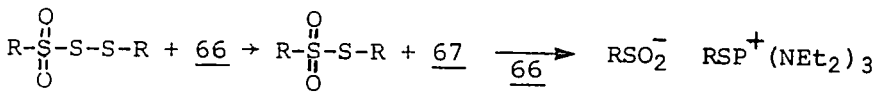
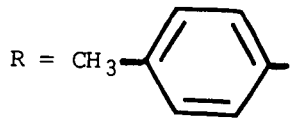
[4] This work has been published: D.N. Harpp, J.G. Gleason and D.K. Ash, J. Org. Chem., 36, 322 (1971).

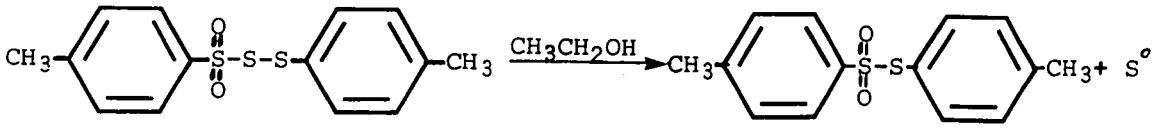


1 43, 40% 87, 60%



p-tolyl p-toluenethiosulfonate (43), phosphonium salt 87, and phosphine sulfide 67. The structure of the phosphonium salt 87 was assigned by its proton nmr which was identical to that obtained in the reaction of 43 with 66 [138].

The interactions described above relate to the desulfurization of sulfenic sulfonic thioanhydrides by trivalent phosphorous compounds. In addition, it was found that p-toluenesulfenic p-toluenesulfonic thioanhydride (1) extruded sulfur in the presence of certain solvents producing



1 43

p-tolyl p-toluenethiosulfonate (43). A summary of the reaction conditions are found in Table XV. This table also summarizes the polarity parameters of the solvent systems used. Although the extrusion of sulfur from certain molecules is known [139], the desulfurization of 1 to 43 is remarkably facile.

The loss of a sulfur atom by α,α'-dithiobisformamidines on treatment with absolute ethanol has been reported [140].

TABLE XV

Sulfur Extrusion from p-Toluenesulfenic p-Toluenesulfonic Thioanhydride (1)

Solvent	Reaction[a]	Dielectric[b] Constant, ε	Z-value[c]	E_T (30)[d] value
Ethanol, absolute	+	24.3	79.6	51.9
Methanol	+	32.6	83.6	55.5
Isopropanol	+	18.3	76.3	48.6
Acetic acid, glacial	+	6.15	79.2	
Silica gel[e]	+		88.	
Dimethyl formamide	+	37.0	68.5	43.8
Dimethyl formamide[f]	+	37.0	68.5	43.8
Acetonitrile	+	36.2	71.3	46.0
Acetone: water (1:1)	+		85.5	
Acetonitrile[g]	+			
Acetonitrile[h]	+			
Benzene	-	2.28	54	34.5
Benzene, refluxing	-	2.28	54	34.5
Diethyl ether	-	4.33		34.6
Diethyl ether, refluxing	-	4.33		34.6
Acetonitrile[i]	-	36.2	71.3	46.0
Ethyl acetate	-	6.02		38.1
Chloroform	-	4.80	63.2	
Tetrahydrofuran	-	2.95		37.4
Acetone	-	20.7	65.7	42.2
Ether, wet	-			
0.012 M HCl in ether	-			
0.12 M HCl in ether	-			

a) At room temperature unless otherwise indicated; +, reaction proceeds to afford 43; -, starting material recovered.

b) Reference 133, p.269.

c) Reference 133, p.301.

d) Reference 133, p.305.

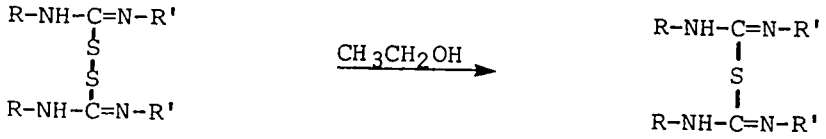
e) Passed through a silica gel column with hexane-chloroform eluant.

f) Distilled from BaO and giving a negative $Ti(iPrO)_4$ test for water.

g) Containing 5 drops of conc.HCl.

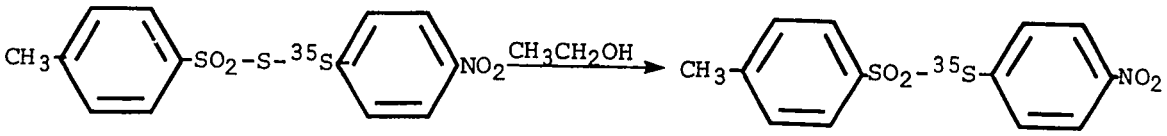
h) Containing 5% diethylamine.

i) Distilled from P_2O_5 and giving a negative $Ti(iPrO)_4$ test for water.



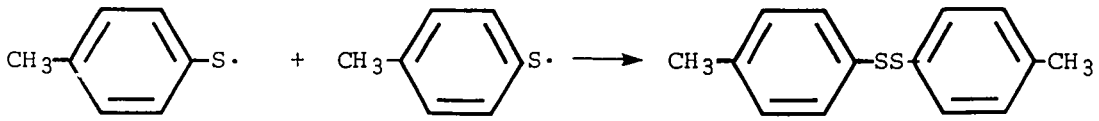
Recently, the extrusion of sulfur from aminothiosulfonates has been observed.[141] This reaction occurs slowly at room temperature and rapidly at boiling temperatures in polar solvents such as acetone, methanol

and 2-propanol to give the corresponding sulfonmorpholides. The decomposition of p-nitrobenzenesulfenic p-toluenesulfonic thioanhydride to the corresponding thiosulfonate on repeated crystallizations from ethanol has been reported.[88(d)] It was shown radiochemically that the central sulfur atom is lost during this conversion.



Some of the possible mechanistic pathways for the loss of sulfur by p-toluenesulfenic p-toluenesulfonic thioanhydride (1) are outlined in Figure 26. Mechanism A, which proceeds via free radicals, appears unlikely as the desulfurization process is unaffected by the application of heat. Starting material is recovered from benzene solution both at room temperature and at reflux. Furthermore, in cases where the desulfurization proceeds, the only product is p-tolyl p-toluenethiosulfonate (43) and no trace of di-p-tolyl disulfide (7) was observed. Two p-tolylthio radicals,

if formed, would be expected to combine to produce disulfide 7.



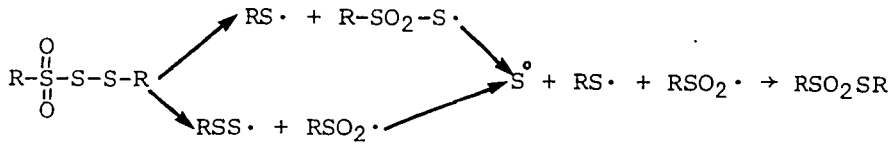
7

Mechanism B appears plausible as the thiosulfonate ion is thought to be in equilibrium with sulfur and the sulfinate ion.[142, 143]

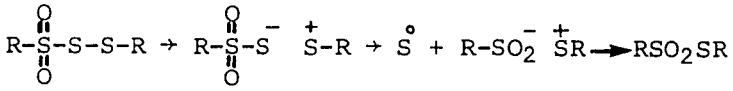
In order to distinguish between mechanism B, which is intermolecular, and mechanism C, which is intramolecular, a crossover experiment between unlabelled and deuterium labelled p-toluenesulfenic p-toluenesulfonic thioanhydride (1) was performed. The requisite thioanhydride-d_2 [93] was synthesized from α-chlorotoluene, by classical means, via the sequence outlined in Figure 27.

For the crossover experiment, equimolar amounts of p-toluenesulfenic p-toluenesulfonic thioanhydride (1) and p-toluenesulfenic p-toluenesulfonic thioanhydride - α, α' - d_2 (93) were stirred in ethanol for 24 hours to effect desulfurization. The product thiosulfonate was isolated and submitted to mass spectral analysis to determine the extent to which crossover had occurred. Table XVb summarizes the ratio of the P, P + 1 and P + 2 peaks in the mass spectra of p-tolyl p-toluenethiosulfonate (43), p-tolyl p-toluenethiosulfonate - α, α' - d_2 (43d) and the crossover reaction product. As seen from the data in Table XVb the product of the reaction exhibits a mass spectrum (spectrum 3) very different to that expected from a 1:1 mixture of d_o and d_2 thiosulfonates (spectrum 5). However, the theoretical mass

Mechanism A



Mechanism B



Mechanism C

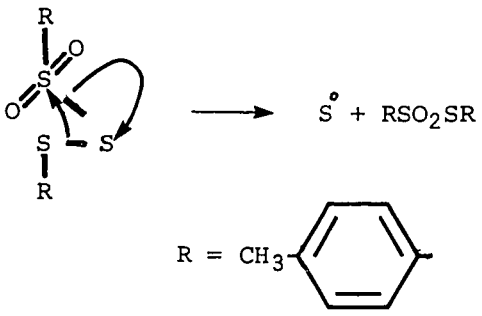


Figure 26 . Possible mechanisms for sulfur extrusion from p-toluenesulfenic p-toluenesulfonic thioanhydride (1).

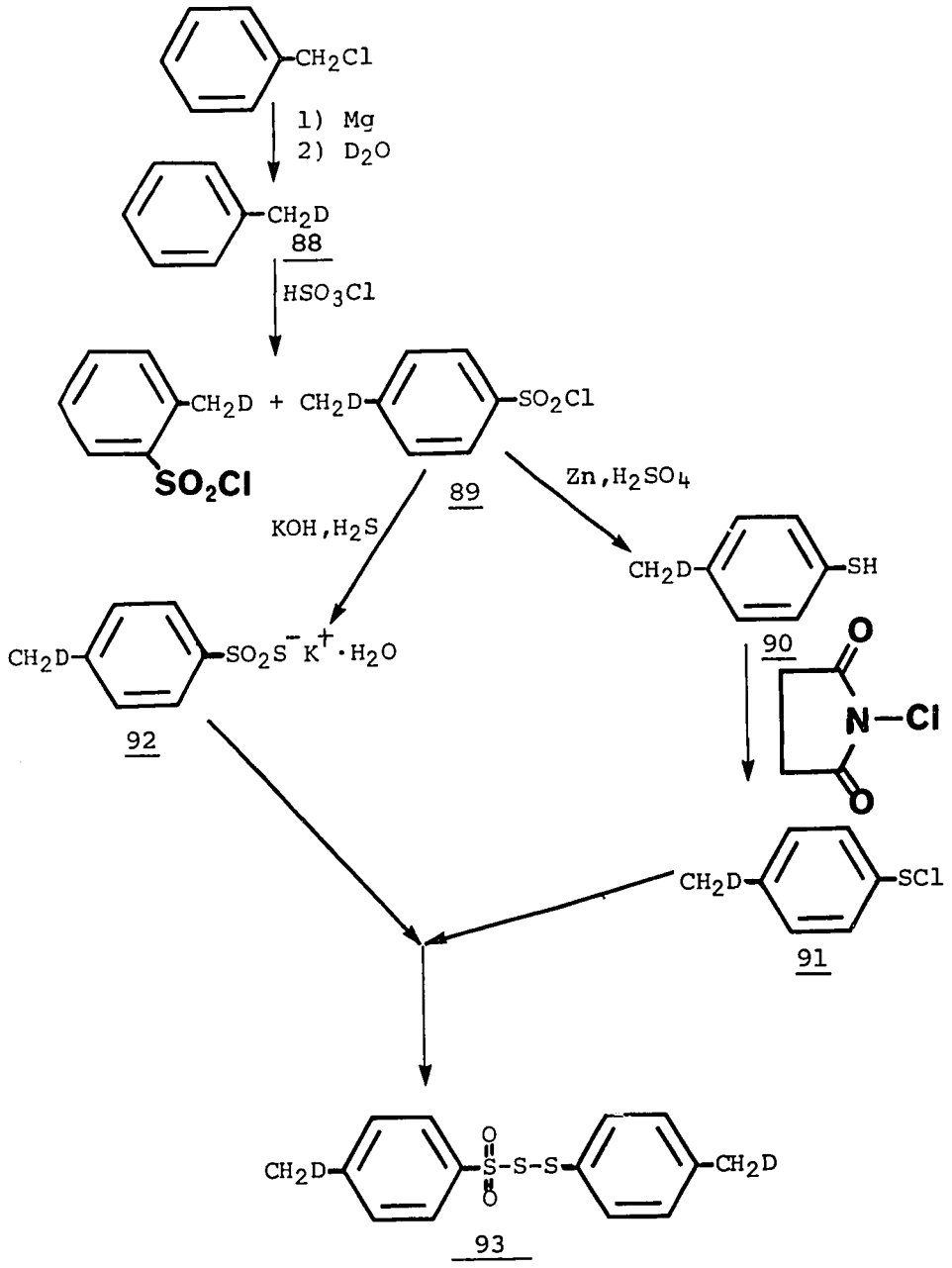


Figure 27. Synthetic route to p-toluenesulfenic p-toluenesulfonic thioanhydride-α,α'-d_2 (93).

spectrum of a 1:2:1 mixture of d_o:d_1:d_2 thiosulfonates (spectrum 6) very closely approximates that of the reaction product indicating that crossover occurred during the desulfurization. This would suggest that the solvolytic desulfurization of sulfenic sulfonic thioanhydride 1 is an intermolecular reaction. However, a 1:1 mixture of 43 and 43d (either finely powdered to give an intimate mixture or equimolar amounts recrystallized together) also exhibits a mass spectrum (spectrum 4) indicative of crossover.

Thus, it is difficult to understand the origins of this crossover phenomenon. It is hard to rationalize ligand exchange by the process of grinding the crystals. Thermal rearrangement in the spectrometer probe seems unlikely (spectra obtained at 40°) as aryl thiosulfonates are thermally stable up to 80°. Further, crossover phenomena of this type after electron bombardment in the spectrometer are quite unexpected in terms of the very low pressure employed (10^{-6} Torr). These experiments therefore are not conclusive in determining whether the crossover occurred during the desulfurization reaction or mass spectral analysis.

TABLE XVb

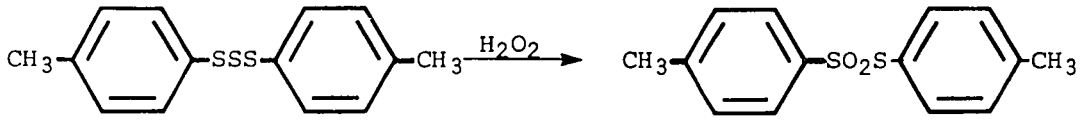
MASS SPECTRA OF THIOSULFONATES

Spectrum	Compound	Relative ratio of peak heights 278(d_o)	279(d_1)	280(d_2)	281	282
1	p-$CH_3C_6H_4SO_2SC_6H_4$ p-CH_3 (43)	1.00	0.36	0.24	0.08	-
2	p-$CH_2DC_6H_4SO_2SC_6H_4$ p CH_2D (43d)	-	0.08	1.00	0.17	0.12
3	crossover reaction product	0.52	1.00	0.64	0.20	0.08
4	1:1 mixture of (43) and (43d)	0.64	1.00	0.79	0.22	0.08
5	theoretical 1:1 mixture of (43) and (43d)[a]	0.50	0.22	0.62	0.12	0.06
6	Theoretical (if crossover occurred)[b]	0.48	1.00	0.65	0.20	0.12

[a] Calculated by adding one-half the intensities of 43 to one-half the intensities of 43d.

[b] Calculated by adding one-quarter the intensities of 43 and one-quarter the intensities of 43d to one-half the intensities of the d_1 compound.

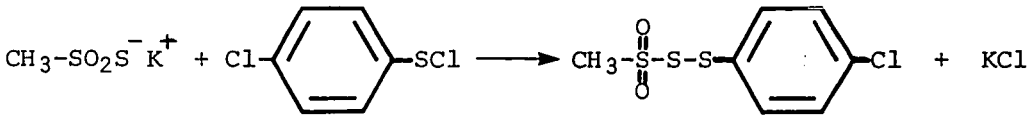
The facile loss of a sulfur atom by p-toluenesulfenic p-toluenesulfonic thioanhydride (1) offers an explanation for the difficulties encountered in the attempted preparation of some other members of this class of compound[88(d)]. For example, the oxidation of di-p-tolyl trisulfide (10) with hydrogen peroxide provided a 40% yield of thiosulfonate 43



10 43

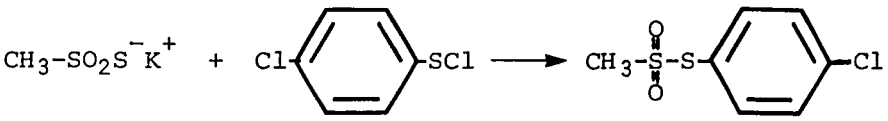
which likely arose via the desulfurization of the initial product, 1, under the reaction conditions.

The reaction of potassium methanethiosulfonate with p-chlorobenzenesulfenyl chloride gave p-chlorobenzenesulfenic methanesulfonic



94

thioanhydride (94) as a crystalline compound whose spectral characteristics were in accord with the assigned structure. During the preparation of an analytical sample, via recrystallization, 94 decomposed. The reaction was repeated twice and in both cases the only product isolated



95

was p-chlorophenyl methanethiosulfonate (95). The attempted preparation of several sulfenic sulfonic thioanhydrides by the interaction of potassium

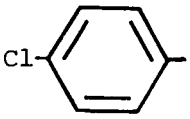
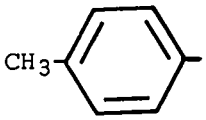
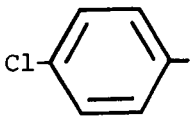
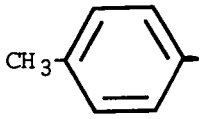
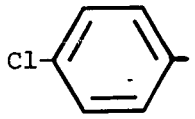
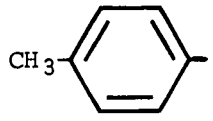
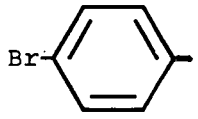
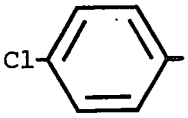
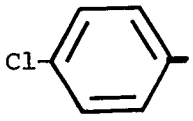
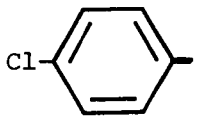
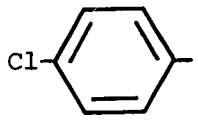
$$RSO_2S^-K^+ + R'SCl \longrightarrow R\text{-}SO_2S\text{-}R'$$

thiosulfonates with sulfenyl chlorides also led to the formation of thiosulfonates. The results are summarized in Table XVI. The mass spectral fragmentation of some of these thiosulfonates is summarized in figures 28-33.

TABLE XVI

REACTION OF POTASSIUM THIOSULFONATES WITH SULFENYL CHLORIDES

$$RSO_2S^-K^+ + R'SCl \longrightarrow RSO_2SR' + KCl$$

R	R'	RSO_2SR' % Yield	Compound #
CH_3-		77	95
		48	96
	CH_3-	48	97
$C_6H_5CH_2$-		87	98
		23	99
	C_6H_5-	36	100
		69	101
C_6H_5-		28	102

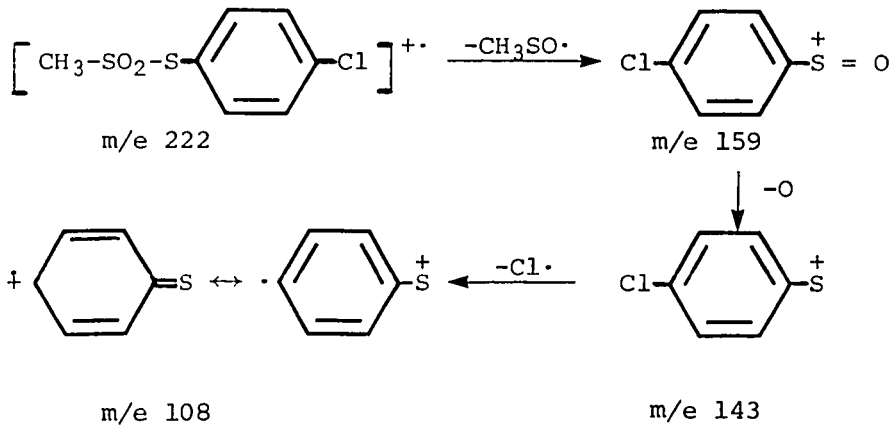


Figure 28. Mass spectral fragmentation pattern of p-chlorophenyl methanethiosulfonate (95).

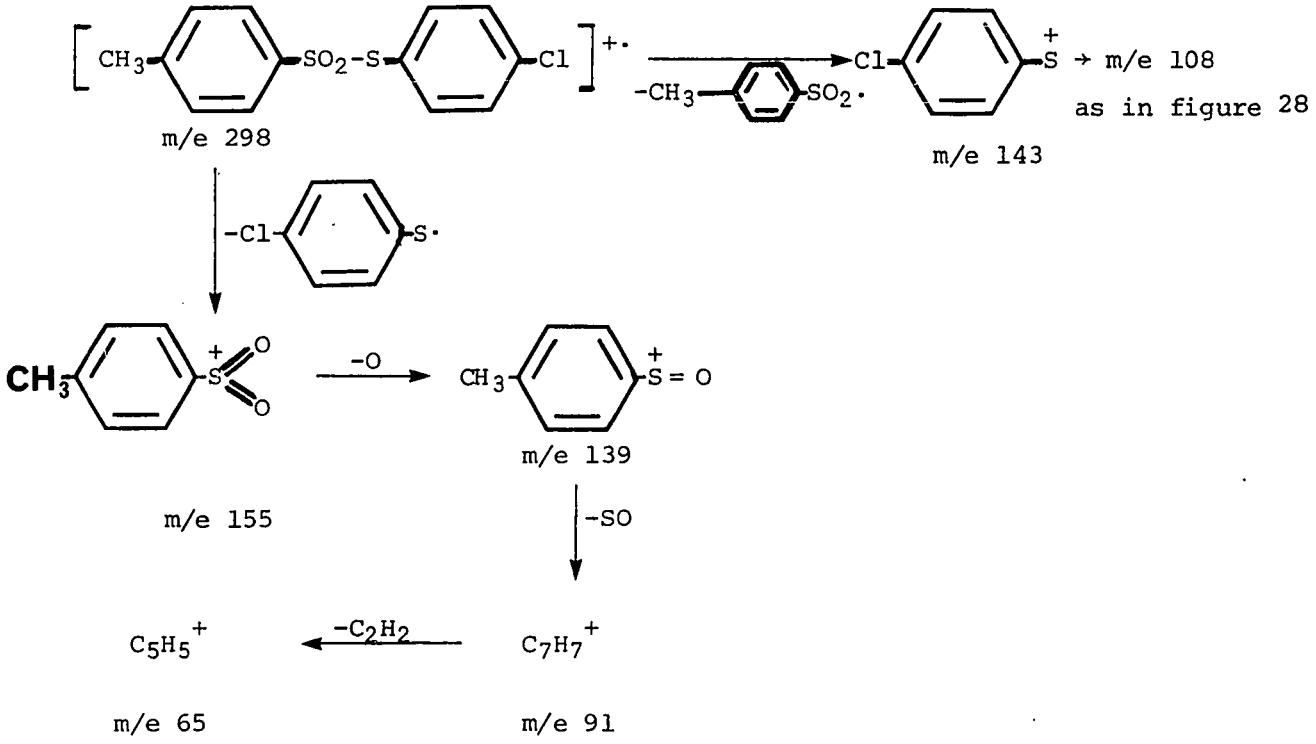


Figure 29. Mass spectral fragmentation pattern of p-chlorophenyl p-toluenethiosulfonate (96).

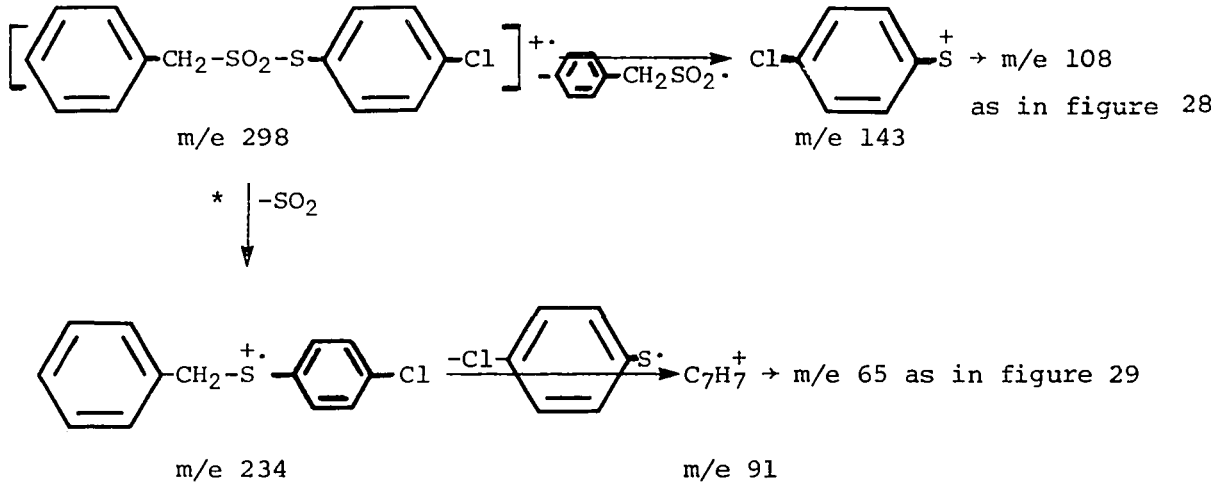


Figure 30 . Mass spectral fragmentation pattern of p-chlorophenyl α-toluenethiosulfonate (98).

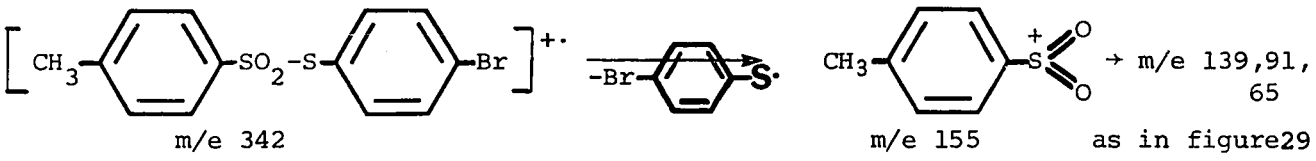


Figure 31. Mass spectral fragmentation pattern of p-bromophenyl p-toluenethiosulfonate (99).

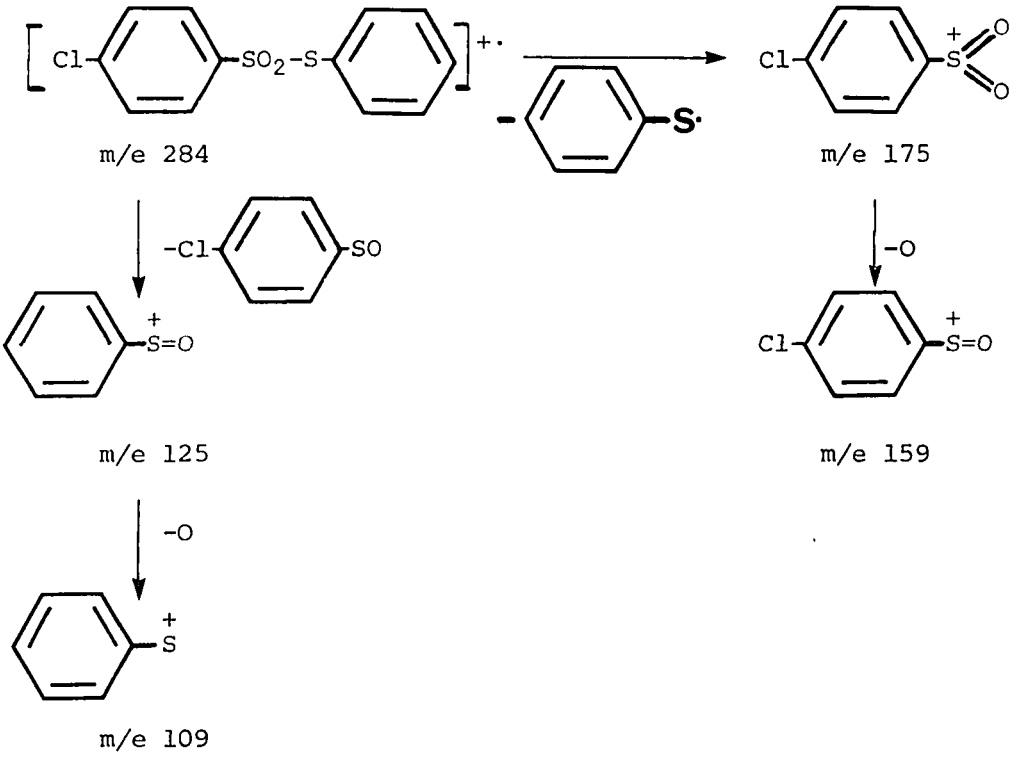


Figure 32. Mass spectral fragmentation pattern of phenyl p-chlorobenzenethiosulfonate (100).

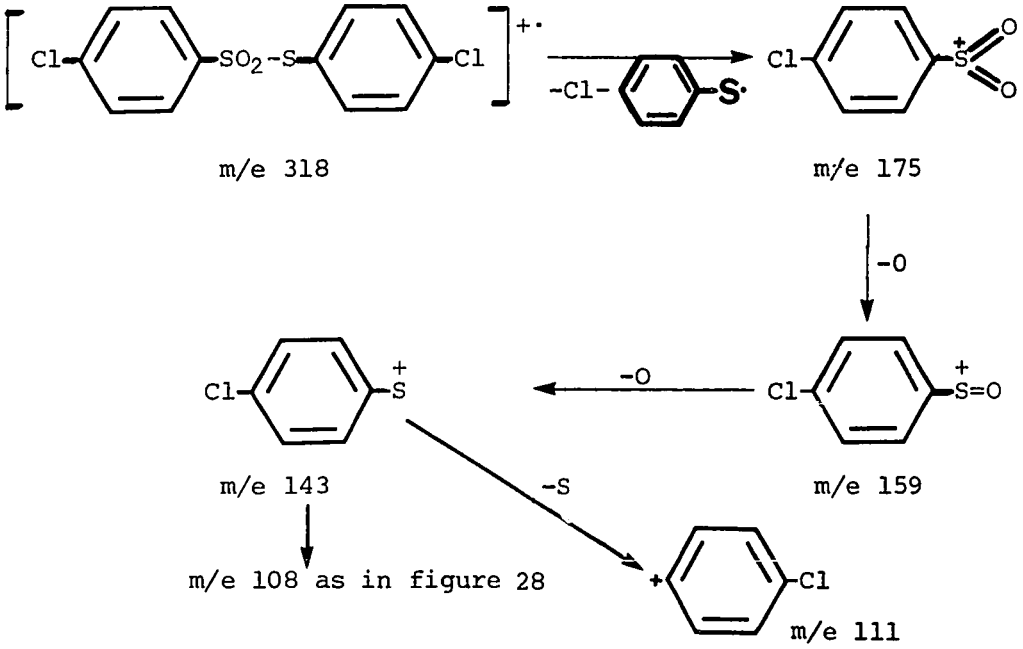


Figure 33 . Mass spectral fragmentation pattern of p-chlorophenyl p-chlorobenzenethiosulfonate (101).

CONCLUSIONS AND CLAIMS TO ORIGINAL WORK

A variety of methods of synthesizing unsymmetric trisulfides were investigated and the most successful reaction involved the interaction of a thiol with an alkyl or aryl phthalimido disulfide. The latter, stable crystalline replacements for alkyl or aryl chlorodisulfides, were synthesized for the first time by a general method *via* the reaction of a thiol with N,N' - thiobisphthalimide.

It was demonstrated that tris(diethylamino) phosphine reacts with a variety of organic trisulfides to afford the corresponding disulfides in high yield. The desulfurization was applicable to alkyl, aralkyl and cyclic trisulfides. Aminophosphines were also shown to desulfurize sulfenic sulfonic thioanhydrides to thiosulfonates and alkyl phthalimido disulfides to N-alkylphthalimides.

A combination of radiochemical and kinetic techniques were used to ascertain the mechanistic pathway of the desulfurization of trisulfides by tris(diethylamino) phosphine. The reaction of aromatic trisulfides was shown to proceed *via* a phosphonium salt formed by nucleophilic attack of the phosphine on the central sulfur atom of the trisulfide in the rate limiting step. The salt decomposes in an S_N2 process to afford products. Triphenylphosphine and tris(diethylamino) phosphine exhibited a dichotomy of behaviour towards aliphatic trisulfides as the former attacked and extruded the central sulfur atom while the latter removed a terminal sulfur atom. Nucleophilic attack of the aminophosphine on a terminal sulfur provided a phosphonium salt in what may be the rate limiting step. Products are formed *via* a S_N2 attack of hydrodisulfide anion on carbon.

The chemistry of sulfenic sulfonic thioanhydrides was studied with particular emphasis on reactions with phosphines. A novel solvolytic desulfurization of this class of compound was also observed.

Finally, the mass spectral behaviour of a variety of these derivatives was examined.

EXPERIMENTAL[1]

Unless stated otherwise, common reagents were obtained from commercial sources and purified when necessary. Melting points were obtained in open capillaries on a Gallenkamp melting point apparatus and are uncorrected. Boiling points are also uncorrected.

Infrared spectra were recorded on a Perkin-Elmer Infracord (Model 137) spectrophotometer, a Perkin-Elmer Model 257 or 337 grating infrared spectrophotometer or a Beckman IR5A spectrometer. Spectra were calibrated with the 1602 cm^{-1} and 1028 cm^{-1} bands of a polystyrene film reference. A Unicam SP-800 ultraviolet spectrophotometer was used for most spectra. For kinetic measurements, a Hitachi-Coleman 124 spectrophotometer, equipped with a Hitachi-Coleman 165 recorder and a Neslab constant temperature regulator, was employed.

Nuclear magnetic resonance spectra were taken on Varian Associates A-60 or T-60 spectrometers. All proton spectra are reported in tau (τ) units relative to tetramethylsilane (TMS). The abbreviations commonly used in the reporting of nmr spectra are: s, singlet; d, doublet; t, triplet; q, quartet and m, multiplet. Mass spectra were obtained on an AEI-MS-902 Mass Spectrometer at 70 eV and are reported in order of decreasing intensity.

Gas chromatographic (vpc) analyses were performed on an F & M Model 5750 Research Chromatograph. Three 6' x 1/8" stainless

[1] Compounds whose spectra appear in Appendix II are indicated by a (●).

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 determination of the activity of the samples used in the radiochemical experiments was carried out on a Baird-Atomic Model 135 scaler timer equipped with a Baird-Atomic Model 255 proportional counter preamplifier. The samples were counted in an atmosphere of 10% methane and 90% argon. Elemental analyses were by Organic Micro-analyses, Montreal, Canada and Scandinavian Microanalytical Laboratories, Herlev, Denmark. Refractive indices were measured on a Carl Zeiss 28241 Refractometer at 25°.

p-Toluenesulfenic p-Toluenesulfonic Thioanhydride (1) was prepared by the method of Brooker, Child and Smiles [88(a)]. To a solution of 9.0g (57 mmol) of p-toluenesulfenyl chloride[144] in 200 ml of anhydrous diethyl ether was added 13.3g (59 mmol) of potassium p-toluenethiosulfonate[145] as a fine powder. The orange colour of the sulfenyl chloride was discharged and a white precipitate of KCl formed. The reaction was stirred for 1.5 hrs. at room temperature, filtered and the filtrate evaporated to dryness. Crystallization of the resulting crude solid from n-hexane gave 16.7g (95%) of pale yellow crystals, mp 68.5-72.5°. Two recrystallizations from n-hexane afforded an analytical sample: mp 77.5-78.5°; ir (KBr) 1340 and 1140 cm^{-1} ($-SO_2-$); nmr (CCl_4) τ 2.15-3.0 (m, 8H), 7.55 (s, 3H), 7.65 (s, 3H); mass spectrum, parent ion m/e 310, fragments at 139, 123, 91, 155 and 65.

Anal. Calcd. for $C_{14}H_{14}O_2S_3$: C, 54.16; H, 4.54; S, 30.99.

Found: C, 54.26; H, 4.49; S, 30.39.

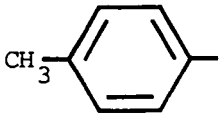
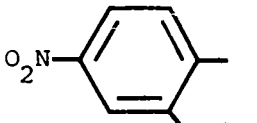
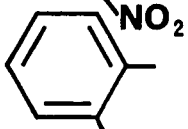
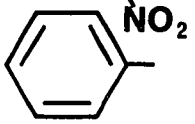
Sulfenic p-Toluenesulfonic Thioanhydrides (2-5) were prepared as described above for 1. The results are summarized in Table XVII and Table XVIII.

Attempted Deoxygenation of p-Toluenesulfenic p-Toluenesulfonic Thioanhydride (1).

A solution of 1.572g (6 mmol) of triphenylphosphine (6) in 50 ml of benzene was added, during 45 mins., to a stirred solution of 0.93g (3 mmol) of 1 in 50 ml of benzene. A white precipitate formed and redissolved. After 5 hours at room temperature the benzene was evaporated in vacuo and the resulting solid chromatographed over silica gel. Elution with 3:1 hexane-chloroform gave 0.423g of yellow oil which, on crystallization from ethanol, afforded 0.326 (44%) of di-p-tolyl disulfide (7) as white needles, mp 44-45.5° (lit.[54] mp 47°). Mixed mp with authentic 7 was undepressed. Elution with 1:1 hexane-chloroform provided, after crystallization from ethanol, 0.775g (88%) of triphenylphosphine sulfide (9), mp 163-166.5° (lit.[56] mp 161°) and mmp162-165.5°. The use of 1:3 hexane-chloroform gave, after crystallization from hexane, 0.765g (92%) of triphenylphosphine oxide (8), mp 154.5-158° (lit.[86] mp 156°) and mmp 155-159°. Further elution with 4:1 chloroform-methanol afforded a white solid which was soluble in cold ethanol and insoluble in hot hexane, benzene, ethyl acetate, diethyl ether, chloroform, methylene chloride and carbon tetrachloride. This solid decomposed during attempted recrystallization.

TABLE XVII

PREPARATION OF SULFENIC p-TOLUENESULFONIC THIOANHYDRIDES

Thioanhydride	R	% Yield	mp	crystallised from
1		95	77.5-78.5°	n-hexane
2		75	149.5-151°[a]	acetic acid
3		76	141.5-143°[b]	acetic acid
4		58	97.5-100°[c]	diethyl ether
5	CH_3CH_2—	89	oil	-

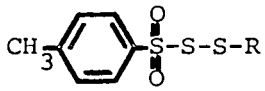
[a] Anal. Calcd. for $C_{13}H_{10}N_2O_6S_3$: C, 40.40; H, 2.61; N, 7.25; S, 24.87.
Found: C, 40.39; H, 2.73; N, 7.22; S, 24.97.

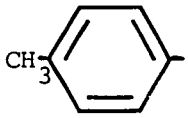
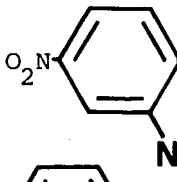
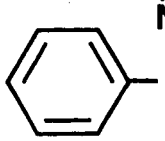
[b] lit. mp 141°[88(a)]

[c] Anal. Calcd. for $C_{13}H_{12}O_2S_3$: C, 52.69; H, 4.08; S, 32.45.
Found: C, 52.92; H, 3.82; S, 32.32.

TABLE XVIII

SPECTRAL PROPERTIES OF SULFENIC p-TOLUENESULFONIC THIOANHYDRIDES[a]



Thioanhydride	R	NMR(τ)	Mass Spectrum[b]
1		2.15-3.0(m,8H), 7.55(s,3H), 7.65(s,3H)[c]	310; 139, 123, 91, 155, 65
2		0.9(m,1H), 1.6(m,2H) 2.1-2.7(m,4H), 7.55(s,3H)[d]	386; 64, 62, 91, 198, 138, 63
4		2.15-2.85(m,9H), 7.65(s,3H)[d]	296; 91, 155, 139, 65, 109, 264
5	CH_3CH_2-	2.15-2.8(m,4H), 7.1(q,2H), 7.55(s,3H), 8.7(t,3H)[c]	248; 91, 155, 65, 216, 124.

[a] All the thioanhydrides exhibited intense absorption in the ir spectrum at 1340 cm^{-1} and 1140 cm^{-1} ($-SO_2-$).

[b] Parent ion followed by major fragments in decreasing order of intensity.

[c] CCl_4

[d] $CDCl_3$

Attempted Deoxygenation of p-Toluenesulfenic p-Toluenesulfonic Thioanhydride (1) with Trichlorosilane.

To a solution of 1.0g (3.2 mmol) of 1 in 50 ml of benzene was added 2.68g (19.8 mmol) of trichlorosilane. The reaction was stirred for 1.5 hrs. at room temperature and then refluxed for 21.5 hrs. Thin layer chromatography indicated no change in the reaction mixture.

Di-p-Tolyl Trisulfide (10).

A solution of 0.744g (6 mmol) of p-toluenethiol in 100 ml of anhydrous ether was added over 140 minutes to a solution of 1.86g (6 mmol) of 1 in 50 ml of anhydrous ether. The reaction was stirred for 21 hrs. at room temperature, refluxed for 3 hrs. and 0.4g (3.2 mmol) of p-toluenethiol was added. After refluxing a further 2.5 hrs., the ether was evaporated in vacuo. Hexane was added, the mixture filtered and the solid obtained recrystallized from ethanol to provide 0.801g of p-tolyl p-toluenethiosulfonate, mp 73-76° (lit.[146] mp 78.5-79.5°), mmp undepressed and ir identical to an authentic sample. The filtrate was chromatographed over silica gel with 1:1 hexane-chloroform eluant. The yellow oil (1.25g) obtained was recrystallized from ethanol to give 0.726g (44%) of 10, mp 78.5-82° (lit.[56] mp 80-81°), mmp undepressed and ir and nmr identical to an authentic sample.

Benzyl Hydrodisulfide (11).

Twenty-five ml of 5.7N HCl in absolute ethanol was added to a suspension of 8.25g (41.6 mmol) of acetic α-toluenesulfenic thioanhydride (63) in 100 ml of absolute ethanol under a nitrogen atmosphere. During

the addition, the disulfide dissolved. The reaction was stirred for 4 hrs. at room temperature, the ethanol and ethyl acetate evaporated in vacuo, and the resulting yellow oil distilled under reduced pressure to yield 5.25g (81%) of 11, bp (0.5 mm) 86-95° (lit.[14(b)] bp (0.01 mm) 65-70°).

Dibenzyl Trisulfide (12).

A solution of 0.31g (2 mmol) of benzyl hydrodisulfide (11) and 0.54g (2 mmol) of N-(benzylthio)phthalimide[97] in 50 ml of benzene was stirred at room temperature. After 15 mins. a precipitate formed. After stirring 20 hrs., the reaction was filtered, the filtrate evaporated to dryness and the resulting solid recrystallized from ethanol to give 0.55g (98%) of 12, as white needles, mp 47-48.5° (lit.[54] mp 49°).

N,N'-Thiobisphthalimide (13) was prepared from phthalimide and sulfur dichloride (14) by the method of Kalnins [147] in a yield of 90%, mp 312-316° (lit.[147] mp 315-317°).

Dibenzyl Trisulfide (12).

A mixture of 0.65g (2 mmol) of 13 and 0.50g (4 mmol) of α-toluenethiol in 50 ml of benzene was stirred for 12 hrs. at room temperature and a white precipitate was noted. The reaction was refluxed and everything dissolved. After 24 hrs. of refluxing, the mixture was cooled to ambient temperature and a white precipitate was collected. The benzene was evaporated from the filtrate and the resulting solid chromatographed over silica gel with 1:1 hexane-chloroform eluant to provide, after crystallization from ethanol, 0.15g (27%) of 12 as white needles, mp 46-47.5° (lit.[54] mp 49°).

Sulfur Dichloride (14).

(Anachemia Chemicals, technical grade) was purified by fractional distillation at atmospheric pressure and the red liquid bp 50-60° was collected. To this, ca. 0.1% PCl_5 was added. This portion was fractionally distilled into a receiver containing PCl_5, bp 58-59° (lit.[148] bp 59°).

Symmetric trisulfides were prepared by the procedure described by Schöberl and Wagner[71(a)]. A solution of two molar equivalents of a thiol in anhydrous ether was added to a solution of 14 in ether. After stirring, the ether was evaporated in vacuo and the resulting material was crystallized or distilled as appropriate. The symmetric trisulfides prepared by this method are summarized in Table XIXand Table XX.

Exo-3,4,5-trithiatricyclo [5.2.1.$0^{2.6}$] decane (26) was obtained in 76% yield via the sulfuration of bicyclo [2.2.1]hept-2-ene with sulfur and ammonia in dimethylformamide as described by Shields and Kurtz [27]. The compound was fractionally distilled under vacuum, bp (0.15) 104-110°; nmr (CCl_4) τ 6.4 (d, 2H), 7.4-7.6 (m, 2H), 7.85-9.05 (m, 6H); mass spectrum, parent ion m/e 190, fragments at 66, 93, 126.

Reaction of 1,3-Propanedithiol with Sulfur Dichloride (14).

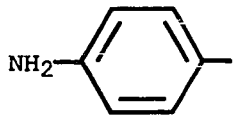
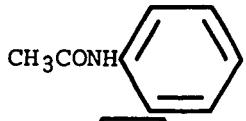
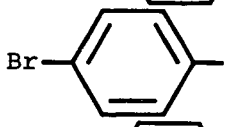
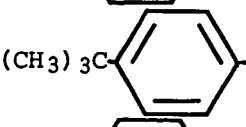
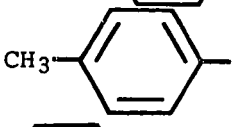
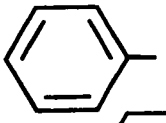
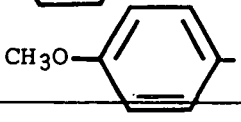
A solution of 3.24g (30 mmol) of 1,3-propanedithiol in 100 ml of anhydrous diethyl ether was added, during 1.5 hrs., to a solution of 3.10g (30 mmol) of 14 in 50 ml of dry ether under a nitrogen atmosphere.

TABLE XIX

PREPARATION OF SYMMETRIC TRISULFIDES

$$2\ RSH + SCl_2 \longrightarrow RSSSR + 2\ HCl$$

14

Trisulfide	R	% Yield	mp	bp (mm)	lit.mp/bp (mm)
15	$CH_3(CH_2)_4$-	61	-	121.5-124°(0.2)	76-96°(1.0)[149]
16	$CH_3CH_2CH_2$-	53	-	92-96° (3.0)	68-69°(0.9)[150]
17●	CH_3O-CO-CH_2-	78	-	123-126°(0.07)[a]	-
12	$C_6H_5CH_2$-	82	48-48.5°	-	49°[54]
18	$(CH_3)_2CH$-	67	-	42-43°(0.015)[b]	75-76°(5)[150]
19	$(CH_3)_3C$-	66	-	48-52°(0.01)[c]	86°(4)[28]
20		78	228-230°[d]	-	∿ 200°[151]
21		74	217.5-220°	-	213-214.5°[151]
22		78	68-71°	-	70-71°[56]
23		79	52.5-54°	-	51-52°[56]
10		86	82-84°[e]	-	80-81°[56]
24		84	-	oil[f]	ca. -5°[56]
25		85	73-76°	-	73-74°[56]

a) Anal. Calcd. for $C_6H_{10}O_4S_3$: C, 29.74; H, 4.16; S, 39.70.
Found: C, 29.95; H, 4.28; S, 39.94.

b) n_D^{25} 1.535 (lit.[150] n_D^{25} 1.5351); c) n_D^{25} 1.5195 (lit.[28] n_D^{20} 1.5225).

d) Isolated as the dihydrochloride.

e) Anal. Calcd. for $C_{14}H_{14}S_3$: C, 60.39; H, 5.07; S, 34.54.
Found: C, 60.11; H, 5.04; S, 34.34.

f) Decomposed on attempted distillation. Collected yellow oil bp(0.5 mm) 156-171° which crystallized, mp 59-61°. This decomposition to diphenyl disulfide has been reported[65].

TABLE XX

SPECTRAL PROPERTIES OF SYMMETRIC TRISULFIDES

R-S-S-S-R

Trisulfide	R	NMR(τ)[a]	Mass Spectrum[b]
15	$CH_3(CH_2)_4$-	7.15(t,2H), 8.0-8.8(m,6H) 9.1(t,3H)	238; 71, 55, 70, 206, 136, 103
16	$CH_3CH_2CH_2$-	7.1(t,2H), 8.15(m,2H), 8.9(t,3H)	182; 75, 70, 85, 76, 108
17●	CH_3O-CO-CH_2-	6.2(s,3H), 6.3(s,2H)	242; 59, 106, 95, 74, 138, 210
12	$C_6H_5CH_2$-	2.8(s,5H), 6.05(s,2H)	278; 91, 182, 213, 123
18	$(CH_3)_2CH$-	6.8(m,1H), 8.6(d,6H)	182; 43, 75, 98
19	$(CH_3)_3C$-	8.6(s)	210; 57, 90, 154, 75, 76
10	p$CH_3C_6H_4$-	2.5-3.1(m,4H), 7.7(s,3H)	278; 123, 91, 246, 155
24	C_6H_5-	2.4-3.0(m)	250; 186, 218, 109, 110, 185, 65

a CCl_4

b Parent ion followed by fragments in decreasing order of intensity

HCl was evolved and a solid precipitated. After 30 mins. of stirring at room temperature, the reaction was filtered and 3.6g of a yellow material collected. Crystallization from chloroform provided a white solid, mp 72-76°, which was not characterized. The desired 1,2,3-trithiane (27) has mp 44°[24].

Reaction of 1,4-Butanedithiol with Sulfur Dichloride (14).

A solution of 2.45g (20 mmol) of 1,4-butanedithiol in 100 ml of anhydrous diethyl ether and a solution of 2.05g (20 mmol) of 14 in 100 ml of dry ether were added simultaneously with stirring, over 2 hrs., to 100 ml of ether at room temperature. Hydrogen chloride gas was evolved and a precipitate formed. The reaction was allowed to stand for ca. 12 hrs., the precipitate was filtered and collected. Evaporation of the ether from the filtrate yielded a solid. Neither solid had the properties expected of 1,2,3-trithepane (28) as neither would sublime at 100° and 0.3 mm.

Meso-α,α'-Dibromoadipic Acid (29) was prepared from adipic acid by the method of Gleason and Harpp[152] in 14% yield, mp 174-181° (lit.[153] mp 192-193°).

Meso-α,α'-Dimercaptoadipic Acid (30) was prepared in 35% yield from meso-α,α'-dibromoadipic acid (29) by the procedure of Fredga[154], mp 181.5-183 (lit.[154] mp 183°).

Reaction of Meso-α,α'-dimercaptoadipic Acid (30) with Sulfur Dichloride (14).

A solution of 0.42g (2 mmol) of 30 in 75 ml of tetrahydrofuran was added during one hr., to a stirred solution of 0.21g (2 mmol) of 14 in 50 ml of tetrahydrofuran at room temperature. Hydrogen chloride gas was evolved and the solution changed from deep to pale yellow in colour. After stirring for one hr., the solvent was evaporated in vacuo to yield a pale yellow oil which solidified on standing. The solid was insoluble in hot hexane and in boiling water. Filtration gave a gummy solid which could not be characterized.

Meso-α,α'-dimercapto Dimethyl Adipate (32)

A suspension of 2.0g (9.5 mmol) of meso-α,α'-dimercaptoadipic acid (30) in 125 ml of methanol was cooled in an ice bath and treated with gaseous HCl for ca. 60 minutes during which time all of 30 dissolved. The mixture was allowed to stand for 2.5 hrs. and the methanol evaporated in vacuo. After allowing the resultant oil to stand for ca. 12 hrs., ether was added, dried over anhydrous Na_2SO_4 and evaporated to give 2.25g of a white solid. Recrystallization from n-hexane provided 1.85g (82%) of diester 32 as white plates, mp 39-41°; nmr (CCl_4) τ 6.25 (s, 6H), 6.55-6.95 (m, 2H), 8.0(d, 2H, SH), 7.9-8.3 (m, 4H). Four recrystallizations from n-hexane yielded an analytical sample, mp 40.5-44.5°.

Anal. Calcd. for $C_8H_{14}O_4S_2$: C, 40.32; H, 5.92.

Found: C, 40.53; H, 5.94.

Reaction of Meso-α,α'-dimercapto dimethyl adipate (32) with Sulfur Dichloride (14).

A solution of 0.475g (2 mmol) of 32 in 50 ml of anhydrous diethyl ether was added dropwise during 30 mins.to a solution of 0.210g (2 mmol) of 14 in 100 ml of dry ether. HCl was evolved as the colour of the reaction mixture went from yellow to colourless and a white precipitate coated the flask. The solvent was evaporated to provide a very pale yellow oil; vpc (LAC column) indicated ca. 80% purity and a retention time identical to meso-3,6-dicarbomethoxy-1,2-dithiane ir (film) 1760-1740 (-C=O) and 1450 cm^{-1} (-C-O); nmr ($CDCl_3$) τ 6.15 (s, 8H), 7.65-8.05 (m, 4H); nmr (CCl_4) τ 6.2 (s), 6.25 (s), 7.75-8.15 (m); mass spectrum, parent ion m/e 268, fragments at 238, 236, 206, 177, 145, 120, 118, 84. Column chromatography over silica gel with 4:1 benzene-methanol gave 0.2g of oil (ca. 85% pure, vpc) and 0.35g (ca. 90% pure, vpc) for a total yield of 0.55g (102%).

Disodium Trimethylene Thiosulfate (34) was prepared in 94% yield from 1,3-dibromopropane by the method of Milligan and Swan[24].

1,2,3-Trithiane (27) was prepared in 56% yield from disodium trimethylene thiosulfate (34) by the procedure of Milligan and Swan[24], mp 43.5-46.5° (lit.[24] mp 44°).

Disodium o-phenylene Dithiosulfate (36) was synthesized in 31% yield from α,α'-dibromo-o-xylene by the method of Milligan and Swan[24].

2,3,4-Benzotrithiepin (37) was prepared in 72% yield from disodium o-phenylene dithiosulfate (36) as described in the literature[24], mp 101-104.5° (lit.[24] mp 101-102°).

Esterification of Meso-α,α'-dibromoadipic Acid (29).

A solution of 3.05g (10 mmol) of meso-α,α'-dibromoadipic acid (29) in 100 ml of methanol was cooled in an ice bath and gaseous HCl was bubbled through for 35 mins. After standing for 14 hrs., the methanol was evaporated in vacuo to give a green oil. Diethyl ether was added, dried over anhydrous Na_2SO_4, and evaporated to leave a pale green oil. The oil was dissolved in cold methanol and cooled in dry ice until crystals formed. Filtration provided 2.05g, mp 50-61°. Three recrystallizations from methanol yielded 0.25g (7.5%) of meso-α,α'-dibromo dimethyl adipate (39), mp 68.5-72.5° (lit.[155] mp 75-76°).

α,α'-Dibromo dimethyl adipate was prepared by the method of Gleason and Harpp[152]. A suspension of 73.0g (0.50 mol) of adipic acid in 248g (2.08 mol) of thionyl chloride was refluxed for one hr. until all the adipic acid had dissolved. After cooling, 300 ml of carbon tetrachloride and 200g (1.12 mol) of N-bromosuccinimide were added and the reaction refluxed for 1.5 hrs. until all the solid in the flask was floating. The colour of bromine was noted. The reaction was cooled to room temperature, filtered, and the filtrate evaporated in vacuo to leave a pale orange oil. The oil was cooled in an ice bath and 100 ml of methanol was added, during 30 minutes, with stirring. Hydrogen chloride gas was evolved as the reaction mixture became warm.

The methanol was evaporated in vacuo and the resultant oil cooled to ca. -15° overnight. The crystals which formed were collected by filtration and recrystallized from methanol to yield 26.8g (16.5%), mp 74.5-77.5°. One recrystallization provided 23.35g of meso-α,α'-dibromo dimethyl adipate (39) as white needles, mp 75.5-79° (lit.[155] mp 75-76°).

The filtrate was cooled to ca. -15° and filtered to yield a solid which was crystallized from methanol and 6.6g, mp 115-120° was obtained. Recrystallization from methanol provided 4.1g, mp 115-118°. The filtrate was evaporated to dryness in vacuo to give 104g of a yellow oil which was fractionally distilled under reduced pressure. After an initial forerun, d,l-α,α'-dibromo dimethyl adipate (38) was collected as a pale yellow oil, 22.6g bp(2.5-3.1 mm) 132-136°. On standing some crystals formed, these were filtered off and 21.2g of 38 remained. Another fraction bp (3.3-3.6 mm) 136-141° (lit.[155] bp (14 mm) 169-170°) weighing 14.7g was collected, filtered to remove crystals, leaving 13.55g of 38. Total yield of d,l-α,α'-dibromo dimethyl adipate (38) was 33.75g (20.5%).

The stereochemical purity of 38 and 39 was determined by vpc using the UC-W98 column with the oven programmed from 80-300° with the temperature increasing 20°/minute. Helium pressure was 50 psi while oxygen and hydrogen were 30 psi and 5 psi respectively. Compound 39 exhibited only one peak with a retention time of 7.8 minutes. The d,l diester 38 was > 95% pure as the major peak had a retention time of 6.2 minutes while the minor peak (< 5%) corresponded to 39.

Attempted Preparation of Disodium Meso-α,α'-adipic Acid Dithiosulfate (40).

A mixture of 3.05g (10 mmol) of meso-α,α'-dibromoadipic acid (29) and 5.0g (20 mmol) of sodium thiosulfate pentahydrate was refluxed in 30 ml of ethanol plus 30 ml of water for one hour. A pale yellow solid formed. The reaction was cooled and the solvent evaporated in vacuo. The resulting solid was extracted (soxhlet) with ethanol and the solvent evaporated from the extract. Recrystallization from ethanol gave a yellow solid which was not characterized.

Attempted Preparation of Disodium Meso-α,α'-adipic Acid Dithiosulfate (40).

A mixture of 3.05g (10 mmol) of meso-α,α'-dibromoadipic acid (29) and 1.5g (15 mmol) of sodium carbonate was stirred in 30 ml of water until everything dissolved. 5.0g (20 mmol) of sodium thiosulfate pentahydrate and 30 ml of ethanol were added and the reaction was refluxed for one hour. It was cooled to room temperature, let stand ca. 20 hrs., and evaporated to dryness. A solution of the resultant material in 20 ml of water was acidic. Evaporation of the water gave a sticky white substance which was extracted (soxhlet) with ethanol. Evaporation of the solvent from the extract yielded a white solid which was not characterized.

Attempted Preparation of Disodium Meso-α,α'-dimethyl Adipate Dithiosulfate (41).

A mixture of 3.3g (10 mmol) of meso-α,α'-dibromo dimethyl adipate (39) and 5.0g (20 mmol) of sodium thiosulfate pentahydrate was refluxed in 60 ml of methanol plus 60 ml of water for 3 hrs. Everything dissolved but after 15 mins. a yellow solid precipitated and the reaction became acidic (ca. pH 5). The reaction was cooled to room temperature, the solvent evaporated in vacuo and the resulting white solid dried over P_2O_5 under reduced pressure. This solid (6.15g) was extracted with methanol and the extract was evaporated to dryness giving 5.6g of white solid. Recrystallization from methanol provided 1.2g of white crystals, ir (KBr) 3430 (water of hydration), 1755 (-C=O), 1230, 1048 and 648 cm^{-1} (-S-SO_3).

Attempted Preparation of cis-3,7-dicarbomethoxy-1,2,3-trithepane (33).

A mixture of 3.3g (10 mmol) of meso-α,α'-dibromo dimethyl adipate (39) and 5.0g (20 mmol) of sodium thiosulfate pentahydrate was refluxed for 1.5 hrs. in 125 ml of methanol and 25 ml of water. The reaction was cooled to room temperature, evaporated to dryness and dried overnight at ca. 1 mm. The resulting white solid was extracted (soxhlet) with methanol, the extract was allowed to stand for 7 days and then evaporated to dryness to yield a white solid which was dried at 60° and ca. 1 mm to a constant weight of 5.3g.

This solid was added to 100 ml of 0.25M phosphate buffer (2.3g KH_2PO_4 and 8.9g $Na_2HPO_4 \cdot 7H_2O$ in 200 ml of water) and 3 ml of 36% formaldehyde. A solution of 2.4g (10 mmol) of sodium sulfide

nonahydrate in 50 ml of water was added dropwise during 45 mins. to the buffered solution. Hydrochloric acid was added as required to maintain pH 8 and the reaction was stirred for 30 mins. The aqueous solution was extracted with ether and the ether layer was washed with water, dried over anhydrous sodium sulfate and evaporated to dryness. The resulting oil was uncharacterizable.

Reaction of 2,4-Dinitrobenzenesulfenic p-Toluenesulfonic Thioanhydride (2) with Sodium p-Toluenethiolate (42).

A suspension of 2.2g (6.85 mmol) of 2 in 50 ml of absolute ethanol was stirred, at room temperature under a nitrogen atmosphere, and 1.0g (6.85 mmol) of 42 in 10 ml of absolute ethanol was added. The reaction mixture turned very dark and after one hour it was filtered to provide 1.0g (45.5%) of recovered 2 as a yellow solid whose ir spectrum was identical to that of authentic 2,4-dinitrobenzenesulfenic p-toluenesulfonic thioanhydride (2). The ethanol was evaporated from the filtrate in vacuo to leave a solid which was washed with chloroform. Evaporation of the chloroform gave a yellow solid which was recrystallized twice from ethanol to yield 0.331g (39%) of di-p-tolyl disulfide (7), mp and mmp 42-44° (lit.[54] mp 47°). The ir spectrum of 7 obtained in this reaction was superimposable on that of an authentic sample. The chloroform insoluble material weighed 1.3 g and the red solid had mp > 270°. It was soluble in water and insoluble in carbon tetrachloride, diethyl ether and benzene.

Attempted Preparation of p-Tolyl Benzyl Trisulfide.

A solution of 0.57g (4.6 mmol) of α-toluenethiol in 50 ml of anhydrous diethyl ether was added, during 30 mins., to a refluxing solution of 0.93g (3 mmol) of p-toluenesulfenic p-toluenesulfonic thioanhydride (1) in 25 ml of ether under a nitrogen atmosphere. The reaction was refluxed 96 hrs. and allowed to stand 12 hrs. The addition of n-hexane and filtration provided 0.229g of p-toluenesulfinic acid as white crystals, mp 82-84° (lit.[156] mp 86-87°); ir (KBr) 2550-2300 (-O-H), 1095 and 1030 cm^{-1}(-S=O); nmr ($CDCl_3$) τ 2.3-2.8 (m, 4H), 7.58 (s, 3H). The filtrate provided an uncharacterizable oil.

Ethanethiol (44) (Anachemia Chemical Co.) was fractionally distilled at atmospheric pressure and the fraction bp 35-36° (lit.[157] bp 37°) collected.

Attempted Preparation of Ethyl Benzyl Trisulfide.

A solution of 1.55g (25 mmol) of ethanethiol (44) in 50 ml of anhydrous diethyl ether was added, during 2hrs., to a stirred solution of 3.10g (30 mmol) of sulfur dichloride (14) in 50 ml of dry ether under a nitrogen atmosphere at room temperature. Hydrogen chloride gas was evolved. After stirring for 20 mins. a solution of 3.72g (30 mmol) of α-toluenethiol in 50 ml of ether was added during 15 mins. The reaction was stirred for one hour and the ether evaporated in vacuo to give 6.0g of yellow oil which was distilled under reduced pressure. Diethyl trisulfide (45), 0.65g, was obtained as a pale yellow liquid, bp (0.07 mm) 25-29° (lit.[28] bp (3 mm) 57°); nmr (CCl_4) τ 7.15 (q, 2H),

8.6 (t, 3H); mass spectrum, parent ion m/e 154, fragments at 61, 66, 94, 122, 62, 93. The bright orange liquid, bp (0.04 mm) 137-161°, deposited white crystals of dibenzyl trisulfide (12) on standing, mp 45-46.5° (lit.[54] mp 49°), whose ir spectrum was identical to that of an authentic sample.

Attempted Preparation of p-Tolyl Benzyl Trisulfide.

A solution of 1.86g (15 mmol) of p-toluenethiol in 50 ml of anhydrous diethyl ether was added, during one hour, to a stirred solution of 1.55g (15 mmol) of sulfur dichloride (14) in 50 ml of dry ether under a nitrogen atmosphere at room temperature. The mixture was stirred for one hour and a solution of 1.86g (15 mmol) of α-toluenethiol in 50 ml of ether was added during 25 min. The reaction was stirred for 14.5 hrs., the ether evaporated in vacuo and α-toluenethiol distilled from the resultant oil, bp(0.015) 28.5-30° (lit.[158] bp 194-195°). The residue, 3.4g, was chromatographed over silica gel to provide 1.05g of di-p-tolyl trisulfide (10) which was crystallized from hexane to yield a sample, mp 80.5-82° (lit.[56] mp 80-81°) and mmp undepressed. Further elution gave 1.45g of a yellow oil which was soluble in cold hexane, ethyl acetate, benzene and acetic acid and which oiled out of ethanol and methanol solutions. The oil was distilled under vacuum to give 0.54g, bp(0.07 mm) 142-151°, of a liquid whose nmr spectrum was indicative of a mixture of trisulfides.

Triphenylmethanethiol (46) was prepared in 88% yield from triphenylmethanol by the procedure of Hiskey and Kepler[159], mp 107-108° (lit.[159] mp 106-107°).

Triphenylmethyl chlorodisulfide (47)●

A solution of 6.0g (21.8 mmol) of triphenylmethanethiol (46) in 80 ml of anhydrous diethyl ether was added, during one hour, to a solution of 3.10g (30 mmol) of sulfur dichloride (14) in 50 ml of dry ether which was cooled in a dry ice/acetone bath. A yellow solid formed, the reaction was warmed to room temperature and filtered to give, after crystallization from hexane, 4.55g of triphenylmethyl chlorodisulfide (47), mp 91-94°. This was recrystallized once from hexane to provide a sample, mp 93-95°. A further 0.68g was obtained by evaporating the ether from the filtrate. Total yield of 47 was 5.23g (70%). Nmr ($CDCl_3$) exhibits one sharp singlet at 2.67 τ; mass spectrum, no parent ion, fragment at 243.

Triphenylmethyl p-chlorophenyl trisulfide (48)●

A stirred suspension of 1.0g (2.92 mmol) of triphenylmethyl chlorodisulfide (47) in 80 ml of anhydrous diethyl ether was cooled in a dry ice/acetone bath and a solution of 0.425g (3 mmol) of p-chlorobenzenethiol in 20 ml of dry ether was added during 20 mins. The reaction was warmed to room temperature, over a 90 min. period, and the ether evaporated in vacuo. The residue was chromatographed over silica gel and eluted with hexane to give 0.660g (50%) of 48 as a yellow solid, mp 84-93°. Recrystallization from acetone and then

hexane provided an analytical sample, mp 99.5-100°; nmr (CCl_4) showed a multiplet at 2.6-2.9 τ.

Anal. Calcd. for $C_{25}H_{19}ClS_3$: C, 66.56; H, 4.23; S, 21.32. Found: C, 66.48; H, 4.30; S, 21.13.

Triphenylmethyl 2-naphthyl trisulfide (49)●

A stirred suspension of 1.0g (2.92 mmol) of triphenylmethyl chlorodisulfide (47) in 80 ml of anhydrous diethyl ether was cooled in a dry ice/acetone bath and a solution of 0.48g (3 mmol) of 2-naphthalenethiol in 20 ml of dry ether was added during 15 mins. The reaction was warmed to room temperature over one hour and stirred for a further 2.5 hrs. The ether was evaporated in vacuo and the resulting oil was allowed to stand ca. 12 hrs. A small amount of acetone was added and on standing a solid formed. Petroleum ether was added and the solid filtered to give, in two crops, 1.076g (79%) of 49 as a yellow solid, mp 100-103°. Two recrystallizations from n-hexane provided an analytical sample, mp 103-105°; nmr (CCl_4) indicated a multiplet at 2.2-2.9 τ.

Anal. Calcd. for $C_{29}H_{22}S_3$: C, 74.64; H, 4.75; S, 20.61. Found: C, 74.59; H, 5.08; S, 20.18.

Attempted Preparation of Ethyl Chlorodisulfide (50)

A) 1.86g (30 mmol) of ethanethiol (44) was added to a solution of 5.15g (50 mmol) of sulfur dichloride (14) in 50 ml of anhydrous diethyl ether. The solution remained orange as the reaction became hot. After stirring for 3 hrs. the mixture was flash evaporated at room

temperature and 120 mm pressure. The pressure was reduced to 60 mm and the 2.7g of orange liquid which remained was kept on dry ice for ca. 12 hrs. This was distilled to give 1.0g (26%) of impure ethyl chlorodisulfide (50) as an orange liquid bp (12 mm) 35-36.5° (lit.[30] bp (13 mm) 30-32°). The product was judged impure by the nmr (CCl_4) spectrum which exhibited 2 quartets of unequal intensity at 6.95 τ and 2 triplets of unequal intensity at 8.55 τ.

B) Dropwise addition of 20.3g (328 mmol) of ethanethiol (44) to 40.7g (395 mmol) of sulfur dichloride (14), which was cooled to 0° in an ice bath, resulted in the evolution of HCl. The orange liquid was distilled under vacuum and 37.0g (88%) of ethyl chlorodisulfide (50), bp (7-8 mm) 24-32° (lit.[30] bp (13mm) 30-32°) was collected. The nmr spectrum was as in A above and integration indicated a purity of 90-92%.

Attempted Preparation of Benzyl Chlorodisulfide (51)

A) α-Toluenethiol (2.8g (22.5 mmol)) was added dropwise to 3.10g (30 mmol) of sulfur dichloride (14) which was cooled in a dry ice/acetone bath. A violent reaction occurred and HCl was evolved. The reaction was warmed to room temperature and the resulting bright orange liquid was kept on dry ice for 18 hrs. This was distilled fractionally, under vacuum, but, aside from some forerun which collected in dry ice traps, nothing distilled at 0.18 mm and a bath temperature of 160°. The liquid in the distillation flask decomposed as it became bright red-purple in colour.

B) α-Toluenethiol (10.0g (80 mmol)) was added dropwise during 15 mins. to 10.3g (100 mmol) of sulfur dichloride (14) cooled in an ice-water bath. The reaction was stirred 2.5 hrs. and distilled under

reduced pressure through a short path system to provide a sample bp (1.05 mm) 21-34°; nmr (CCl_4) τ 2.7 (s, 5H), 5.5 (s, 2H) and a sample bp (1.7 mm) 34-37°; nmr (CCl_4) as above. Total yield was 2.6g (17%).

Attempted Preparation of 2-Naphthyl Chlorodisulfide (52)

A) A solution of 3.5g (22 mmol) of 2-naphthalene in 80 ml of anhydrous diethyl ether was added, during 35 mins., to a stirred solution of 3.10g (30 mmol) of sulfur dichloride (14) in 50 ml of dry ether which was cooled in a dry ice/acetone bath. This was warmed to room temperature, during 1.5 hrs., and the ether evaporated in vacuo to give an orange liquid. On cooling in dry ice a yellow solid formed. Hexane was added and the solid filtered. Recrystallization from hexane provided a yellow solid which, on drying over P_2O_5 in vacuo in the dark, decomposed, as evidenced by the formation of green solid mixed in with the yellow.

B) The reaction in A above was repeated to give 3.6g of a yellow solid (some green coloured material was present) mp 31-45°. Attempted crystallization from hexane resulted in decomposition.

Attempted Preparation of Ethyl Phenyl Trisulfide

1.72g (15.6 mmol) of benzenethiol was added to a solution of 2.0g (15.6 mmol) of ethyl chlorodisulfide (50) in 40 ml of anhydrous diethyl ether and the reaction was stirred for 1.5 hrs. The solvent was evaporated and the residue fractionally distilled under vacuum to provide 0.466g, bp (0.075 mm) 92-110° (lit.[83] bp (0.01 mm) 67-69°;

nmr (CCl_4) τ 2.3-2.9 (m, 5H), 7.15 (q, 2H, each peak split), 8.65 (t, 3H, each peak split). Redistillation by short path afforded a fraction bp(0.07 mm) 92-100° whose nmr indicated the presence of more than one ethyl group.

Attempted Preparation of Ethyl n-Propyl Trisulfide

1.22g (15.6 mmol) of n-propanethiol was added to a solution of 2.0g (15.6 mmol) of ethyl chlorodisulfide (50) in 40 ml of anhydrous diethyl ether and the reaction was stirred for one hour. The solvent was evaporated in vacuo and the residue chromatographed over silica gel to provide 2.283g of a yellow oil homogeneous on tlc; nmr (CCl_4) τ 6.9-7.55 (m, 4H), 8.0-9.15 (m, 10H); mass spectrum, parent ions at m/e 182 (di-n-propyl trisulfide (16)),168 (ethyl n-propyl trisulfide), 154 (diethyl trisulfide (45)). Fractional distillation under reduced pressure did not yield a constant boiling fraction.

Attempted Preparation of Ethyl t-Butyl Trisulfide

A) 3.5g (39 mmol) of 2-methyl-2-propanethiol was added dropwise to 5.0g (39 mmol) of ethyl chlorodisulfide (50) which was cooled in an ice bath. The reaction was stirred for 40 hrs. and distilled to provide 2.85g, bp (7mm) 73-79°. Chromatography on a silica gel column with n-hexane as eluant gave 2.4g of light yellow oil, nmr (CCl_4) τ 7.15 (q, 2H), 8.65 (t, 9H). The product was impure by vpc and decomposed on attempted purification by preparatory vpc.

B) 3.5g (39 mmol) of 2-methyl-2-propanethiol was added dropwise to 5.0g (39 mmol) of ethyl chlorodisulfide (50) in an ice-water bath. The reaction was stirred 16 hrs. and chromatographed over silica gel with n-hexane eluant to provide 4.4g of liquid. Fractional distillation under reduced pressure yielded 0.876g, bp(0.12 mm) 37-40°; nmr (CCl_4) τ 7.15 (q, 2H) 8.65 (t, 14H); mass spectrum, parent ions at m/e 210(di-t-butyl trisulfide (19)), 182 (ethyl t-butyl trisulfide), 154 (diethyl trisulfide (45)). Redistillation under vacuum gave 0.390g bp (0.08 mm) 35-37°; mass spectrum as above.

Attempted Preparation of Ethyl Benzyl Trisulfide

7.7g (62 mmol) of α-toluenethiol was added dropwise to 8.0g (62 mmol) of ethyl chlorodisulfide (50) cooled in a dry ice/acetone bath during 15 mins. The reaction was stirred one hour, during which time it warmed to room temperature, and fractionally distilled under reduced pressure. No constant boiling fraction was obtained and the highest boiling material had bp (0.15 mm) 82° (lit.[30] bp (0.1 mm) 92-94°).

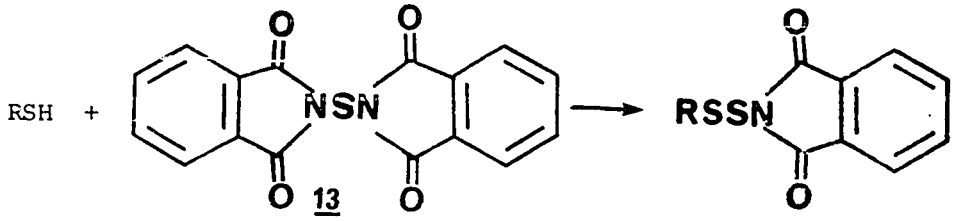
The following is a representative procedure for the preparation of alkyl phthalimido disulfides. The compounds prepared by this method (54 - 59) are summarized in Table XXI and Table XXII and their spectral properties are found in Table XXIII.

p-Tolyl Phthalimido Disulfide (59)

A mixture of 6.5g (20 mmol) of N,N'-thiobisphthalimide (13)[147] and 2.25g (18 mmol) of p-toluenethiol was refluxed in 100 ml of benzene for 7 hrs. On cooling to room temperature a solid precipitated.

TABLE XXI

PREPARATION OF ALKYL AND ARYL PHTHALIMIDO DISULFIDES



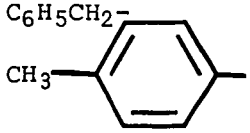
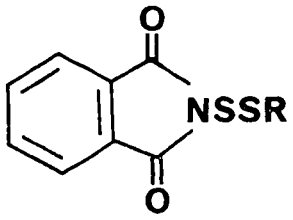
Disulfide	R	Reaction Time (hr.)	Yield %	Mp, °C
54	$CH_3CH_2CH_2$-	17	75	49-50.5
55	CH_3O-CO-CH_2-	18	77	76-76.5
56	$(CH_3)_2CH$-	22	74	101.5-103
57	$(CH_3)_3C$-	17	74	103.5-105.5
58	$C_6H_5CH_2$-	1.5	90	133.5-135.5
59		7	81	124.5-125.5

TABLE XXII

ANALYTICAL DATA ON ALKYL AND ARYL PHTHALIMIDO DISULFIDES



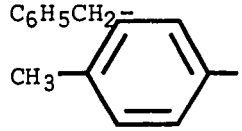
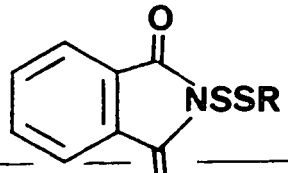
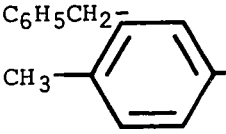
Disulfide	R	Calcd. %			Found, %		
		C	H	S	C	H	S
54	$CH_3CH_2CH_2$-	52.16	4.38	-	52.39	4.42	-
55	CH_3O-CO-CH_2-	46.65	3.20	-	46.60	3.75	-
56	$(CH_3)_2CH$-	52.16	4.38	-	52.25	4.49	-
57	$(CH_3)_3C$-	53.91	4.90	23.98	53.89	5.18	24.76
58	$C_6H_5CH_2$-	59.75	3.68	21.27	59.79	3.65	21.25
59		59.75	3.68	21.27	59.76	3.50	21.05

TABLE XXIII

SPECTRAL PROPERTIES OF ALKYL AND ARYL PHTHALIMIDO DISULFIDES[a]



Disulfides	R	NMR(τ)	Mass Spectrum[b]
54	$CH_3CH_2CH_2$-	2.1(m,4H),6.95(t,2H),8.1(m,2H), 8.9(t,3H)[c]	253; 64,130,76,104
55	CH_3O-CO-CH_2-	2.3(m,4H),6.1(s,2H),6.35(s,3H)[d]	283; 147,103,76,179
56	$(CH_3)_2CH$-	2.15(m,4H),6.6(m,1H),8.55(d,6H)[c]	253; 64,211,130,104,147
57	$(CH_3)_3C$-	2.05(m,4H),8.6(s,9H)[c]	267; 210,64,57,130,76,104
58	$C_6H_5CH_2$-	2.05(m,4H),2.55(m,5H),5.65(s,2H)[d]	301; 91,236,76,104,147,65
59		1.75(m,4H),2.25(q,4H),7.25(s,3H)[d]	301; 123,91,104,154,76

a) The ir(KBr) spectra of these compounds all show strong absorptions at 1690-1720, 1250-1290, 1035-1065 and 710-725 cm^{-1} due to the phthalimido group as well as bands attributed to the alkyl or aryl substituent.

b) Parent ion followed by major fragments in decreasing order of intensity.

c) CCl_4

d) $CDCl_3$

Filtration gave 2.25g (85%) of phthalimide. The filtrate was evaporated to dryness in vacuo and the resulting solid crystallized from ethanol to provide 3.85g of white needles, mp 124.5-126°. The mother liquor yielded a further 0.55g, mp 123-124°. The total yield was 4.4g (81%) of p-tolyl phthalimido disulfide (59). Two recrystallizations from ethanol afforded an analytical sample: mp 124.5-125.5°; ir (KBr): 1705 (-N-CO-), 1275, 1050, 875, 825 (p-C_6H_4) and 725 cm^{-1} (o-C_6H_4).

Reaction of α-Toluenethiol with p-Tolyl Phthalimido Disulfide (59)

A mixture of 0.9 (3 mmol) of 59 and 0.37g (3 mmol) of α-toluenethiol in 30 ml of benzene was stirred at room temperature for 35 hrs. and then refluxed for 13 hrs. The reaction was cooled to room temperature, the benzene evaporated in vacuo, and the resulting solid crystallized from ethanol. The crystals (phthalimide) were filtered off, the ethanol evaporated from the filtrate and the residue chromatographed over silica gel with 3:1 hexane-chloroform eluant. The yellow oil eluted from the column exhibited 3 spots on tlc on silica gel with n-hexane eluant and was likely a mixture of di-p-tolyl (10), dibenzyl (12) and p-tolyl benzyl trisulfides.

Reaction of p-Toluenethiol with Benzyl Phthalimido Disulfide (58)

A mixture of 0.9g (3 mmol) of 58 and 0.35g (3 mmol) of p-toluenethiol in 30 ml of benzene was stirred for 5.5 hrs. at room temperature and then refluxed 43 hrs. The disappearance of the thiol was monitored by vpc. The reaction was cooled to room temperature and the 0.3g of solid which precipitated was filtered off.

The benzene was evaporated from the filtrate and the resulting semi-solid oiled out of ethanol on attempted crystallization. The oil was chromatographed over silica gel with n-hexane eluant. All fractions collected were shown to be mixtures of 10, 12 and p-tolyl benzyl trisulfide by vpc and nmr spectroscopy.

p-Bromophenylmethanethiol (53)

A mixture of 10.0g (40 mmol) of p-bromophenylmethyl bromide and 8.5g (80 mmol) of thiourea was refluxed for 5 hrs. in 50 ml of ethanol. The reaction was cooled to room temperature and the ethanol evaporated in vacuo to provide a solid. Fifty ml of water and 8g (200 mmol) of sodium hydroxide pellets were added and the mixture refluxed for 13 hrs. The reaction was cooled to room temperature and acidified with concentrated hydrochloric acid until acidic. This was extracted with three 50 ml portions of chloroform, the chloroform was washed with 50 ml of water, dried over anhydrous sodium sulfate and evaporated in vacuo to give a brown oil which crystallized on dry ice but liquified on warming. Short path distillation under reduced pressure provided 5.9g (73%) of p-bromophenylmethanethiol (53) as a colourless liquid, bp (0.35 mm) 75-78° (lit.[160] mp 25-27°); nmr (CCl_4) τ 2.5-2.9 (m, 4H), 6.35 (d, 2H), 8.4 (t, 1H).

Reaction of p-Bromophenylmethanethiol (53) with Benzyl Phthalimido Disulfide (58)

Reflux 3.0g (10 mmol) of 58 and 2.05g (10 mmol) of p-bromophenylmethanethiol (53) in 100 ml of ethanol for 2.5 hrs. All of the thiol had reacted as determined by vpc. The reaction was cooled to room

temperature and the ethanol evaporated in vacuo to provide a pale yellow solid. The addition of 50 ml of benzene and filtration of the insoluble white solid afforded 1.35g (92%) of phthalimide, mp 231-236° (lit.[161] mp 238°). Evaporation of the benzene from the filtrate gave an oil which did not crystallize from ethanol-benzene, and was chromatographed over silica gel with petroleum ether (30-60°) as eluant to provide a yellow oil. The nmr (CCl_4) of this oil showed it to be a mixture of trisulfides due to the many absorptions in the benzylic (4.8-5.7 τ) region.

n-Propyl Benzyl Trisulfide (60)

A mixture of 12.65g (50 mmol) of n-propyl phthalimido disulfide (54) and 6.2g (50 mmol) of α-toluenethiol in 150 ml of benzene was refluxed for 160 hrs. The reaction was cooled to room temperature and the solid which crystallized out was filtered to give 5.0g (68%) of phthalimide. The benzene was evaporated from the filtrate and the residue chromatographed over silica gel with petroleum ether (30-60°) as eluant. Elution provided 3.5g (30%) of trisulfide 60 as a pale yellow oil; nmr (CCl_4) τ 2.7 (m, 5H), 5.95 (s, 2H), 7.2 (t, 2H), 8.25 (m, 2H), 9.0 (t, 3H). Analysis by vpc on the LAC column indicated a purity of > 95%. With the oven programmed from 100-220° with the temperature increasing 20°/min and the helium, oxygen and hydrogen pressures at 50, 30 and 5 psi respectively, 60 exhibited a retention time of 5.6 minutes.

Further elution from the column gave 3.4g of a fraction containing ca. 50% of trisulfide 60 as estimated by vpc. Fractional distillation of this liquid provided a fraction bp (0.3 mm) 116-118° which was less pure by vpc.

i-Propyl Benzyl Trisulfide (61)●

A mixture of 12.65g (50 mmol) of i-propyl phthalimido disulfide (56) and 6.2g (50 mmol) of α-toluenethiol in 150 ml of benzene was refluxed for 111 hrs. The reaction was cooled to room temperature and the solid which crystallized out was filtered to give 5.65g (77%) of phthalimide. The benzene was evaporated from the filtrate and the residue chromatographed over silica gel with n-hexane as eluant. The purity of fractions was monitored by tlc and vpc. Elution provided 7.7g (67%) of trisulfide 61 as a yellow oil whose purity was estimated by vpc to be > 90%. The oil was fractionally distilled under reduced pressure and the fraction bp (0.35 mm) 87-115° was collected. Distillation by short path in vacuo provided 0.7g of i-propyl benzyl trisulfide (61) as a pale yellow oil, bp (0.4 mm) 111-116°; nmr (CCl_4) τ 2.9 (s, 5H), 6.05 (s, 2H), 6.95 (m, 1H), 8.7 (d, 6H). Analysis by vpc on the LAC column indicated a purity of > 95%. Under the same conditions as for 60, the trisulfide 61 exhibited a retention time of 5.0 minutes.

Benzyl p-Toluenethiosulfonate (62) was prepared in 87% yield from potassium p-toluenethiosulfonate[145] and α-bromotoluene by the method of Boldyrev, mp 53-59° (lit.[162] mp 55-57°).

Acetic α-Toluenesulfenic Thioanhydride (63)

A solution of 5.0g (50 mmol) of triethylamine in 20 ml of chloroform was added, during 20 mins., to a stirred solution of 14.0g (50 mmol) of benzyl p-toluenethiosulfonate (62) and 4.25g (50 mmol) of thioacetic S-acid (64) in 150 ml of chloroform at room temperature. After stirring one hour, the chloroform solution was washed with six 150 ml

portions of saturated sodium chloride solution, dried over anhydrous magnesium sulfate and evaporated. The residue was chromatographed over silica gel with benzene eluant to provide an oil which crystallized on standing. Recrystallization from petroleum ether (30-60°) afforded 5.7g of 63, mp 56-59° (lit.[163] mp 58-59°). The mother liquors gave a further 1.65g for a total yield of 7.35g (74%). Nmr ($CDCl_3$) τ 2.75 (s, 5H), 4.1 (s, 2H), 7.7 (s, 3H).

Thioacetic S-acid (64) (Aldrich Chemical Co.) was fractionally distilled at atmospheric pressure before use, bp 87-90° (lit.[164] bp 88-91.5°).

2-Propanesulfenyl Chloride (65) was prepared in 77% yield from di-isopropyl disulfide and chlorine by the method of Brintzinger et al.[165] bp (20-50 mm) ca.25° (lit.[166] bp (45 mm) 36°). Nmr (neat) τ 6.55 (m, 1H), 8.6 (d, 6H).

i-Propyl Benzyl Trisulfide (61)

A solution of 2.7g (25.4 mmol) of 2-propanesulfenyl chloride (65) in 50 ml of anhydrous diethyl ether was added, during 30 mins., to a stirred solution of 4.0g (25.6 mmol) of benzyl hydrodisulfide (11) in 100 ml of dry ether under a nitrogen atmosphere at room temperature. After stirring for one hour, the ether was evaporated in vacuo and the resulting liquid fractionally distilled under reduced pressure. This afforded 0.80g (14%) of 61 as a colourless liquid, bp (0.1 mm) 88-91°; nmr (CCl_4) τ 2.75 (s, 5H), 6.1 (s, 2H), 7.35 (m, 1H), 8.75 (d, 6H); mass spectrum, parent ion m/e 230, fragments at 91, 92, 198, 65.

Tris(diethylamino)phosphine (66) was prepared in 36% yield from phosphorous trichloride and diethylamine by the method of Gleason[167] bp (0.1 mm) 68° (lit.[167] bp (0.5 mm) 80-84°).

The following is a representative procedure for the preparation of symmetric disulfides via the desulfurization of the corresponding trisulfides with tris(diethylamino) phosphine (66). Disulfides synthesized by this method are summarized in Table XXIV.

Desulfurization of Di-p-Tolyl Trisulfide (10)

A solution of 0.70g (2.5 mmol) of di-p-tolyl trisulfide (10) and 0.63g (2.5 mmol) of tris(diethylamino) phosphine (66) in 100 ml of anhydrous diethyl ether was stirred for 2.5 hrs. at room temperature. The ether was evaporated in vacuo to give a yellow oil which was chromatographed over silica gel with 1:1 hexane-chloroform eluant. Collection of the first material to elute afforded a yellow oil which was crystallized from ethanol to provide 0.50g (81%) of di-p-tolyl disulfide (7) as white needles, mp and mmp 44-47° (lit.[54] mp 47°).

Desulfurization of Dibenzyl Trisulfide (12) with Triphenylphosphine (6)

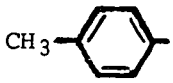
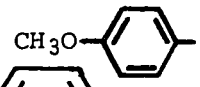
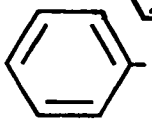
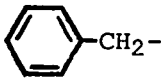
A solution of 0.60g (2.16 mmol) of 12 and 0.565g (2.16 mmol) of 6 in 10 ml of anhydrous diethyl ether was stirred for 1.5 hrs. at room temperature under a nitrogen atmosphere. The ether was evaporated in vacuo and the resulting oil allowed to stand ca. 12 hrs. as crystals formed. These were filtered and washed with hexane to give 0.78g, mp 138-149°, which, on recrystallization from ethanol, afforded 0.472g (75%) of triphenylphosphine sulfide (9), mp 161-163° (lit.[56] mp 161°).

TABLE XXIV

DESULFURIZATION OF TRISULFIDES BY TRIS(DIETHYLAMINO)PHOSPHINE

$$RSSSR + [(CH_3CH_2)_2N]_3P \longrightarrow RSSR + [(CH_3CH_2)_2N]_3P = S$$

66 67

Trisulfide	R	% Yield	mp	lit.mp	Disulfide
10		81	44-47°	47°[51]	7
25		62	36.5-38°	44-45°[53]	68
24		92	61-62°	61-62°[53]	69
12		94	68-71.5°	71°[51]	70
15	$CH_3(CH_2)_4$-	61	-	-	71
16	$CH_3CH_2CH_2$-	80	-[a]	-	72
17	CH_3O-CO-CH_2-	91	-[b]	-	73

a) One peak on vpc; nmr (CCl_4) τ 7.35 (t, 2H), 8.3 (m, 2H), 9.0 (t, 3H); mass spectrum, parent ion m/e 150, fragments at 43, 108.

b) Same retention time as authentic 73 on UCW98 column; nmr (CCl_4) τ 6.25 (s, 3H), 6.4 (s, 2H).

The hexane was evaporated from the filtrate to provide 0.259g (49%) of dibenzyl disulfide (70) as white crystals, mp 55-60°. Three crystallizations from ethanol afforded 0.080g (15%) of 70, mp 66-67.5° (lit.[54] mp 71°).

Tris(dimethylamino)phosphine (74) (Aldrich Chemical Co.) was fractionally distilled under vacuum before use, bp (17 mm) 56-57° (lit.[103] bp(12 mm) 49-51°).

Desulfurization of 2,3,4-Benzotrithiepin (77)

A solution of 0.8g (5 mmol) of aminophosphine 74 in 50 ml of benzene was added to a solution of 1.0g (5 mmol) of 77 in 100 ml of benzene and the reaction stirred for 30 mins. at room temperature. Evaporation of the benzene in vacuo gave a pale yellow oil which was chromatographed over silica gel with hexane eluant. Elution provided a white solid which was crystallized from methanol to afford 0.65g (77%) of 2,3-benzodithiin (75) as white needles, mp 77.5-79° (lit.[168] mp 80°).

Desulfurization of Exo-3,4,5-trithiatricyclo [5.2.1.$0^{2.6}$]decane (26) with Tris(dimethylamino)phosphine (74)

1.65g (10 mmol) of 74 was added to a solution of 1.9g (10mmol) of 26 in 50 ml of benzene. After stirring for 3 hrs. at room temperature, the benzene was evaporated in vacuo to give a yellow oil. Chromatography over silica gel with 2:1 hexane-chloroform eluant provided 1.15g of a viscous yellow oil with a retention time identical to that of 26 on vpc; nmr (CCl_4) τ 6.35 (d, 0.7H), 6.45-6.75 (m, 1H), 7.3-7.6 (m, 2H), 7.95-9.05 (m, 6H). Further elution gave 0.4g of a mixture of the above

oil and tris(dimethylamino)phosphine sulfide. Continued elution afforded 1.8g (92%) of the aminophosphine sulfide.

Desulfurization of Exo-3,4,5-trithiatricyclo [5.2.1.$0^{2.6}$] decane (26) with Triphenylphosphine (6)

1.3g (5 mmol) of 6 was added to a solution of 0.95g (5 mmol) of 26 in 50 ml of benzene at room temperature. After stirring for 48 hrs. the benzene was evaporated to give a white solid. The solid was heated with ethanol and filtered to provide 0.7g of white solid, mp 98-135°; nmr ($CDCl_3$) τ 6.65 (s, 2H), 7.35-7.55 (m, 2H), 8.0-9.0 (m, 8H). Evaporation of the filtrate and recrystallization from ethanol gave 1.15g (78%) of triphenylphosphine sulfide (9) as white needles, mp 163-168° (lit.[56] mp 161°).

Desulfurization of i-Propyl Benzyl Trisulfide (61)

A solution of 0.25g (1.08 mmol) of 61 and 0.30g (1.2 mmol) of aminophosphine 66 in 10 ml of anhydrous diethyl ether was stirred for 2 hrs. at room temperature under a nitrogen atmosphere. The ether was evaporated in vacuo and the resulting oil chromatographed over silica gel with 1:1 hexane-chloroform eluant. Elution provided 0.205g (96%) of i-propyl benzyl disulfide (80)● as a colourless oil; nmr (CCl_4) τ 2.75 (s, 5H), 6.2 (s, 2H), 7.4 (m, 1H), 8.8 (d, 6H); mass spectrum, parent ion m/e 198, fragments at 91, 65, 92.

Desulfurization of n-Propyl Benzyl Trisulfide (60)

A solution of 2.3g (10 mmol) of 60 and 1.65g (10 mmol) of aminophosphine 74 in 30 ml of benzene was stirred at room temperature for one hour. The benzene was evaporated in vacuo and the resulting

oil chromatographed over silica gel with petroleum ether (30-60°) as eluant. Elution provided n-propyl benzyl disulfide (81) as a yellow oil, nmr (CCl_4) τ 2.7 (s, 5H), 6.15 (s, 2H), 7.65 (t, 2H), 8.55 (m, 2H), 9.1 (t, 3H).

Desulfurization of Benzyl Phthalimido Disulfide (58).

A solution of 1.5g (5 mmol) of 58 and 1.7g (10 mmol) of aminophosphine 74 in 50 ml of benzene was stirred at room temperature. The reaction turned cloudy and then became clear yellow. Heat was evolved. After 30 mins. the benzene was evaporated under vacuum to give a yellow solid which was crystallized from ethanol to afford 0.7g of N-benzylphthalimide (82) as white needles, mp 114-115° (lit.[169] mp 116°). The mother liquor provided a further 0.25g, mp 108-114°. The total yield was 0.95g (80%).

Desulfurization of n-Propyl Phthalimido Disulfide (54).

A solution of 0.505g (2 mmol) of 54 and 0.7g (4.2 mmol) of aminophosphine 74 in 30 ml of benzene was stirred at room temperature. Heat was evolved and a yellow colour developed. After 30 mins. the benzene was evaporated in vacuo to yield a colourless oil which crystallized on standing. Recrystallization from ethanol provided 0.233g (62%) of N-n-propylphthalimide (83) as white needles, mp 62.5-65° (lit.[170] mp 64.5°).

Desulfurization of i-Propyl Phthalimido Disulfide (56).

A solution of 1.25g (5 mmol) of 56 and 1.7g (10 mmol) of aminophosphine 74 in 50 ml of benzene was stirred at room temperature. Heat was evolved. After 40 mins. the benzene was removed under vacuum to give an oil which crystallized on standing on dry ice. Recrystallization from ethanol provided 0.2g (21%) of N-i-propylphthalimide (84) as white needles, mp 80-83° (lit.[171] mp 86°).

Attempted Desulfurization of Carbomethoxymethyl Phthalimido Disulfide (55).

A solution of 1.15g (4 mmol) of 55 and 1.35g (8 mmol) of aminophosphine 74 in 30 ml of benzene was stirred at room temperature. Heat was evolved, a yellow colour formed and a solid precipitated. After one hour the reaction was filtered to yield phthalimide, mp 232-234.5° (lit.[161] mp 238°). Evaporation of the benzene from the filtrate provided a brown oil which was not characterized.

Desulfurization of p-Tolyl Phthalimido Disulfide (59).

A solution of 1.5g (5 mmol) of 59 and 0.85g (5.2 mmol) of aminophosphine 74 in 50 ml of benzene was stirred at room temperature. The reaction became cloudy and an oil separated out. After 4 hrs. the stirring was stopped. On standing 4 days, the oil was replaced by crystals. Filtration afforded 0.35g of phthalimide, mp 230-233° (lit.[161] mp 238°) and mmp undepressed. Evaporation of the filtrate to dryness gave a solid plus a liquid. The addition of 5 ml of hexane and filtration provided 0.5g, mp 145-165°. Recrystallization from ethanol-benzene yielded 0.2g (15%) of N-(p-tolyl-thio)phthalimide (85), mp 200.5-203.5° (lit.[48] mp 200.5-203°).

Desulfurization of t-Butyl Phthalimido Disulfide (57).

A solution of 1.0g (5 mmol) of tri-n-butylphosphine in 5 ml of benzene was added to a stirred solution of 1.35g (5 mmol) of 57 in 20 ml of benzene under a nitrogen atmosphere at room temperature. The reaction turned pale yellow and heat developed. After 30 mins. the benzene was evaporated under vacuum to give a solid plus a liquid. Addition of 5 ml of hexane and filtration provided 0.7g of N-(t-butylthio)phthalimide (86) as a white solid, mp 125.5-128.5° (lit.[97] mp 130-131°), mmp undepressed. The mother liquor afforded a further 0.15g, mp 128-132° for a total yield of 0.85g (73%).

Radiochemical Experiments

The equipment described earlier was used to determine the radiochemical activity of the samples. On standardization the plateau area was centered at 2325 volts with pulse height = 2. All samples were counted on shelf #1 after being mounted on cardboard and covered with a mylar film.

Sulfur Dichloride - ^{35}S (14*) was purchased from Amersham/Searle (3.3 mCi., 0.068g). Of this, 0.021g was diluted with 25g of unlabelled sulfur dichloride (14) which had been distilled twice, bp 60° (lit.[148] bp 59°).

Dibenzyl Trisulfide - ^{35}S (12*) was prepared from sulfur dichloride-^{35}S (14*) and α-toluenethiol in 67% yield as described for the unlabelled compound, mp 47.5-49° (lit.[54] mp 49°).

Di-p-Tolyl Trisulfide - ^{35}S(10*) was prepared in 53% yield from sulfur dichloride-^{35}S(14*) and p-toluenethiol as described for the unlabelled compound, mp 83.5-85.5° (lit.[56] mp 80-81°).

Desulfurization of Dibenzyl Trisulfide - ^{35}S(12*) with Triphenylphosphine (6)

A solution of 0.400g (1.44 mmol) of 12* and 0.380g (1.45 mmol) of 6 in 100 ml of anhydrous diethyl ether was stirred for 2 hrs. at

room temperature. The ether was evaporated and the resulting white solid chromatographed over silica gel. Elution with 1:1 hexane-chloroform provided 0.218g (62%) of dibenzyl disulfide (70), mp 66.5-69.5° (lit.[54] mp 71°). Elution with chloroform afforded 0.236g (56%) of triphenylphosphine sulfide (9*), mp 159-162° (lit.[56] mp 161°).

Desulfurization of Dibenzyl Trisulfide -^{35}S(12*) with Tris(diethylamino)phosphine (66) was carried out as for the unlabelled compound to provide a 69% yield of dibenzyl disulfide (70*), mp 66-70.5° (lit.[54] mp 71°) and a 91% yield of tris(diethylamino)phosphine sulfide (67) as a yellow oil.

Desulfurization of Dibenzyl Trisulfide -^{35}S(12*) with Tri-n-butyphosphine

A solution of 0.7g (2.52 mmol) of 12* and 0.6g (2.96 mmol) of tri-n-butylphosphine in 100 ml of anhydrous diethyl ether was stirred under a nitrogen atmosphere for 45 mins. The ether was evaporated and the residue chromatographed over silica gel. Elution with 3:1 hexane-chloroform provided, after 3 recrystallizations from ethanol, 0.090g (15%) of dibenzyl disulfide (70*), mp 64-68° (lit.[54] mp 71°). Elution with 1:3 hexane-chloroform gave 0.519g (91%) of tri-n-butylphosphine sulfide as a yellow oil.

Desulfurization of Di-p-tolyl Trisulfide -^{35}S(10*) with Triphenylphosphine (6)

A solution of 0.525g (1.89 mmol) of 10* and 0.50g (1.91 mmol) of 6 in 100 ml of anhydrous diethyl ether was stirred for one hour. The

ether was evaporated and the resulting solid chromatographed over silica gel. Elution with 1:1 hexane-chloroform provided, after crystallization from ethanol, 0.195g (42%) of di-p-tolyl disulfide (7), mp 41-45° (lit.[51] mp 47°). Elution with chloroform afforded, after crystallization from ethanol, 0.340g (61%) of triphenylphosphine sulfide (9*), mp 160.5-164° (lit.[56] mp 161°).

Desulfurization of Di-p-tolyl Trisulfide -^{35}S(10*) with Tris(diethylamino)phosphine (66) was accomplished as described for the unlabelled compound to provide a 56% yield of di-p-tolyl disulfide (7), mp 44-45° (lit.[51] mp 47°) and a 85% yield of phosphine sulfide 67 as a yellow oil.

Table XXV gives the results of the determination of the radiochemical activity of the samples discussed above.

TABLE XXV

	Reaction	Compound	Weight (g.)	Dis-integrations	Time (min.)	Activity (mCi mole^{-1})
1)	12* + 6 ⟶ 70 + 9	12*	0.00846	19,061	2.0	0.138
		70	0.01027	14,384	10.0	0.014
		9	0.00904	16,663	2.0	0.122
2)	12* + 66 ⟶ 70 + 67	12*	0.00846	18,712	2.0	0.138
		70	0.00834	20,776	2.0	0.137
		67	0.00923	4,839	10.0	0.006
3)	12* + $(nBu)_3P$ ⟶ 70 + $(nBu)_3P{=}S$	12*	0.00689	32,590	6.0	0.098
		70	0.00713	9,258	6.0	0.024
		$(nBu)_3P{=}S$	0.00315	12,650	6.0	0.071
4)	10* + 6 ⟶ 7 + 9	10*	0.01023	22,580	6.0	0.046
		7	0.01087	758	6.0	<0.001
		9	0.01053	22,196	6.0	0.046
5)	10* + 66 ⟶ 7 + 67	10*	0.01023	28,010	6.0	0.057
		7	0.00707	1,200	10.0	0.002
		67	0.00770	34,030	10.0	0.056

Kinetics of Desulfurization. All materials were recrystallized or redistilled before use in these kinetic experiments. Benzene and cyclohexane were dried over and distilled from sodium before use while ethyl acetate was dried and distilled from phosphorous pentoxide. A Hitachi-Coleman 124 Spectrophotometer equipped with a Hitachi-Coleman 165 recorder and a Neslab constant temperature regulator (±0.1°C) was utilized at constant wavelength to monitor the disappearance of trisulfide with time. The solutions of trisulfide and phosphine were equilibrated for a minimum of 15 minutes before each run. Every run was carried out in duplicate.

Pseudo first order conditions were used for the reactions with an excess of (at least 20 fold) tris(diethylamino) phosphine (66). The values of the pseudo first order rate constant (k') were calculated from plots of ln $(Ao-A\infty)/(At-A\infty)$ versus time by the method of least squares. All calculations were performed using an IBM 360/50 computer. The rate constants were calculated from the initial portion of the curve for which first order kinetics were seen to be valid.

Reaction of p-Toluenesulfenic p-Toluenesulfonic Thioanhydride (1) with Three Moles of Triphenylphosphine (6).

A solution of 2.36g (9 mmol) of 6 in 50 ml of benzene was added over one hour to 0.93g (3 mmol) of 1 dissolved in 50 ml of benzene at room temperature. A precipitate formed and then redissolved after 2 hrs. The reaction was stirred for 6 hrs., the benzene evaporated in vacuum, and the residue chromatographed over silica gel. Elution with 3:1 hexane-chloroform gave 0.50g (68%) of di-p-tolyl disulfide (7) as a yellow oil which, on crystallization from ethanol, afforded white needles, mp 44.5-46.5° (lit.[54] mp 47°). Elution with 1:1 hexane-chloroform provided, after crystallization from ethanol, 0.75g (85%) of triphenylphosphine sulfide (9), mp 158-160.5° (lit.[56] mp 161°). The use of 1:3 hexane-chloroform as eluant gave, after crystallization from diethyl ether, 0.95g (57%) of triphenylphosphine oxide (8), mp 156-159° (lit.[86] mp 156°). The melting points of 7, 8 and 9 were undepressed on admixture with authentic samples.

Reaction of p-Toluenesulfenic p-Toluenesulfonic Thioanhydride (1) with Equimolar Triphenylphosphine (6).

A solution of 0.26g (1 mmol) of 6 in 50 ml of benzene was added over 40 mins. to 0.31g (1 mmol) of 1 dissolved in 50 ml of benzene. The reaction was stirred for 4 hrs. at room temperature, the benzene evaporated in vacuum, and the residue chromatographed over silica gel. Elution with 1:1 petroleum ether (30-60°)-chloroform gave a pale yellow solid, which, on crystallization from ethanol, afforded 0.20g (68%) of triphenylphosphine sulfide (9), mp 163-165 (lit.[56] mp 161°). The filtrate was evaporated to

dryness and crystallized from ethanol to produce 0.23g (81%) of p-tolyl p-toluenethiosulfonate (43), mp and mmp 70-74° (lit.[172] mp 78.5-79.5°).

Reaction of p-Toluenesulfenic p-Toluenesulfonic Thioanhydride (1) with Tris(diethylamino)phosphine (66).

A solution of 0.25g (1 mmol) of 66 in 25 ml of benzene was added slowly to 0.31g (1 mmol) of 1 dissolved in 10 ml of benzene. The reaction was stirred for 6.5 hrs. at room temperature and the benzene was removed under vacuum. The residue was heated with n-hexane and an insoluble oil 87 (0.35g, 60%) separated out, nmr ($CDCl_3$) τ 2.75 (m, 8H), 6.85 (m, 12H), 7.62 (d, 3H, J_{PH} = 2.5 Hz), 7.69 (s, 3H), 8.85 (t, 18H) (lit.[138]). The hexane soluble portion was chromatographed over silica gel. Elution with 1:1 hexane-chloroform afforded 0.10g (40%) of p-tolyl p-toluenethiosulfonate (43), which, after crystallization from ethanol, gave white crystals, mp and mmp 74-78° (lit.[172] mp 78.5-79.5°). Further elution gave 0.15g of tris(diethylamino)phosphine sulfide (67).

Sulfur Extrusion from p-Toluenesulfenic p-Toluenesulfonic Thioanhydride (1) in Methanol.

The procedure outlined here is typical of the sulfur extrusion reactions summarized in Table XXVI. A solution of 0.200g (0.65 mmol) of 1 in 20 ml of methanol was stirred at room temperature. After 24 hrs. the solvent was removed in vacuo to afford 0.203g of crude p-tolyl p-toluenethiosulfonate (43) whose infrared spectrum was superimposable on that of an authentic sample. Crystallization from n-hexane gave 0.110g (61%) of 43, mp 72.5-75° (lit.[172] mp 78.5-79.5°). Mmp with authentic 43 was

undepressed but admixture with 1 resulted in a sample mp < 58-62°. It was found that as little as 5% of 1 added to 43 will cause a noticeable change in the ir spectrum so that the crude samples of 43 obtained in these reactions must contain less than 5% of unreacted p-toluenesulfenic p-toluenesulfonic thioanhydride (1).

Attempted Sulfur Extrusion from p-Toluenesulfenic p-Toluenesulfonic Thioanhydride (1).

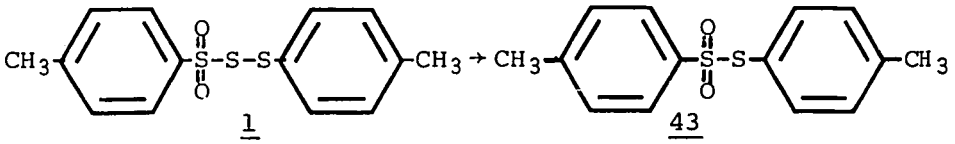
The procedure outlined here is typical of the attempted extrusion reactions summarized in Table XXVI in which 1 was recovered unchanged. A solution of 0.200g (0.65 mmol) of 1 in 20 ml of ethyl acetate was stirred at room temperature. After 23 hrs., the solvent was evaporated in vacuo to provide 0.209g of a crude solid whose infrared spectrum was identical to that of authentic 1. Crystallization from n-hexane afforded 0.134g (67%) of recovered starting material, mp 72-74° and mmp with authentic 1 68-71°. Admixture with 43 gave a sample mp < 59-65°.

Toluene-α-d_1 (88).

A mixture of 48.8g (2.0 mol) of magnesium turnings and 200 ml of anhydrous diethyl ether, in a 2 ℓ. three necked flask fitted with a mechanical stirrer, a condenser with a drying tube and an addition funnel with a gas inlet tube, was flushed with nitrogen. A small amount (ca.1.5 ml) of α-chlorotoluene was added and the reaction was initiated. A solution of 253.2g (2.0 mol) of α-chlorotoluene in 1 ℓ. of dry ether was added over 45 mins. as the temperature was controlled by an ice bath. The reaction mixture was refluxed for 15 mins. and then cooled in ice. Eighty grams (4.0 moles) of deuterium oxide (Merck, Sharpe and Dohme, min. isotopic purity 99.7%) was added dropwise to maintain gentle refluxing. After the

TABLE XXVI[a]

SULFUR EXTRUSION FROM p-TOLUENESULFENIC p-TOLUENESULFONIC THIOANHYDRIDE (1)



1 → 43

Solvent	Recovery of 1, %	Yield of 43, %
Ethanol, absolute	-	48
Methanol	-	61
Isopropanol	-	32
Acetic acid glacial	-	52
Silica gel column[b]	-	37
Dimethyl formamide	-	72
Dimethyl formamide, dry[c]	-	51
Acetonitrile	-	74
Acetone: water (1:1)	-	50
Acetonitrile + 5 drops conc. HCl	-	-
Acetronitrile + 5% $(CH_3CH_2)_2NH$	-	-
Benzene	68	-
Benzene, reflux	49	-
Diethyl ether	64	-
Diethyl ether, reflux	50	-
Acetonitrile, dry[d]	64	-
Ethyl acetate	67	-
Chloroform	58	-
Tetrahydrofuran	56	-
Acetone	65	-
Diethyl ether, wet[e]	40	-
0.012 M HCl in ether	90	-
0.12 M HCl in ether	85	-

a) Unless stated otherwise, the reaction was stirred for ca. 24 hours at room temperature and worked up as in the typical procedure on p.176.

b) Chromatographed over silica gel with hexane-chloroform eluant.

c) Distilled from BaO bp 152.5°; gave a negative test for water with $Ti(i\text{-}PrO)_4$.

d) Distilled from P_2O_5, bp 82°; gave a negative test for water with $Ti(i\text{-}PrO)_4$.

e) Ether was shaken with water and gave a positive test for water with $Ti(i\text{-}PrO)_4$.

addition, the reaction was refluxed for 15 mins. and cooled.

The reaction mixture was added, in small portions, to 600 ml of water and 200 ml of concentrated hydrochloric acid which had been cooled in an ice bath. The ether layer was decanted and 100 ml of ether was added and decanted. The combined ether layers were dried over anhydrous sodium sulfate and evaporated in vacuo, with a bath temperature ca. 25°, to afford 280 ml of yellow liquid. Fractional distillation at atmospheric pressure gave, after a forerun of 120 ml of diethyl ether (bp ca. 35°), 107.95g (58%) of toluene-α-d_1 (88) as a colourless liquid, bp 110-111° (lit.[173] bp 110.6°); nmr (neat) τ 2.95 (s, 5H), 7.87 (t, 2H, J_{HD} = 2 Hz); mass spectrum, parent peak at m/e 93, fragments at 92, 91, 66, 65. Integration of the nmr signals gave a value of 97.5% deuterium incorporation.

p-Toluenesulfonyl chloride-α-d_1 (89) was prepared in 31% yield from toluene-α-d_1 (88) essentially as described by Vogel[174], mp 66-69.5° (lit.[175] mp 71°); nmr ($CDCl_3$) τ 2.27 (m, 4H), 7.5 (t, 2H, J_{DH}= 2 Hz); mass spectrum, parent peak at m/e 191, fragments at 92, 156, 66, 125. The ratio of the ions at m/e 191 and 190 indicated a deuterium content of 97.3%.

Evaporation of the filtrate and fractional distillation by the procedure of Vogel[174] gave a 37% yield of a 7:3 mixture of ortho to para toluenesulfonyl chlorides, bp (17 mm) 140-142° (lit.[174] bp (10 mm) 126°); nmr ($CDCl_3$) τ 1.85-2.7 (m), 7.3 (t, J_{DH} =2 Hz), 7.5 (t, J_{DH} = 2 Hz). The isomer ratio was determined by integration of the signals at 7.3 and 7.5 τ .

p-Toluenethiol-α-d_1 (90) was prepared in 45% yield from p-toluenesulfonyl chloride-α-d_1 (89) according to the procedure of Vogel[176], mp 41-44° (lit.[177] mp 42-43°); nmr ($CDCl_3$) τ 2.95 (m, 4H), 6.7 (s, 1H), 7.75 (t, 2H, J_{DH} = 2 Hz); mass spectrum, parent ion m/e 125 fragments at 92, 124, 91, 80, 78. Integration of the nmr signals gave a deuterium content of 97.5%.

p-Toluenesulfenyl chloride-α-d_1 (91) was prepared in 74% yield from p-toluenethiol-α-d_1 (90) by the method of Emde[144], bp (0.55 mm) 63-65° (lit.[178] bp (6 mm) 94°); nmr (CCl_4) τ 2.65 (m, 4H), 7.68 (t, 2H, J_{HD} = 2 Hz). Integration of the nmr signals indicated a deuterium content of 98.5%.

Potassium p-Toluenethiosulfonate-α-d_1 (92) was prepared in 55% yield from p-toluenesulfonyl chloride-α-d_1 (89) as described by Boldyrev and co-workers[145].

p-Toluenesulfenic p-Toluenesulfonic Thioanhydride-α,α'-d_2 (93) was prepared in 68% yield from potassium p-toluenethiosulfonate-α-d_1 (92) and p-toluenesulfenyl chloride-α-d_1 (91) as described on p.130, mp 71-74°; mmp 72-76.5°; nmr (CCl_4) τ 1.8-3.0 (m, 8H), 7.65 (m, 4H); mass spectrum, parent ion m/e 312, fragments at 280, 248, 216, 156, 140, 125, 124, 92. Integration of the nmr signals indicated a deuterium content of 99.1%.

p-Tolyl p-Toluenethiosulfonate-α,α'-d_2 (43d) was prepared in 75% yield from 93 as described on p.176, mp and mmp 73-77° (lit.[172] mp 78.5-79.5°); nmr (CCl_4) τ 2.7 (m, 8H), 7.6 (m, 4H); mass spectrum, parent ion at m/e 280, fragments at 140, 92, 124, 156. Nmr integration indicated a deuterium content of 98%.

Crossover Desulfurization of p-Toluenesulfenic p-Toluenesulfonic Thioanhydride (1) and p-Toluenesulfenic p-Toluenesulfonic Thioanhydride - $\alpha, \alpha' - d_2$ (93).

A solution of 0.100g (0.32 mmol) of 1 and 0.100g (0.32 mmol) of 93 in 20 ml of absolute ethanol was stirred at room temperature for 23.5 hrs. A yellow oily semi-solid was noted at the bottom of the flask. The solvent was evaporated to provide an oil which crystallized on standing. Recrystallization from n-hexane followed by recrystallization from ethanol gave 0.071g of thiosulfonate, mp 73-75.5°. The mother liquor afforded a further 0.050g, mp 71-74° for a total yield of 0.121g (67%).

Oxidation of di-p-Tolyl Trisulfide (10) with Hydrogen Peroxide.

A solution of 2.8g (10 mmol) of di-p-tolyl trisulfide (10) in 100 ml of methylene chloride plus 10 ml of glacial acetic acid was treated with 0.7g (20 mmol, 2 ml of 35% solution) of hydrogen peroxide and stirred for 43 hrs. at room temperature. A further 0.7g (20 mmol) of peroxide was added and the reaction stirred for 22 hrs. at which point an additional 0.7g (20 mmol) was added. The formation of a yellow precipitate was noted. After a total of 70 hrs., the methylene chloride was evaporated in vacuo and the residue poured over ice-water to provide a yellow solid. Filtration and recrystallization from n-hexane gave 1.6g of pale yellow crystals. Recrystallization from the same solvent afforded 1.1g (40%) of p-tolyl p-toluenethiosulfonate (43) as white crystals, mp 77-80° (lit.[172] mp 78.5-79.5°) and mmp with an authentic sample undepressed.

p-Chlorobenzenesulfenic Methanesulfonic Thioanhydride (94)●.

To a stirred solution of 4.5g (25 mmol) of p-chlorobenzenesulfenyl chloride[178] in 100 ml of anhydrous diethyl ether was added 4.2g (28 mmol) of potassium methanethiosulfonate as a fine powder. After 5 mins., 0.4g (2.7 mmol) of the thiosulfonate salt was added and this was repeated at 50 mins. and at 80 mins. The reaction was stirred for 17 hrs. at room temperature and filtered to remove the KCl which had formed. The ether was evaporated from the filtrate under vacuum to yield a yellow solid, which, on crystallization from diethyl ether, provided 4.5g (71%) of 94, mp 36-39°. Three recrystallizations from ether afforded a sample mp 37.5-39.5°; ir (KBr) 1320 and 1140 cm^{-1} ($-SO_2-$); nmr (CCl_4) τ 2.5 (m, 4H), 6.78 (s, 3H); mass spectrum, parent ion at m/e 254, fragments at 143, 108, 175, 159. An attempt at further purification led to decomposition.

The following is a representative procedure for the isolation of thiosulfonates during the attempted preparation of sulfenic sulfonic thioanhydrides. A summary of the thiosulfonates obtained is found in Table XXVII and the spectral characteristics of these compounds are collected in Table XXVIII.

p-Chlorophenyl Methanethiosulfonate (95).

To a solution of 2.25g (12.6 mmol) of p-chlorobenzenesulfenyl chloride[178] in 50 ml of anhydrous diethyl ether was added 2.7g (18 mmol) of potassium methanethiosulfonate as a fine powder. After 15 mins. the orange colour of the sulfenyl chloride was discharged and a white precipitate had formed. Filtration, after 3 hrs. of stirring at room temperature, gave 1.7g of KCl plus unreacted thiosulfonate salt. Evaporation of the ether from the filtrate afforded a yellow solid which was crystallized from ether to provide 2.25g (77%) of 95. Recrystallization from ether yielded a sample, mp 99.5-102° (lit.[179] mp 102-103°).

TABLE XXVII

PREPARATION OF THIOSULFONATES

$RSO_2S^-K^+ + R'SCl \longrightarrow RSO_2SR' + KCl$

Compound	R	R'	% Yield	mp, °C	lit.mp, °C
95	CH_3-	$pClC_6H_4$-	77	99.5-102	102-103[179]
96	$pCH_3C_6H_4$-	$pClC_6H_4$-	48	88.5-90	90[180]
97	$pCH_3C_6H_4$-	CH_3-	48	56.5-58.5	57-58[88(c)]
98	$C_6H_5CH_2$-	$pClC_6H_4$-	87	109-110[a]	-
99	$pCH_3C_6H_4$-	$pBrC_6H_4$-	23	97.5-99.5[b]	107[137]
100	$pClC_6H_4$-	C_6H_5-	36	82.5-86	81[180]
101	$pClC_6H_4$-	$pClC_6H_4$-	69	133-137	137-138[181]
102	C_6H_5-	$pClC_6H_4$-	28	68.5-71.5	72-73[180]

a) Anal. Calcd. for $C_{13}H_{11}ClO_2S_2$: C, 52.26; H, 3.71.
Found: C, 52.22; H, 3.84.

b) Anal. Calcd. for $C_{13}H_{11}BrO_2S_2$: C, 45.6; H, 3.2; S. 18.7.
Found: C, 46.07; H, 3.51; S, 19.66

TABLE XXVIII

SPECTRAL PROPERTIES OF THIOSULFONATES[a]

$R-SO_2-S-R'$

Compound	R	R'	Nmr (τ)	Mass spectrum[b]
95	CH_3	$pClC_6H_4$-	2.4(m, 4H), 6.8(s, 3H)[c]	222; 159, 143, 108
96	$pCH_3C_6H_4$-	$pClC_6H_4$-	2.7(m, 8H), 7.6(s, 3H)[d]	298; 91, 155, 139, 65
101	$pClC_6H_4$-	$pClC_6H_4$-	———	318; 159, 175, 111, 143, 108
98	$C_6H_5CH_2$-	$pClC_6H_4$-	2.55(s, 9H), 5.5(s, 2H)[c]	298; 91, 234, 65
99	$pCH_3C_6H_4$-	$pBrC_6H_4$-	2.55(m, 8H), 7.55(s, 3H)[c]	342; 58, 91, 155, 139
100	$pClC_6H_4$	C_6H_5-	———	284; 110, 109, 125, 175, 159

a) All compounds in the table exhibited ir(KBr) 1340-25 and 1145-25 cm^{-1} ($-SO_2-$).

b) Parent ion followed by major fragments in order of decreasing intensity.

c) $CDCl_3$

d) CCl_4

APPENDIX I

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

Program:

```
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 CONCENTRATION  (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,END=500)(HEAD(M),M=1,18)
   50 FORMAT(18A4)
      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)
      DO 35 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,5HRATIC//)
      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 24H2ND 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
      DO10J=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
      DO20I=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. Calculation of Activation Parameters ($\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$) by the Method of Least Squares.

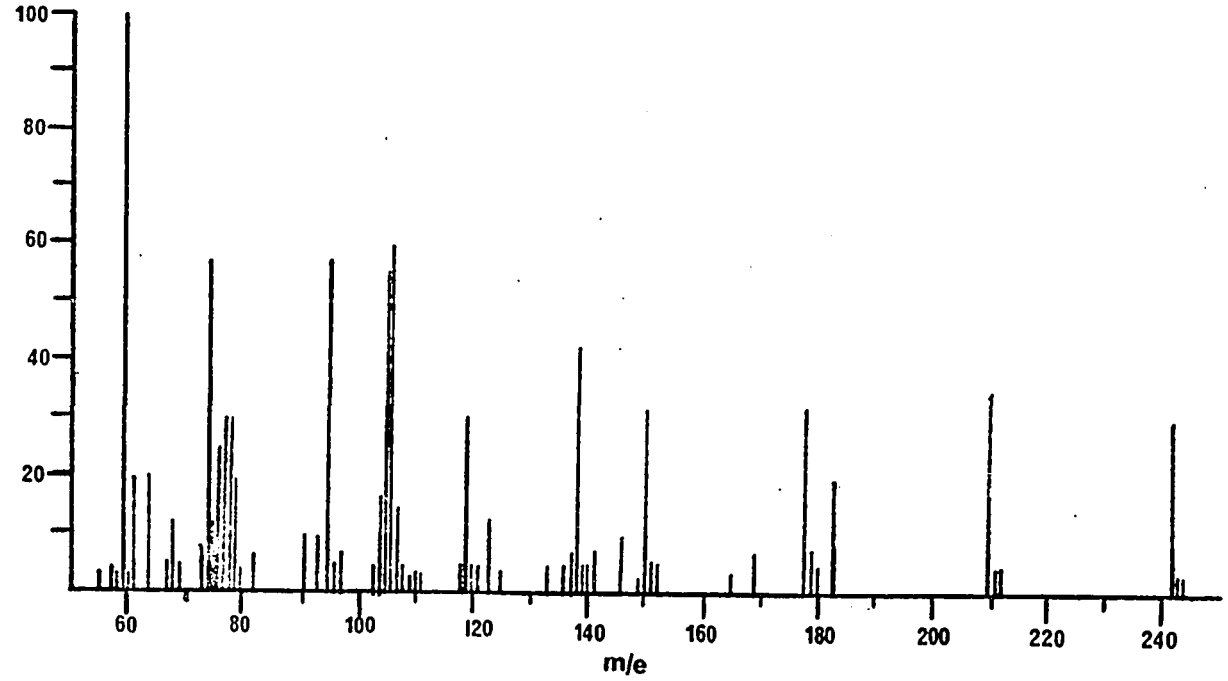
Program:

```
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,8HENTROPY,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
```

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
      DO10J=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
      DO20I=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
```

APPENDIX II



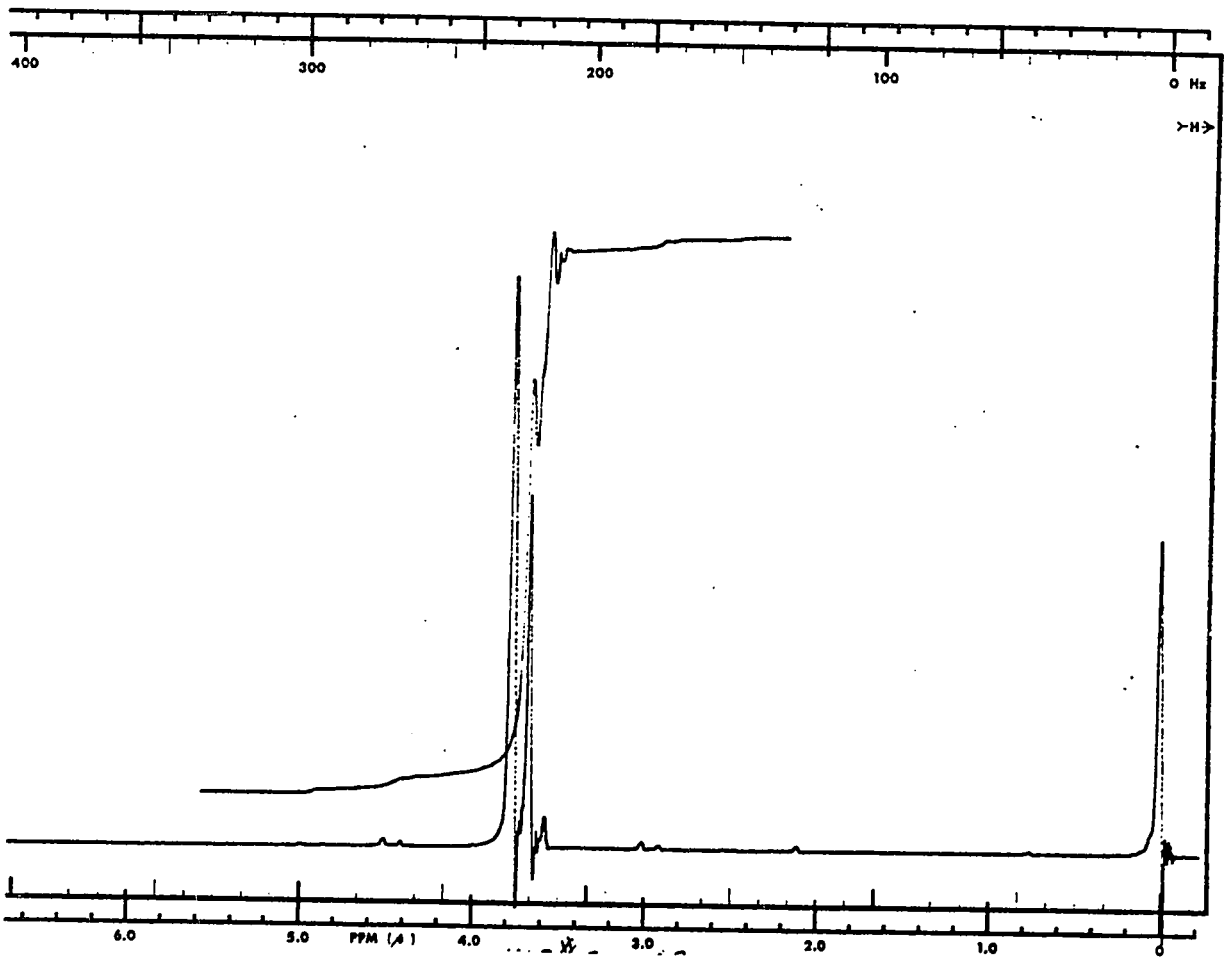


Figure 34. Mass spectrum and nmr spectrum of di-carbomethoxymethyl trisulfide (17).

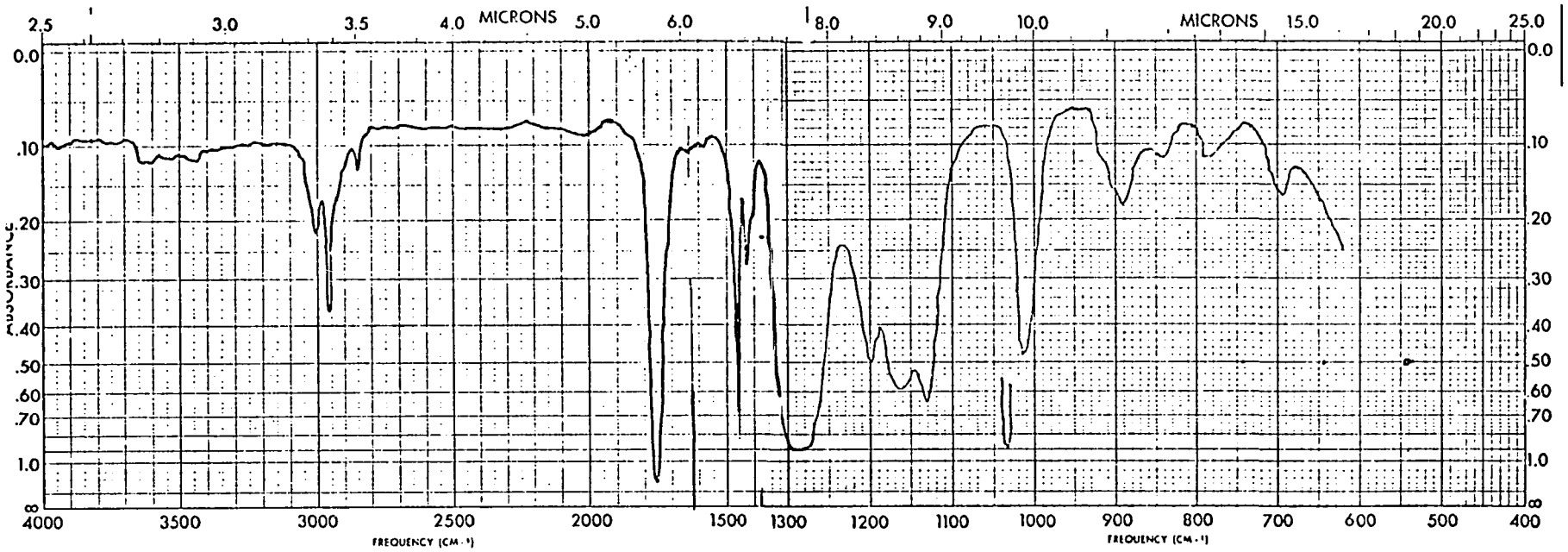


Figure 35. Ir spectrum of di-carbomethoxymethyl trisulfide (17).

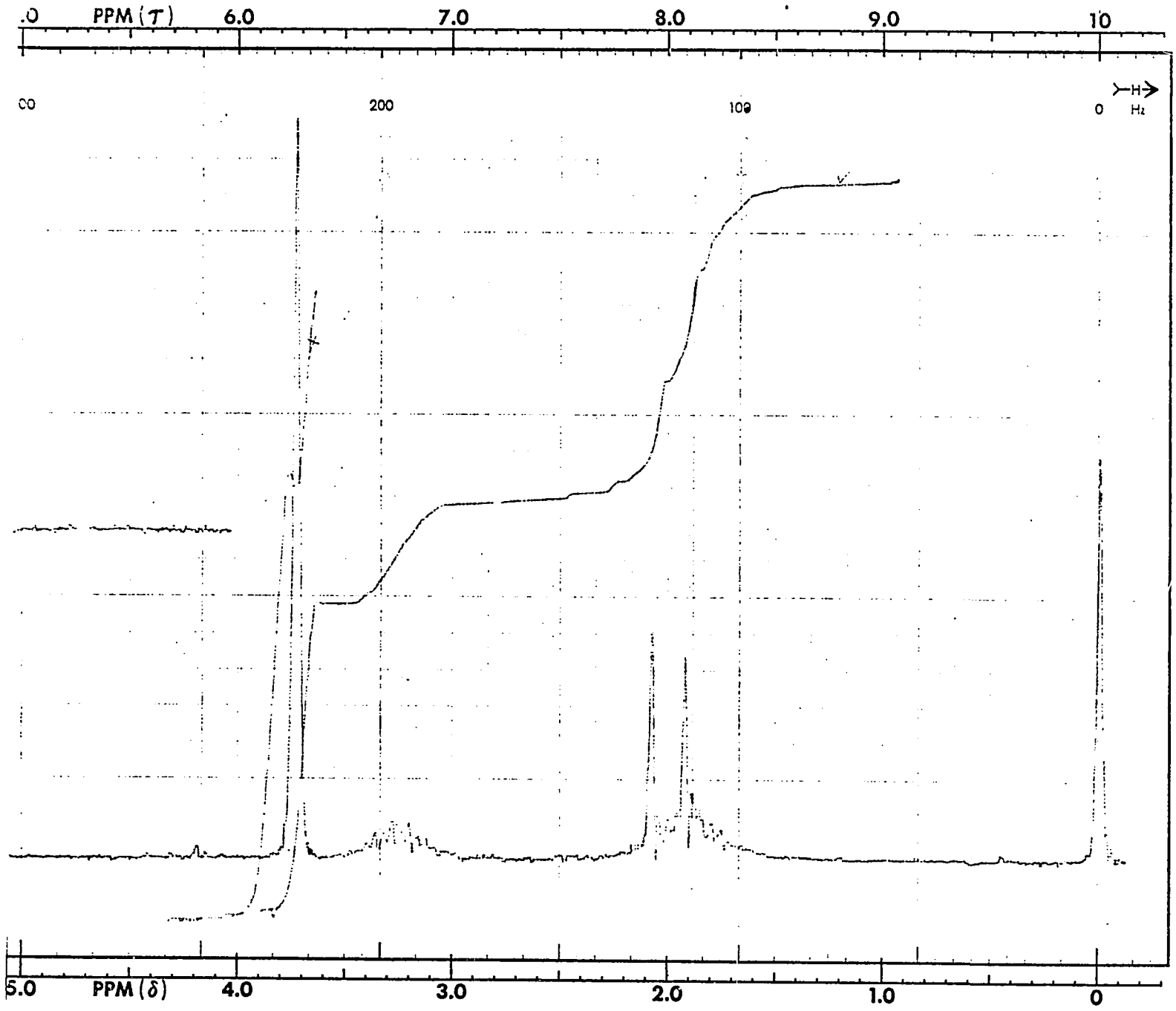


Figure 36. Nmr spectrum of meso - α, α' - dimercapto dimethyl adipate (32).

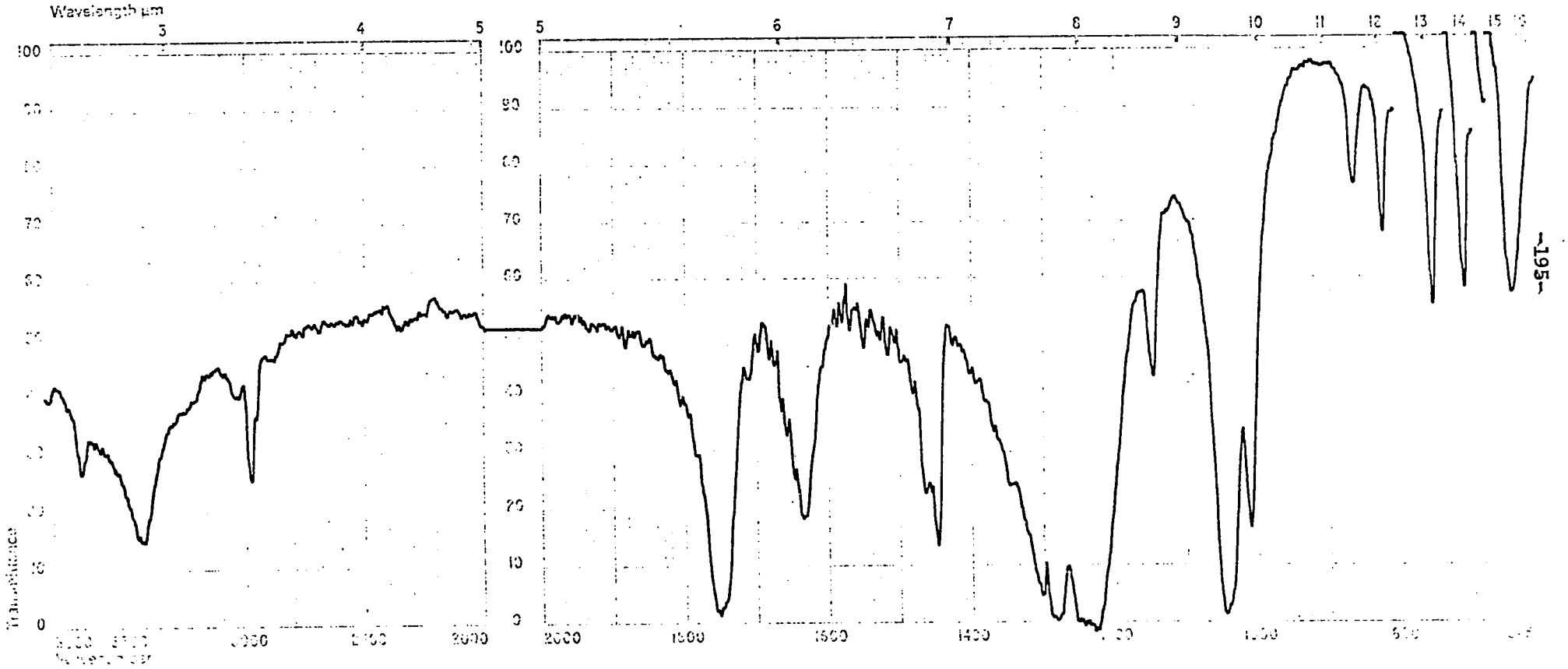


Figure 37. Ir spectrum of disodium meso - α, α' - dimethyl adipate dithiosulfate (41).

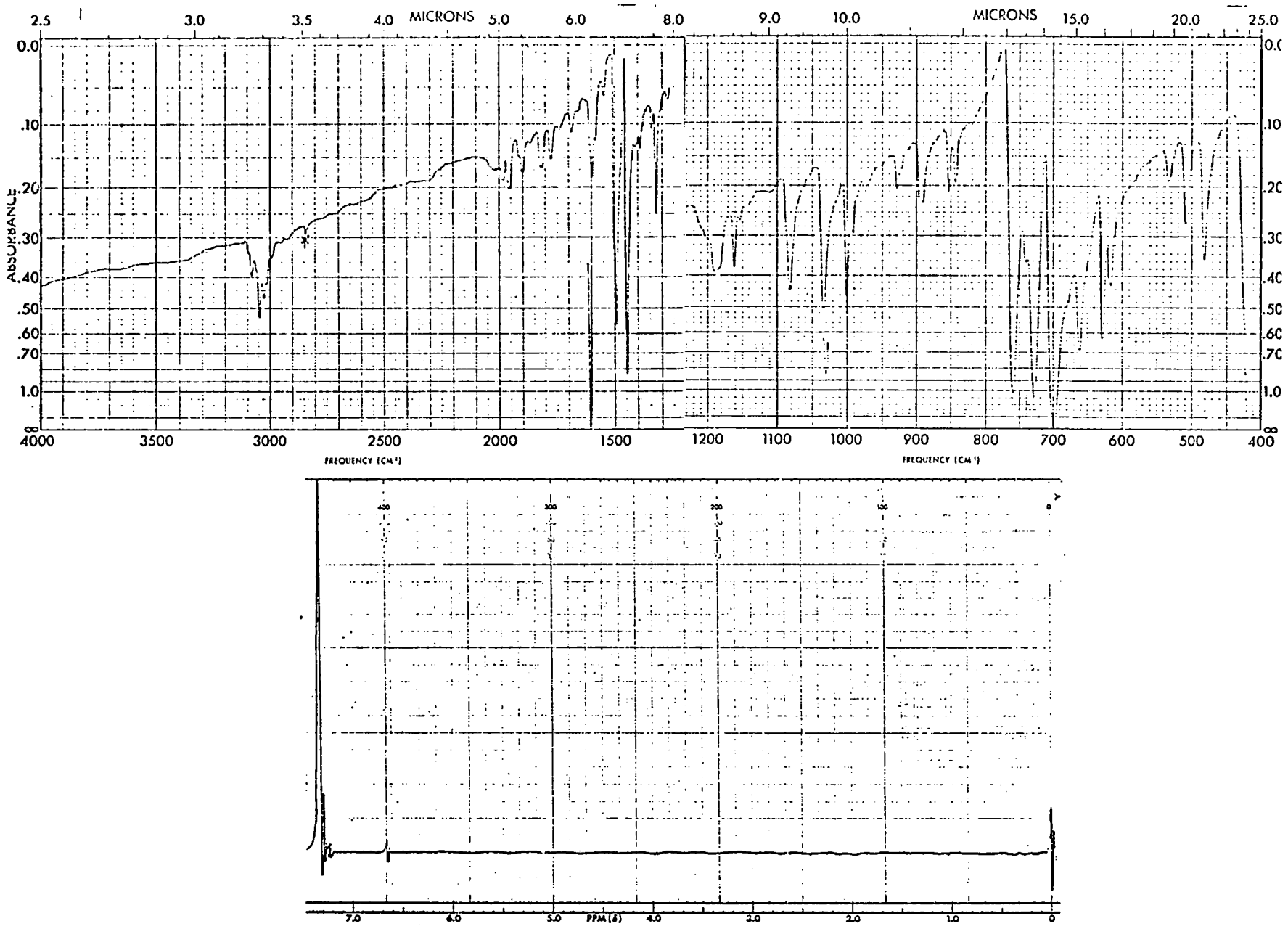


Figure 38. Ir and nmr spectra of triphenylmethyl chlorodisulfide (47).

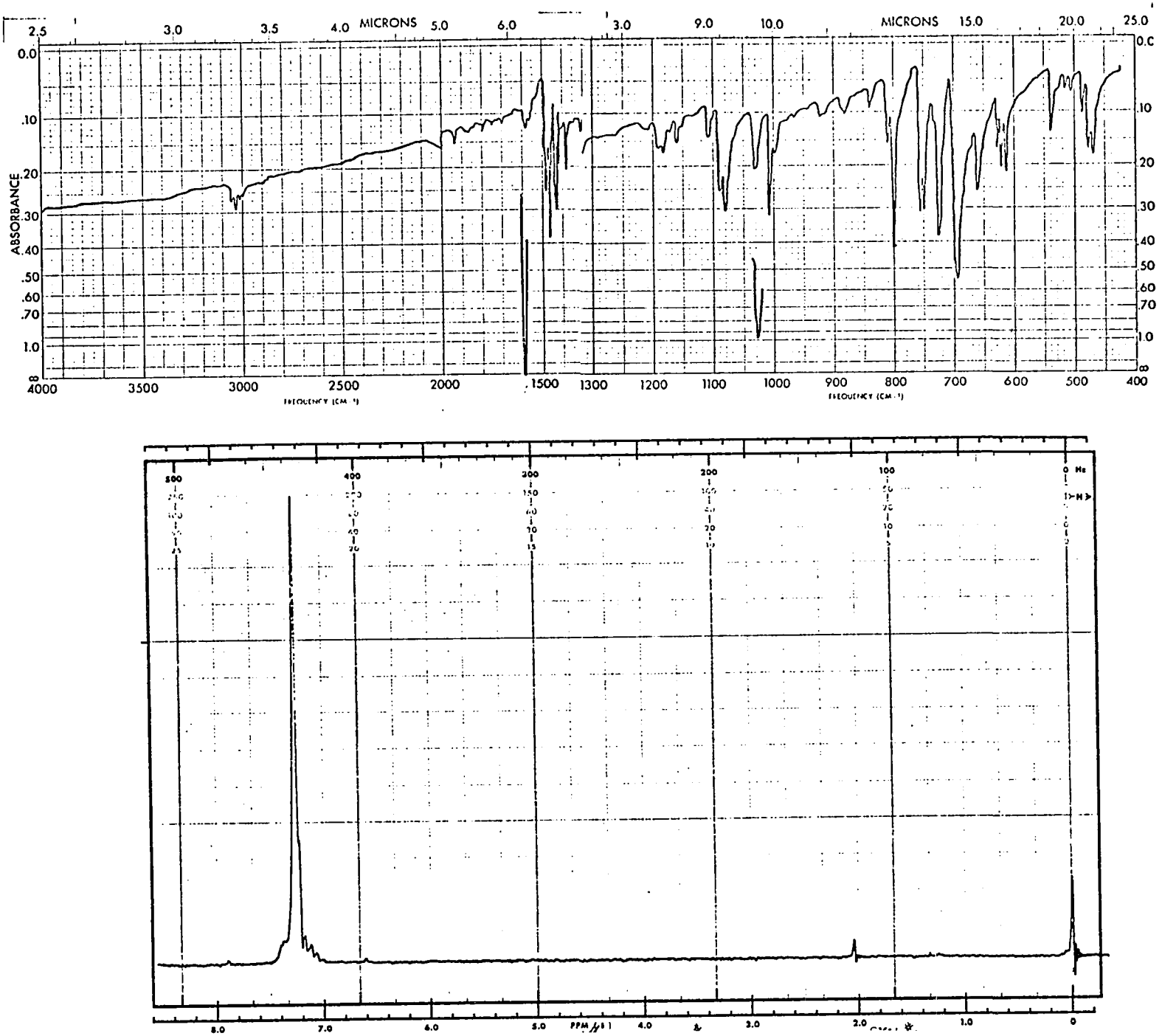


Figure 39. Ir and nmr spectra of triphenylmethyl p-chlorophenyl trisulfide (48).

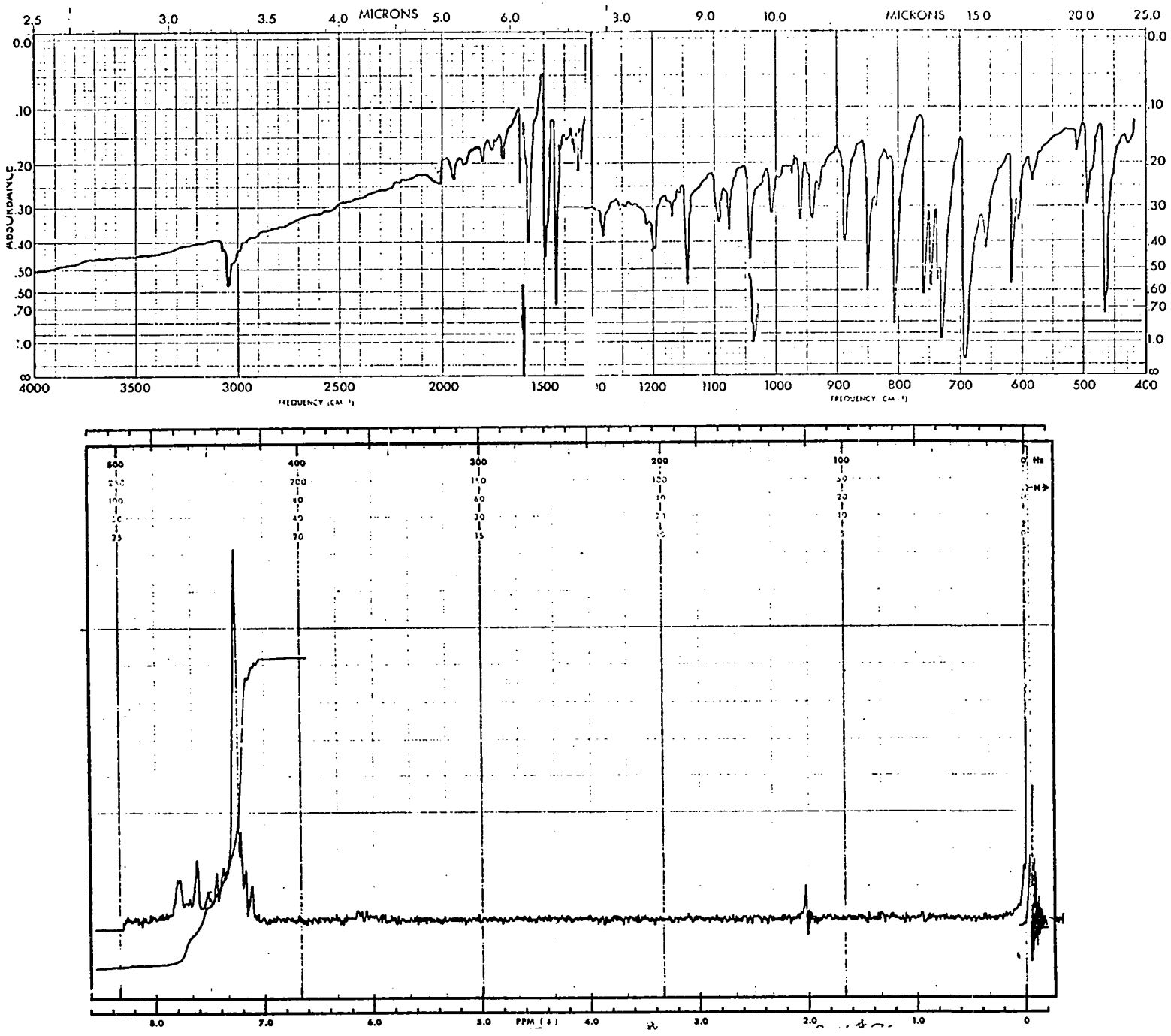


Figure 40. Ir and nmr spectra of triphenylmethyl β-naphthyl trisulfide (49).

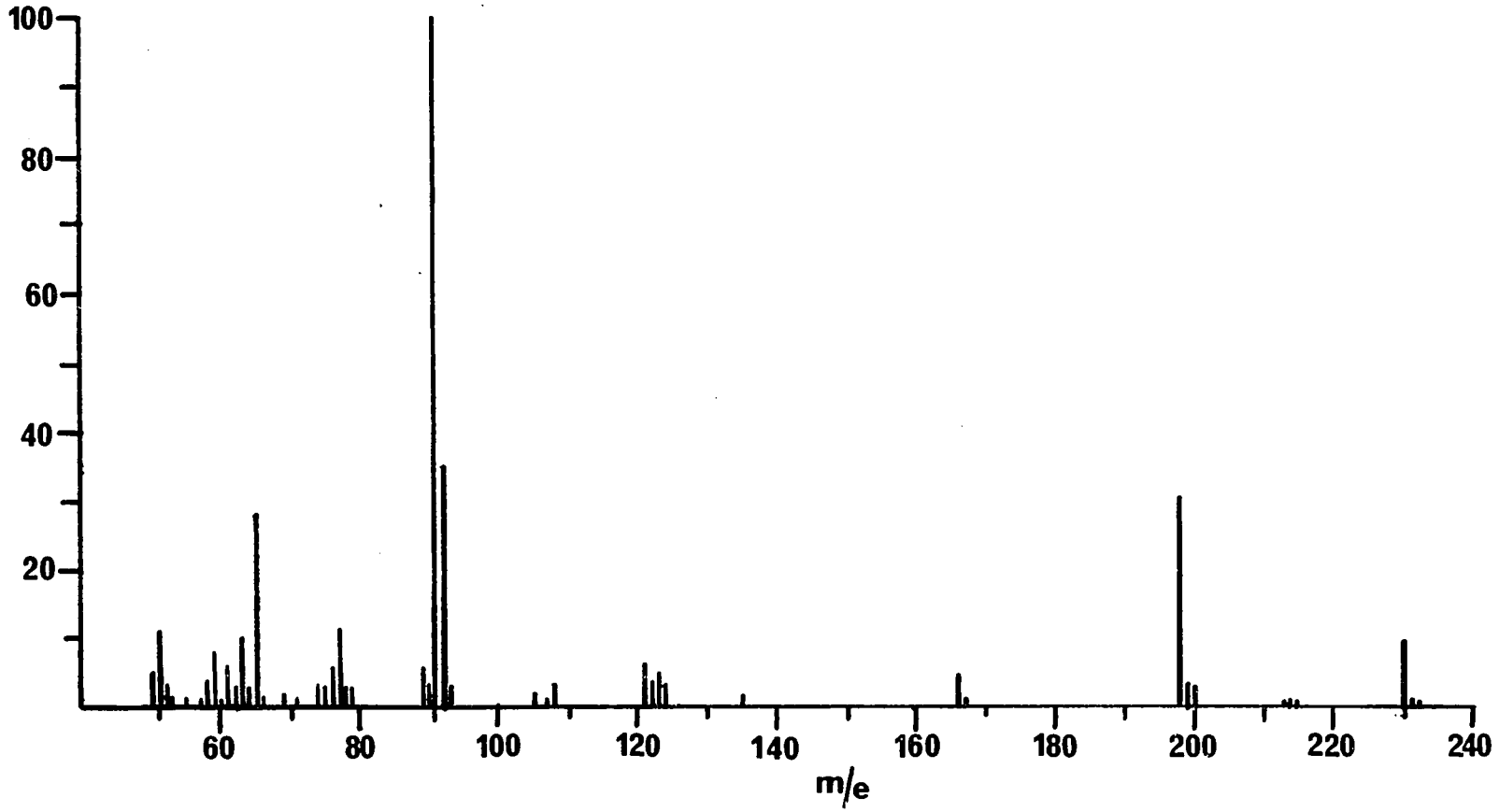
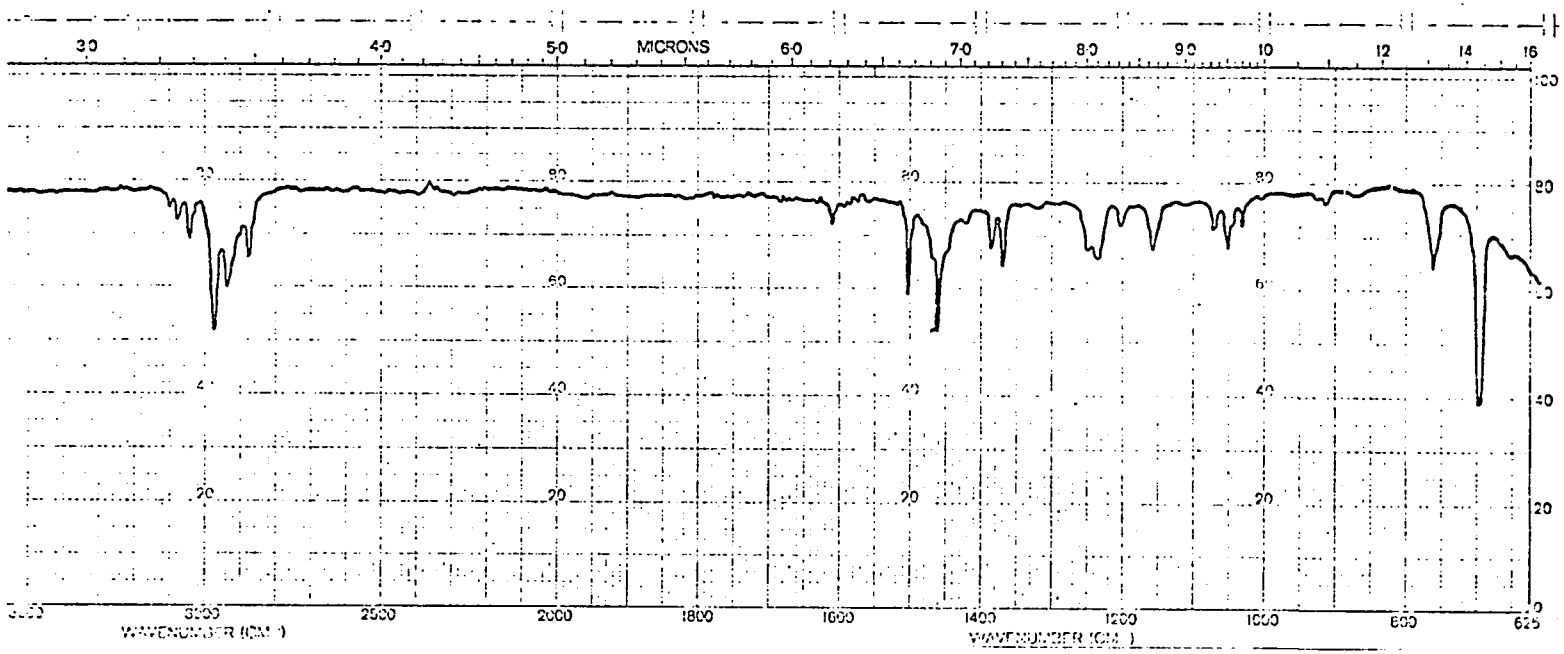


Figure 41. Mass spectrum of isopropyl benzyl trisulfide (61).



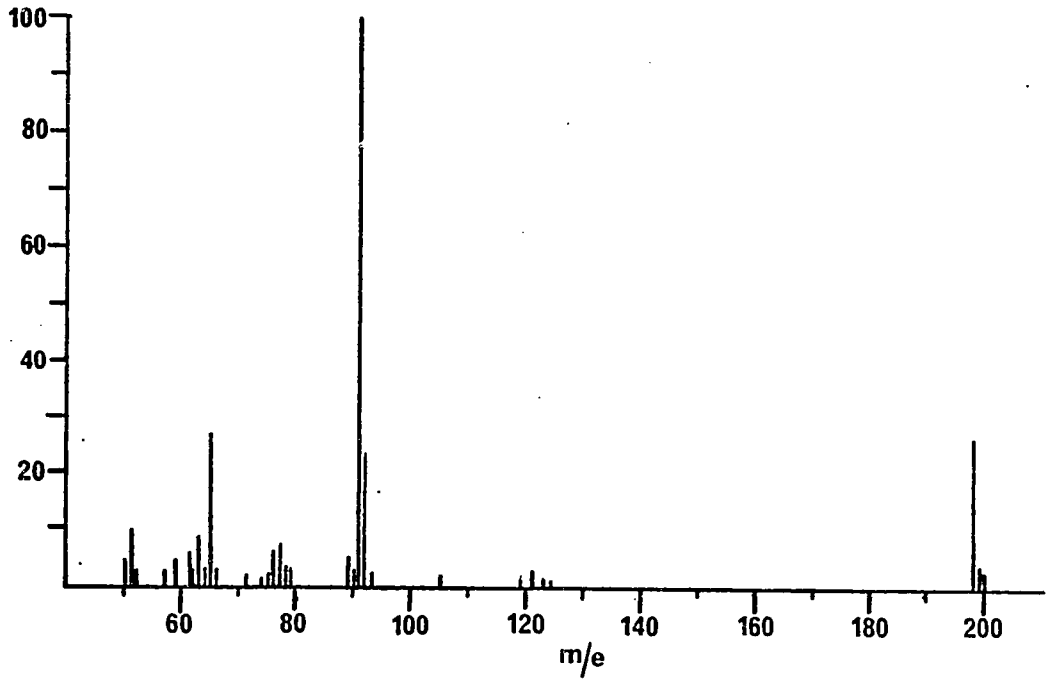
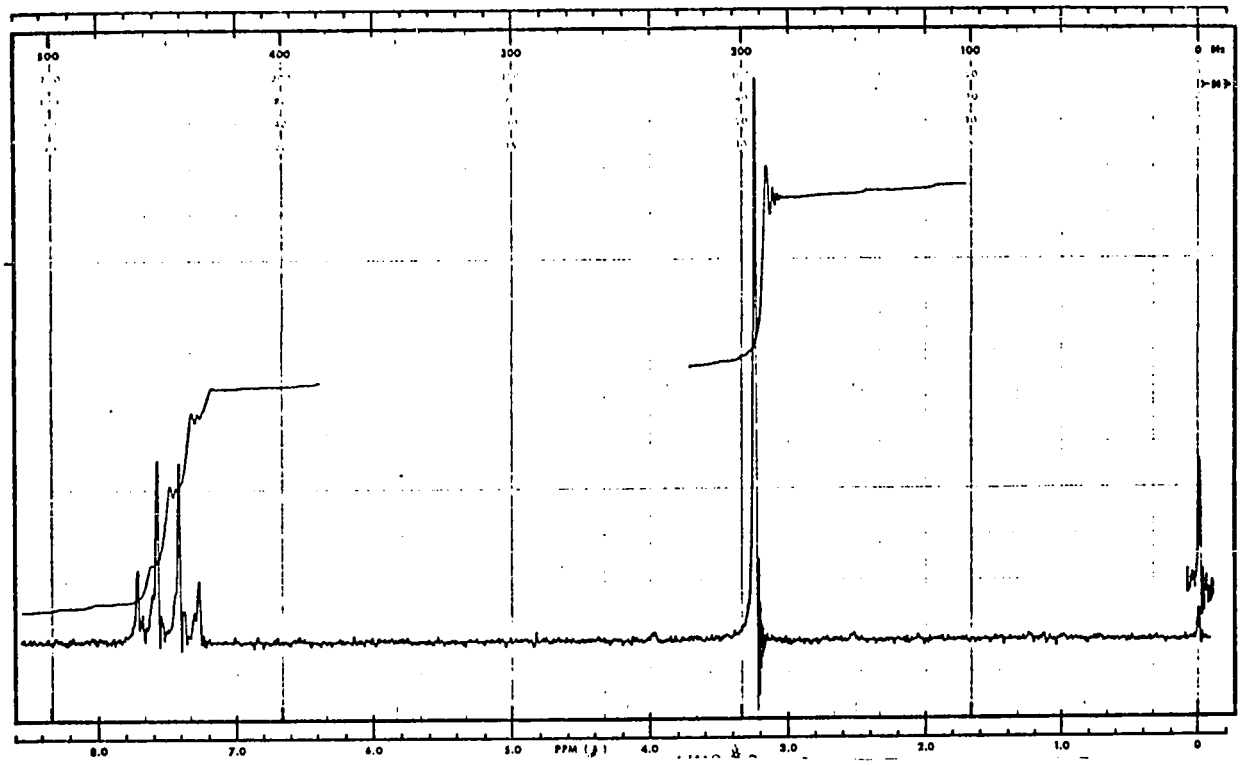


Figure 42. Ir and mass spectra of isopropyl benzyl disulfide (80).



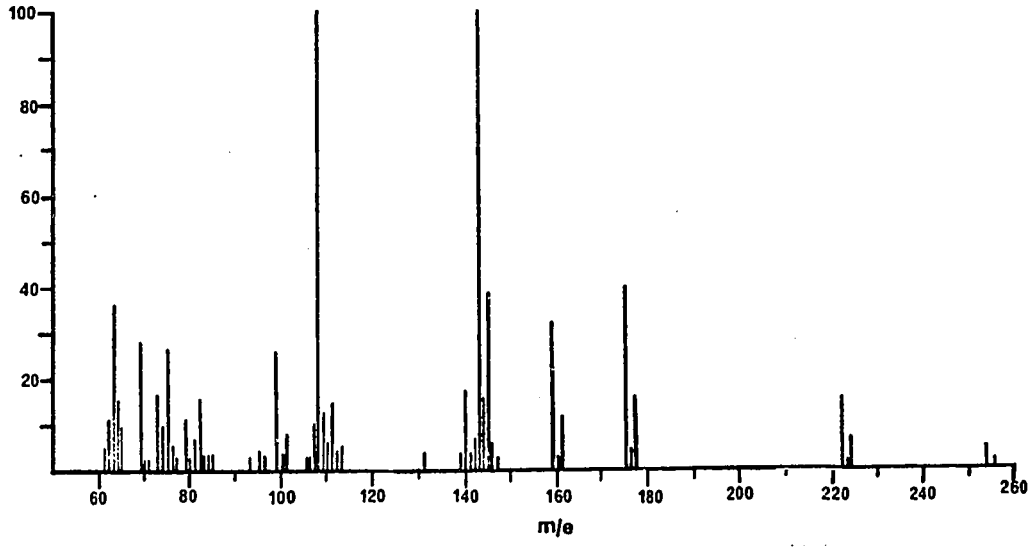


Figure 43. Nmr and mass spectra of p-chlorobenzenesulfenic methanesulfonic thioanhydride (94).

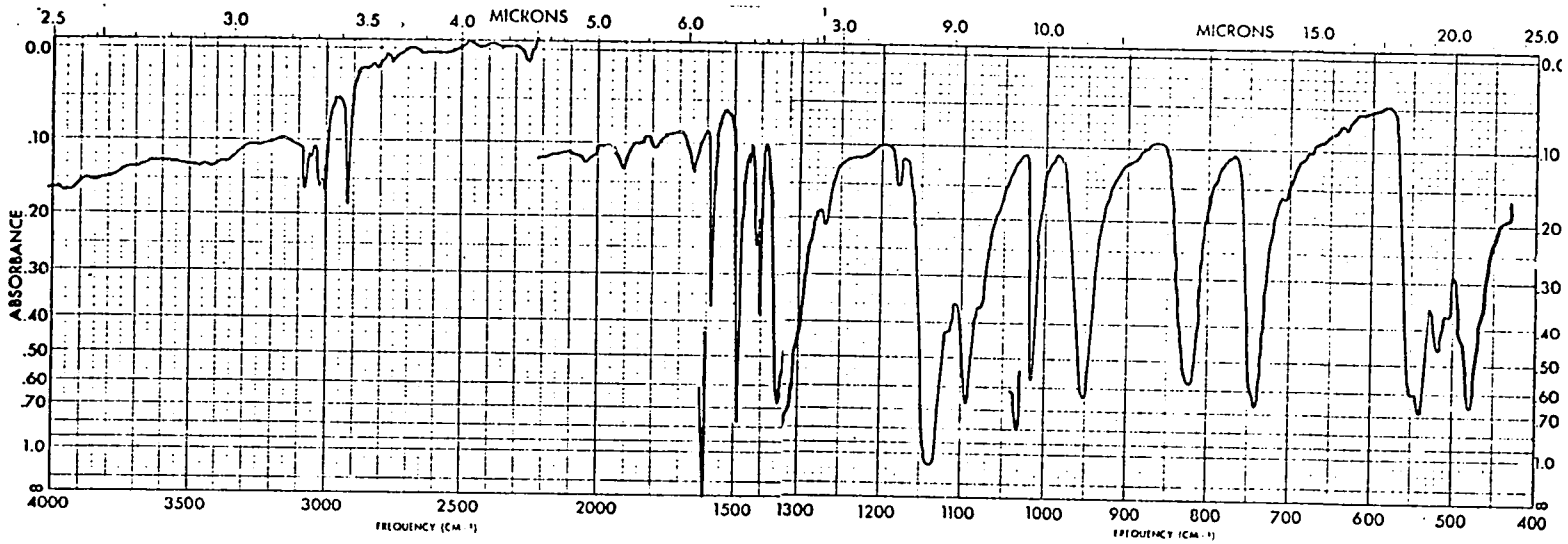
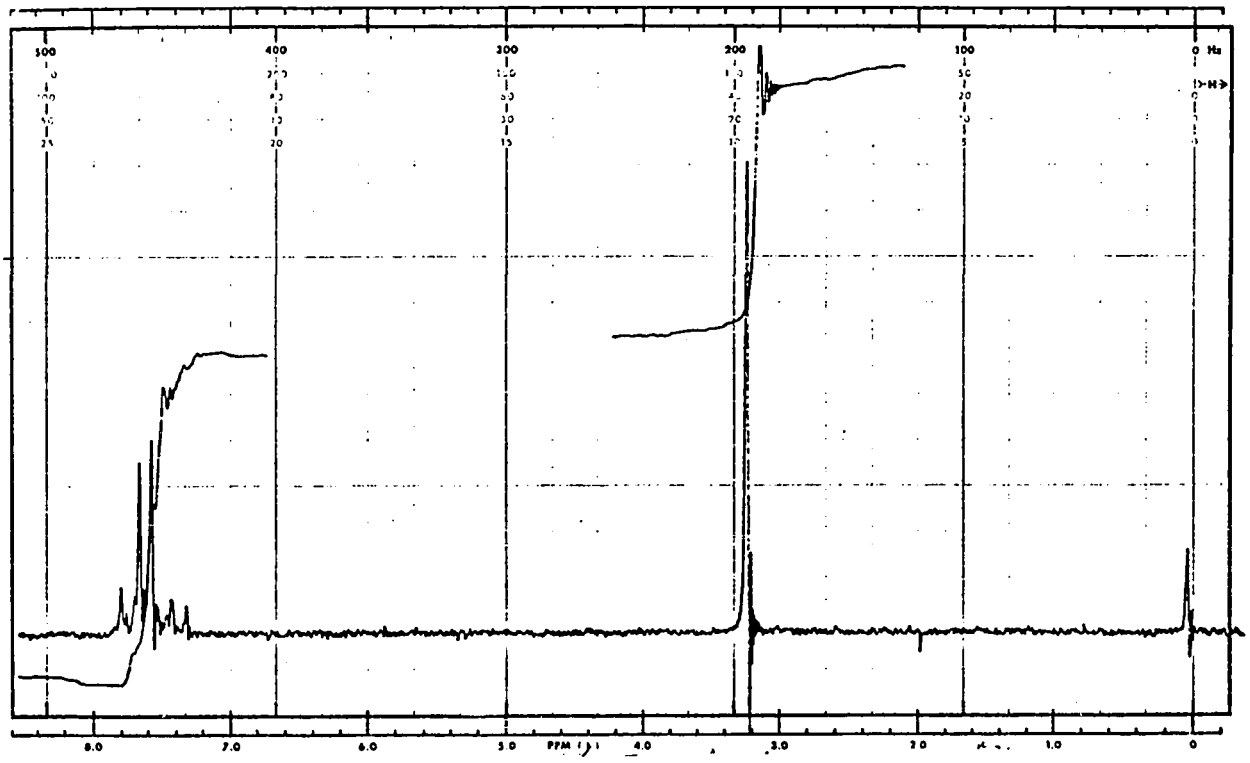


Figure 44. Ir spectrum of p-chlorobenzenesulfenic methanesulfonic thioanhydride (94).



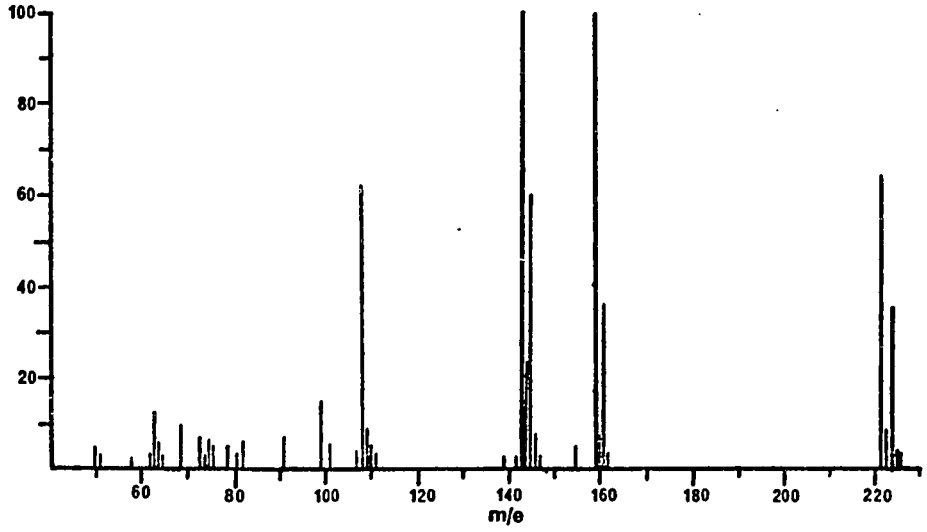


Figure 45. Nmr and mass spectra of p-chlorophenyl methanethiosulfonate (95).

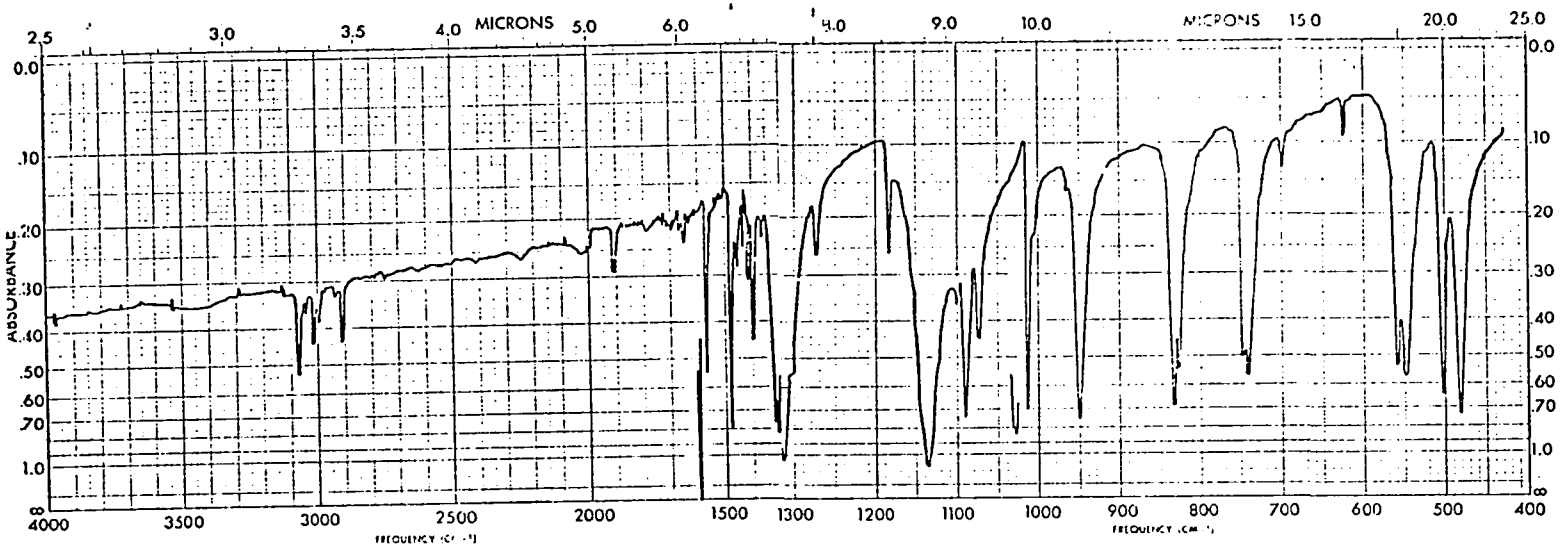


Figure 46. Ir spectrum of p-chlorophenyl methanethiosulfonate (95).

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