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TITLE **STUDIES IN THE SYNTHESIS AND
FUNGICIDAL ACTIVITY OF SOME
SUBSTITUTED BENZYL 2-HYDROXYETHYL
OLIGOSULPHIDES AND RELATED
COMPOUNDS**

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DEGREE **Ph.D**

**AWARDING
BODY** **University of North London**

DATE **1994**

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The University of North London
in collaboration with
British Technology Group PLC
and
The Department of Plant Science
Obafemi Awolowo University, Ile-Ife, Nigeria

Studies in the Synthesis and Fungicidal Activity
of some Substituted Benzyl 2-Hydroxyethyl Oligosulphides
and Related Compounds

by

Ezekiel Temidayo Ayodele, B.Sc., M.Sc. (Ife)

A thesis submitted in partial fulfilment of the
requirements of the University of North London for the
degree of Doctor of Philosophy

August 1994



Dedicated to my wife Funmilayo

and children Tolulope, Tobiloba and Toluwaleke.

Studies in the synthesis and fungicidal activity of some substituted benzyl 2-hydroxyethyl oligosulphides and related compounds

E.T. AYODELE (1994)

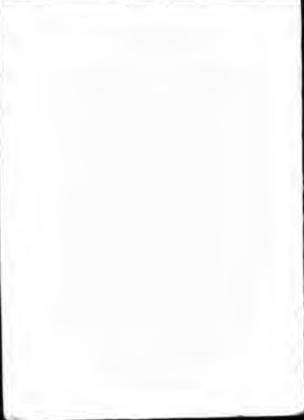
Abstract

Unsymmetrical compounds of the general type: $\text{ArCH}_2(\text{S})_n\text{CH}_2\text{CH}_2\text{OH}$ ($n = 1-4$, $\text{Ar} = o\text{-}$ or $p\text{-ClC}_6\text{H}_4$, $o\text{-}$ or $p\text{-MeC}_6\text{H}_4$, Ph , $p\text{-MeOC}_6\text{H}_4$) have been prepared as analogues of the trisulphide $\text{PhCH}_2\text{SSSCH}_2\text{CH}_2\text{OH}$ which occurs naturally in the stem and root of the plant *Petiveria alliacea*. In addition, disulphides ($n = 2$) were prepared with $\text{Ar} = p\text{-FC}_6\text{H}_4$ or $\text{Ar} = \text{benzothiazol-2-yl}$. Also, tri- and tetra-sulphides with $\text{Ar} = 2\text{-furyl}$ were prepared. The unsymmetrical trisulphides were prepared by the reaction of sulphur dichloride with two mercaptans, and the tetrasulphides were prepared by the reaction of sulphur monochloride with two mercaptans as appropriate. Unsymmetrical disulphides were prepared by the reaction of 2-hydroxyethylthioisothiuronium chloride with substituted benzyl mercaptans in the presence of sodium hydrogen carbonate. Unsymmetrical monosulphides ($n = 1$) were prepared by the reaction of benzyl or substituted benzyl mercaptans with chloroethanol and sodium hydroxide.

The symmetrical trisulphides of the type: $\text{ArCH}_2\text{SSSCH}_2\text{Ar}$, (where Ar is as defined above), were prepared by the reaction of the corresponding benzylthioisothiuronium chlorides with dimethylamine. Some phthalimido disulphides of the type: $\text{PhthNSSCH}_2\text{Ar}$, where Ar is as defined above, were prepared by the reaction of *N,N'*-thiobisphthalimide with benzyl or various substituted benzyl mercaptans.

^1H nmr, ^{13}C nmr and mass spectroscopy of the various compounds are discussed in detail. All the techniques, in addition to elemental analysis, were useful in the characterization of the compounds.

In vitro test results of compounds against *Fusarium culmorum*, *Fusarium oxysporium* and *Gaeumomyces graminis* showed that most of them were fungicidal and that activity does not depend on the number of sulphur atoms present. Also, some of the compounds were tested *in vivo* against five fungi that included *Erysiphe graminis* on barley seedlings, *Botrytis fabae* on bean seedlings, *Podosphaera leucotricha* on apple seedlings, *Uromyces viciae-fabae* on bean seedlings and *Phytophthora infestans* on potato leaf. Most compounds tested were found to be fungicidal against these organisms. The para-fluoro substituted unsymmetrical disulphide gave the greatest spectrum of disease control, reducing infection in all host-pathogen systems examined. The compounds were phytotoxic at concentrations greater than 0.33%.



Acknowledgement

I wish to express my sincere gratitude to my Supervisors Prof. H.R. Hudson (Professor of Chemistry, University of North London), Prof. Max Pianka (Pesticide Consultant, formerly Head of Organic Synthesis, Murphy Chemical Ltd and Laboratory Head, Glaxo Group Research Ltd) and Dr. I.A.O. Ojo (Senior Lecturer in Chemistry, Chemistry Department, Obafemi Awolowo University, Ile-Ife, Nigeria) for their untiring interest, advice and encouragement throughout the period of this work.

I am indebted to my sponsors, the Overseas Development Administration, University of North London and British Technology Group PLC. The contributions of Drs. Richard A'Court, Paul Matewele, Julius Olaifa and Prof. A.E. Akingbohunge are sincerely appreciated. I wish also to thank the authorities of Ladole Akintola University of Technology, Ogbomoso for a study leave granted me to pursue this work.

I am grateful to Dr. Dale Walters of the Scottish Agricultural College, Auchincruive, for the glasshouse screening of some of the compounds.

Thanks also go to Wimal Dissanayake, John Crowder, Stephen Boyer and Lloyd Williams for their technical assistance.

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CHAPTER ONE

INTRODUCTION AND LITERATURE SURVEY

1 INTRODUCTION AND LITERATURE SURVEY

1.1 Sulphur based agricultural chemicals

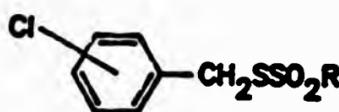
The use of elemental sulphur and its compounds as pesticides was known to the ancient Greeks as early as 1000 B.C.; however, the first ever record to suggest the application of sulphur for the control of pest diseases was not made until 1803 by Forsyth.¹ He recommended a concoction of tobacco, sulphur, quicklime and elder bud for the control of powdery mildew on fruit of trees. The use of sulphur as an effective remedy for the control of peach mildew was also reported to the London Horticultural Society in 1824.² It was suggested that sulphur be painted on heat pipes in green-houses for the control of greenhouse diseases and that the oxidation products of sulphur had fungicidal properties.³ By the middle of the nineteenth century, sulphur had gained a lot of popularity for its fungicidal properties, and its use as a fungicide gradually increased until the fungicidal properties of Bordeaux mixture⁴ in the control of mildew of grapes were discovered.

The introduction of dithiocarbamates for plant disease control during the 1930's marks the beginning of the use of organic chemicals on an important scale for the control of plant diseases. Tisdale et al.⁵ patented compounds of the general molecular formular $X(Y)NCSSZ$, where X is hydrogen or alkyl, Y is hydrogen, alkyl or aryl, and Z is metallic in nature, and thiuram disulphide derivatives, as fungicides,

bactericides, and microbiocides. The use of ethylenebisdi-thiocarbamate as a bactericide, or fungicide was also discovered.⁶ It was reported that disodium ethylenebisdithiocarbamate was highly active against fungi.⁷ This compound, however, appeared to have little future as a practical fungicide because of its instability and water solubility until Henberger et al.⁸ demonstrated that it could be stabilized and made to adhere to foliage. This was accomplished by the addition of zinc sulphate and lime in aqueous solution to this compound, forming zineb (zinc ethylenebisdithiocarbamate) on exposure to air. Thiocyanates and isothiocyanates were found⁹ to show some promise as insecticides as well as fungicides, the most active being ethylene and trimethylene dithiocyanates; other workers confirmed this finding.¹⁰ The lower aliphatic isothiocyanates were found to exhibit only very low activity⁹ possibly because of their high volatility.¹⁰

The xanthates and xanthyl sulphides ROCSSM , $(\text{ROCSS-})_2$, $(\text{ROCS})_2\text{S}$ were screened for their fungistatic properties and it was observed that the most active compound was potassium methyl xanthate; against *Botrytis cinerea* and *Fusarium caeruleum* it was fungistatic up to a rating of 7 on a scale of 1-10. The tuberculostatic, bacteriostatic and fungistatic activities of S-alkylisothiosemicarbazonium iodides and their N⁴-(p-chlorophenyl) derivatives have been studied in vitro¹¹ and the N⁴-(p-chlorophenyl) derivatives were found to be five times more active than the non-substituted S-alkylisothiosemicarbazonium iodides which were only 2% as

active as the parent thiosemicarbazone. The inhibitory effects of some organic sulphur compounds on *Histoplasma capsulatum* have been investigated; eight classes of organic sulphur compounds comprising 42 substances were tested *in vitro* for activity against the yeast phase of *Histoplasma capsulatum*. Activity was found in classes of thiols, thioacids, disulphides, thiosulphonates, sulphinates, and sulphenamides, but the reaction products of thiols with aldehydes or ketones were found unpromising.¹² The thiosulphonates (1)



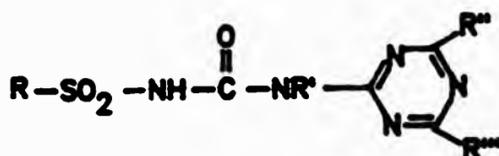
(1)

were patented as antiviral drugs by Shimabara et al.¹³ Also, *N*-phenylsulphenamide and its substituted derivatives have been prepared and patented as fungicides.¹⁴

Only a few studies have been made of the fungicidal activities of alkyl sulphides and mercaptans¹⁵ but none of these compounds showed a high order of activity and they are primarily of academic interest.

Sulphur and its compounds continue to be important agrochemicals, as shown by the large variety of new sulphur-based crop protection chemicals in current development around the world.^{16,17,18} The sulphonylurea herbicides¹⁹ are about one to two orders of magnitude more

active than the standard herbicides used for weed control in agriculture. These sulphonylureas have the general structure (2) shown below.



(2)

The variations on the right-hand side of the molecule possessing activity are relatively few: triazine and pyrimidine rings are allowed and the substituents can be methyl, methoxy or other small radicals. On the left-hand side, many variations are possible with a wide variety of aromatic, heterocyclic and even aliphatic groups. Selectivity against various plant species is obtained with these structural variations.

Sodium tetrathiocarbonate, a new soil fumigant, recently under field development by Union Oil Co. of California, is made from carbon disulphide, sulphur and caustic soda.²⁰ Tetrathiocarbonate gives a broad spectrum control of nematodes, nitrifying bacteria, grape *Phylloera* and a wide range of soil fungi.²¹ It is water soluble and can be added with irrigation water and, being low in phytotoxicity, it can be used even on some established plants such as citrus trees and grape vines.

The familiar, sulphur-containing types of agrochemicals

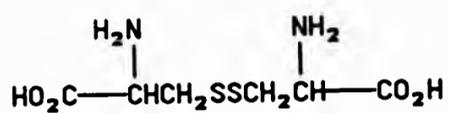


continue to have new variations, mostly in the direction of increased activity towards target organisms and improved selectivity so that non-target organisms are not affected. Thus, new benzylthiocarbamate herbicides and new S-alkyl thiophosphate anticholinesterase insecticides have been developed and introduced recently.²²

1.2 Review of naturally occurring di-, tri-, and poly-sulphides and related compounds

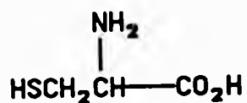
While investigating plant extracts for antibacterial activity, it was observed that a freshly prepared infusion of ground garlic cloves possessed high anti-bacterial activity, when tested by the cylinder-plate method used for the assay of penicillin.²³ It is also known that *Allium sativum*, the common garlic, is endowed with various therapeutic virtues both in legend and in the scientific literature. The antibacterial activity had been attributed to the presence of diallyl disulphide,²³ unstable sulphur in alkyl polysulphides,²⁴ a bacteriophage,²⁵ acrolein or similar unsaturated aldehydes,^{26,27} in the garlic extracts.

As far back as 1922, the disulphide cystine (3) was found in the protein keratin²⁸ which occurs in hair, skin, and nails, and its biological importance was recognized.



(3)

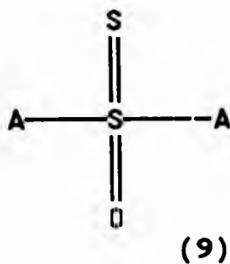
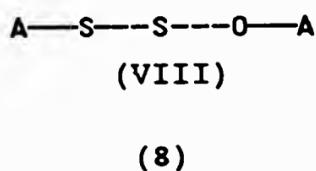
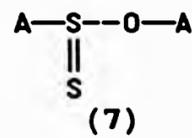
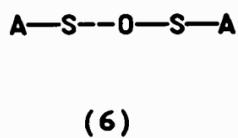
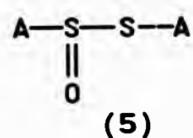
Glutathione, an oxidation-reduction catalyst, was discovered²⁹ in yeast, red blood cells and animal tissues, and was shown to be the tripeptide, glutamyl-cysteinyl-glycine. Its oxidized form was shown to be a derivative of cysteine (4), while its reduced form contained a cystine residue.



(4)

The anti-bacterial agent allicin has been isolated³⁰ from onion in the pure state as a colourless liquid. The compound was found to contain approximately 40% sulphur by weight, and no nitrogen or halogens. The oil cannot be distilled without decomposition, it is irritating to the skin, and the odour is much more characteristic of garlic than the various allyl disulphides. Its action was found to be more bacteriostatic than bactericidal and it is about equally effective against Gram positive and Gram negative organisms. The molecular weight of allicin was found to be approximately 167 and this, together with other analytical

data, indicated an empirical and molecular formula of $C_6H_{10}OS_2$ (molecular weight of 162). Alkaline hydrolysis yielded sulphur dioxide and some allyl disulphide. Five possible structures (5-9), where A represents the allyl group, were proposed.



The most remarkable occurrence of organic disulphides reported so far is that of methyl disulphide in the cavities of quartz of the palaeozoic period.³¹ Methyl disulphide and isopropyl disulphide are present in the odours from *eucalyptus*.³² Allyl disulphide^{33,34} and allyl propyl disulphide^{35,36} are found in the oil of garlic and allyl s-butyl disulphide in *Asafetida*.³⁷ The essential oil of *Agathosma apiculata Meyer* contains 30% of n-butyl 1-pentenyl disulphide.³⁸ Methyl disulphide is also present in the gases from sulphite pulp digesters.³⁹

1.3 Methods of preparation of symmetrical organic disulphides

The first synthetic organic disulphide was made by Zeise who distilled ethyl disulphide from a mixture of potassium ethyl sulphate and barium disulphide.⁴⁰ Other workers: Morin,⁴¹ Cahour,⁴² and Muspratt,⁴³ obtained the same product at a later date.

Because of the importance of the methods of synthesis for this class of compounds, some specific examples already reported in the literature will now be given.

1.3.1 Reaction of alkyl halides with disodium disulphide

Earlier attempts at making symmetrical disulphides used the reaction of an alkyl halide and sodium disulphide^{44,45,46,47} as depicted by the equation in Scheme 1.



Scheme 1

Although alkyl disulphides are obtained in fairly good yields by this method, a problem arises from the fact that sodium "disulphide" is a random mixture of compounds including Na_2S , Na_2S_2 , Na_2S_3 and possibly Na_2S_4 , Na_2S_5 and Na_2S_6 . Therefore, in addition to the alkyl disulphide, other products such as the trisulphides and polysulphides are

formed. For the lower members of the series, this may not be a serious problem because fractionation can be used to separate the disulphides from the polysulphides because of the wide differences in their boiling points.

1.3.2 Reaction of sulphur with organic compounds

The reactions of various organic compounds when heated with sulphur are also known to give disulphides, although products obtained from this kind of reaction are not pure and may contain mono-, di-, and polysulphides depending on the nature of the starting materials and the conditions of heating. However, disulphides have been obtained from phenols,⁴⁸ naphthols,⁴⁹ aniline,⁴⁸ and saturated and unsaturated^{50,51} hydrocarbons. An unsaturated disulphide was reportedly formed from amylene and sulphur under certain conditions.⁵² Dibenzyl disulphide has been obtained from benzophenone in several ways.⁵³ Certain aldehydes and ketones give good yields of disulphides when heated with hydrogen sulphide under controlled conditions.⁵⁴

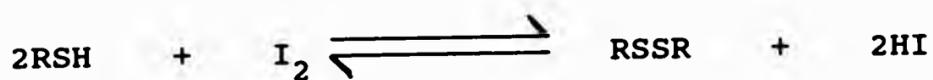
1.3.3 Reaction of sulphur chlorides with organic compounds

Several organic compounds, such as thiophene,⁵⁵ acetoacetanilide,⁵⁶ and aromatic hydrocarbons,⁵⁷ give disulphides when they are treated with sulphur monochloride. Sulphur monochloride acts as a chlorinating, as well as a

sulphurising agent, when it is allowed to react with trithioformaldehyde, producing $(\text{ClCH}_2)_2\text{S}_2$. Some monosulphides and polysulphides are formed in addition to the desired disulphide when sulphur monochloride reacts with ethylene⁵⁸ and amylene.⁵⁹ When *o*-nitrophenylthiosulphenyl chloride, $(\text{o}-\text{O}_2\text{NC}_6\text{H}_4\text{SSCl})$, is added to an unsaturated hydrocarbon a disulphide is formed.⁶⁰

1.3.4 Oxidation of mercaptans

This is the simplest method for the preparation of disulphides, and is depicted in Scheme 2.

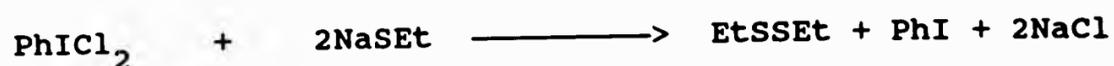


Scheme 2

The hydriodic acid formed is a strong reducing agent and the reaction does not go to completion unless this acid is removed, either by solution in water or by combination with a base.⁶¹ This method also is the neatest way of preparing alkyl disulphides. The thiol is dissolved in benzene, over a layer of water, and iodine is added until it is no longer decolourized. The hydriodic acid that is formed dissolves in the water layer and the benzene solution of the disulphide is separated and fractionated.^{62,63}

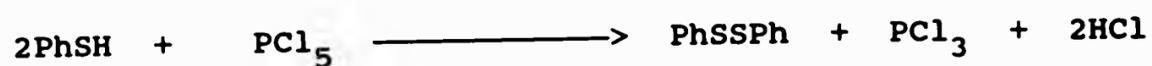
Chlorine can also convert a mercaptan to the

disulphide.⁶⁴ However, care must be taken to conduct the reaction in such a way that it will not be violent. Any other compound that gives up chlorine readily may also be used instead of chlorine, thus phenyliodosochloride reacts with sodium mercaptide⁶⁵ as shown in Scheme 3.



Scheme 3

Phosphorus pentachloride gives up two chlorine atoms when it reacts with phenyl mercaptan, to give the disulphide⁶⁶ (Scheme 4).

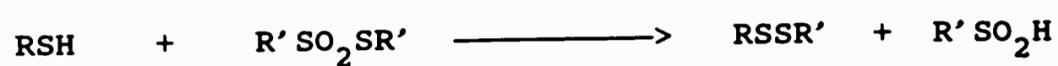


Scheme 4

1.4 Unsymmetrical disulphides and cyclic polymeric disulphides

Unsymmetrical disulphides are sulphides of the general formula RSSR' , where R and R' are different groups. Nucleophilic displacement of a sulphinic acid from thiosulphonates by thiols has been exploited to produce a wide variety of unsymmetrical disulphides.⁶⁷ While the reactions proceed readily and completely in most cases, even at -86°C , subsequent disproportionation of both products is

a complication whose importance varies greatly with structure.⁶⁷ The reaction proceeds according to Scheme 5.



Scheme 5

The relative stabilities of some disulphides toward disproportionation have been studied in detail.^{68,69,70}

The treatment of two mercaptans with bromine has been reported to give a mixture of three disulphides, one of which is unsymmetrical (Scheme 6).⁷¹



Scheme 6

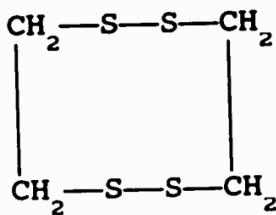
These disulphides may be separated by fractional distillation. Other oxidizing agents have been reportedly used for this reaction.⁷²

The reaction of a mercaptide with Bunte salt has been reported to give an unsymmetrical disulphide⁷³ as shown in Scheme 7.

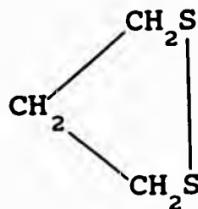


Scheme 7

A neat way of preparing a pure unsymmetrical disulphide is by the reaction a sulphenyl halide with a mercaptide.^{74,75} The reaction of S-alkylthioisothiuronium chloride with a mercaptan, in the presence of a base, also gives pure unsymmetrical disulphide.⁷⁶ The treatment of ethylene⁷⁷ and trimethylene⁷⁸ dimercaptans with bromine yields solids to which structures (10) and (11), respectively, have been assigned.



(10)

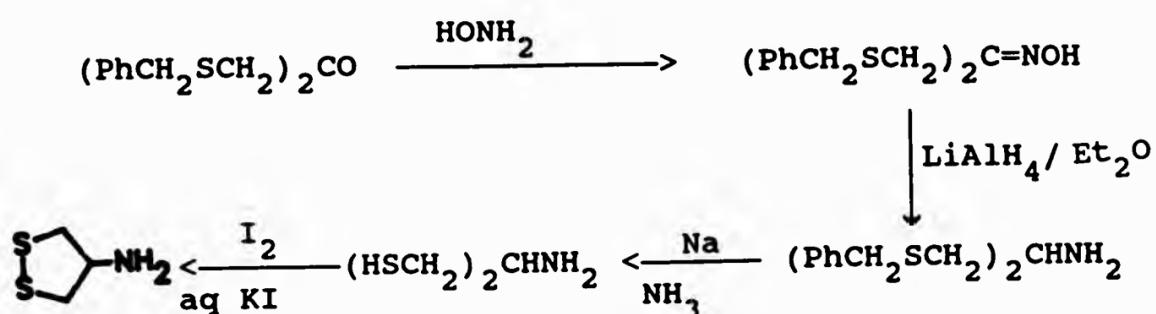


(11)

Compounds of the same composition as (10) were reportedly made in two other ways, one by oxidation of ethylene dimercaptan and the other by the reaction of ethylene bromide with sodium disulphide.⁷⁸

A number of aliphatic disulphides, not previously reported, have been prepared by adaptations of more or less well known methods as mentioned earlier. α, α' -Diethyl-, α, α' -di-n-propyl-, α, α' -di-n-butyl- and α, α' -diphenyl-D, L-cystine have been prepared via hydantoin intermediates.⁷⁹ 9,10-Diphenyl 2-anthranyl disulphide and 2-anthraquinonyl disulphide have been prepared by the reduction of the corresponding sulphonyl chlorides with zinc and acetic

acid.⁸⁰ The preparation of a number of 5- and 6-membered cyclic disulphides has been reported, all of which with one exception were new. The method of Price et al.⁸¹ for the synthesis of naphthalene-1,8-disulphide was simplified and improved upon by these workers.⁸² 4-Amino-1,2-dithiolane has been prepared by the following reaction (Scheme 8).



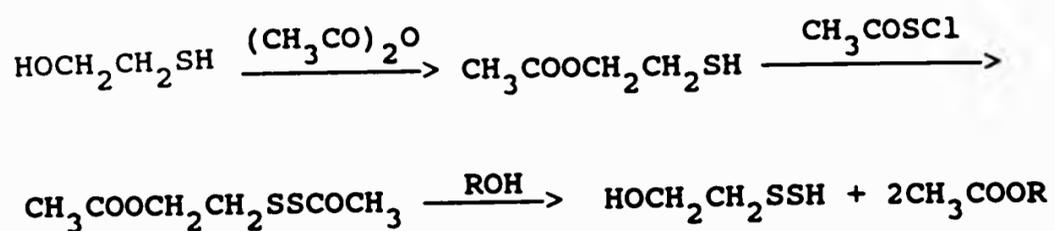
Scheme 8

Eight variously substituted benzoyl disulphides were prepared by the reaction of the corresponding benzoyl chlorides with aqueous sodium disulphide.⁸³ Leek-type flavourings have been prepared by the reaction of aliphatic thiosulphinates with an alkali metal sulphide and were identified as a mixture of aliphatic disulphides (30%) and trisulphides.⁸⁴

This review on these classes of compounds would be incomplete if alkyl hydrodisulphides and the chemistry of disulphides were not included since these explain certain peculiar properties of these compounds.

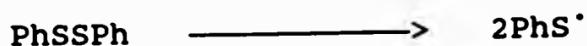
Alkyl hydrodisulphides synthesised so far are methyl,⁸⁵ ethyl,⁸⁶ benzyl,⁸⁷ benzhydryl,⁸⁸ and trityl⁸⁹ hydrodisulphides, the latter three of which have been reported to be stable for a few weeks. The lower members are only stable for a few minutes after being isolated in a pure state. Compounds containing the hydrodisulphide, -SSH, group have been postulated by biochemists as intermediates in various enzymatic reactions.^{90,91} However, alanyl hydrodisulphide, $\text{HO}_2\text{CCH}(\text{NH}_2)\text{CH}_2\text{SSH}$, which has been named thiocystine and proposed as an intermediate of the enzymatic cleavage of cystine, has never been isolated.⁹² Only circumstantial evidence is available to support the intermediate formation of thiocystine⁹³ and similar polysulphonic species containing labile sulphur.

The preparation of 2-hydroxyethyl hydrodisulphide has been reported,⁹⁴ as shown in Scheme 9. This compound was said to be unstable and the workers were unable to obtain accurate analytical results; however, they claimed that the nmr spectrum showed proton signals due to the -SSH, -OH, and $-\text{CH}_2\text{CH}_2-$ groups only. It was suggested that a trace amount of the corresponding trisulphide was present as impurity.



Scheme 9

Disulphides are susceptible to decomposition,⁹⁵ due to the lability of the sulphur-sulphur bond. It is known that diphenyl disulphide dissociates into free radicals (Scheme 10).⁹⁶



Scheme 10

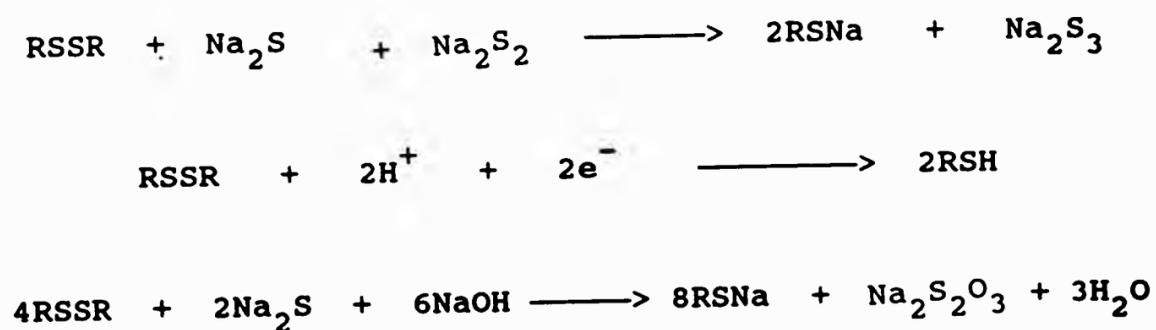
Aryl disulphides are also decomposed by ultraviolet light but the quantum yield is small.⁹⁷ Diphenyl disulphide is decomposed by aluminium chloride to give the mono-sulphide and other products.⁹⁸ The primary decomposition products of dibenzyl disulphide were reported to be stilbene, hydrogen sulphide, and sulphur (Scheme 11).⁹⁹



Scheme 11

Aliphatic disulphides are not very stable to heat, di-n-propyl disulphide being the highest member of the series that can be distilled at atmospheric pressure. The pyrolysis of an aliphatic disulphide gives a mixture which was reported to contain mercaptan, mono-sulphide and hydrogen sulphide.¹⁰⁰

An interesting important fact about disulphides is the ease and completeness with which they are reduced to mercaptans. With sodium sulphide or the disulphide they are reduced to mercaptans (Scheme 12).^{101,102}



Scheme 12

In the presence of water, triphenylphosphine reduces diphenyl sulphide to the mercaptan.¹⁰³

Disulphides undergo oxidation with hydrogen peroxide to give sulphenic acids¹⁰⁴ or oxidation may stop at RSO_2SR .¹⁰⁵ Perbenzoic acid was reported to give a lower oxidation product, RSOSR ,¹⁰⁶ or RSO_2SR .¹⁰⁷ Whether the oxidation product of an unsymmetrical aryl disulphide by a peracid is $\text{ArSO}_2\text{SAr}'$ or $\text{ArSSO}_2\text{Ar}'$ depends on the substituents in the

aryl groups.¹⁰⁸

1.5 Review of biological activity of the plant

Petiveria alliacea

Petiveria alliacea is a plant which can be found mainly in the tropical regions of Venezuela, Colombia, Puerto Rico and several parts of Africa. It was found¹⁰⁹ that the young and active part of the plant was resistant to 2,4-D when treated with a solution spray (0.075%). It has also been reported that this plant shows resistance to diuron.¹¹⁰

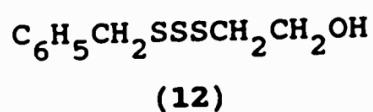
Alcohol, acetone, and petroleum ether extracts, and powders from *Petiveria alliacea*, have been tested for toxicity on adult houseflies, mosquito larvae, and thirteen other insect species and leaf feeders, and found to show low activity.¹¹¹ When an alcohol extract of the dried ground bark and leaves of the plant was tested for the presence of alkaloids, a negative result was obtained, thus showing that any medicinal or biological activity possessed by this plant must be due to substances other than alkaloids.¹¹²

A systematic and quantitative study has been reported on the volatile isothiocyanates obtained from the seeds of *Petiveria alliacea*.¹¹³ Isothiocyanates of the general molecular formula RNCS, where R = Me, allyl, isopropyl, s-butyl, 3-butenyl, benzyl and phenylethyl were said to be present.

Thin-layer chromatographic analysis for coumarins in

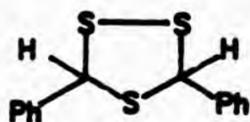
the ether extracts of the root of this plant has shown the presence of nineteen coumarins. Also, preliminary tests for other active substances in the root of this plant have shown that tannins, essential oils, anthracene derivatives, saponins, alkaloids, triterpenoids or flavinoids are absent.¹¹⁴

The isolation, structural elucidation and synthesis¹¹⁵ of an antimicrobial substance from *Petiveria alliacea* has been reported, the active component being obtained from the chloroform-soluble fraction of the total water-alcohol extract of the stems and roots of the plant. The authors identified the compound (12) by nmr and mass spectroscopy.



They also prepared the active compound (12) by the reaction of sulphur dichloride with benzyl mercaptan and mercaptoethanol.

Trithiolaniacin (13), a novel trithiolane, has also been isolated from the chloroform extract of the wet root of *Petiveria alliacea* collected at the end of the rainy season.¹¹⁶



(13)

The structure of this compound (13) was determined by spectroscopic methods. Other products including benzaldehyde, benzoic acid, *trans*-stilbene, and sulphur were also claimed to be present in the chloroform extract.

A phytochemical study of *Petiveria alliacea* has been reported.¹¹⁷ The plant was found¹¹⁸ to show higher nitrate values at the end of summer than at the onset of winter. When the vegetal materials from this plant were digested *in vitro*, nitrates were obtained 1.5-2.5 h from the start of digestion and the maximum accumulation of nitrites (from nitrate reduction) occurred at 4 h.

The alcoholic extracts of various parts of *Petiveria alliacea* and of other plants, particularly the non-saponifiable portions of these extracts, have been tested for their ability to protect mice against a lethal injection of *Escherichia coli*.¹¹⁹ When injected at 50 mg kg⁻¹ the extracts, and/or the non-saponifiable portions of this plant, have protective activity. This activity was associated with the lipophilic constituents of the non-saponifiable fraction and occurred especially with plant extracts known for their skin-healing properties.

A highly polar compound isolated from *Petiveria alliacea*, was shown to be *trans*-*N*-methyl-4-methoxyproline, on the basis of its microanalytical and spectral data. Dibenzyl trisulphide, previously unknown as a natural product, was also claimed to be isolated from the root of the plant.¹²⁰

Compounds $\text{PhCH}_2\text{XCH}_2\text{Y}$, where $\text{X} = \text{S}_2$ (14), S_3 (15); $\text{Y} =$

Ph, CH₂OH, when X = S₂; then Y = Ph (16), have been found useful for prophylactic and therapeutic treatment of liver disorders.¹²¹ When the roots of *Petiveria alliacea* were extracted with methanol, and the extract treated with water and ethyl acetate, the organic layer of which was chromatographed on silica gel, the following compounds were obtained.¹²¹

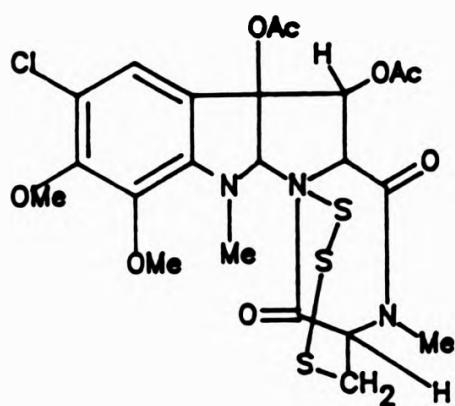


It was also found that a mixture of PhCH₂SSCH₂Ph and PhCH₂SSSCH₂Ph at 200 mg kg⁻¹ showed 69% and 78% improvement of abnormal blood coagulation time and glutamate-pyruvate transaminase in *D*-galactosome-induced liver disorder in rats.

Synthetic analogues and derivatives of the active component (12) of *Petiveria alliacea* have also attracted interest.¹¹⁵ Some polysulphide mixtures containing PhCH₂SSCH₂CH₂Cl (26%), PhCH₂SSSCH₂CH₂Cl (56%) and PhCH₂SSSSCH₂CH₂Cl (18%) were found¹²² to inhibit the growth of *Staphylococcus aureus* and *Mycobacterium tuberculosis* at 12.5 g cm³ and *Candida albicans* and *Trichopyton mentagrophytes* at 6.3 g cm³.

1.6 Trisulphide from the fungus *Pithomyces chartarum*

Sporidesmin (17) has been isolated from the fungus *Pithomyces chartarum*.¹²³



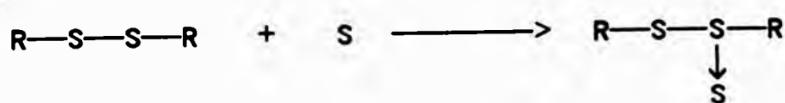
(17)

It is one of the metabolites responsible for liver damage and facial eczema in sheep. The authors assigned structure (17) that corresponds to the cysteine analogue of sporidesmin with three sulphur atoms linked together in an unusual eight membered ring.

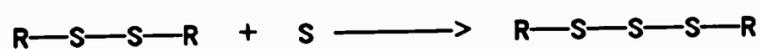
1.7 Structure of organic trisulphides

The question that has arisen over the years is the disposition of the third sulphur atom in an organic trisulphide, since there is no doubt that there is a sulphur

atom attached to each of the alkyl carbon atoms by a fixed bond. Also, much had been made of the fact that sulphur can be added to a disulphide,¹²⁴ or removed from a trisulphide or higher polysulphide. It had been suggested¹²⁵ that the extra sulphur is added to one of the sulphur atoms of the disulphide instead of being inserted between them (Scheme 13).



or



Scheme 13

Various structures have been proposed^{126,127} and these have been reviewed.^{128,129} It had also been claimed that in the oxidation of ethyl trisulphide, tetrasulphide, and pentasulphide, all are converted to the trisulphoxide EtSOSOSOEt , which was taken as establishing the basic structure EtSSSEt in all cases,¹³⁰ and inferring that the structures of the tetrasulphide and pentasulphide are,

respectively, as follows:

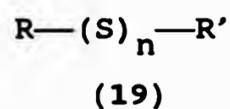
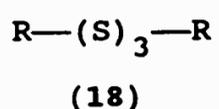
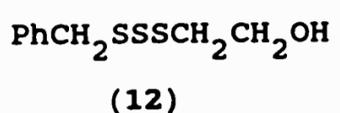


The known lability of the S-S bond does not support the above argument. This lability is manifested in chemical reactions and may have little or nothing to do with the validity of conclusions deduced from physical measurements.^{131,132} It was claimed that electron¹³³ and X-ray diffraction data, and Raman,¹³² ultraviolet,^{131,132} and X-ray emission spectra, indicate the presence of zig-zag sulphur chains as opposed to conclusions obtained from measurements of dipole moment, parachor, and viscosity which are considered less reliable.¹³² A two-fold axis of symmetry, shown by X-rays, appeared to exclude the possibility that sulphur atoms are attached to the chain.¹³³ From a study of the crystal structure of β,β' -diiododiethyl trisulphide, it was concluded that the zig-zag chain in the sulphur atoms is the correct one.

1.8 Aims of the present investigation

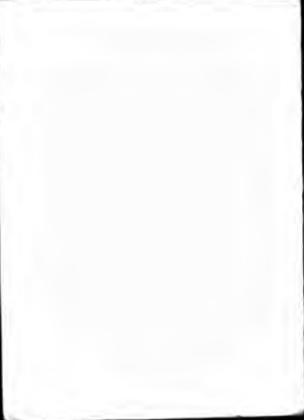
From the above review of the biological activity of the plant *Petiveria alliacea* and the chemistry of the oligosulphides, and in the light of current work on the plant *Petiveria alliacea* at the Department of Plant Science,

Obafemi Awolowo University, Ile-Ife, it became of interest to study in more detail compounds of the following types.



The present programme of study is therefore concerned with an investigation of the following.

- (i) Methods for the preparation of oligosulphides of type 19, in which the number of sulphur atoms may vary and in which the terminal groups R and R' include heterocyclic and other structures not previously found in compounds of this type.
- (ii) The preparation of the trisulphide (12) by different methods, since the earlier method¹¹⁵ was reported to give symmetrical trisulphide in addition to the desired unsymmetrical trisulphide.
- (iii) The preparation of symmetrical trisulphides of type 18, in order to compare their biological activity with that of the unsymmetrical trisulphides.
- (iv) The possible inclusion of other hetero atoms such as oxygen in place of one of the sulphur atoms in the oligosulphide chain, to give compounds of the type RSSOR'.
- (v) The characterisation of the synthesised compounds using elemental analysis and spectroscopic methods, including nmr, mass spectrometry, and infrared and uv spectroscopy where appropriate, and discussion of the spectroscopic



properties of the compounds.

- (vi) The chemical properties of the new compounds, particularly their thermal stability and propensity to disproportionation.
- (vii) The screening of the compounds for their biological activity.
- (vii) A detailed discussion of the reactions that have been studied including their possible mechanisms.

CHAPTER TWO

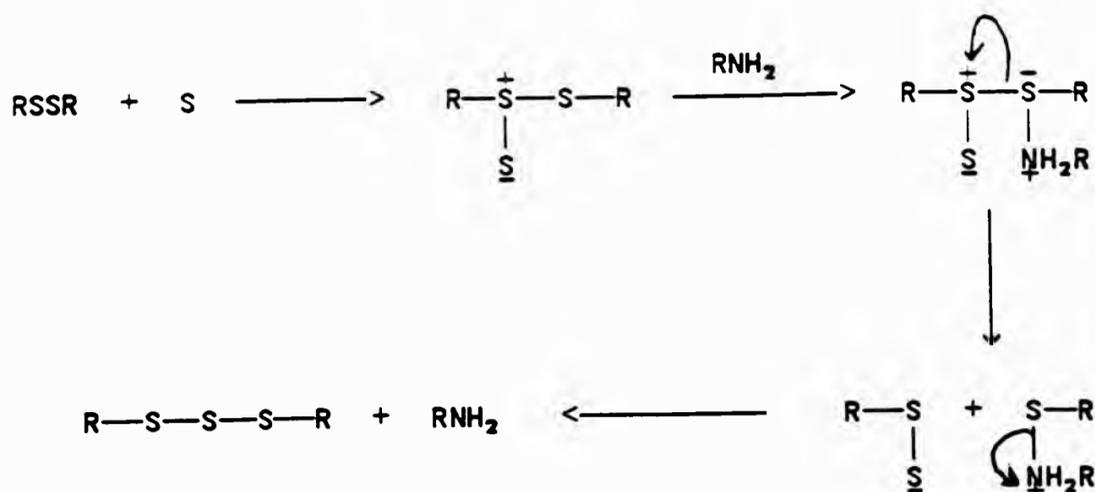
DISCUSSION

2 DISCUSSION

2.1 Introduction

Polysulphides of an order higher than two have been known for many years;¹³⁴ likewise, their interconvertibility was separately recognized by various earlier investigators. It was observed¹³⁴ that diethyl disulphide gave higher order polysulphides when heated in a sealed tube experiment with sulphur and ammonia. The reverse reaction was observed by Twiss when polysulphides were destructively distilled at atmospheric pressure.¹³⁵

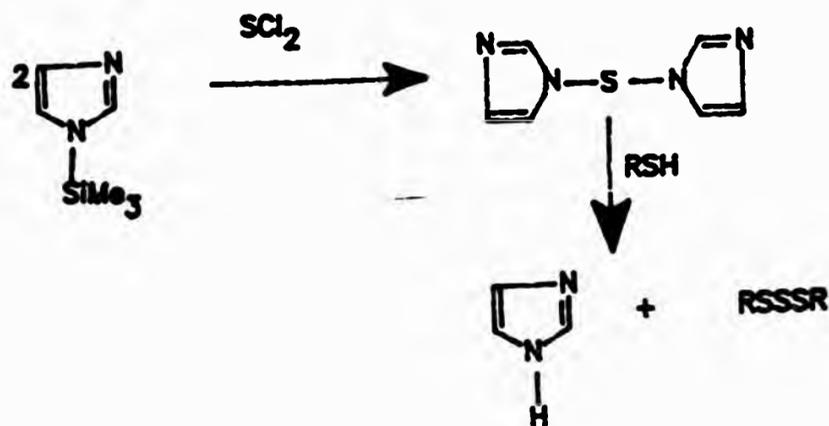
A possible mechanism by which a linear disulphide becomes a linear trisulphide on reaction with sulphur in the presence of an amine has been suggested.¹³⁶ It would logically involve initially the addition of a sulphur atom to one of the disulphide sulphur atoms. The resulting positive charge on the latter, attracting some of the neighbouring electrons and aided by approach of the amino group to the neighbouring sulphur, would induce the splitting of the S-S disulphide bond and the recombination of the fragments into a linear chain of three sulphur atoms as shown in Scheme 14.



Scheme 14

A route such as this, while unsupported except for the structures of the initial and final materials, represents a logical explanation of the observed phenomenon.¹³⁶

During the screening of natural products for insecticidal activity, Banerji *et al.* found that allyl di- and tri-sulphides showed considerable larvicidal activity.¹³⁷ They therefore synthesised different di- and tri-sulphides and tested them for bioactivity. A scheme used by these workers (15) involved the reaction of di-imidazolyl sulphide with a mercaptan.



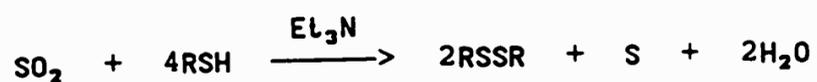
Scheme 15

Although there are several excellent methods for the synthesis of disulphides, only a few are available for trisulphides,¹³⁸ mainly because of the greater thermal instability of trisulphides.¹³⁹ However, dialkyl trisulphides have been synthesised with various degrees of purity by a number of methods, e.g. the reaction of sulphur dichloride with thiols (Scheme 16).¹⁴⁰



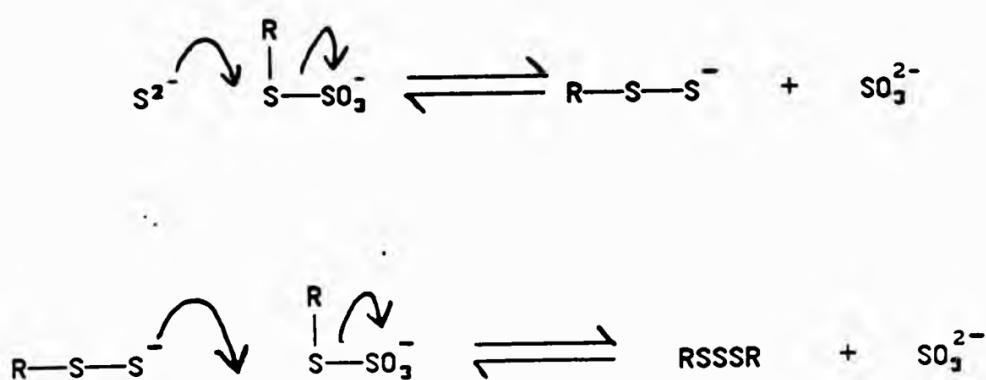
Scheme 16

Akiyama has prepared dialkyl trisulphides by the reduction of sulphur dioxide with thiols.¹⁴¹ The weakness of his method was that a mixture of products was obtained. He considered the reaction to be catalyzed by a sulphur dioxide-triethylamine adduct since ten times as much sulphur dioxide as triethylamine was used (Scheme 17).



Scheme 17

The reactions of Bunte salts (which are salts of S-alkyl or S-aryl hydrogen thiosulphates) with sodium sulphide or sodium mercaptide have been reported to give alkyl or aryl trisulphides.¹⁴² It was proposed that this reaction involved two nucleophilic displacements as depicted in Scheme 18.



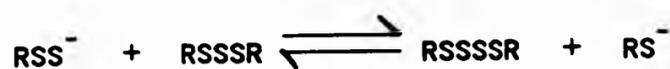
Scheme 18

In some cases disulphides were reported as being formed,¹⁴² but this side reaction could be suppressed by the addition of a layer of light petroleum to the stirred mixture in order to extract the trisulphide from the aqueous phase. This presumably minimizes the reaction of trisulphide with liberated sulphite ion which could give the disulphide and thiosulphate ion according to Scheme 19.



Scheme 19

In all cases, tetrasulphides were also formed (Scheme 20) and the relative proportions of di-, tri-, and tetrasulphides were determined by gas-liquid chromatography.

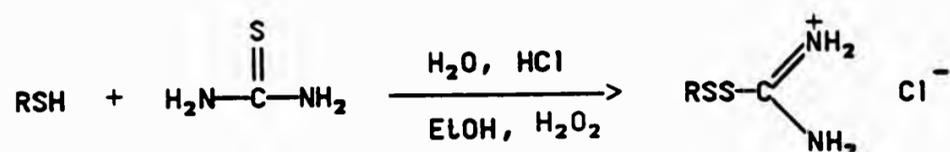


Scheme 20

When this reaction was carried out in the presence of formaldehyde, a product containing dimethyl disulphide and dimethyl trisulphide in the ratio 2:98 was reportedly obtained¹⁴² and, in fact, in some experiments the presence of disulphide could not be detected. However, tetrasulphide was formed in addition, showing that this method is not suitable for the synthesis of pure symmetrical trisulphides.

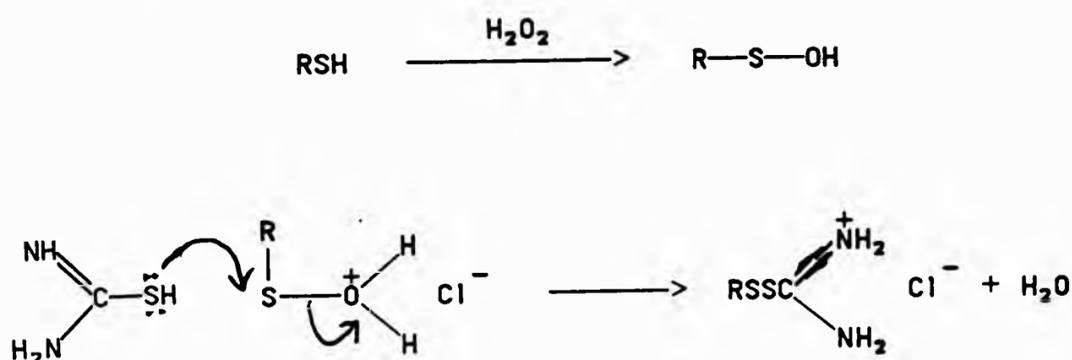
2.2 Symmetrical trisulphides

Because of the limitations^{136,142,143} of the methods discussed above for the synthesis of symmetrical trisulphides, the method used in the present work involved the reaction of an S-benzylthioisothiuronium chloride with an amine. Various S-benzylthioisothiuronium chlorides were easily prepared in good yield by the method of Sirakawa et al.¹⁴⁴ The reaction proceeds according to Scheme 21.



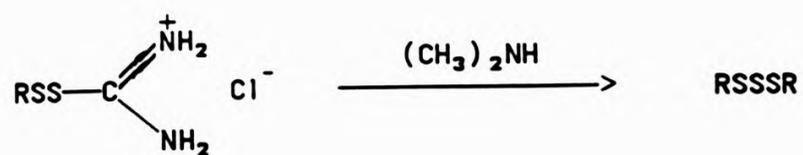
Scheme 21

A mechanism which was proposed¹⁴⁴ involves oxidation of the thiol to the corresponding sulphenic acid, and then reaction of the sulphenic acid with thiourea to give the *S*-benzylthioisothiuronium chloride (Scheme 22).



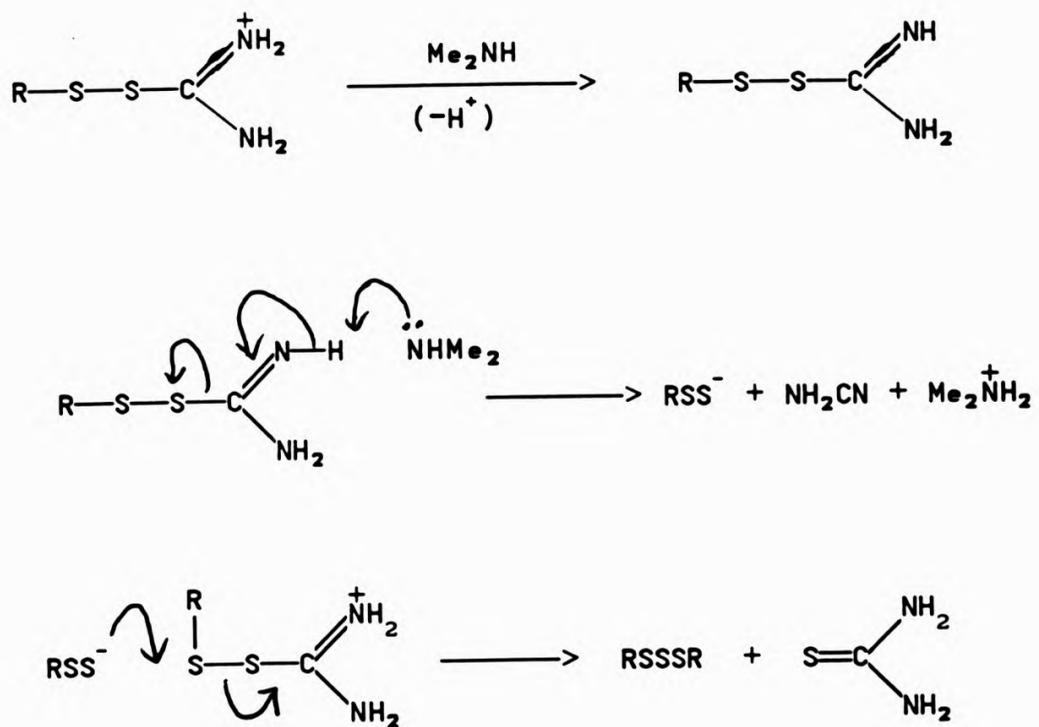
Scheme 22

The symmetrical trisulphides were prepared¹⁴⁴ by treating the corresponding *S*-benzylthioisothiuronium chlorides with dimethylamine (Scheme 23). On addition of dimethylamine to a solution of the *S*-benzylthioisothiuronium chloride in methanol, with vigorous stirring, a solid (the product) was precipitated out after 20 to 35 minutes.



Scheme 23

A mechanism that has been proposed for this reaction is depicted in Scheme 24.



Scheme 24

A list of symmetrical trisulphides prepared by this method, including their elemental analysis, nmr and mass spectral data, is presented in Table 1.

Table 1 Symmetrical trisulphides $\text{ArCH}_2\text{SSSCH}_2\text{Ar}$

Ar	Found (%)			δ_{H}	m/z (%)
	(Calculated)				
	C	H	S		
Ph	60.58 (60.41)	5.14 (5.08)	34.28 (34.53)	4.02 (s, 4H) 7.30 (m, 10H)	277 ($[\text{M} - 1]^+$, 31)
<i>p</i> -MeC ₆ H ₄	61.90 (62.10)	6.17 (5.93)	31.16 (31.38)	2.32 (s, 6H) 4.01 (s, 4H) 7.27 (m, 8H)	306 (M^+ , 2)
<i>o</i> -MeC ₆ H ₄	61.96 (62.69)	5.74 (5.93)	31.30 (31.38)	3.78 (s, 6H) 4.00 (s, 4H) 7.23 (m, 8H)	306 (M^+ , 17)
<i>o</i> -ClC ₆ H ₄	48.26 (48.41)	3.39 (3.49)	27.50 (27.68)	4.14 (s, 4H) 7.35 (m, 8H)	347 (M^+ , 9)
<i>p</i> -ClC ₆ H ₄	48.51 (48.41)	3.51 (3.49)	27.55 (27.68)	3.97 (s, 4H) 7.27 (m, 8H)	347 (M^+ , 4)
<i>p</i> -MeOC ₆ H ₄	56.80 (56.77)	5.33 (5.37)	29.20 (28.40)	2.38 (s, 6H) 4.06 (s, 4H) 7.20 (m, 8H)	338 (M^+ , 11)

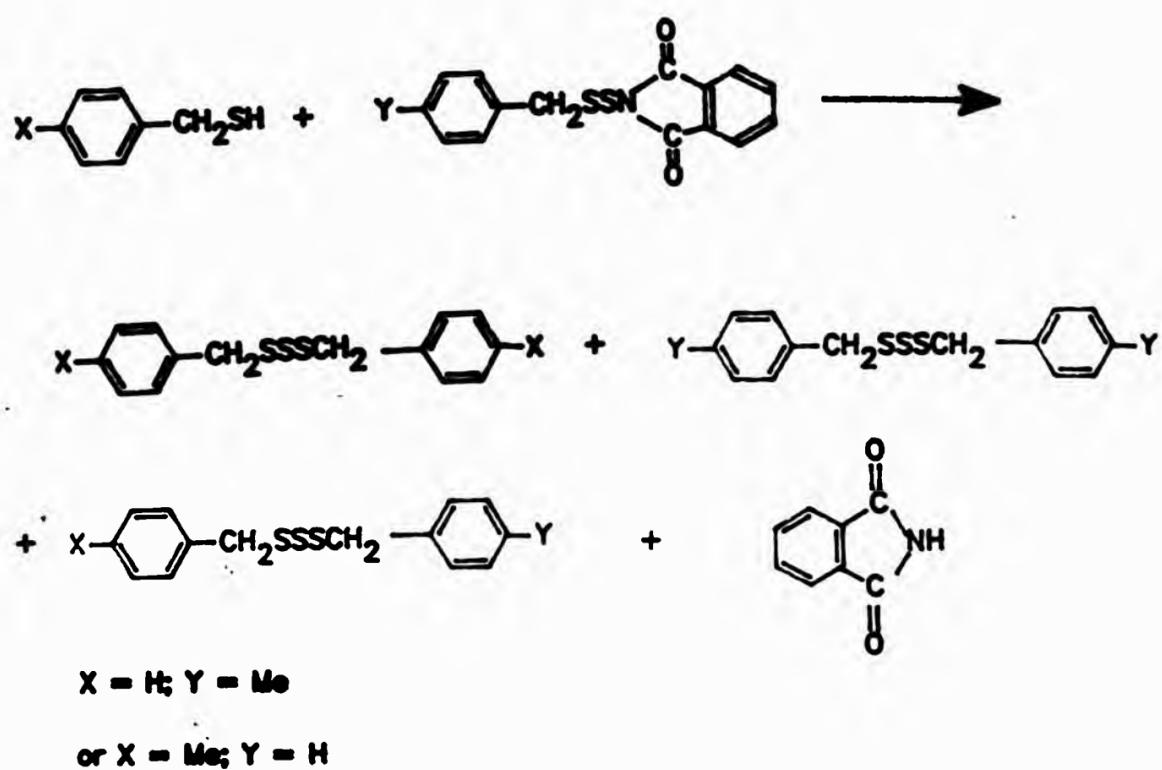
2.3 Unsymmetrical trisulphides

Organosulphur compounds of the general formula R₁SSR₂' are known to be of biological importance and several have been isolated from natural sources.¹⁴⁵⁻¹⁴⁷ A variety of both symmetrical and unsymmetrical trisulphides has been isolated from the onion family (genus *Allium*), including allyl n-propyl trisulphide, allyl but-2-enyl trisulphide, allyl s-butyl trisulphide, and diallyl trisulphide.

2.4 Synthesis of unsymmetrical trisulphides

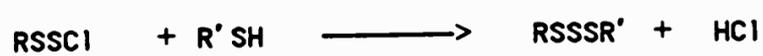
Although the preparation of symmetrical trisulphides is straightforward and well documented,^{138,140} the synthesis of unsymmetrical trisulphides is more complex. Problems in the synthesis of benzyl-containing di- and tri-sulphides have been reported previously. Hiskey et al.¹⁴⁸ reported that benzyl 2-hydroxyethyl disulphide disproportionates rapidly. The finding that isopropyl 2-hydroxyethyl trisulphide was unchanged after three months at 25 °C suggested that the instability of Hiskey's compound was due to the benzyl rather than the hydroxyethyl group.¹⁴⁹ Furthermore, Harp et al.¹⁵⁰ reported that the attempted preparation of benzyl 4-methylphenyl trisulphide, from either benzyl mercaptan and 4-methylphenyl phthalimido disulphide, or 4-thiocresol and benzyl phthalimido disulphide, yielded mixtures containing both of the symmetrical trisulphides as well as the desired

product (Scheme 25).



Scheme 25

Some other methods have also been reported for the synthesis of unsymmetrical trisulphides. The reactions of mercaptans with alkyl,¹⁵¹ acyl,¹⁵² and aryl chlorodisulphides,¹⁵³ were reported to give unsymmetrical trisulphides (Scheme 26).



Scheme 26

The limitation of this method is that chlorodisulphides are relatively unavailable and are unstable.

Also reported as a method of preparation for this class of compound is the interaction of an *N*-arylamidithiosulphite with a mercaptan (Scheme 27).



Scheme 27

A problem associated with this method is that the desired unsymmetrical trisulphide is formed together with an equivalent amount of symmetrical disulphide, which makes isolation of the pure trisulphide difficult.¹⁵⁴

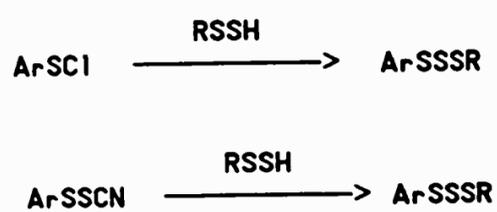
The preparation of moderate yields of unsymmetrical trisulphides only, via deoxygenation of dialkanesulphonic thioanhydrides by triphenylphosphine has been reported (Scheme 28).¹⁵⁵



Scheme 28

Also, unsymmetrical trisulphides can be prepared by the reactions of arenesulphenyl chlorides or thiocyanates with alkyl hydrodisulphides,¹⁵⁶ although the non-availability and instability of hydrodisulphides make this method

unattractive (Scheme 29).



Scheme 29

The synthesis of compounds of the type RSSSR' where R = benzyl or a substituted benzyl group and R' = HOCH₂CH₂, is an important focus of this work. The method used consisted of three major steps which are described in some detail below.¹⁵⁰

Step 1

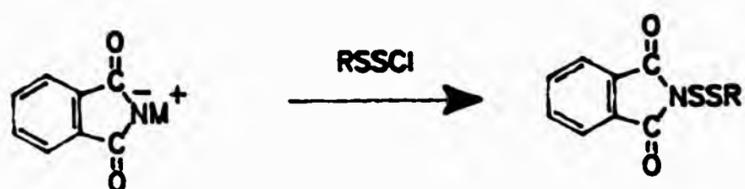
N,N'-Thiobisphthalimide was prepared readily by the reaction of phthalimide with freshly distilled sulphur monochloride (Scheme 30).¹⁵⁷ On dropwise addition of sulphur monochloride to a vigorously stirred solution of phthalimide in anhydrous *N,N*-dimethylformamide, a yellow precipitate appeared after 25 min and the mixture was then stirred at 28 °C for a further 20 h. The product was isolated by filtration and recrystallisation and the infrared spectrum exhibited no =NH, -NH₂, or COOH bands.



Scheme 30

Step 2

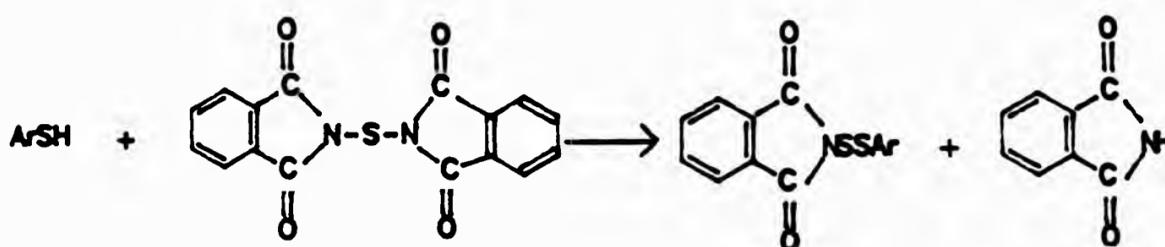
The second step involved the synthesis of the benzyl phthalimido disulphide. The first three closely related examples of this class of compound to be reported¹⁵⁸ were prepared by the reaction of an alkali metal derivative of phthalimide with a thiosulphenyl chloride (Scheme 31).



Scheme' 31

Due to the unavailability and instability of thiosulphenyl chlorides, this method was not considered to be suitable.^{159,160}

Also, it had been found that aryl mercaptans undergo nucleophilic reaction with *N,N'*-thiobisphthalimide to give the corresponding aryl phthalimido disulphide (Scheme 32).¹⁵⁹



Scheme 32

Using a similar scheme in the present investigation, a series of substituted benzyl phthalimido disulphides was prepared, all of which are new compounds. An advantage of this method is that the precipitation of phthalimide from the cold reaction mixture is a good indication that the reaction has taken place and may be used quantitatively to monitor the extent of reaction. The products obtained were all crystalline solids and were well characterized as shown in Table 2.

Table 2 Phthalimido disulphides PhthNSSCH₂R
and PhthNSSCH₂CH₂OH

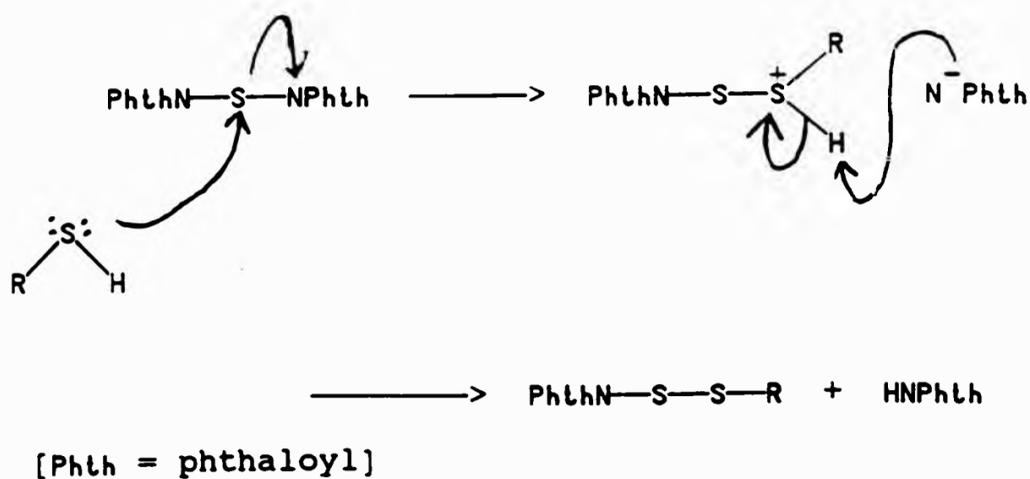
R	Found (%)				δ_H	m/z (%)
	(Calculated)					
	C	H	N	S		
C ₆ H ₅	59.73	3.66	4.80	21.23	4.30(s, 2H)	301(M ⁺ , 24)
	(59.75)	(3.68)	(4.65)	(21.27)	7.25(m, 5H)	
					7.85(m, 4H)	
o-ClC ₆ H ₄	53.71	2.96	4.18	19.10	4.32(s, 2H)	335(M ⁺ , 1)
	(53.65)	(3.01)	(4.17)	(19.08)	7.23(m, 4H)	
					7.84(m, 4H)	
p-ClC ₆ H ₄	53.69	2.99	4.17	19.20	4.38(s, 2H)	335(M ⁺ , 2)
	(53.65)	(3.01)	(4.17)	(19.08)	7.25(m, 4H)	
					7.85(m, 4H)	
o-MeC ₆ H ₄	60.76	4.21	8.89	20.21	2.33(s, 3H)	315(M ⁺ , 10)
	(60.94)	(4.16)	(8.89)	(20.33)	4.37(s, 2H)	
					7.25(m, 4H)	
					7.85(m, 4H)	

contd./

Table 2 contd.

$p\text{-MeC}_6\text{H}_4$	60.89	4.25	8.67	20.21	2.30(s, 3H)	315(M ⁺ ,13)
	(60.94)	(4.16)	(8.89)	(20.33)	4.30(s, 2H)	
					7.25(m, 4H)	
					7.85(m, 4H)	
$p\text{-MeOC}_6\text{H}_4$	58.06	3.97	4.26	19.40	3.78(s, 3H)	331(M ⁺ ,12)
	(58.00)	(3.96)	(4.23)	(19.36)	4.30(s, 2H)	
					6.85(m, 2H)	
					7.35(m, 2H)	
				7.85(m, 4H)		
HOCH_2	47.05	3.51	5.72	25.15	2.59(s, 1H)	255(M ⁺ ,23)
	(47.06)	(3.56)	(5.49)	(25.13)	2.89(t, 2H)	
					3.79(t, 2H)	
					7.28(m, 4H)	

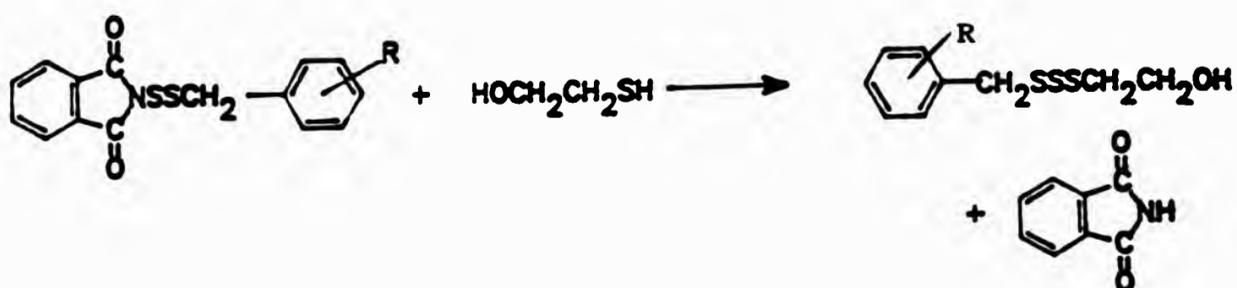
It is proposed that a phthalimido group is displaced from the N,N' -thiobisphthalimide by nucleophilic attack on the sulphur atom by the mercaptan. The phthalimido group is known¹⁵⁰ to be a very good leaving group, and the formation of phthalimide in the reaction mixture supports this mechanism (Scheme 33).



Scheme 33

Step three

This involved the reaction of 2-mercaptoethanol with the substituted benzylphthalimido disulphide and is summarized in Scheme 34.¹⁶⁰



Scheme 34

Reaction proceeds on refluxing a solution of the phthalimido disulphide and mercaptoethanol in toluene. The duration of reaction depends on the molecular complexity of the

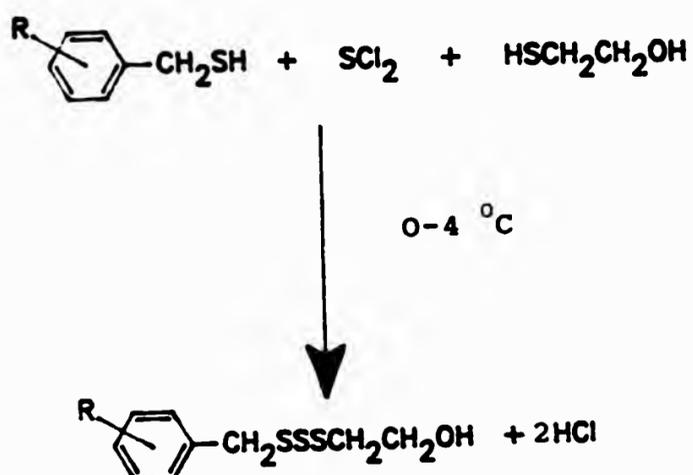
phthalimido disulphide, thus for the first member of the series, the reaction was completed in about 150 h. A longer period of time was required for higher members. When the reaction mixture was allowed to cool down, phthalimide crystallized out in all cases and this again was a good indication that the reaction had occurred. The method used in this synthesis is highly reproducible because the repeated preparation of 2-hydroxyethyl benzyl trisulphide gave a product whose analytical and other spectral properties were similar to those obtained in the first preparation. A nucleophilic attack by the sulphur atom of the mercaptan on the phthalimido disulphide is proposed for this reaction, the phthalimido group being a good leaving group which is cleaved off and then picks up a proton to form phthalimide which precipitated out on cooling. The reaction is therefore proposed to proceed by an S_N2 mechanism in which both mercaptoethanol and the phthalimido disulphide are involved in the rate-determining step. Apart from the products formed, there is no proof yet for this mechanism; a detailed kinetic study of the reaction will be required to establish this.

From the available 1H nmr, ^{13}C nmr and mass spectra it was established that small amounts (ca. 4%) of the respective symmetrical trisulphides were also formed alongside the desired products, possibly by disproportionation of the product arising from the prolonged heating (average 150 h) that the reaction mixture was subjected to. Attempts to effect complete separation by

column chromatography were unsuccessful.

2.5 Reaction of mercaptans with sulphur dichloride

The reactions of mercaptoethanol and various substituted benzyl mercaptans with sulphur dichloride were carried out in order to obtain various substituted benzyl 2-hydroxyethyl trisulphides. Although this method¹¹⁵ had been used previously to prepare this type of compound and separations were carried out by preparative tlc, we were able to design a suitable column chromatographic technique and obtained better yields. The reaction is as shown in Scheme 35. Also, Table 3 contains a list of the compounds prepared and their analytical, nmr, and mass spectral results.



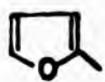
Scheme 35

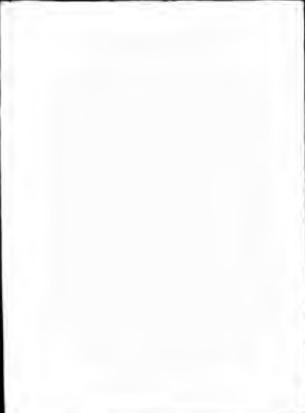
Table 3 Unsymmetrical Trisulphides $\text{ArCH}_2\text{SSSCH}_2\text{CH}_2\text{OH}$

Ar	Found (%)			δ_{H}	m/z (%)
	(Calculated)				
	C	H	S		
C_6H_5	46.33	5.24	41.50	2.57(s, 1H)	232(M^+ , 3)
	(46.51)	(5.21)	(41.51)	2.92(t, 2H)	
				3.85(t, 2H)	
				4.07(s, 2H)	
				7.03(m, 5H)	
<i>p</i> -MeC ₆ H ₄	48.83	5.78	39.00	2.31(s, 3H)	246(M^+ , 2)
	(48.73)	(5.74)	(39.03)	2.64(s, 1H)	
				2.93(t, 2H)	
				3.86(t, 2H)	
				4.04(s, 2H)	
			7.17(m, 4H)		
<i>o</i> -MeC ₆ H ₄	48.76	5.72	38.80	2.38(s, 3H)	246(M^+ , 2)
	(48.73)	(5.74)	(39.03)	2.41(s, 1H)	
				2.94(t, 2H)	
				3.87(t, 2H)	
				4.11(s, 2H)	
			7.16(m, 4H)		

contd./

Table 3 contd.

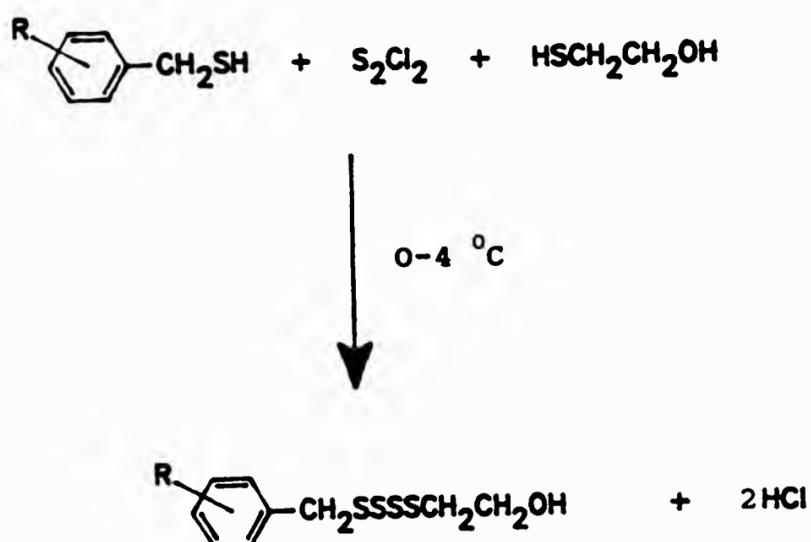
$p\text{-ClC}_6\text{H}_4$	40.27	4.29	36.36	2.40(s, 1H)	266(M ⁺ , 2)
	(40.51)	(4.16)	(36.02)	2.97(t, 2H)	
				3.89(t, 2H)	
				4.04(s, 2H)	
				7.28(m, 4H)	
$o\text{-ClC}_6\text{H}_4$	40.40	4.20	36.20	2.41(s, 1H)	266(M ⁺ , 2)
	(40.51)	(4.16)	(36.02)	2.97(t, 2H)	
				3.91(t, 2H)	
				4.19(s, 2H)	
				7.23(m, 2H)	
			7.33(m, 2H)		
	38.17	4.78	43.40	2.52(s, 1H)	222(M ⁺ , 2)
	(37.81)	(4.54)	(43.26)	2.98(t, 2H)	
				3.90(t, 2H)	
				4.09(s, 2H)	
				6.33(m, 2H)	
			7.40(m, 1H)		
$p\text{-MeOC}_6\text{H}_4$	45.82	5.36	36.80	2.40(s, 1H)	262(M ⁺ , 2)
	(45.76)	(5.39)	(36.65)	2.88(t, 2H)	
				3.92(t, 2H)	
				4.01(s, 2H)	
				4.84(s, 3H)	
			7.35(m, 4H)		



Sulphur dichloride was not stable to atmospheric moisture and, as a result, all reactions were carried out using well dried ether and under inert conditions. It was possible to isolate and separate the small amounts of symmetrical trisulphides that were formed as side products by column chromatography, thereby giving the desired unsymmetrical trisulphides almost totally free from the symmetrical derivatives for the first time.

2.6 Unsymmetrical Tetrasulphides

The reaction of sulphur monochloride with an equimolar mixture of mercaptoethanol and benzyl mercaptan (or substituted benzyl mercaptan) in dried absolute ether, under inert conditions and in the cold, was used to prepare a series of unsymmetrical tetrasulphides. The reaction is shown in Scheme 36.¹¹⁵ These reactions were carried out under inert conditions because of the moisture sensitiveness of sulphur monochloride, since any slight contact with air will decompose it to elemental sulphur.



Scheme 36

In addition to the desired product, a small amount of the symmetrical tetrasulphide was also formed. Column chromatography was used to separate this and any other



impurities. The procedure used involved eluting first with petroleum ether (b.p. 40-60 °C), followed by mixtures of petroleum ether and dichloromethane in various proportions. Tlc was used to monitor the various eluants and the desired product was finally eluted with dichloromethane. A possible impurity, bis(2-hydroxyethyl) tetrasulphide may have been retained on the column. Using this method, a series of unsymmetrical tetrasulphides was prepared, some of which were new. Table 4 gives a list of these compounds together with their analytical and spectral results. From these results, we can deduce that the various compounds were pure and that the method is versatile.

Table 4 Unsymmetrical Tetrasulphides $\text{ArCH}_2\text{SSSSCH}_2\text{CH}_2\text{OH}$

Ar	Found (%)			δ_{H}	m/z (%)
	(Calculated)				
	C	H	S		
C_6H_5	40.71	4.54	48.60	2.30(s, 1H)	264(M^+ , 2)
	(40.74)	(4.58)	(48.56)	3.05(t, 2H)	
				3.90(t, 2H)	
				4.15(s, 2H)	
				7.32(m, 5H)	
<i>p</i> -MeOC ₆ H ₄	40.83	4.78	43.30	2.61(s, 1H)	294(M^+ , 2)
	(40.82)	(4.80)	(43.50)	3.05(t, 2H)	
				3.77(s, 3H)	
				3.92(t, 2H)	
				4.12(s, 2H)	
				6.87(m, 2H)	
			7.22(m, 2H)		
<i>p</i> -ClC ₆ H ₄	36.23	3.69	42.79	2.13(s, 1H)	298(M^+ , 3)
	(36.19)	(3.71)	(42.85)	3.07(t, 2H)	
				3.92(t, 2H)	
				4.11(s, 2H)	
				7.29(m, 4H)	

contd./

Table 4 contd.

o-MeC ₆ H ₄	43.20	5.14	45.80	2.21(s, 1H)	278(M ⁺ , 2)
	(43.17)	(5.07)	(46.00)	2.40(s, 3H)	
				3.06(t, 2H)	
				3.91(t, 2H)	
				4.18(s, 2H)	
				7.18(m, 4H)	
p-MeC ₆ H ₄	43.28	4.98	45.76	2.33(s, 1H)	278(M ⁺ , 2)
	(43.17)	(5.07)	(46.00)	2.38(s, 3H)	
				3.05(t, 2H)	
				3.90(t, 2H)	
				4.12(s, 2H)	
				7.19(m, 4H)	
	32.96	3.86	50.29	2.57(s, 1H)	254(M ⁺ , 4)
	(33.08)	(3.97)	(50.36)	2.99(t, 2H)	
				3.92(t, 2H)	
				4.11(s, 2H)	
				6.39(m, 2H)	
				7.47(m, 1H)	

2.7 Unsymmetrical disulphides

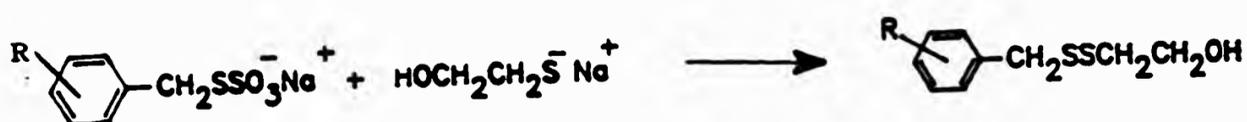
Using the reaction Schemes 37, 38, and 39¹⁶¹ to prepare unsymmetrical disulphides, we found that small amounts of



Scheme 37



Scheme 38

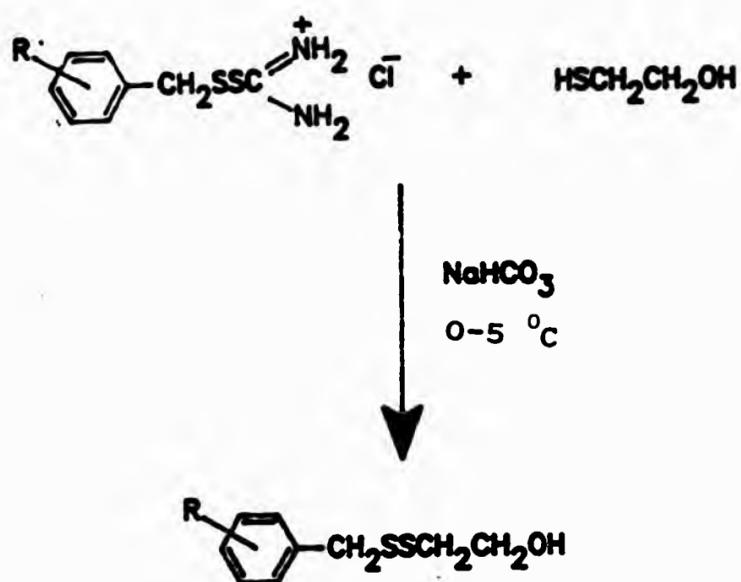


Schemes 39

the symmetrical disulphides were also formed together with the desired products. This may be due to a rearrangement reaction involving the Bunte salt in Scheme 37 above, or it may be that part of the product undergoes disproportionation

to give the symmetrical disulphide as suggested by Hiskey et al.¹⁴⁸

Using another method, apparently for the first time for making this type of compound, we were able to prepare pure unsymmetrical disulphides. This method involved the reaction of an *S*-benzylthioisothiuronium chloride with mercaptoethanol under alkaline conditions as shown in Scheme 40.



Scheme 40

The list of compounds prepared by this method and their analytical and spectral results is presented in Table 5.

Table 5 Unsymmetrical Disulphides $RCH_2SSCH_2CH_2OH$
and $H_2C=CHCH_2SSCH_2CH_2OH$

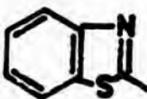
R	Found (%)			δ_H	m/z (%)
	(Calculated)				
	C	H	S		
<i>o</i> -ClC ₆ H ₄	46.43	4.87	28.00	2.54 (t, 2H)	234 (M ⁺ , 5)
	(46.05)	(4.73)	(27.26)	2.80 (s, 1H)	
				3.71 (t, 2H)	
				3.99 (s, 2H)	
				7.17 (m, 4H)	
<i>p</i> -MeOC ₆ H ₄	52.13	6.15	27.42	2.47 (s, 1H)	230 (M ⁺ , 2)
	(52.16)	(6.13)	(27.83)	2.54 (t, 2H)	
				3.74 (t, 2H)	
				3.77 (s, 3H)	
				3.85 (s, 2H)	
			7.00 (m, 4H)		
<i>p</i> -MeC ₆ H ₄	56.11	6.68	29.84	2.31 (s, 3H)	214 (M ⁺ , 5)
	(56.04)	(6.60)	(29.89)	2.49 (s, 1H)	
				2.53 (t, 2H)	
				3.69 (t, 2H)	
				3.84 (s, 2H)	
			7.17 (m, 4H)		

contd./

Table 5 contd.

$o\text{-MeC}_6\text{H}_4$	56.14	6.59	29.89	2.38(s, 3H)	214(M ⁺ , 4)
	(56.04)	(6.60)	(29.89)	2.48(t, 2H)	
				2.49(s, 1H)	
				3.67(t, 2H)	
				3.91(s, 2H)	
				7.15(m, 4H)	
C_6H_5	54.04	5.97	32.20	2.34(s, 1H)	200(M ⁺ , 8)
	(53.99)	(6.04)	(31.97)	2.49(t, 2H)	
				3.68(t, 2H)	
				3.88(s, 2H)	
				7.30(m, 5H)	
$p\text{-ClC}_6\text{H}_4$	46.13	4.67	27.10	2.36(s, 1H)	234(M ⁺ , 2)
	(46.05)	(4.73)	(27.26)	2.56(t, 2H)	
				3.73(t, 2H)	
				3.84(s, 2H)	
				7.27(m, 4H)	
$p\text{-FC}_6\text{H}_4$	49.49	5.04	29.10	2.41(s, 1H)	218(M ⁺ , 9)
	(49.55)	(5.08)	(29.33)	2.54(t, 2H)	
				3.73(t, 2H)	
				3.86(s, 2H)	
				7.00(m, 2H)	
				7.17(m, 2H)	contd./

Table 5 contd.

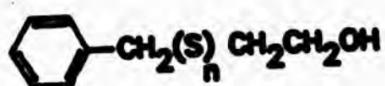
	44.36	3.84	39.52	3.07(t, 2H)	243(M ⁺ , 8)
	(44.41)	(3.73)	(39.52)	3.89(t, 2H)	
				4.68(s, 1H)	
				7.36(m, 2H)	
				7.85(m, 2H)	
H ₂ C=CH	39.92	6.70	42.57	2.69(s, 1H)	150(M ⁺ , 54)
	(39.99)	(6.72)	(42.62)	2.84(t, 2H)	
				3.34(d, 2H)	
				3.84(t, 2H)	
				5.19(m, 2H)	
				5.86(m, 1H)	

These results confirmed that the various compounds were pure. The absence of a molecular ion peak due to symmetrical aryl disulphide in the mass spectra of the products indicated the absence of these disulphides and that the compounds did not undergo disproportionation of the type reported by Hiskey *et al.*¹⁴⁸ The benzyl and substituted benzyl groups are therefore stable in this class of compound. The advantage of the method used (Scheme 40) in the present investigations was that all reactions were carried out under cold conditions and a good chromatographic

technique was used in the separation of undesired side products. The yields (60-75%) for the various reactions were good.

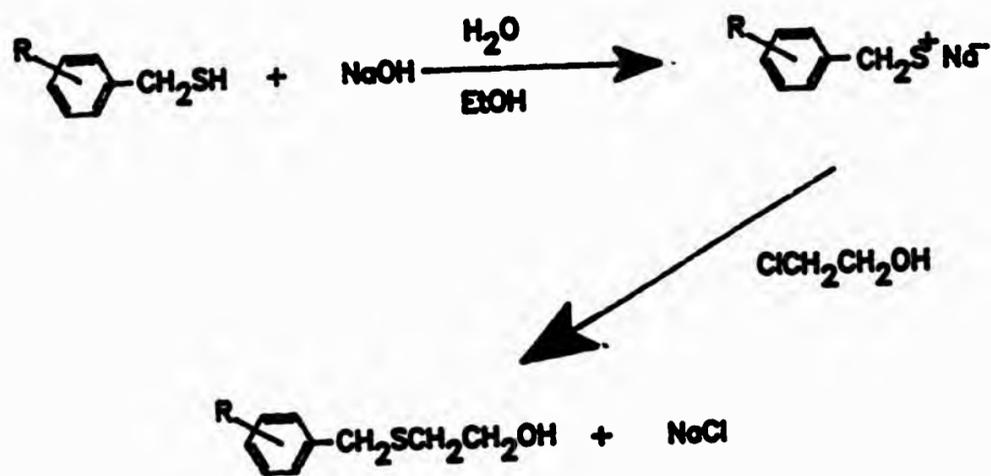
2.8 Unsymmetrical Monosulphides

The various unsymmetrical monosulphides prepared in this work were known; They were prepared so that their fungicidal activity could be compared with that of the unsymmetrical compounds of the types:



were $n = 2, 3$ and 4 .

In the preparation of the monosulphides ($n = 1$), the reaction of a benzyl sodium mercaptide with chloroethanol was used¹⁶² and gave an almost quantitative yield of the various products. The reaction is shown in Scheme 41.



Scheme 41

The list of compounds prepared together with their analytical and spectral results, is presented in Table 6.

Table 6 Unsymmetrical Monosulphides $\text{ArCH}_2\text{SCH}_2\text{CH}_2\text{OH}$

Ar	Found (%)			δ_{H}	m/z (%)
	(Calculated)				
	C	H	S		
C_6H_5	64.17	7.20	18.80	2.55(t, 2H)	168(M ⁺ , 27)
	(64.26)	(7.21)	(19.02)	2.88(s, 1H)	
				3.63(t, 2H)	
				3.67(s, 2H)	
				7.27(m, 5H)	
o-ClC ₆ H ₄	53.36	5.53	15.90	2.64(t, 2H)	202(M ⁺ , 10)
	(53.33)	(5.49)	(15.79)	3.06(s, 1H)	
				3.68(t, 2H)	
				3.81(s, 2H)	
				7.17(m, 2H)	
			7.32(m, 2H)		
o-MeC ₆ H ₄	65.80	7.70	17.80	2.38(s, 3H)	182(M ⁺ , 49)
	(65.80)	(7.67)	(17.59)	2.61(s, 1H)	
				2.68(t, 2H)	
				3.66(t, 2H)	
				3.71(s, 2H)	
			7.15(m, 4H)	contd./	

Table 6 contd.

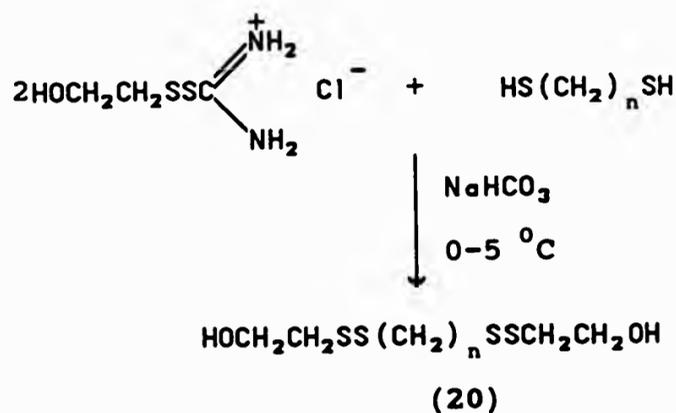
$p\text{-MeOC}_6\text{H}_4$	60.84	7.11	15.90	2.58(s, 1H)	198(M ⁺ , 30)
	(60.58)	(7.12)	(16.14)	2.60(t, 2H)	
				3.67(t, 2H)	
				3.78(s, 3H)	
				3.87(s, 2H)	
				6.82(m, 2H)	
				7.20(m, 2H)	
$p\text{-MeC}_6\text{H}_4$	65.78	7.74	17.63	2.31(s, 3H)	182(M ⁺ , 42)
	(65.80)	(7.67)	(17.59)	2.59(s, 1H)	
				2.61(t, 2H)	
				3.64(t, 2H)	
				3.66(s, 2H)	
				7.16(m, 4H)	
$p\text{-ClC}_6\text{H}_4$	53.29	5.46	15.84	2.66(t, 2H)	202(M ⁺ , 12)
	(53.33)	(5.49)	(15.79)	3.04(s, 1H)	
				3.69(t, 2H)	
				3.79(s, 2H)	
				7.27(m, 4H)	

The usual procedure was to dissolve the mercaptan and alkali in the minimum amount of water, followed by dilution with absolute ethanol and addition of the alkyl halide at

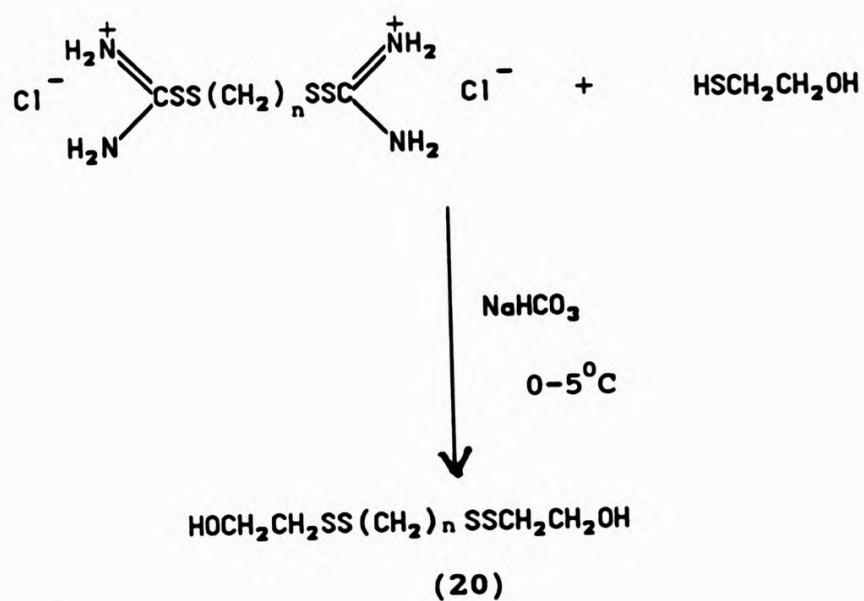
such a rate that the reaction, which was exothermic, was kept under control. However, attention must be paid to the fact that a mercaptan in an alkaline medium may be oxidised to the disulphide and that the rate of oxidation depends on the length and manner of exposure to air. Therefore in all the experiments involving the preparation of these monosulphides, inert conditions were used. Column chromatography was also utilized to remove any trace of disulphide formed.

2.9 Alkane-bis- α,ω -(2-hydroxyethyl disulphide)s

Two methods were used to prepare these novel compounds (20), the first of which involved the reaction of S-(2-hydroxyethylthio)isothiuronium chloride with an α,ω -dimercaptoalkane in alkaline medium as depicted in Scheme 42.



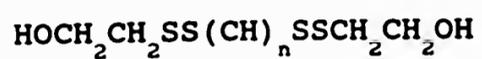
Scheme 42



Scheme 44

Analytical and spectral results, presented in Table 7, showed that these compounds were pure, irrespective of the reaction route employed.

Table 7 Alkane-bis- α,ω -(2-hydroxyethyl)disulphide)s



n	Found (%)			δ_{H}	m/z (%)
	(Calculated)				
	C	H	S		
2	29.27	5.73	51.99	2.32 (t, 4H)	246 (M^+ , 5)
	(29.26)	(5.74)	(52.04)	2.68 (t, 4H)	
				2.96 (s, 2H)	
				3.84 (t, 4H)	
3	32.31	6.18	49.00	2.12 (q, 2H)	260 (M^+ , 3)
	(32.31)	(6.20)	(49.17)	2.87 (dt, 8H)	
				3.11 (s, 2H)	
				3.87 (t, 4H)	
4	35.03	6.62	46.67	1.82 (q, 4H)	274 ¹ (M^+ , 2)
	(35.09)	(6.70)	(46.61)	2.71 (s, 2H)	
				2.74 (t, 4H)	
				2.86 (t, 4H)	
				3.87 (t, 4H)	

¹Exact molecular mass (m/z) : Found (M^+) 274.0190. $\text{C}_8\text{H}_{18}\text{O}_2\text{S}_4$ requires 274.0186.

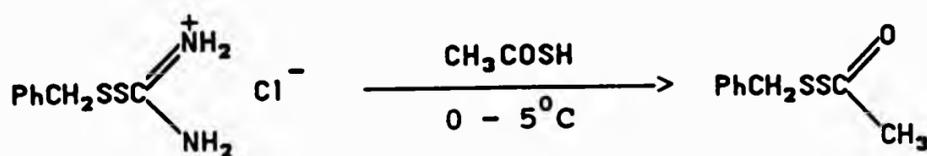
2.10 Symmetrical and other unsymmetrical disulphides

Using different methods as appropriate, some symmetrical and unsymmetrical disulphides were prepared. Dibenzyl disulphide was prepared by the method of Baroni¹⁶³ as depicted in Scheme 45.



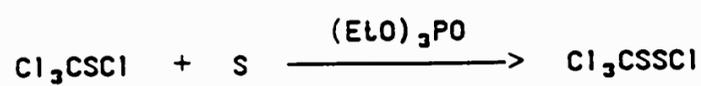
Scheme 45

Acetyl benzyl disulphide was prepared as reported by the reaction of S-benzylthioisothiuronium chloride with thioacetic acid and this reaction is shown in Scheme 46.¹¹⁴



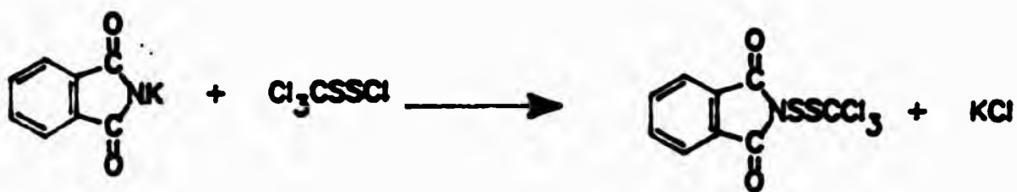
Scheme 46

Trichloromethanethiosulphenyl chloride was prepared by heating under reflux trichloromethanesulphenyl chloride, sulphur, and a catalytic amount of triethyl phosphate, as shown in Scheme 47.¹⁶⁴



Scheme 47

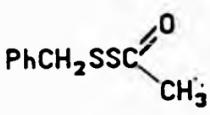
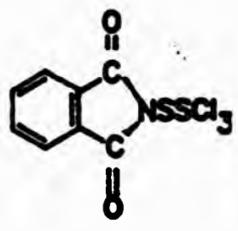
Trichloromethyl phthalimido disulphide was prepared by the reaction of potassium phthalimide with trichloromethanethio-sulphenyl chloride as shown in Scheme 48.¹⁶⁵



Scheme 48

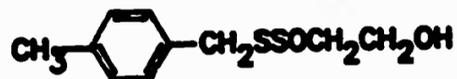
Analytical and other spectral results (Table 8) showed that these compounds were pure.

Table 8. Symmetrical and unsymmetrical disulphides

Compounds	Found (%)			δ_H	m/z (%)
	(Calculated)				
	C	H	S		
$\text{PhCH}_2\text{SSCH}_2\text{Ph}$	67.89 (68.26)	5.83 (5.74)	25.80 (25.99)	3.56(s, 4H) 7.28(m, 10H)	246(M ⁺ , 60)
	54.51 (54.52)	5.04 (5.09)	32.50 (32.32)	2.31(s, 3H) 3.91(s, 2H) 7.29(m, 5H)	198(M ⁺ , 50)
	32.95 (32.89)	1.27 (1.23)	19.40 (19.48)	7.31(m, 4H)	316(M ⁺ , 48)
Cl_3CSSCl	5.62 (5.51)	- (-)	29.34 (29.55)	-	218(M ⁺ , 10)

2.11 Compound of the type: RSSOR'

An attempt made to prepare the following compound:



via the oxidation of 4-methylbenzyl 2-hydroxyethyl disulphide using hydrogen peroxide or perchlorobenzoic acid was unsuccessful. A possible explanation is that this

compound might not be stable under laboratory conditions. It was also noticed that the liquid product changed colour from pale yellow to dark brown only a few minutes after isolation from the reaction mixture. Elemental analysis showed that this is not the expected product.

2.12 Stability of compounds of the type $\text{ArCH}_2(\text{S})_n\text{CH}_2\text{CH}_2\text{OH}$

Benzyl 2-hydroxyethyl mono-, di-, tri-, tetra-sulphide were analysed by tlc and ^1H nmr after they had been stored under laboratory conditions for about 14 months. The tlc was carried out in petroleum ether (b.p.40-60 $^\circ\text{C}$)/ CH_2Cl_2 (ratio 2:1). In the benzyl 2-hydroxyethyl mono- and di- sulphide, a single spot was observed and the R_f values were 0.71 and 0.68, respectively. For benzyl 2-hydroxyethyl trisulphide two spots were observed with R_f values of 0.68 and 0.23 respectively. Also, for benzyl 2-hydroxyethyl tetrasulphide two spots were observed with R_f values of 0.67 and 0.22, respectively.

The ^1H nmr spectrum of benzyl 2-hydroxyethyl trisulphide showed the presence of bis(2-hydroxyethyl) trisulphide because triplets due to the methylene protons of bis(2-hydroxyethyl) trisulphide were observed at δ 2.58 and 3.69 in addition to those due to the original compound (δ 2.91 and 3.83). Also, the ^1H nmr of benzyl 2-hydroxyethyl tetrasulphide showed the presence of bis(2-hydroxyethyl) tetrasulphide because triplets which may be due to the

methylene protons of bis(2-hydroxyethyl) tetrasulphide were observed at δ 2.61 and 3.58 in addition to those due to the original compound (δ 3.03 and 3.92).

The ^1H nmr spectra of benzyl 2-hydroxyethyl mono- and di-sulphide, showed the absence of any impurities after samples of both compounds were heated to 50 $^\circ\text{C}$ for 3 h and 100 $^\circ\text{C}$ for 3 h.

From this stability study, it was found that benzyl 2-hydroxyethyl mono- and di-sulphide were stable under laboratory conditions for about 14 months while benzyl 2-hydroxyethyl tri- and tetra-sulphide were not. Both compounds undergo disproportionation after a period of storage. The disproportionation products contain bis(2-hydroxyethyl) tri-, and tetra-sulphide respectively. Another possible disproportionation product which is bis(benzyl) tri-, and tetra- sulphide respectively was not observed in the ^1H nmr.

2.13

¹H nmr Spectroscopy

2.13.1 Introduction

Nuclear magnetic resonance spectroscopy is a powerful tool that gives useful information about the nature of the immediate environment of nuclei with spin property. It is a very useful technique in establishing molecular structure of compounds. In the present study, the technique was particularly useful for confirmation of the structures of the various compounds synthesised.

2.13.2 Compounds of the type:



The general ¹H nmr chemical shifts observed for these compounds are summarised in Table 9. The ¹H nmr spectra of the symmetrical trisulphides provide evidence that the compounds have a highly symmetrical structure with respect to the two methylene groups because they exhibit a sharp singlet at δ 3.97-4.14 and this is the only diagnostic peak for this class of compound.

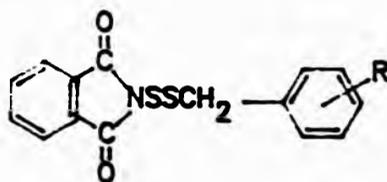
Table 9. ^1H nmr data for symmetrical trisulphides $\text{ArCH}_2\text{SSSCH}_2\text{Ar}$ in CDCl_3

Group	δ_{H} /ppm	Multiplicity
Ar^{a}	7.20-7.35	m
$-\text{CH}_2-$	3.97-4.14	s
$-\text{CH}_3$	2.32-2.38	s
$-\text{OCH}_3$	3.78	s

$^{\text{a}}\text{Ar} = \text{Ph}, p\text{-MeC}_6\text{H}_4, o\text{-MeC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, o\text{-ClC}_6\text{H}_4.$

As expected, all the compounds gave peaks at δ 7.20-7.35 and multiplets were observed in all cases, these peaks being assigned to the aromatic protons. A singlet peak at δ 2.32-2.38 was observed when a methyl substituent was present in the benzene ring. The protons of methoxy substituents gave a signal downfield at δ 3.78, because of the electronegativity of the oxygen atom. In this class of compound the proton nmr spectrum is relatively simple and the peaks are easily assigned to their respective hydrogen atoms in the molecule. A typical spectrum for this class of compound is presented in Figure 1.

2.13.3 Compounds of the type:



The chemical shifts for this class of compound are summarised in Table 10.

Table 10. ¹H nmr data for phthalimido disulphides PhthNSSAr in CDCl₃

Group	δ_{H} /ppm	Multiplicity
Ar ^a	7.84-7.85	m
Ar ^b	7.23-7.35	m
-CH ₂ -	4.30-4.38	s
-OCH ₃	3.78	s
-CH ₃	2.30-2.33	s

^aAr = phthalimido group.

^bAr = Ph, o-ClC₆H₄, o-MeC₆H₄, p-MeOC₆H₄, p-MeC₆H₄, p-ClC₆H₄.

For compounds in this class, the peaks at δ 7.84-7.85 were assigned to the protons of the benzene ring of the phthalimido group; they are shifted downfield because of the effect of the oxygen of the carbonyl groups. Next to these peaks, but well distinguishable from them, are peaks at δ 7.23-7.35 which are assigned to the protons of the other

benzene ring present in the molecule. Further evidence for this assignment lies in the fact that the protons of the benzene ring in compounds in which no phthalimido group is present gave peaks at δ 7.19-7.35. As in the symmetrical trisulphides, the singlet methylene proton peak at δ 4.30-4.38 is diagnostic of this class of compound. The spectra for this class of compound are quite simple and the protons are easily assigned to their respective peaks. A typical spectrum is presented in Figure 2.

2.13.4 Compounds of the type:



The usual chemical shifts for this class of compound are summarised in Table 11. The protons of the methoxy group (R = MeO) absorb well downfield at δ 3.87 when compared with those of the methyl group (R = Me) at δ 2.31-2.38. This is also due to the electronegative effect of the oxygen atom of the methoxy group. Also, for the same reason, the protons of the methylene group adjacent to oxygen in the ethoxy group HOCH₂CH₂ give a signal that is downfield at δ 3.85-3.92 when compared to that adjacent to sulphur (SCH₂CH₂) at δ 2.88-2.98, oxygen being more electronegative than sulphur. The methylene protons in both cases give a triplet because of coupling to the two hydrogen atoms of the adjacent CH₂ group. In compounds in which electron donating groups such

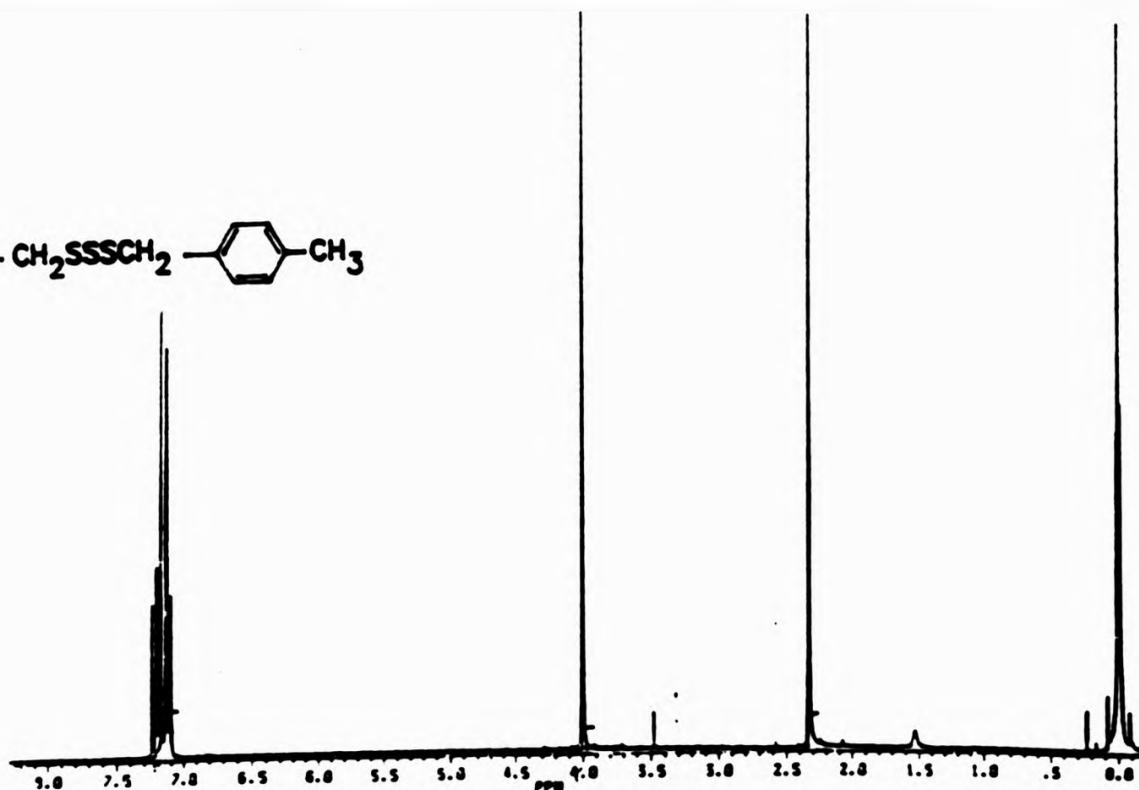


Figure 1: ^1H nmr spectrum (250 MHz) of di-(4-methylbenzyl) trisulphide in CDCl_3

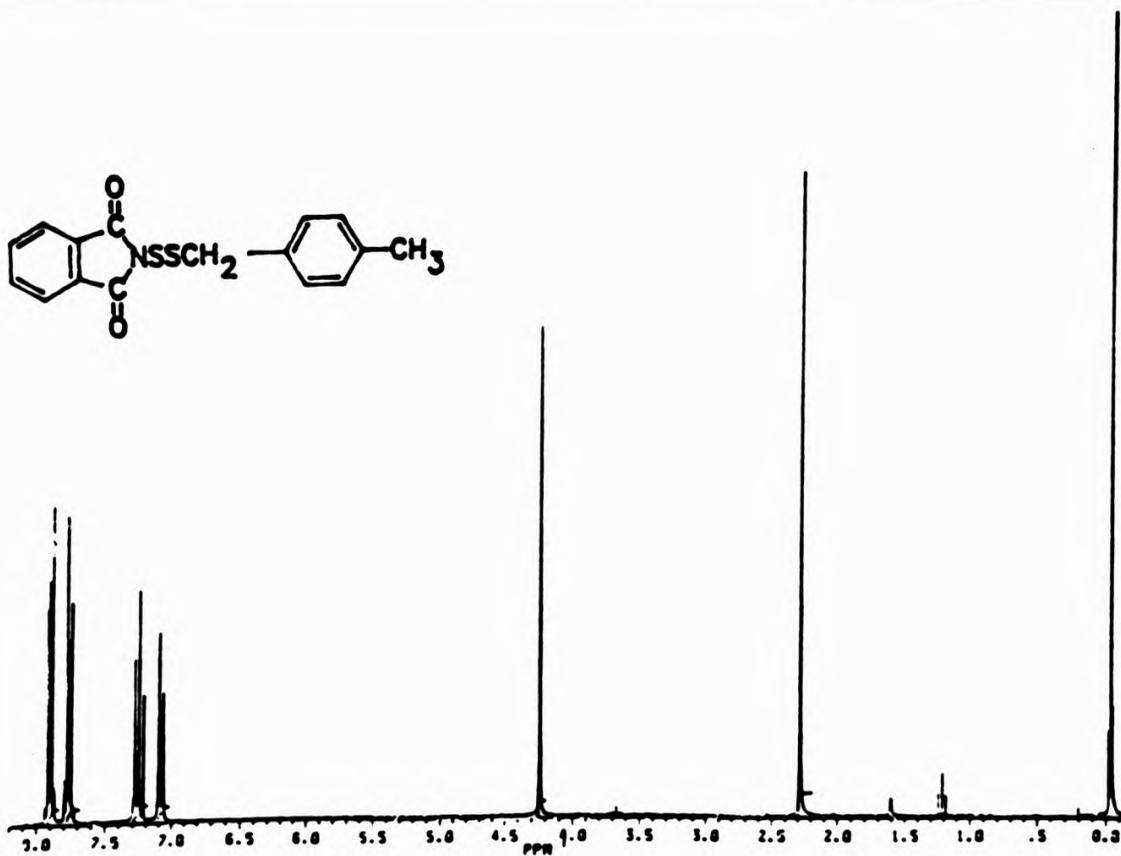
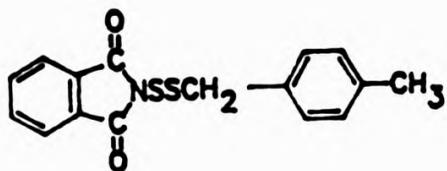


Figure 2: ^1H nmr spectrum (250 MHz) of 4-methylbenzyl phthalimido disulphide in CDCl_3

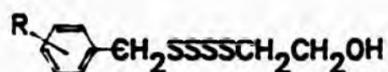
as methyl are present as substituents in the benzene ring, the OH proton absorbs slightly downfield from the protons of the methyl group. This is not the case for unsymmetrical tetrasulphides and may be due to the longer sulphur chain in the tetrasulphides. The CH₂ protons of the benzyl group give a singlet signal at δ 4.01-4.19 and absorption in this region is fairly constant for all the compounds. The proton nmr spectra of this class of compound confirmed their purity (ca. 98%) and they were quite simple. A typical spectrum is presented in Figure 3.

Table 11. ¹H nmr data for unsymmetrical trisulphides
ArCH₂SSSCH₂CH₂OH in CDCl₃

Group	$\delta_{\text{H}}/\text{ppm}$	Multiplicity	Coupling constant (J/Hz)
Ar ^a	7.16-7.35	m	-
ArCH ₂	4.01-4.19	s	-
OH	2.31-2.64	s	-
SCH ₂ CH ₂	2.88-2.98	t	³ J _{HCCH} = 6
HOCH ₂ CH ₂	3.85-3.92	t	³ J _{HCCH} = 6
CH ₃	2.31-2.38	s	-
CH ₃ O	3.87	s	-

^aAr = Ph, o-MeC₆H₄, o-ClC₆H₄, p-ClC₆H₄, p-MeC₆H₄, p-ClC₆H₄,
p-MeOC₆H₄.

2.13.5 Compounds of the type:



The usual chemical shifts for this class of compound are summarised in Table 12.

Table 12. ^1H nmr data for unsymmetrical tetrasulphides
 $\text{ArCH}_2\text{SSSSCH}_2\text{CH}_2\text{OH}$ in CDCl_3

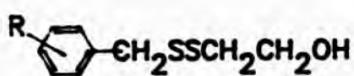
Group	$\delta_{\text{H}}/\text{ppm}$	Multiplicity	Coupling constant J/Hz
Ar^{a}	7.19-7.32	m	-
ArCH_2	4.11-4.18	s	-
HOCH_2CH_2	3.90-3.92	t	$^3J_{\text{HCCH}} = 6$
CH_3O	3.77	s	-
SCH_2CH_2	3.05-3.07	t	$^3J_{\text{HCCH}} = 6$
CH_3	2.34-2.40	s	-
OH	2.13-2.33	s	-

$^{\text{a}}\text{Ar} = \text{Ph}, o\text{-ClC}_6\text{H}_4, p\text{-MeC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, o\text{-MeC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4.$

Absorption at δ 7.19-7.32 is assigned to the benzene ring protons, and a singlet in the region δ 4.11-4.18 is due to the benzyl CH_2 protons. The methylene protons adjacent to

oxygen in the ethoxy group (HOCH_2CH_2) absorb well downfield at δ 3.90-3.92 when compared to those adjacent to sulphur (SCH_2CH_2) which gave signal at δ 3.05-3.07, due to the electronegative effect of the oxygen atom as mentioned above. Both sets of methylene protons are triplets because of their being coupled to each other. Also, as in the previous class of compound, the methoxy group protons ($\text{R} = \text{MeO}$) absorb well downfield at δ 3.77 as compared with the methyl protons ($\text{R} = \text{Me}$) which give signal at δ 2.34-2.40. The proton nmr spectra of this class of compound confirmed their purity (ca. 97%) and the different protons were easily assigned. A typical spectrum is presented in Figure 4.

2.13.6 Compounds of the type:



The chemical shifts for this class of compound are presented in Table 13. Protons of the benzene ring give a multiplet at δ 7.00-7.30, the benzyl methylene protons give a singlet at δ 3.84-3.99, and the protons of the methylene group adjacent to oxygen in the ethoxy group (HOCH_2CH_2) give a signal at δ 3.67-3.74, which is downfield compared to that for the CH_2 protons adjacent to sulphur (SCH_2CH_2), which resonate at δ 2.48-2.54. Both sets of methylene protons are triplets being coupled to one another. The methoxy group protons ($\text{R} = \text{MeO}$)

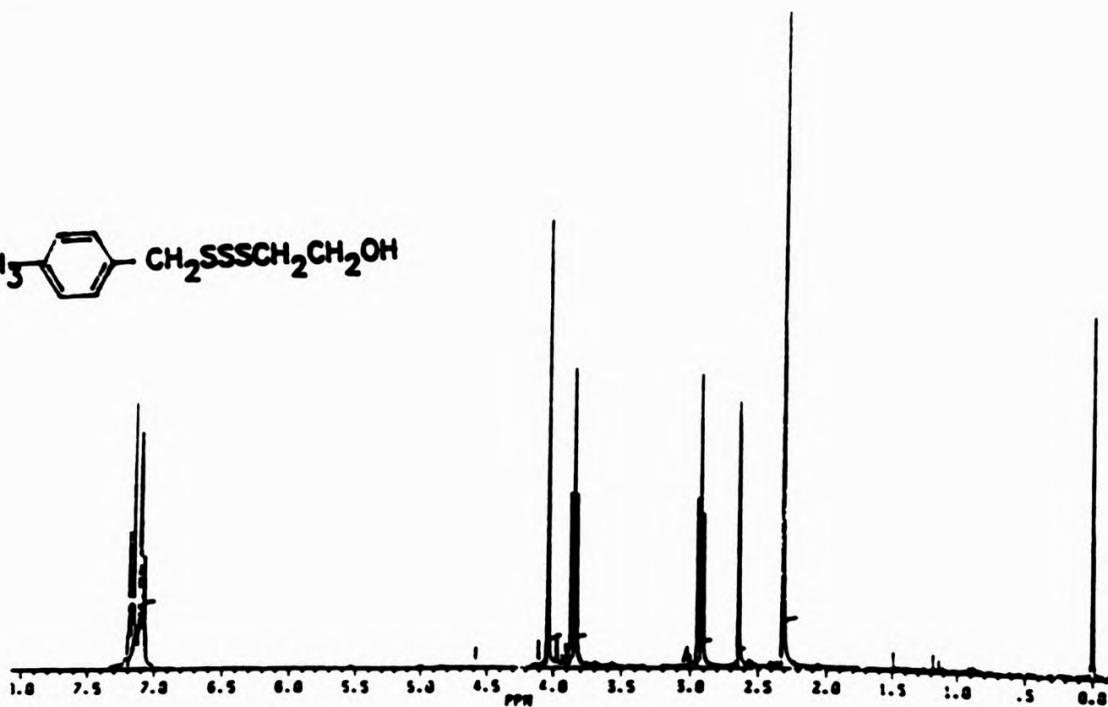
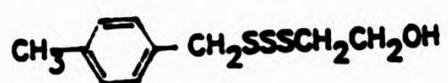


Figure 3: ^1H nmr spectrum (250 MHz) of 4-methylbenzyl
2-hydroxyethyl trisulphide in CDCl_3

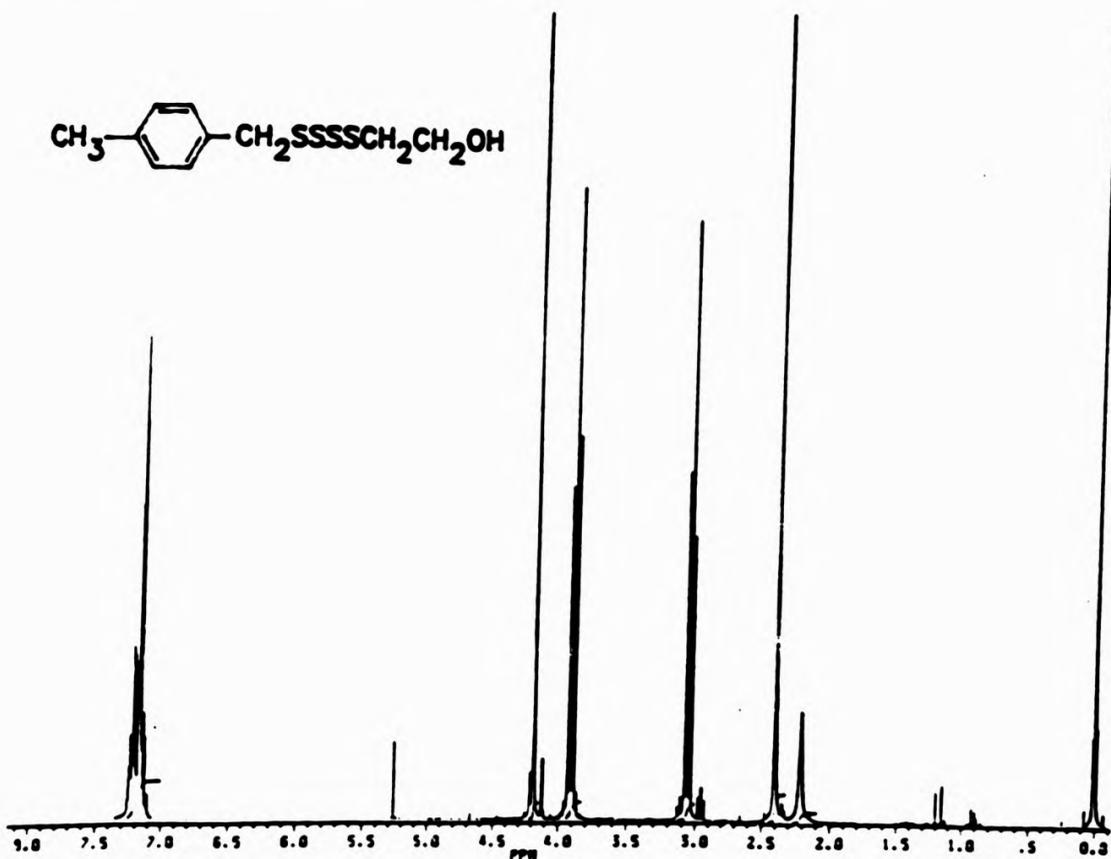


Figure 4: ^1H nmr spectrum (250 MHz) of 4-methylbenzyl
2-hydroxyethyl tetrasulphide in CDCl_3

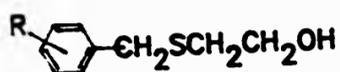
also gave a singlet well downfield at δ 3.77 when compared with the protons of the methyl group ($R = \text{Me}$), which resonate at δ 2.31-2.38. As for other classes of compound, the proton nmr spectra confirm their purity (ca. 99%) and all the hydrogen atoms are easily assigned to their respective signals. A typical spectrum is presented in Figure 5.

Table 13. ^1H nmr data for unsymmetrical disulphides
 $\text{ArCH}_2\text{SSCH}_2\text{CH}_2\text{OH}$ in CDCl_3

Group	δ_{H} /ppm	Multiplicity	Coupling constant (J/Hz)
Ar^{a}	7.00-7.30	m	-
ArCH_2	3.84-3.99	s	-
CH_3O	3.77	s	-
HOCH_2CH_2	3.67-3.74	t	$^3J_{\text{HCCH}} = 6$
SCH_2CH_2	2.48-2.54	t	$^3J_{\text{HCCH}} = 6$
CH_3	2.31-2.38	s	-
OH	2.34-2.80	s	-

^aAr = Ph, *o*-ClC₆H₄, *p*-MeC₆H₄, *p*-MeOC₆H₄, *o*-MeC₆H₄, *p*-ClC₆H₄,
p-FC₆H₄.

2.13.7 Compounds of the type:



The chemical shifts for compounds of this class are presented in Table 14.

Table 14. ^1H nmr data for unsymmetrical monosulphides
 $\text{ArCH}_2\text{SCH}_2\text{CH}_2\text{OH}$ in CDCl_3

Group	δ_{H} /ppm	Multiplicity	Coupling constant (J/Hz)
Ar^{a}	7.15-7.27	m	-
ArCH_2	3.66-3.81	s	-
CH_3O	3.78	s	-
HOCH_2CH_2	3.63-3.68	t	$^3J_{\text{HCCH}} = 6$
OH	2.59-3.06	s	-
SCH_2CH_2	2.55-2.68	t	$^3J_{\text{HCCH}} = 6$
CH_3	2.31-2.38	s	-

$^{\text{a}}\text{Ar} = \text{Ph}, o\text{-MeC}_6\text{H}_4, o\text{-ClC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, p\text{-MeC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4.$

The triplet at δ 3.63-3.68 which is assigned to the methylene group adjacent to oxygen (HOCH_2CH_2) is well downfield when compared to the second triplet at δ 2.55-2.68, due to the methylene group adjacent to sulphur

(SCH₂CH₂). This first triplet was not well resolved in most of the compounds, however, when the spectra were run in deuterated water the peaks became well resolved and were of comparable intensity to the peaks of the second triplet. This showed that the protons of the OH group exhibited long range coupling with those of the methylene group (HOCH₂CH₂) although this was weak. In all the compounds of this class, the hydroxy protons gave a singlet more downfield than the methylene group (SCH₂CH₂) protons, although this was not found to be the case for other higher order oligosulphides discussed earlier. The multiplet at δ 7.15-7.27 is assigned to the protons of the benzene ring and the singlet at δ 3.66-3.81 to the protons of the benzyl methylene group. Again, as in previous classes of compound, the methoxy protons (R = MeO) showed a singlet well downfield at δ 3.78 when compared with the singlet of the protons of the methyl group (R = Me) that resonate at δ 2.31-2.38. A typical spectrum for this class of compound is presented in Figure 6.

2.13.8 Compounds of the type:



The chemical shifts of compounds in this class are presented in Table 15. The protons of the central methylene group when

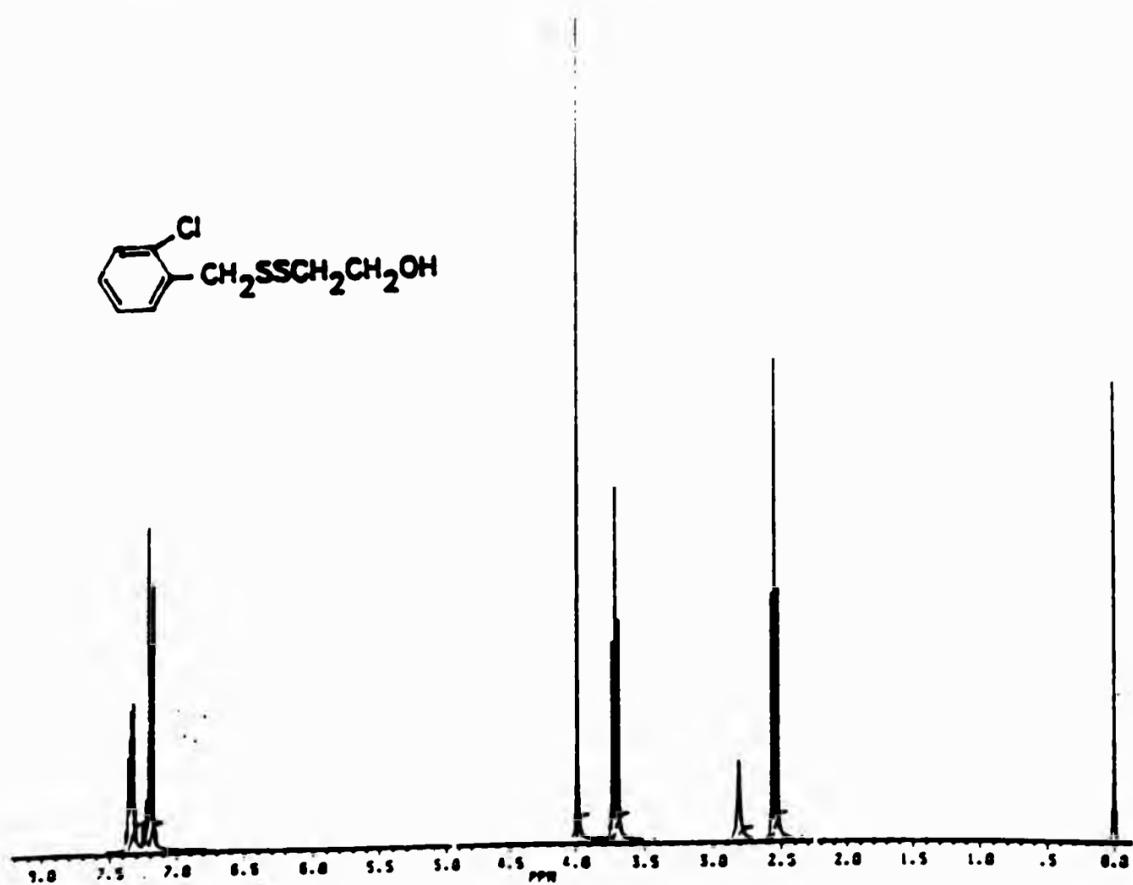


Figure 5: ^1H nmr spectrum (250 MHz) of 2-chlorobenzyl
2-hydroxyethyl disulphide in CDCl_3

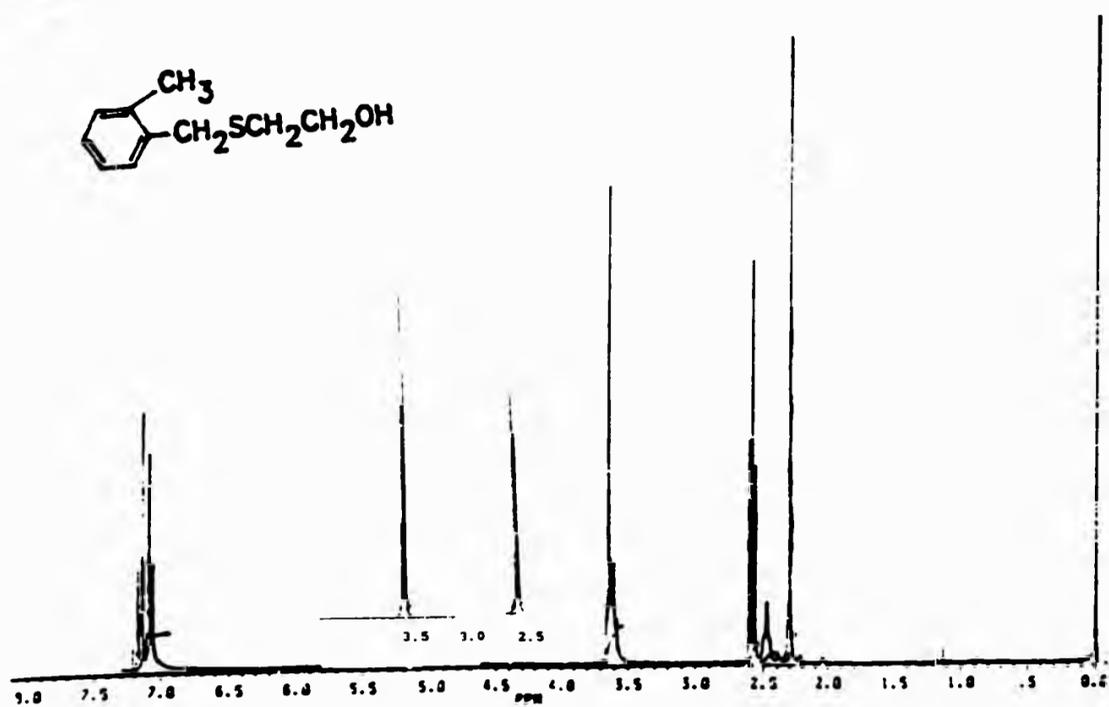


Figure 6: ^1H nmr spectrum (250 MHz) of 2-methylbenzyl
2-hydroxyethyl monosulphide in CDCl_3

n=3 (SCH₂CH₂CH₂S) gave a quintet at δ 1.97, and the protons of the two methylene groups on either side (SCH₂CH₂CH₂S) gave a triplet at δ 2.85. The protons of the methylene group adjacent to sulphur in the the hydroxyethyl group (HOCH₂CH₂) gave a triplet at δ 2.86 whilst those adjacent to oxygen, HOCH₂, were shifted downfield at δ 3.84-3.87 where they resonate as a triplet. The hydroxy protons gave a broad peak at δ 3.11-3.71. A typical spectrum is presented in Figure 7.

Table 15. ¹H nmr data for alkane bis-α,ω-(2-hydroxyethyl-disulphide)s HOCH₂CH₂SS(CH₂)_nSSCH₂CH₂OH in CDCl₃

Group	δ _H /ppm	Multiplicity	Coupling Constant (J/Hz)
SCH ₂ (CH ₂) _{n-2} CH ₂ S	1.82-2.12	q	-
SCH ₂ (CH ₂) _{n-2} CH ₂ S	2.32-2.87	t	³ J _{HCCH} = 6
HOCH ₂ CH ₂ S	2.68-2.87	t	³ J _{HCCH} = 6
OH	3.11-3.71	b	-
HOCH ₂	3.84-3.87	t	³ J _{HCCH} = 6

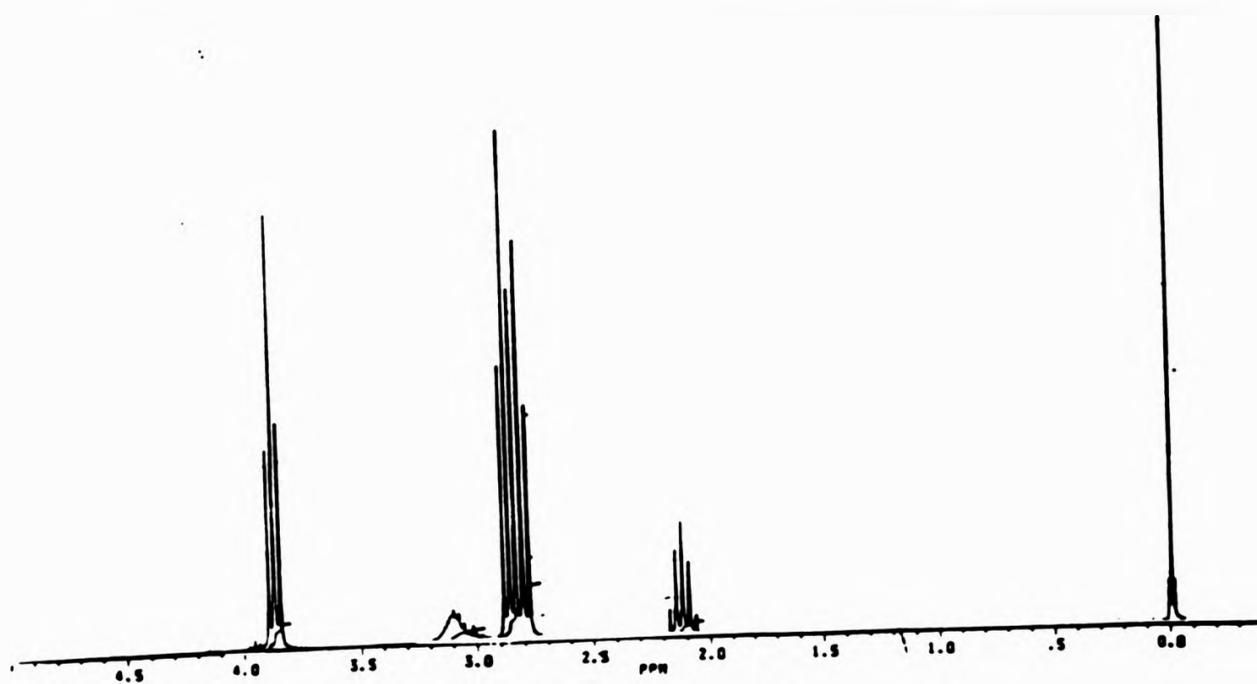
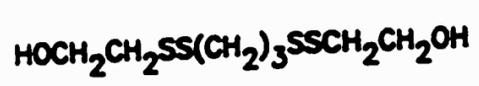


Figure 7: ¹H nmr spectrum (250 MHz) of propane bis- α,ω -(2-hydroxyethyl)disulphide) in CDCl_3

¹³C nmr spectra of most of the compounds synthesised in this work were found to be useful for the confirmation of their structures. The various peaks due to the respective carbon atoms were easily assigned, and the spectra provided further evidence for the purity of most of the compounds. Like the ¹H nmr spectra, the ¹³C nmr of most of the compounds shared similar features.

2.14.1 Compounds of the type:



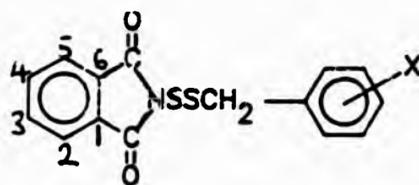
The chemical shifts for this class of compound are presented in Table 16. The electron-withdrawing effect of the oxygen atom of the methoxy group causes the ArC-4 carbon atom to absorb downfield at δ 159.1. The methoxy carbon, which gives a signal at δ 55.24, was shifted downfield when compared with the signal for the methyl carbon at δ 19.33-21.17, due to the electronegative effect of the oxygen atom of the methoxy group. The methylene carbon of the the benzyl group (ArCH₂S) resonates at δ 40.48-43.11 and this range is fairly constant for all the compounds in this class.

Table 16. ^{13}C nmr data for symmetrical trisulphides
 $\text{ArCH}_2\text{SSSCH}_2\text{Ar}$ in CDCl_3

Group Ar	δ_c /ppm						
	ArCH ₂	ArC-1	ArC-3	ArC-2	ArC-5	ArC-6	ArC-4
<i>p</i> -MeOC ₆ H ₄ ^a	42.6	113.5	128.4	130.5	128.4	130.5	159.1
<i>o</i> -ClC ₆ H ₄	40.5	126.7	129.0	131.7	129.8	134.3	134.3
<i>p</i> -MeC ₆ H ₄ ^b	42.9	129.3	128.8	133.4	128.8	133.4	137.3
<i>p</i> -ClC ₆ H ₄	42.3	128.8	130.7	133.5	130.7	133.5	135.0
<i>o</i> -MeC ₆ H ₄ ^c	41.2	126.0	128.0	130.6	134.0	137.0	137.5
Ph	43.1	127.6	128.6	129.4	128.6	129.4	136.5

^aMethoxy carbon gives signal at δ 55.2. ^bMethyl carbon gives signal at δ 21.2. ^cMethyl carbon gives signal at δ 19.3.

2.14.2 Compounds of the type:



The chemical shifts for compounds in this class are presented in Table 17. The carbonyl carbon atoms absorb well downfield at δ 167-169 and this range was constant for all the compounds. The methylene carbon of the benzyl group (ArCH_2) gave a signal at δ 42.6-45.7. The absorptions of the phthalimido aromatic carbons ArC-1',6' ArC-2',5' and ArC-3',4' were shifted downfield when compared to those of

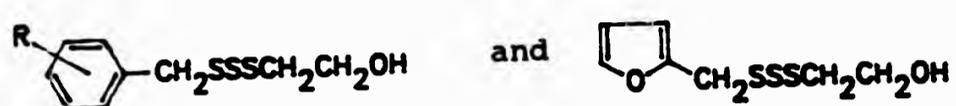
the carbons of the aryl ArC-1 and ArC-4 of the benzyl group because of their proximity to the oxygen of the carbonyl groups. Also, the carbon of the methoxy group absorbed downfield when compared with that of the methyl group.

Table 17. ^{13}C nmr data for phthalimido disulphides PhthNSSAr^a in CDCl_3

Group	δ_c /ppm						
	ArCH ₂	ArC-1	ArC-3	ArC-2	ArC-5	ArC-6	ArC-4
Ar							
<i>o</i> -ClC ₆ H ₄	43.1	124.1	126.8	129.7	126.7	129.6	131.9
<i>p</i> -MeC ₆ H ₄ ^b	45.2	129.3	124.0	129.3	124.0	129.3	132.2
<i>p</i> -ClC ₆ H ₄	43.5	124.2	126.8	129.7	126.8	129.7	131.3
Ph	42.6	125.1	127.3	130.0	127.3	130.0	131.8
<i>o</i> -MeC ₆ H ₄ ^c	45.7	124.5	129.1	130.1	129.1	130.1	132.4
<i>p</i> -MeOC ₆ H ₄ ^d	45.3	113.7	125.7	130.3	125.7	130.3	158.3

^aIn all compounds, ArC-3',4' give signal at δ 132.2-134.4; ArC-2',5' give signal at δ 134.1-135.0; ArC-1',6' give signal at δ 134.8-138.6; C=O carbon gives signal at δ 167.6-169.6. ^bMethyl carbon gives signal at δ 21.1. ^cMethyl carbon gives signal at δ 20.9. ^dMethoxy carbon gives signal at δ 25.8.

2.14.3 Compounds of the type:



The chemical shifts for this class of compound are presented in Table 18.

Table 18. ^{13}C nmr data for unsymmetrical trisulphides $\text{ArCH}_2\text{SSSCH}_2\text{CH}_2\text{OH}$ in CDCl_3

Group Ar	δ_c/ppm								
	SCH_2	ArCH_2	HOCH_2	ArC-1	ArC-3	ArC-2	ArC-5	ArC-6	ArC-4
$p\text{-MeC}_6\text{H}_4^a$	41.3	42.9	59.7	127.0	133.1	129.3	133.1	129.3	137.1
$o\text{-ClC}_6\text{H}_4$	40.6	41.5	59.6	125.9	126.7	131.7	127.1	129.8	134.0
Ph	41.3	43.0	59.6	127.6	128.6	129.4	128.6	129.4	136.2
$o\text{-MeC}_6\text{H}_4^b$	41.4	43.0	60.0	127.2	133.2	128.5	133.8	129.4	137.4
$p\text{-ClC}_6\text{H}_4$	40.3	41.4	59.5	126.6	129.8	131.6	129.8	131.6	133.8
$p\text{-MeOC}_6\text{H}_4^c$	41.3	43.0	59.2	114.2	129.5	131.4	129.5	131.4	158.9
2-Furyl ^d	35.3	41.7	59.6						

^aMethyl carbon gives signal at δ 21.1.

^bMethyl carbon gives signal at δ 22.3.

^cMethoxy carbon gives signal at δ 55.1.

^dC-3, C-4, C-2 and C-5 of the furyl ring give signals at δ 109.5, 110.6, 142.7 and 149.2 respectively.

The chemical shift of the carbon atom of the methylene group adjacent to the hydroxy group (HOCH_2) is well downfield at around δ 60 for most of the compounds, while that of the CH_2 group adjacent to sulphur (SCH_2CH_2) gives a signal at δ 40.3-41.3, which is only slightly upfield when compared with the methylene carbon of the benzyl group (ArCH_2) at δ 41.4-43.0. Again the chemical shift of the carbon of the methoxy group was shifted well downfield, at δ 55.1, when compared with that of the methyl group at δ 21.1-22.3. In the furfuryl compound, the signals at δ 109.5 and 110.6 are due to C-3 and C-4 of the furyl ring and those at δ 142.7 and 149.2, which are assigned to C-2 and C-5 of this ring, are downfield due to the proximity of oxygen. Lastly, the well downfield absorption of ArC-4 of the benzene ring in 4-methoxybenzyl 2-hydroxyethyl trisulphide (when compared with the absorption of similar carbon atoms of compounds with different substituent in the ring) may be due the electron-withdrawing inductive effect of the oxygen atom of the methoxy group in this compound.

2.14.4 Compounds of the type:



The chemical shifts for this class of compound are presented

in Table 19. The absorption of the carbon atom of the methylene group adjacent to the hydroxy group (HOCH_2) is downfield at δ 60 and this is fairly constant for all the compounds. The carbon atom adjacent to sulphur in the group (SCH_2CH_2), resonates at δ 41.6-41.7, except for that of 2-furfuryl 2-hydroxyethyl tetrasulphide which gives a signal at δ 35.38. In 2-furfuryl 2-hydroxyethyl tetrasulphide, absorptions at δ 109.6 and 110.0 which are upfield compared with those of the other two carbon atoms, are assigned to C-3 and C-4 of the furyl ring. The downfield signals at δ 143.0 and 149.6 are assigned to the furyl C-2 and C-5 respectively because of their proximity to the oxygen of the furyl ring. Lastly the well downfield absorption for ArC-4 in 4-methoxybenzyl 2-hydroxyethyl tetrasulphide is due to the electron-withdrawing effect of the oxygen atom of the methoxy group.

Table 19. ^{13}C nmr data for unsymmetrical tetrasulphides
 $\text{ArCH}_2\text{SSSSCH}_2\text{CH}_2\text{OH}$ in CDCl_3

Group Ar	δ_c/ppm								
	SCH_2	ArCH_2	HOCH_2	ArC-1	ArC-3	ArC-2	ArC-5	ArC-6	ArC-4
<i>o</i> - $\text{MeC}_6\text{H}_4^{\text{a}}$	41.8	42.8	60.0	126.1	128.3	130.8	127.9	130.2	137.1
Ph	41.6	43.3	59.8	127.7	128.7	129.4	128.7	129.4	136.0
<i>p</i> - $\text{MeOC}_6\text{H}_4^{\text{b}}$	41.6	43.1	59.8	114.5	130.6	131.3	130.6	131.3	159.1
<i>p</i> - ClC_6H_4	41.7	43.4	59.6	126.5	128.5	130.8	128.5	130.8	134.6
<i>p</i> - $\text{MeC}_6\text{H}_4^{\text{c}}$	41.7	42.8	60.0	126.1	128.2	130.7	128.2	130.7	136.9
2-Furyl ^d	35.4	41.8	60.0						

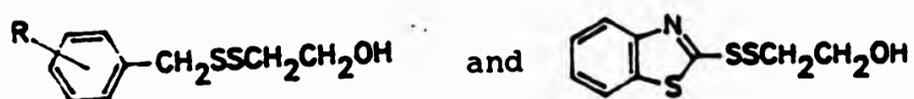
^aMethyl carbon gives signal at δ 19.5.

^bMethoxy carbon gives signal at δ 55.2.

^cMethyl carbon gives signal at δ 19.3.

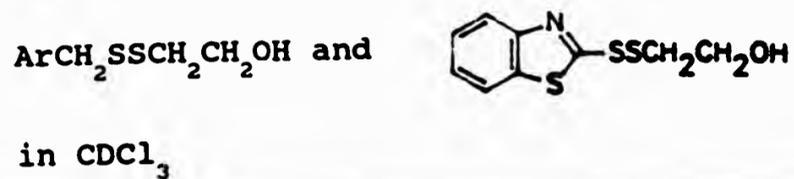
^dC-3, C-4, C-2 and C-5 of the furyl ring give signals at δ 109.6, 111.0, 143.0 and 149.6 respectively.

2.14.5 Compounds of the type:



The chemical shifts for this class of compounds are presented in Table 20.

Table 20. ^{13}C nmr data for unsymmetrical disulphides



Group Ar	δ_c /ppm								
	SCH_2	ArCH_2	HOCH_2	ArC-1	ArC-3	ArC-2	ArC-5	ArC-6	ArC-4
$p\text{-MeOC}_6\text{H}_4^a$	40.8	42.7	60.1	113.8	129.2	130.4	129.2	130.4	159.0
$o\text{-MeC}_6\text{H}_4^b$	40.8	41.4	60.0	125.9	134.6	127.8	134.1	130.5	136.7
$o\text{-ClC}_6\text{H}_4$	40.8	40.9	60.1	126.7	134.0	129.7	133.9	131.4	134.7
Ph	40.7	43.3	60.1	127.5	128.8	129.3	128.8	129.3	137.1
$p\text{-ClC}_6\text{H}_4$	40.9	42.6	60.2	128.7	130.6	133.4	130.6	133.4	135.7
$p\text{-MeC}_6\text{H}_4^c$	40.8	43.2	60.1	129.1	129.2	134.0	129.2	134.0	137.2
$p\text{-FC}_6\text{H}_4$	40.8	42.5	60.1	115.6	130.9	133.0	130.9	133.0	160.3
benzothia- zol-2-yl ^d	42.6		59.1						

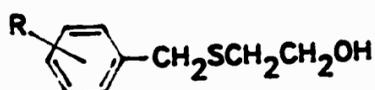
^aMethoxy carbon gives signal at δ 55.2.

^bMethyl carbon gives signal at δ 19.2.

^cMethyl carbon gives signal at δ 21.1. ^dArC-2, ArC-3,4, ArC-5 ArC-6 and ArC-1 of the benzene ring in benzothiazol-2-yl compound give signals at δ 124.9, 126.5, 135.8, 153.4 and 170.9, respectively. In this compound, the benzothiazol-2-yl group is attached directly to sulphur i.e. benzyl CH_2 is not present as in other compounds.

The absorption of the carbon of the methylene group adjacent to the hydroxy group (HOCH_2) is downfield at about δ 60.0 when compared to that of the carbon adjacent to sulphur SCH_2CH_2 at δ 41. These δ values are almost constant for all the compounds except benzothiazol-2-yl 2-hydroxyethyl disulphide, whose methylene group that is adjacent to sulphur (SCH_2CH_2) resonates at δ 42.6. The absorption of the carbon of the methoxy group is shifted downfield when compared with that of the methyl group. The absorption of the carbon of ArC-4 is also shifted downfield in 4-methoxybenzyl 2-hydroxyethyl disulphide (δ 159.0) and in 4-fluorobenzyl 2-hydroxyethyl disulphide (δ 160.3) when compared with the other carbon atoms in the benzene ring because of the electron-withdrawing effect of the oxygen and fluorine atoms. Lastly, the carbon of the benzyl group (ArCH_2) gave a signal at δ 40.9-43.2.

2.14.6 Compounds of the type:



The chemical shifts for this class of compounds are presented in Table 21. An interesting feature of the chemical shifts is that the absorption of the carbon adjacent to sulphur (SCH_2CH_2) and that of the benzyl group (ArCH_2S) is shifted upfield when compared with the absorption of similar carbon atoms in the unsymmetrical di-, tri-, and tetra-sulphides. A possible explanation for this

may be that the presence of more than one electronegative sulphur atom in the disulphide and other polysulphides leads to more electron attracting effect hence the shifting of the absorption of these carbon atoms downfield in the unsymmetrical di-, tri- and tetra-sulphides. However, the methylene carbon adjacent to the hydroxy group (HOCH_2) gives an absorption at about δ 60 for all the compounds in this class. In 4-methoxybenzyl 2-hydroxyethyl monosulphide, the chemical shift of ArC-4 is similarly downfield when compared with δ values of other carbon atoms in the compound. Also, the absorption of the methoxy carbon is shifted downfield at δ 55.2 when compared with methyl at δ 19.1-21.1.

Table 21. ^{13}C nmr data for unsymmetrical monosulphides

$\text{ArCH}_2\text{SCH}_2\text{CH}_2\text{OH}$ in CDCl_3

Group Ar	δ_c /ppm								
	SCH_2	ArCH_2	HOCH_2	ArC-1	ArC-3	ArC-2	ArC-5	ArC-6	ArC-4
$o\text{-ClC}_6\text{H}_4$	33.2	34.4	60.5	126.8	133.8	129.7	133.2	130.7	135.8
$o\text{-MeC}_6\text{H}_4^a$	33.8	34.5	60.4	125.9	135.6	127.4	135.0	129.6	136.6
$p\text{-MeOC}_6\text{H}_4^b$	34.2	35.1	60.3	114.0	129.9	135.3	129.9	135.3	158.7
Ph	33.8	35.3	60.2	128.6	129.2	130.1	129.2	130.1	131.5
$p\text{-ClC}_6\text{H}_4$	33.5	34.7	60.4	128.7	129.4	132.1	129.4	132.1	134.9
$p\text{-MeC}_6\text{H}_4^c$	34.2	35.4	60.2	128.7	129.2	134.9	129.2	134.9	136.8

^aMethyl carbon gives signal at δ 19.1. ^bMethoxy carbon gives signal at δ 55.2. ^cMethyl carbon gives signal at δ 21.1.

The methylene carbon of the benzylic group (ArCH_2S) in unsymmetrical di-, tri-, and tetra-sulphides respectively resonates at a fairly constant chemical shift value ($\delta = \text{ca. } 43$), while that of the unsymmetrical monosulphides absorbs upfield at $\delta 35$. An explanation for this has been provided above. However, the presence of additional sulphur atoms in unsymmetrical tri- and tetra-sulphides does not significantly affect δ values of the methylene carbon atom of the benzylic group in these compounds because these δ values are about equal to those obtained for the methylene carbon of the benzylic group in unsymmetrical disulphides.

The absorption of the methylene carbon of the benzylic group in unsymmetrical mono-, di-, tri-, and tetra-sulphides does not show any significant dependence on the substituents in the benzene ring because the chemical shift values obtained for this carbon atom in the various compounds are fairly constant as shown in Tables 18, 19, 20, and 21.

2.14.7 Effects of substituents in the benzene ring on chemical shifts of the carbon atoms of the ring

It is known¹⁶⁶ that chemical shifts of the carbon atoms in the benzene ring depend on the substituents in the ring. This dependence has been explained using the empirical

relationship below.

$$\delta_c (k) = 128.5 + \sum_i A(i)(R) \dots\dots(a)$$

where $A(i)(R)$ = chemical shift increment for substituent R in the i^{th} position (i.e. ArC-1, ortho, meta or para).

$\delta_c (k)$ = chemical shift of the carbon atom of the benzene ring.

The chemical shift increment $A(i)$ for various substituents (R) in the i^{th} position has been determined and tabulated,¹⁶⁶ however, the chemical shift increment for R = CH_2S has not been quoted in any of these tables. Substituting the chemical shift values obtained for ArC-4 in 4-methoxybenzyl 2-hydroxyethyl mono-, di-, tri-, and tetra-sulphides respectively in equation (a), the chemical shift increment due to CH_2S is calculated to be -0.975. The same value was obtained when chemical shift values for ArC-1 in 2-methylbenzyl 2-hydroxyethyl mono-, di-, tri-, and tetra-sulphides respectively were substituted in equation (a).

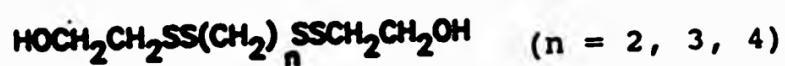
In all compounds of the type $\text{ArCH}_2(\text{S})_n\text{CH}_2\text{CH}_2\text{OH}$ ($n = 1, 2, 3, 4$), the experimental chemical shift values obtained for the carbon atoms in the benzene ring agree with the calculated values obtained from the equation (b).

$$\delta_c (k) = 128.5 + Ai(R) - 0.975 \dots (b)$$

$$= 127.525 + Ai(R)$$

The above results show that in these classes of compound, the chemical shift of the carbon atoms in the benzene ring depends on the substituents in the ring and a general agreement with literature values was obtained.

2.14.8 Compounds of the type:



The chemical shifts for this class of compounds are presented in Table 22.

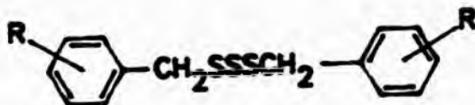
Table 22. ^{13}C nmr data for alkane-bis- α,ω -(2-hydroxyethyl-disulphide)s $\text{HOCH}_2\text{CH}_2\text{SS}(\text{CH}_2)_n\text{SSCH}_2\text{CH}_2\text{OH}$ in CDCl_3

n	δ_c / ppm			
	$\text{SCH}_2(\text{CH}_2)_{n-2}\text{CH}_2\text{S}$	$\text{SCH}_2(\text{CH}_2)_{n-2}\text{CH}_2\text{S}$	$\text{HOCH}_2\text{CH}_2\text{S}$	HOCH_2
2	—	38.2	40.9	60.2
3	28.1	37.0	41.1	60.1
4	27.7	38.4	41.1	60.3

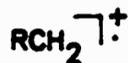
The absorptions of the carbon of the methylene group adjacent to the hydroxy group (HOCH_2) is shifted downfield at about δ 60 when compared with those adjacent to sulphur ($\text{HOCH}_2\text{CH}_2\text{S}$) which resonate at δ 41. The absorptions of the carbon adjacent to sulphur of the group $\text{SCH}_2(\text{CH}_2)_{n-2}\text{CH}_2\text{S}$ was also shifted downfield when compared with those of the central methylene group(s). The δ values for the carbon in each position were fairly constant for the various compounds.

The mass spectra of the compounds were determined by conventional electron impact (E.I.) ionization. The quoted m/z values for fragment ions containing one or more chlorine atoms refer to ions containing the ^{35}Cl isotope. Fragment ions containing chlorine give rise to characteristic isotope patterns depending on the number of chlorine atoms present, the peaks being separated by two units due to the ^{35}Cl and ^{37}Cl isotopes (natural abundance of ^{35}Cl and ^{37}Cl isotopes is approximately 3:1, respectively).

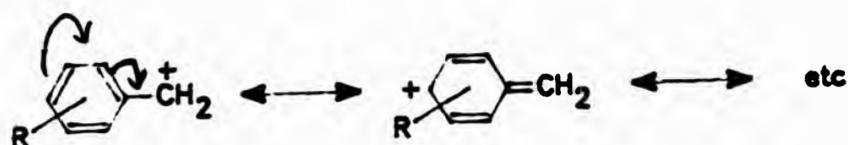
2.15.1 Compounds of the type:



These compounds all gave relatively weak molecular ions under electron impact conditions except for the first member of the group, dibenzyl trisulphide, for which only the $[M-1]^+$ peak was observed. The generally observed fragment ions are shown in Table 23. The compounds (R = H, o- or p-Me, p-MeO, o- or p-Cl) showed fragment ions at m/z 91, 105, 121, and 125, respectively, which are characteristic of the fragment:

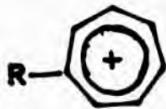


This ion is formed very readily in the ionization chamber because of the relative ease with which the C-S bond is broken, and in all cases the base peak was due to this fragment ion. This type of ion is stabilised by delocalisation of the benzene ring electrons (Scheme 49).



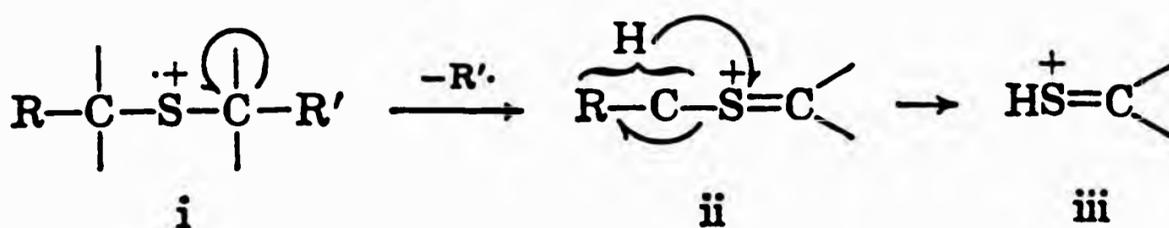
Scheme 49

It might also be formulated as the highly stable tropylium ion:



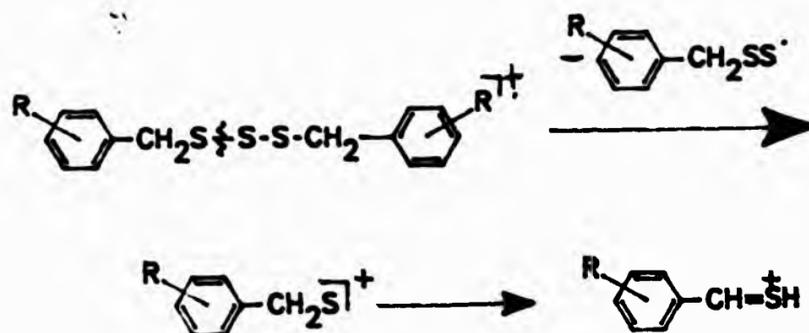
It was found by Levy *et al.*¹⁶⁷ that fragments arising from α -cleavage and carbon-sulphur bond cleavage dominated the fragmentation of thioethers upon electron bombardment. Also, the direction of carbon-sulphur bond cleavage in sulphides has been reported by Carl Djerassi *et al.*¹⁶⁸ Through a deuterium-labelling experiment, they demonstrated that the hydrogen transfer to sulphur (ii-iii) (Scheme 50) is not a four-centre process as had been originally postulated¹⁶⁹ for the formation of the analogous fragment in ethers. Rather, four-, five-, and six-membered cyclic transition states transferring the secondary hydrogen to sulphur are equally favoured. However, if a choice between secondary and primary hydrogen is available, they claimed that the transfer of the

former predominates.¹⁷⁰

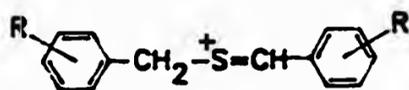


Scheme 50

The compounds in the present studies also showed fragment ions at 123, 137, 153, and 157, respectively, which are indicative of an ion formed by S-S cleavage, possibly with hydrogen transfer to give the more stable sulphonium ion, as follows:



Also, peaks at 213, 241, 273, and 281 respectively are assigned to a sulphonium ion:



which arises from the loss of two sulphur atoms and a hydrogen atom.

Table 23. Principal ions in the E.I. mass spectra of symmetrical trisulphides $\text{ArCH}_2\text{SSSCH}_2\text{Ar}$

Ar	m/z (%)				
	M^{\dagger}	ArCH_2^{\dagger}	$\text{ArCH}_2\text{S}^{\dagger}$	M-SSH^{\dagger}	M-S^{\dagger}
Ph	- ^a	91/100	123/36	213/54	246/12
<i>o</i> -MeC ₆ H ₄	306/17	105/100	137/17	241/43	274/1
<i>p</i> -MeC ₆ H ₄	306/2	105/100	137/5	241/12	274/1
<i>p</i> -MeOC ₆ H ₄	338/11	121/41	153/58	273/29	306/1
<i>p</i> -ClC ₆ H ₄	346/4	125/100	157/11	281/13	314/1
<i>o</i> -ClC ₆ H ₄	346/9	125/100	157/7	281/12	314/1

^am/z 277 (8%), [M-1]⁺ observed.

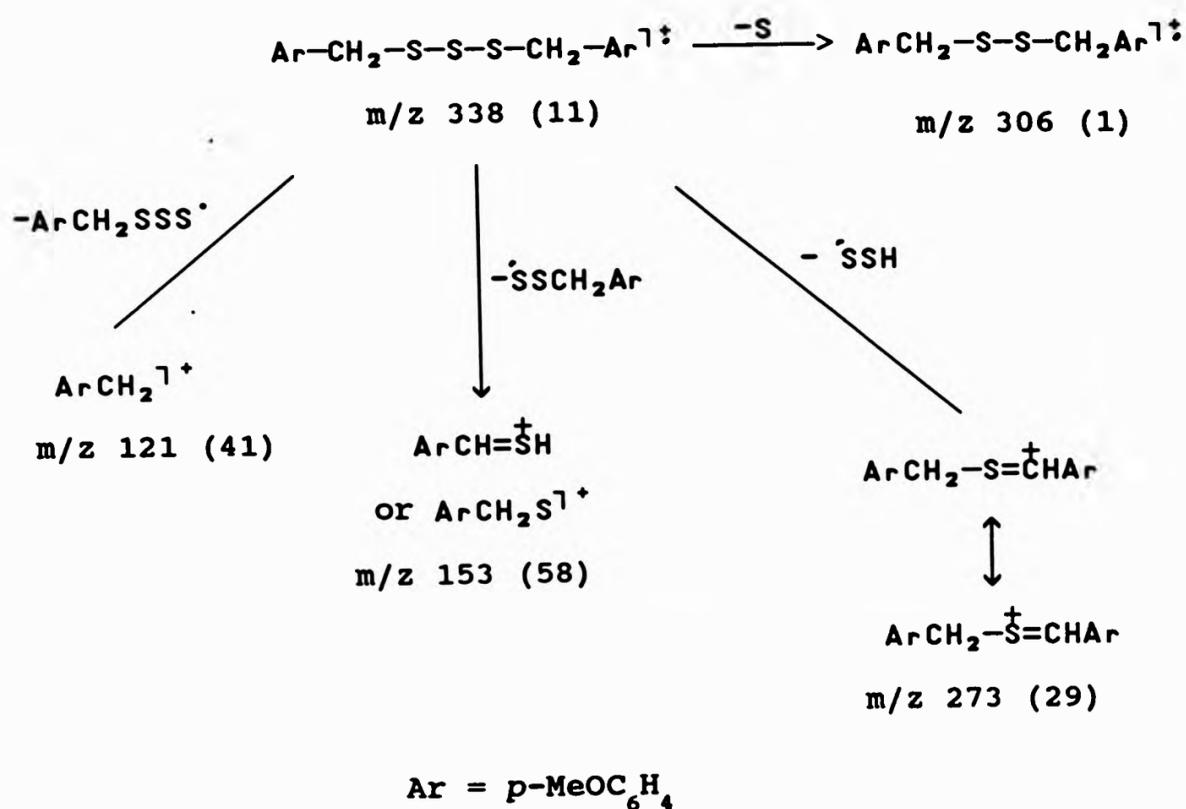
Lastly, the peaks at 246, 274, 306, and 314 for each of the compounds, respectively, are characteristic of the symmetrical disulphide ion:



which arises from the loss of one sulphur atom from the parent molecular ion. Except for dibenzyl trisulphide, these peaks are generally of low intensities. There are some other peaks with very low intensities that cannot be accounted

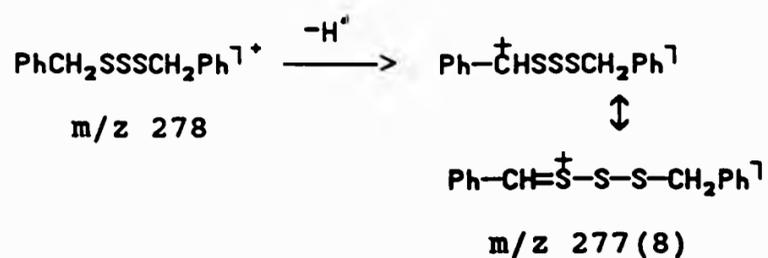
for.

The fragmentation pattern of di-(4-methoxybenzyl) trisulphide, as a representative of the group, is given in Scheme 51. The mass spectrum of di-(2-methylbenzyl) trisulphide in Figure 8 is also presented as typical for this class of compound.



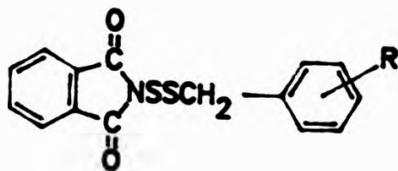
Scheme 51

In dibenzyl trisulphide, the formation of the [M-1]⁺ peak may be due to the loss of hydrogen from the molecular ion as depicted in Scheme 52.



Scheme 52

2.15.2 Compounds of the type:



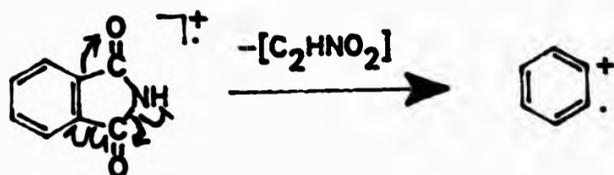
These compounds all gave relatively weak molecular ions under E.I. conditions except 2-chlorobenzyl phthalimido disulphide which gave a peak at $[M-1]^+$. The observed fragment ions are shown in Table 24 with their respective m/z values and relative intensities.

Table 24. Principal ions in the E.I. mass spectra of phthalimido disulphides PhthNSSCH₂R

R	m/z (%) ^{a,b}				
	M ⁺	M-SSH ⁺	RCH ₂ S ⁺	RCH ₂ ⁺	C ₆ H ₄ ⁺
Ph	301/24	236/46	123/43	91/100	76/15
p-ClC ₆ H ₄	335/2	270/16	157/8	125/94	76/18
o-ClC ₆ H ₄	- ^c	270/19	157/12	125/92	76/21
o-MeC ₆ H ₄	315/10	250/12	137/26	105/100	76/16
p-MeC ₆ H ₄	315/13	250/13	137/21	105/100	76/23
p-MeOC ₆ H ₄	331/12	266/14	153/27	121/100	76/28
HOCH ₂	255/23	-	-	45/56	76/100

^aPeak observed at m/z 147 in all compounds. ^bPeak observed at m/z 210 and m/z 178 in all compounds except 2-hydroxyethyl phthalimido disulphide (R = HOCH₂) where m/z 211 and 179 were observed. ^cm/z 334 (9%), [M-1]⁺ observed.

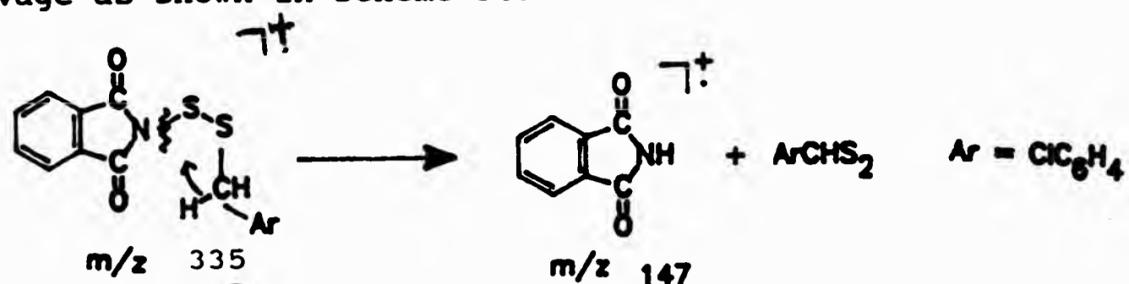
All the compounds gave a fragment at m/z 76 which is due to the ion C₆H₄⁺. This may possibly be formed as a result of intramolecular rearrangement involving the phthalimide cation radical (m/z 147) as shown Scheme 53.



Scheme 53

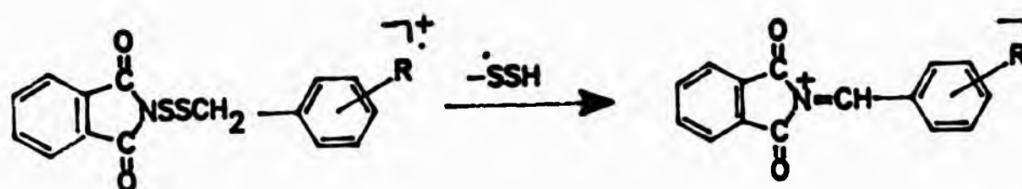
The elimination of C_2HNO_2 is equivalent to the loss of a molecule each of CO and HNCO.

The phthalimide cation radical may be formed by N-S cleavage as shown in Scheme 54.



Scheme 54

The compounds gave fragment ions at m/z 236, 250, 266, and 269 respectively which are characteristic of the molecular ion having lost $\cdot SSH$ (Scheme 55).

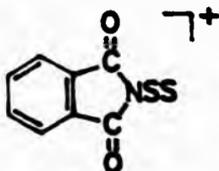


Scheme 55

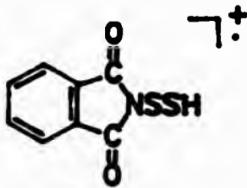
This type of loss was observed for symmetrical trisulphides as discussed earlier on. The fact that S or SSH are not lost from 2-hydroxyethyl phthalimido disulphide is an indication that the C-S-S-N linkage in this compound is very strong and that it cannot be broken under these conditions. The electronic effect of the benzene ring in the benzyl series

might make the cleavage of this bond easier.

All the compounds gave a fragment ion at m/z 210 (except 2-hydroxyethylphthalimido disulphide which gave $m/z = 211$), which is characteristic of the ion:

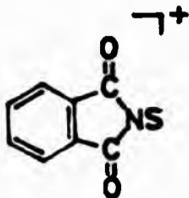


This ion may be formed as a result of the loss of ArCH_2^\cdot from the molecular ion. In the case of 2-hydroxyethyl phthalimido disulphide, the ion:

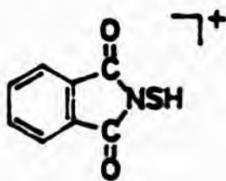


may be formed by C-S cleavage and hydrogen transfer.

Also, all the benzyl compounds gave a peak at m/z 178 which is assigned to the fragment ion:

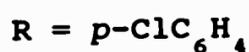
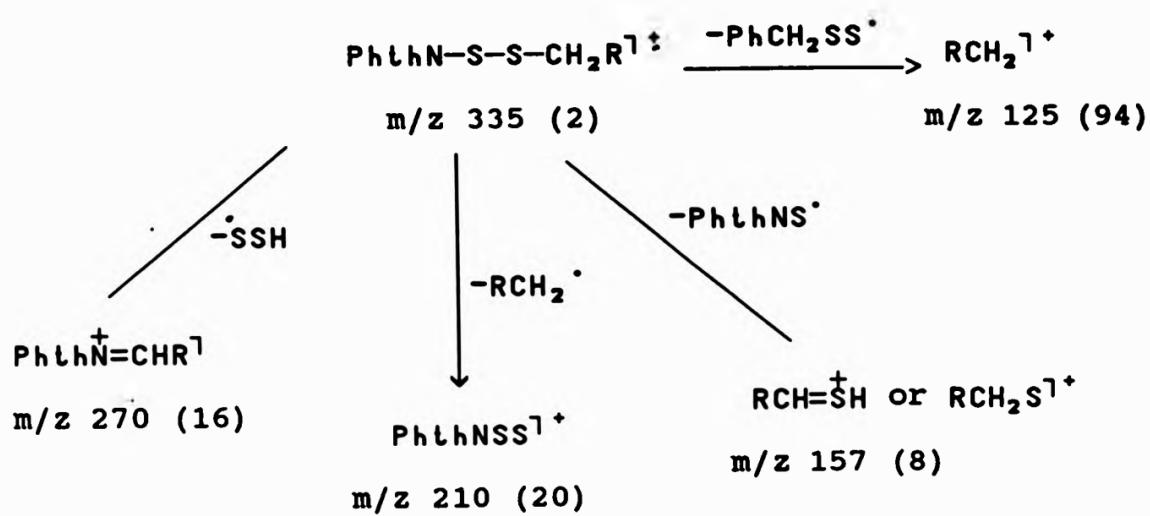


formed by S-S cleavage and the loss of $\text{RCH}_2\text{S}^\cdot$ from the molecular ion. In the spectrum of 2-hydroxyethyl phthalimido disulphide, the peak observed at m/z 179 is assigned to the ion:



which may be formed by S-S cleavage and hydrogen transfer.

The possible fragmentation pattern of 4-chlorobenzyl phthalimido disulphide as a representative of this class of compound is given in Scheme 56. Also presented is the mass spectrum of 4-methoxybenzyl phthalimido disulphide in Figure 9, as a typical mass spectrum for this class of compound.



Scheme 56

2.15.3 Dibenzyl disulphide

This compound gave a strong molecular ion under electron impact condition. Fragment ions were also observed at m/z 155, 123, and 91. The fragmentation pattern of this compound is presented in Scheme 57.

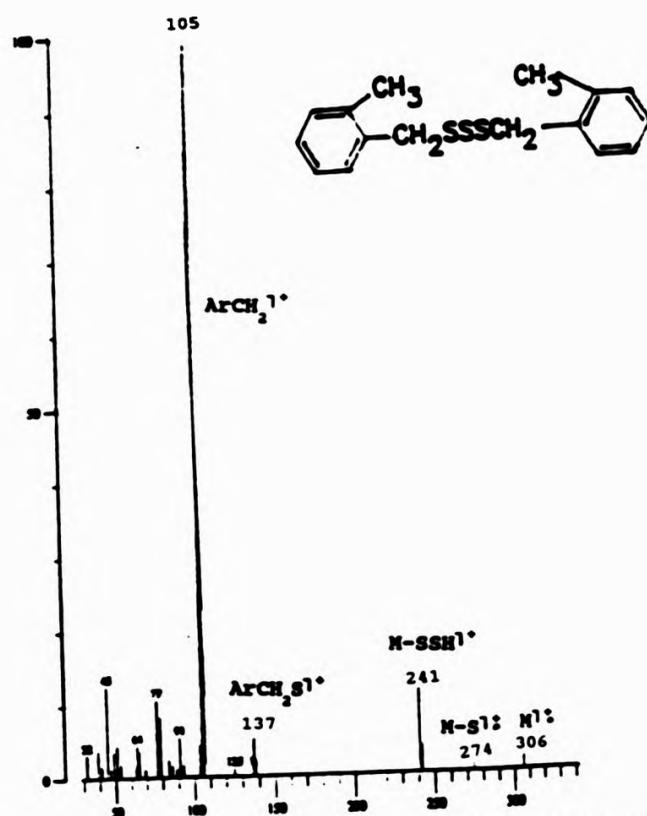


Figure 8: Mass spectrum of di-(2-methylbenzyl) trisulphide

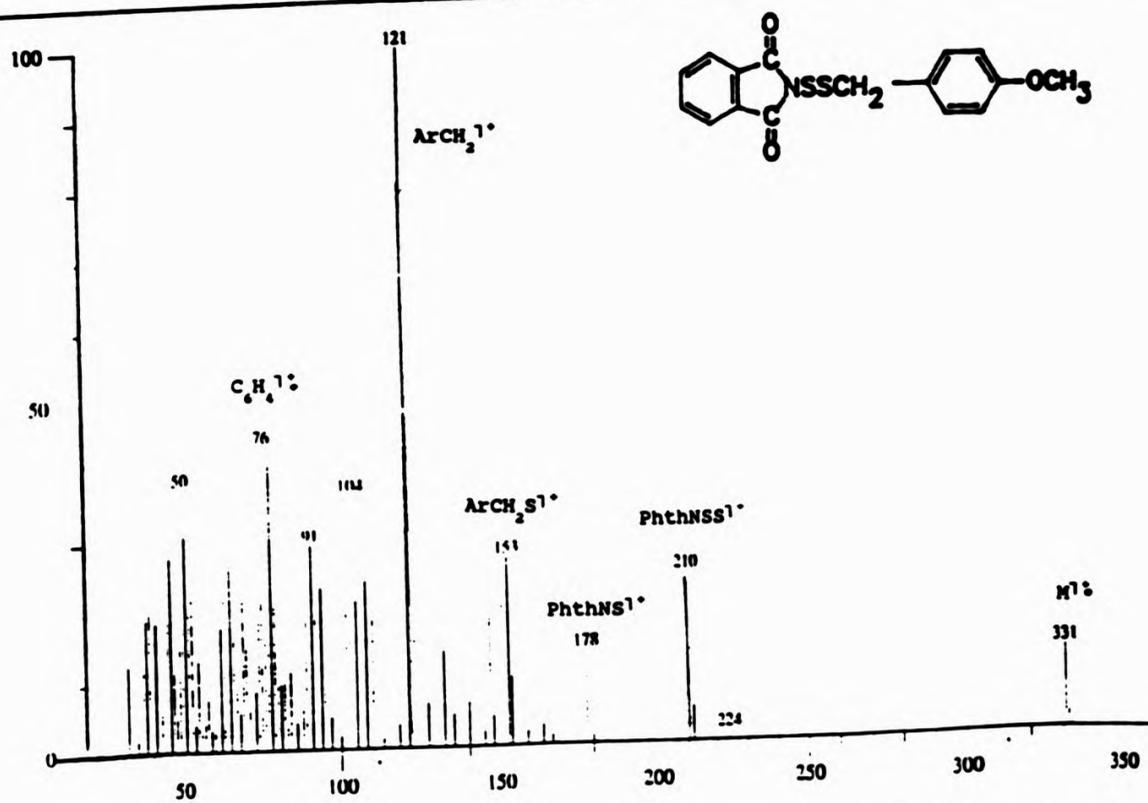
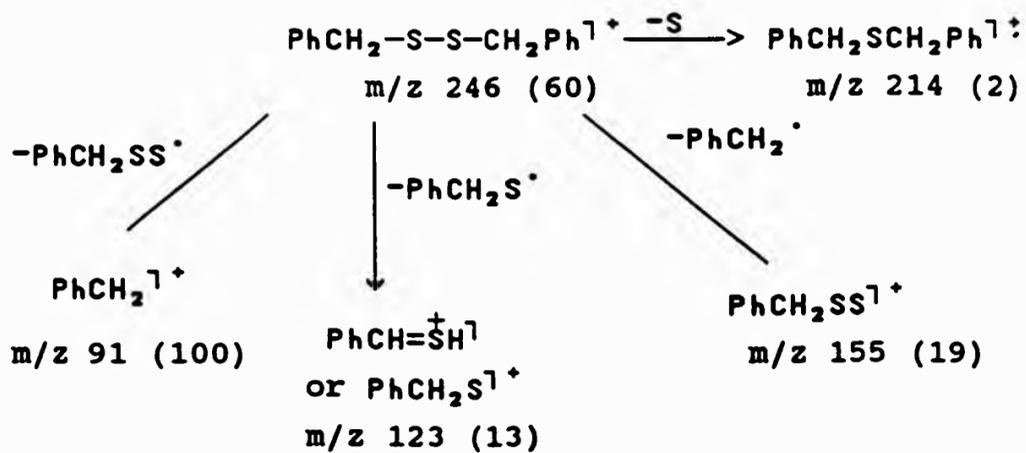


Figure 9: Mass spectrum of 4-methoxybenzyl phthalimido disulphide.



Scheme 57

2.15.4 Compounds of the type:

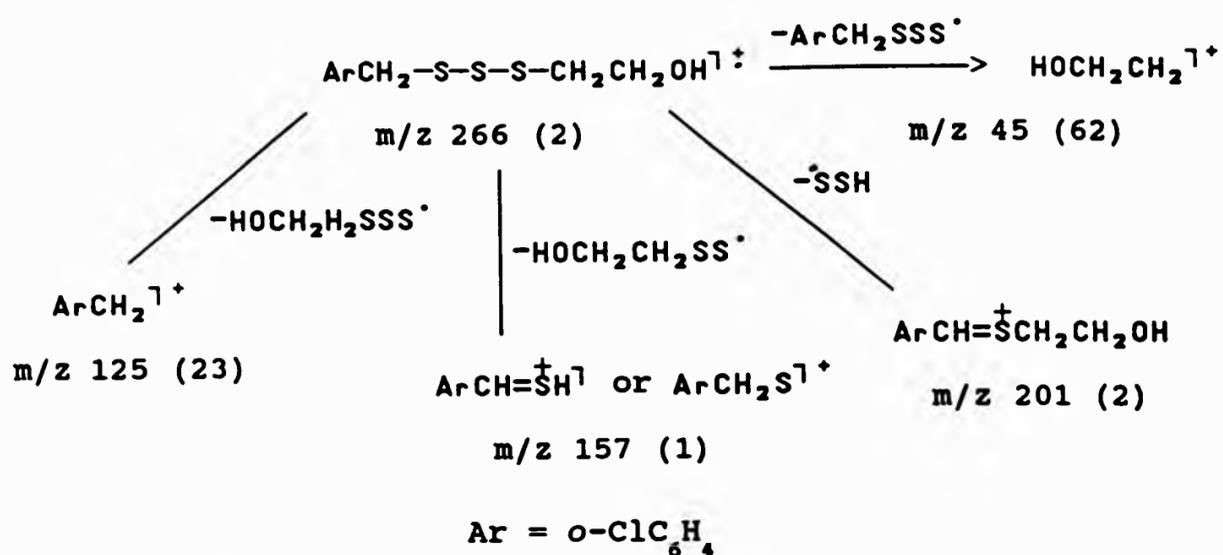


For all the compounds in this class, the molecular ion peak was observed, this was weak in all compounds except in benzyl 2-hydroxyethyl trisulphide where it was fairly strong. The principal ions in the mass spectra of unsymmetrical trisulphides are presented in Table 25. Also, in Figure 10, the mass spectrum of benzyl 2-hydroxyethyl trisulphide is shown as a typical spectrum for this type of compound.

Table 25. Principal ions in the E.I. mass spectrum of unsymmetrical trisulphides $\text{ArCH}_2\text{SSSCH}_2\text{CH}_2\text{OH}$

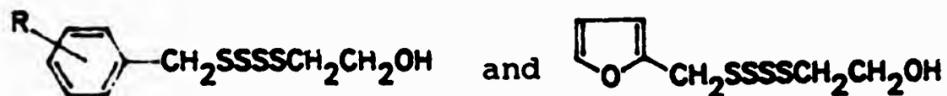
Ar	m/z (%)					
	M^{\ddagger}	M-S^{\ddagger}	M-SSH^{\ddagger}	$\text{RCH}_2\text{S}^{\ddagger}$	RCH_2^{\ddagger}	$\text{HOCH}_2\text{CH}_2^{\ddagger}$
Ph	232/12	200/4	167/14	123/23	91/100	45/68
<i>p</i> -MeC ₆ H ₄	246/2	214/2	181/7	137/10	105/100	45/65
<i>o</i> -MeC ₆ H ₄	246/2	214/3	181/3	137/3	105/100	45/58
<i>o</i> -ClC ₆ H ₄	266/1	234/2	201/2	157/3	125/17	45/59
<i>p</i> -ClC ₆ H ₄	266/2	234/1	201/2	157/1	125/23	45/62
<i>p</i> -MeOC ₆ H ₄	262/2	-	197/4	153/2	121/29	45/53
2-Furyl	222/2	-	157/1	-	81/100	45/49

A weak peak corresponding to the loss of one sulphur atom from the molecular ion was observed for most compounds. Also observed was a prominent peak due to the loss of the 'SSH radical, which showed a relative intensity of 14% in the case of Ar = Ph but was relatively weak for the other compounds in the series. Except for the *o*- and *p*-chloro-substituted benzyl 2-hydroxyethyl trisulphide, the base peak for all compounds was the benzyl cation ArCH_2^{\ddagger} . A prominent peak at m/z 45 assigned to $\text{HOCH}_2\text{CH}_2^{\ddagger}$ was also observed in all compounds. The fragmentation pattern of 2-chlorobenzyl 2-hydroxyethyl trisulphide is shown in Scheme 58 as a representative of the class.



Scheme 58

2.15.5 Compounds of the type:



The principal ions in the mass spectra of unsymmetrical tetrasulphides are presented in Table 26. For all the compounds in this class, the molecular ion was observed as a weak peak. Most compounds also gave a weak peak corresponding to the loss of one sulphur atom from the molecular ion. A prominent peak at m/z 200, 214, 234, 230 and 190, assigned to $\text{ArCH}_2\text{SSCH}_2\text{CH}_2\text{OH}^{\dagger}$ (where Ar = Ph, o- and p-MeC₆H₄, p-ClC₆H₄, p-MeOC₆H₄ and 2-furyl, respectively) and corresponding to the loss of two sulphur atoms from the molecular ion, was observed. Except for the o- and p-methyl substituted benzyl 2-hydroxyethyl tetrasulphide, a weak peak

assigned to $\text{ArCH}_2\text{SCH}_2\text{CH}_2\text{OH}^{\dagger\dagger}$ and corresponding to the loss of three sulphur atoms from the molecular ion was also observed. All compounds gave a prominent peak at m/z 45 assigned to $\text{HOCH}_2\text{CH}_2^{\dagger\dagger}$. The base peak for all compounds was the benzyl cation $\text{ArCH}_2^{\dagger\dagger}$. The fragmentation pattern of 4-chlorobenzyl 2-hydroxyethyl tetrasulphide as a representative of the class is shown in Scheme 59 and the mass spectrum of 2-methylbenzyl 2-hydroxyethyl tetrasulphide is presented in Figure 11.

Table 26. Principal ions in the E.I. mass spectra of unsymmetrical tetrasulphides $\text{ArCH}_2\text{SSSSCH}_2\text{CH}_2\text{OH}$

Ar	m/z (%)						
	$M^{\dagger\dagger}$	$M-S^{\dagger\dagger}$	$M-2S^{\dagger\dagger}$	$M-3S^{\dagger\dagger}$	$\text{ArCH}_2S^{\dagger\dagger}$	$\text{ArCH}_2^{\dagger\dagger}$	$\text{HOCH}_2\text{CH}_2^{\dagger\dagger}$
Ph	264/2	-	200/11	167/3	123/29	91/100	45/53
<i>o</i> -MeC ₆ H ₄	278/2	-	214/9	-	137/4	105/100	45/60
<i>p</i> -MeC ₆ H ₄	278/2	-	214/11	-	137/5	105/100	45/49
<i>p</i> -ClC ₆ H ₄	298/3	266/8	234/3	201/5	157/4	125/100	45/59
<i>p</i> -MeOC ₆ H ₄	294/2	-	230/8	198/5	153/5	121/100	45/62
2-Furyl	254/4	222/5	190/9	158/3	113/6	81/100	45/47

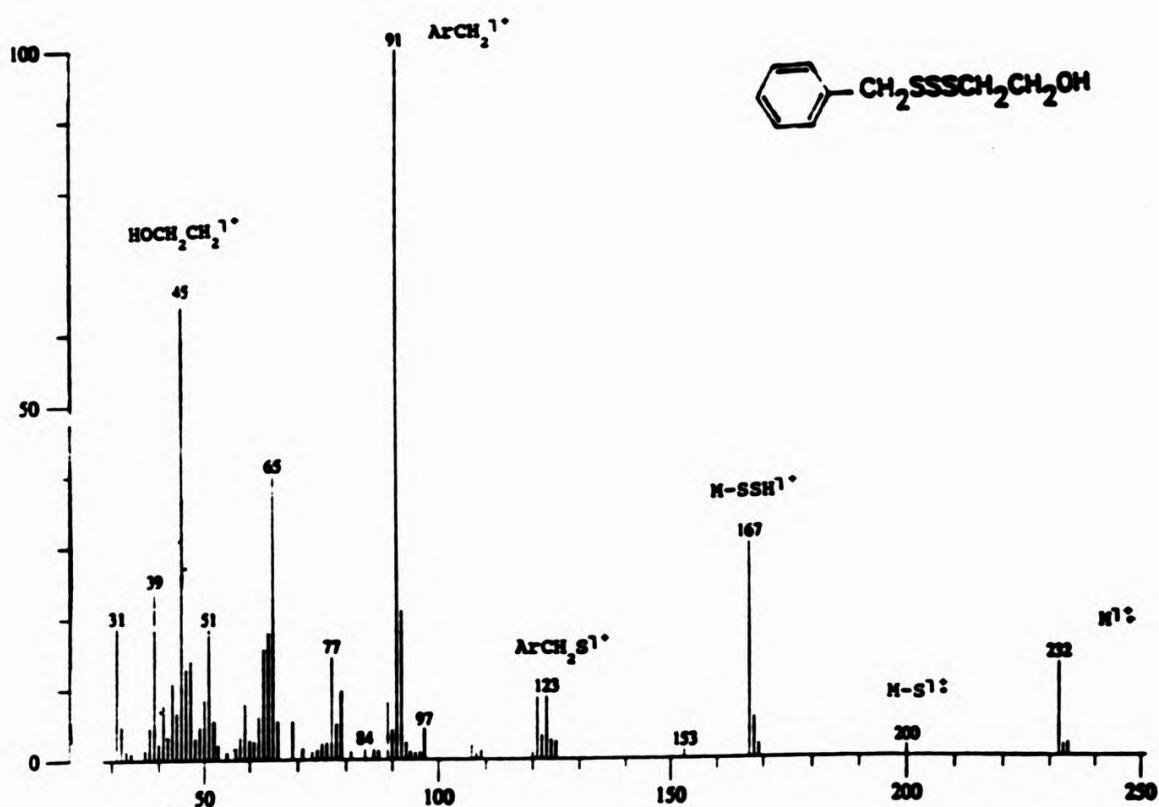


Figure 10: Mass spectrum of benzyl 2-hydroxyethyl trisulphide

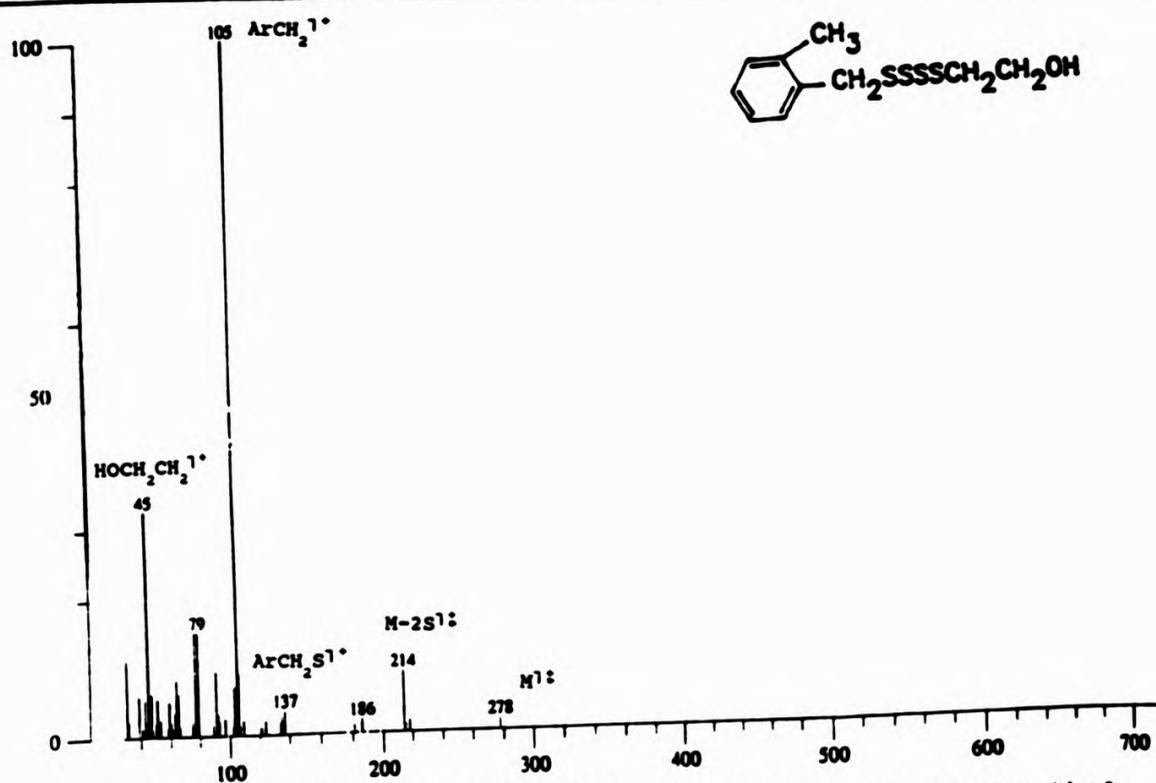
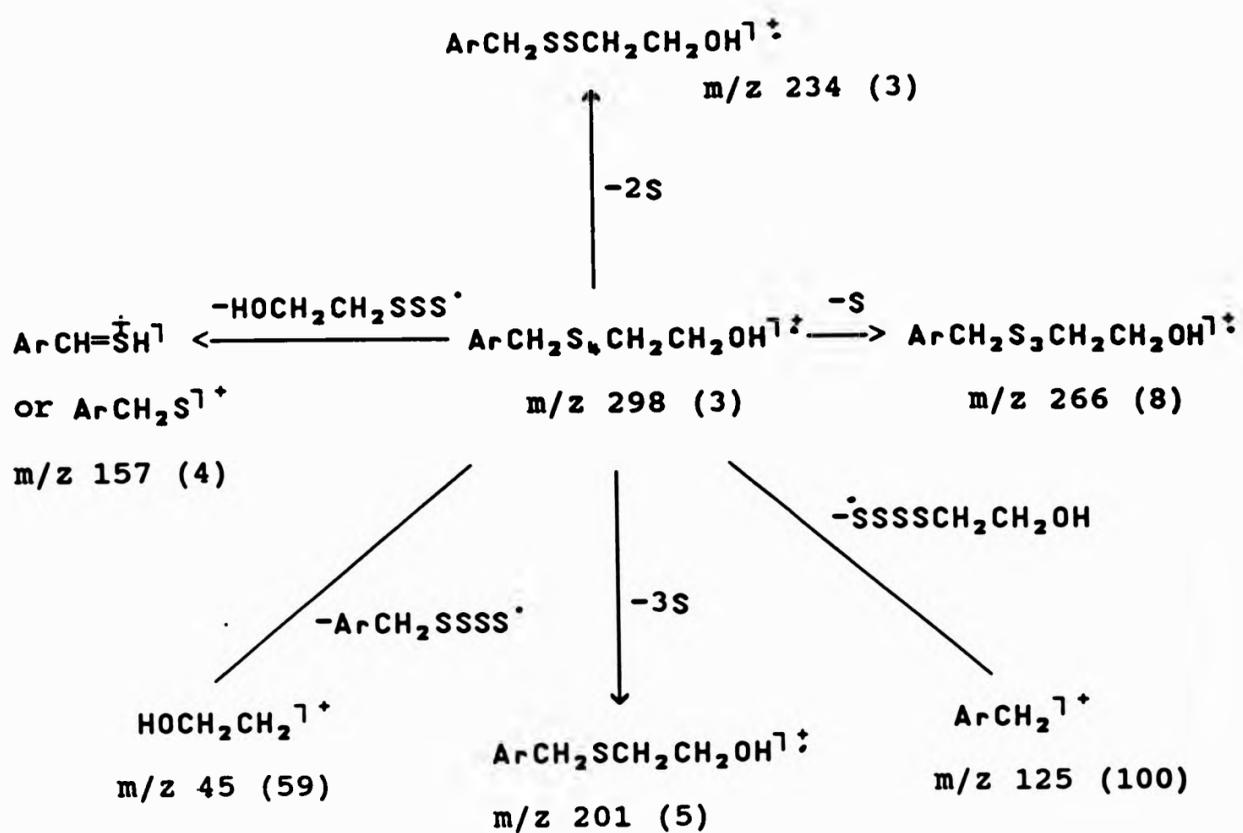


Figure 11: Mass spectrum of 2-methylbenzyl 2-hydroxyethyl tetrasulphide



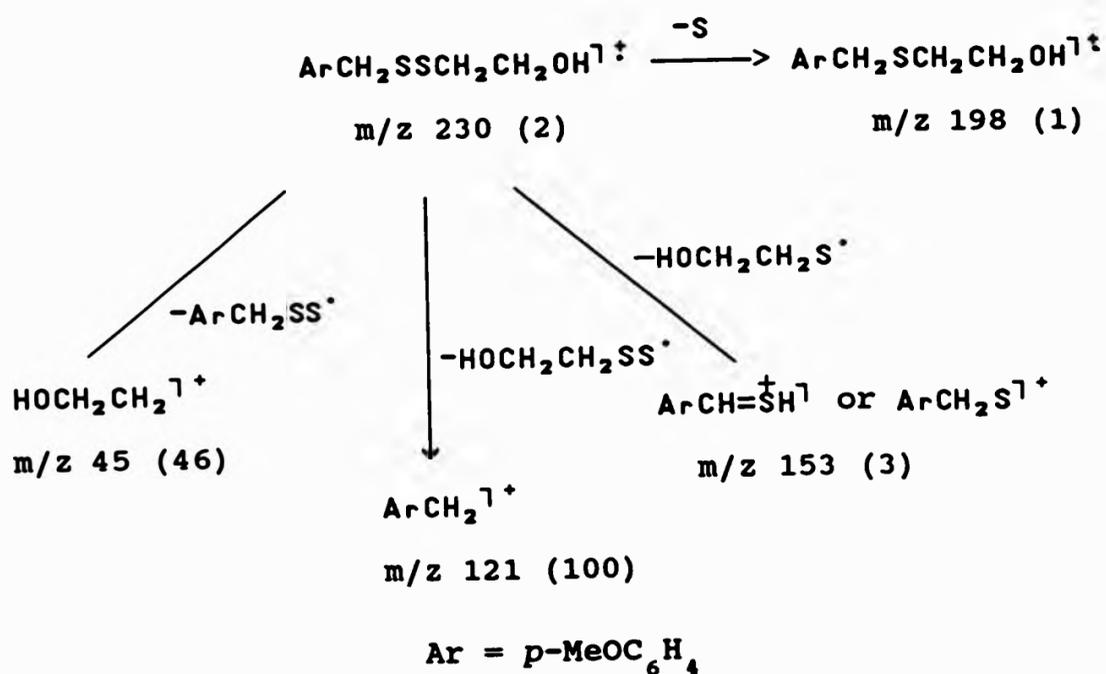
Scheme 59

2.15.6 Compounds of the type:



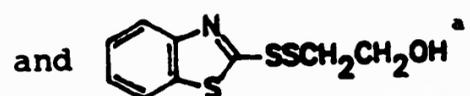
The principal ions in the mass spectra of this class of compound are presented in Table 27. For all compounds, a weak molecular ion peak was observed under E.I. conditions. Except for benzothiazol-2-yl 2-hydroxyethyl disulphide, a weak peak at m/z 168, 182, 202, 198, and 186, assigned to $\text{ArCH}_2\text{SCH}_2\text{CH}_2\text{OH}^{\dagger}$ (where Ar = Ph, o- and p-MeC₆H₄, p- and

$o\text{-ClC}_6\text{H}_4$, $p\text{-MeOC}_6\text{H}_4$ and $p\text{-FC}_6\text{H}_4$ respectively) corresponding to the loss of one sulphur atom from the molecular ion, was also observed. Most compounds gave a weak peak assigned to $\text{ArCH}=\overset{\dagger}{\text{S}}\text{H}$, corresponding to the loss of $\text{HOCH}_2\text{CH}_2\text{S}^\bullet$ from the molecular ion. A prominent peak at m/z 45 assigned to the hydroxyethyl cation $\text{HOCH}_2\text{CH}_2^{\dagger+}$ was observed in all compounds and this was the base peak for the benzothiazol-2-yl 2-hydroxyethyl disulphide. The base peak for all other compounds was the benzyl cation $\text{ArCH}_2^{\dagger+}$. The fragmentation pattern of 4-methoxybenzyl 2-hydroxyethyl disulphide is as depicted in Scheme 60. Also, the mass spectrum of benzyl 2-hydroxyethyl disulphide is presented in Figure 12 as a representative of this class of compound.



Scheme 60

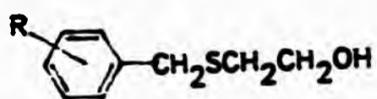
Table 27. Principal ions in the E.I. mass spectra of unsymmetrical disulphides $\text{ArCH}_2\text{SSCH}_2\text{CH}_2\text{OH}$



Ar	m/z (%)				
	M ⁺	M-S ¹⁺	ArCH ₂ S ¹⁺	ArCH ₂ ¹⁺	HOCH ₂ CH ₂ ¹⁺
Ph	200/12	168/2	123/2	91/100	45/56
<i>o</i> -MeC ₆ H ₄	214/4	182/2	137/6	105/100	45/48
<i>p</i> -MeC ₆ H ₄	214/5	182/3	137/8	105/100	45/52
<i>p</i> -ClC ₆ H ₄	234/2	202/1	157/2	125/100	45/43
<i>o</i> -ClC ₆ H ₄	234/5	202/1	157/3	125/100	45/53
<i>p</i> -MeOC ₆ H ₄	230/2	198/1	153/3	121/100	45/46
<i>p</i> -FC ₆ H ₄	218/9	186/2	141/4	109/100	45/56
(benzothiazol-2-yl) ^a	243/8	211/4	-	-	45/100

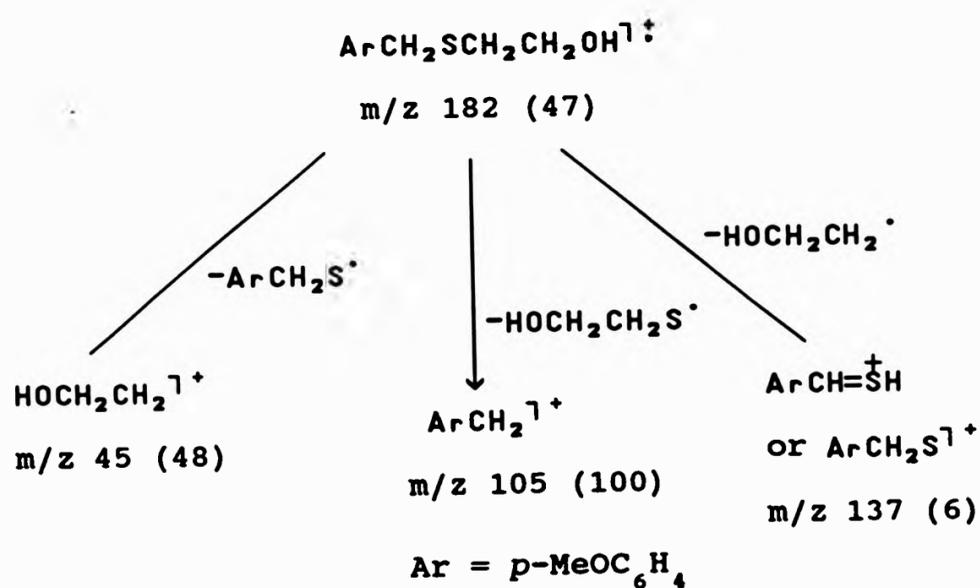
^aStructure as above

2.15.7 Compounds of the type:



The principal ions in the mass spectra of this class of compound are presented in Table 28. For all compounds, the molecular ion peak was observed as a strong peak under E.I. conditions. A prominent peak at m/z 123, 137, 153, and 157,

assigned to $\text{ArCH}=\overset{\ddagger}{\text{S}}\text{H}$ (where $\text{Ar} = \text{Ph}$, *o*- and *p*- MeC_6H_4 , *o*- and *p*- ClC_6H_4 and *p*- MeOC_6H_4 respectively) corresponding to the loss of $\text{HOCH}_2\text{CH}_2^\cdot$ from the molecular ion, was observed. All compounds gave a prominent peak at m/z 45 assigned to the hydroxyethyl cation $\text{HOCH}_2\text{CH}_2^{\ddagger+}$. The base peak for all compounds was the benzyl cation $\text{ArCH}_2^{\ddagger+}$. The fragmentation pattern of 4-methoxybenzyl 2-hydroxyethyl monosulphide as a representative of the class is shown in Scheme 61. The mass spectrum of 4-methylbenzyl 2-hydroxyethyl monosulphide is presented in Figure 13.



Scheme 61

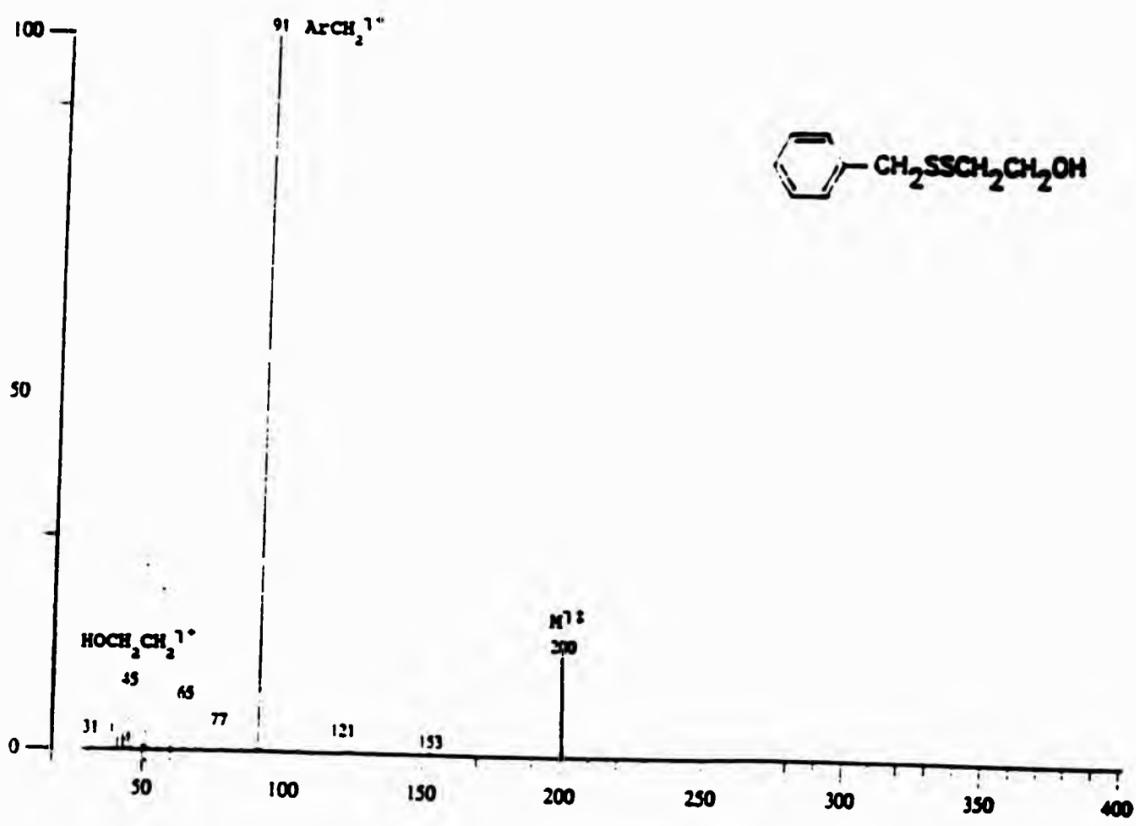


Figure 12: Mass spectrum of benzyl 2-hydroxyethyl disulphide

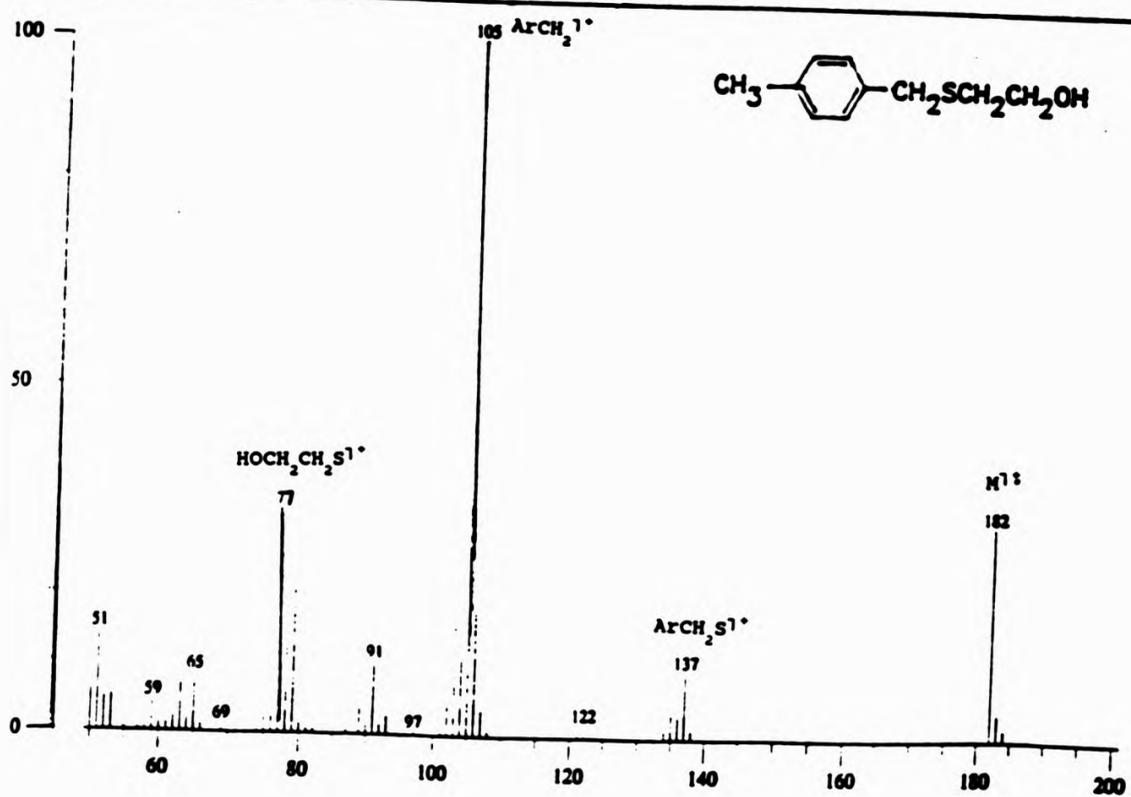
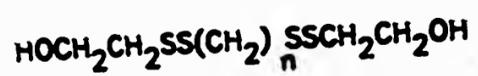


Figure 13: Mass spectrum of 4-methylbenzyl 2-hydroxyethyl monosulphide

Table 28. Principal ions in the E.I. mass spectra of unsymmetrical monosulphides $\text{ArCH}_2\text{SCH}_2\text{CH}_2\text{OH}$

Ar	m/z (%)			
	$\text{M}^{\cdot+}$	$\text{ArCH}_2\text{S}^{\cdot+}$	$\text{ArCH}_2^{\cdot+}$	$\text{HOCH}_2\text{CH}_2^{\cdot+}$
Ph	168/27	123/22	91/100	45/54
<i>o</i> -MeC ₆ H ₄	182/47	137/6	105/100	45/48
<i>o</i> -ClC ₆ H ₄	202/10	157/9	125/100	45/61
<i>p</i> -ClC ₆ H ₄	202/12	157/9	125/100	45/50
<i>o</i> -MeOC ₆ H ₄	198/30	153/3	121/100	45/47
<i>p</i> -MeC ₆ H ₄	182/42	137/5	105/100	45/54

2.15.8 Compounds of the type:



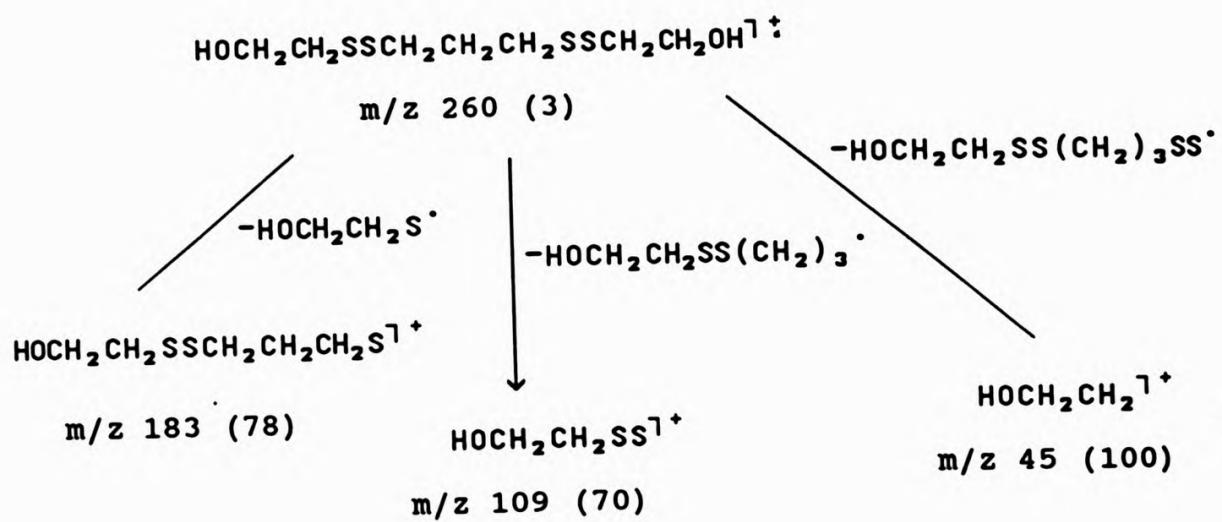
The principal ions in the mass spectra of this class of compound are presented in Table 29.

Table 29. Principal ions in the E.I. mass spectra of
 alkane- α,ω -bis(2-hydroxyethyl disulphide)s
 $\text{HOCH}_2\text{CH}_2\text{SS}(\text{CH}_2)_n\text{SSCH}_2\text{CH}_2\text{OH}$

n	m/z (%)			
	$\text{M}^{\cdot+}$	$\text{M}-\text{HOCH}_2\text{CH}_2\text{S}^{\cdot+}$	$\text{HOCH}_2\text{CH}_2\text{SS}^{\cdot+}$	$\text{HOCH}_2\text{CH}_2^{\cdot+}$
2	246/5	-	109/65	45/100
3	260/22	183/78	109/45	45/100
4	274/2	197/100	109/8	45/35

For all the compounds, the molecular ion peak was observed, this peak was weak except in the compound (where $n = 3$). The compounds (where $n = 3$ and $n = 4$), gave a prominent peak at m/z 183 and 197 respectively corresponding to the loss of the radical $\text{HOCH}_2\text{CH}_2\text{S}^{\cdot}$ from their parent molecular ion. All the compounds gave a prominent peak at m/z 109 assigned to $\text{HOCH}_2\text{CH}_2\text{SS}^{\cdot+}$. Except the compound where $n = 4$ in which the base peak at m/z 197 and due to the molecular ion having lost the cation radical $\text{HOCH}_2\text{CH}_2\text{S}^{\cdot+}$, the base peak of other compounds was the hydroxyethyl cation $\text{HOCH}_2\text{CH}_2^{\cdot+}$. In the compound (where $n = 4$), the strong peak at m/z 120 may be due to the molecular ion having lost the fragment ion $\text{HOCH}_2\text{CH}_2\text{SSCH}_2\text{CH}_2\text{OH}^{\cdot+}$. The fragmentation pattern of propane- α,ω -bis(2-hydroxyethyl disulphide) as a representative of the class is shown in Scheme 62. Also, the

mass spectrum of butane- α,ω -bis(2-hydroxyethyl disulphide) is presented in Figure 14.



Scheme 62

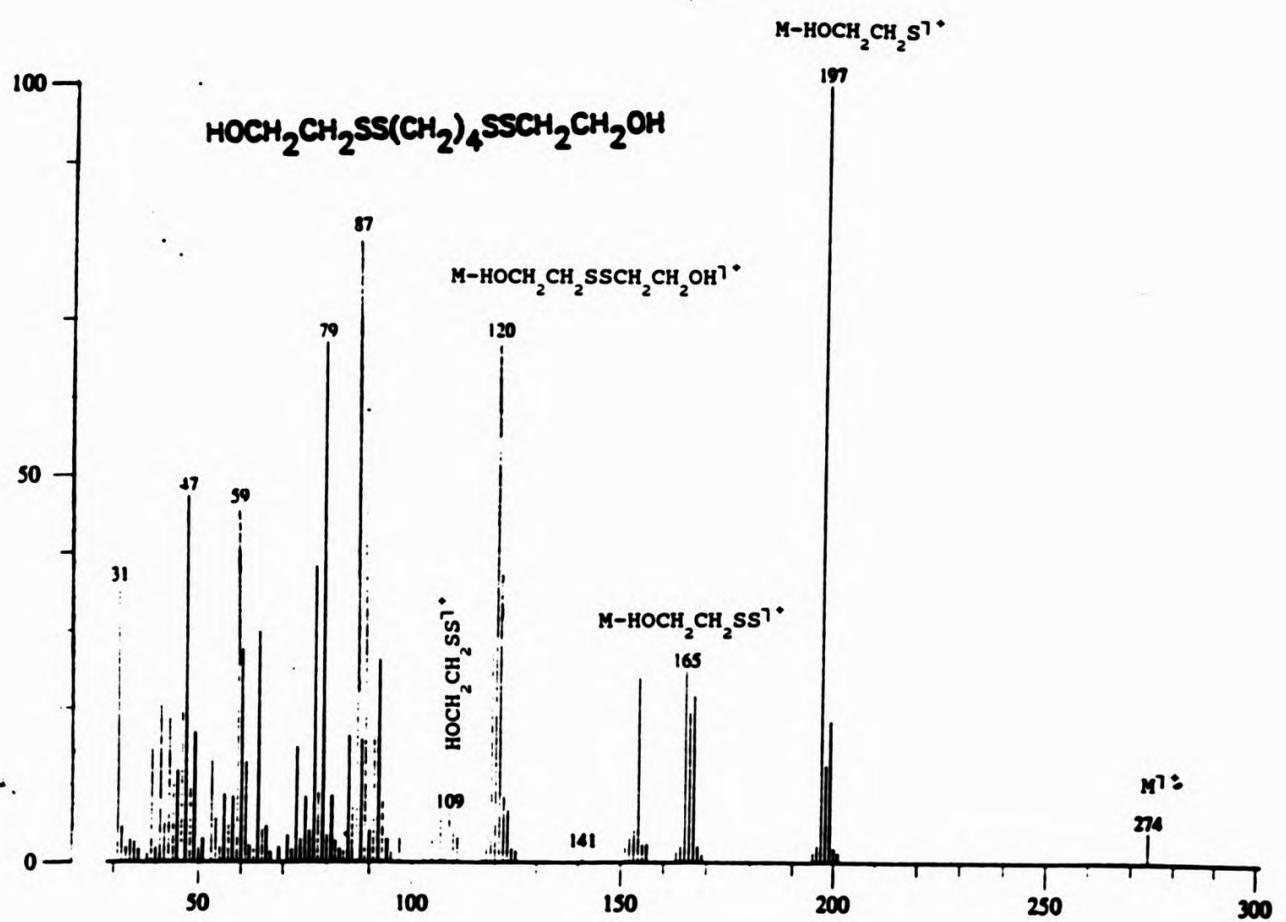


Figure 14: Mass spectrum of butane- α,ω -bis(2-hydroxyethyl-disulphide)

CHAPTER THREE

BIOLOGICAL ACTIVITY

3.1 Fungicidal screening: results and discussion

The various compounds were tested for fungicidal activity as described in the experimental section. The fungal organisms against which the compounds were tested are shown in Table 30.

Table 30. Organisms and the corresponding diseases

Fungi	Diseases
(1) <i>Fusarium culmorum</i>	Pre-emergence seedling blight, root and foot rot in cereals.
(2) <i>Fusarium oxysporium</i>	Vascular wilt or damping off disease, rot and ear blight.
(3) <i>Gaeumomyces graminis</i>	Crown sheath rot on rice, take-all on wheat, barley, rye, and corn.

The *in vitro* testing of the compounds was carried out in the Life Science Department of the University of North London. Germination of spores was assessed by measuring the diameter of growth of each plate and comparing it with the control. The percentage inhibition (%I) of growth was calculated by

using the following equation.

$$\%I = \frac{d_c - d}{d_c} \times 100$$

d = diameter of growth for plate treated with chemical

d_c = diameter of growth for control plate

The %I were then ranked according to the key below.

Key

%I

0 = ≤ 10

1 = 11-20

2 = 21-49

3 = 50-79

4 = ≥ 80

- = Not tested

The results of this *in vitro* test are shown in Tables 31, 32, 33, 34, 35, 36, 37, 38 and 39.

Table 31. *In vitro* test results for $\text{ArCH}_2\text{SSSCH}_2\text{CH}_2\text{OH}$

Ar	(1)			(2)			(3)		
	10	100	1000	10	100	1000	10	100	1000
C_6H_4	1	2	4	1	2	4	1	2	4
<i>o</i> -ClC ₆ H ₄	2	2	4	2	3	4	2	3	4
<i>p</i> -MeC ₆ H ₄	2	3	4	2	2	4	2	3	4
<i>p</i> -MeOC ₆ H ₄	2	3	4	2	3	4	2	3	4

Table 32. *In vitro* test results for $\text{ArCH}_2\text{SSSSSCH}_2\text{CH}_2\text{OH}$

Ar	(1)			(2)			(3)		
	10	100	1000	10	100	1000	10	100	1000
C_6H_4	2	2	4	2	3	4	2	2	4
<i>o</i> -MeC ₆ H ₄	1	3	4	1	3	4	1	3	4
<i>p</i> -ClC ₆ H ₄	2	3	4	2	3	4	1	2	4
<i>p</i> -MeOC ₆ H ₄	1	2	4	1	3	4	1	2	4
<i>p</i> -MeC ₆ H ₄	1	2	4	1	2	4	1	3	4
	1	2	4	1	2	4	1	2	4

Table 33. *In vitro* test results for $\text{ArCH}_2\text{SSCH}_2\text{CH}_2\text{OH}$

Ar	(1)			(2)			(3)		
	10	100	1000	10	100	1000	10	100	1000
C_6H_4	0	3	4	1	3	4	2	3	4
<i>o</i> -Cl C_6H_4	0	3	4	2	3	4	2	4	4
<i>o</i> -Me C_6H_4	1	3	4	1	3	4	2	4	4
<i>p</i> -MeOC C_6H_4	1	3	4	2	3	4	2	4	4
<i>p</i> -FC C_6H_4	2	3	4	2	3	4	3	4	4

Table 34. *In vitro* test results for $\text{ArCH}_2\text{SCH}_2\text{CH}_2\text{OH}$

Ar	(1)			(2)			(3)		
	10	100	1000	10	100	1000	10	100	1000
C_6H_4	2	3	4	1	2	4	1	2	4
<i>o</i> -Cl C_6H_4	2	2	4	1	2	4	0	2	4
<i>o</i> -Me C_6H_4	2	3	4	1	2	4	0	1	4
<i>p</i> -MeOC C_6H_4	2	3	4	1	2	4	1	2	4
<i>p</i> -Cl C_6H_4	2	3	4	0	1	4	1	2	4

Table 35. *In vitro* test results for ArCH₂SSSCH₂Ar

Ar	(1)			(2)			(3)		
	10	100	1000	10	100	1000	10	100	1000
C ₆ H ₄	0	0	2	0	0	2	-	-	-
<i>o</i> -MeC ₆ H ₄	0	0	2	0	0	2	-	-	-
<i>o</i> -ClC ₆ H ₄	0	0	2	0	0	2	-	-	-
<i>p</i> -MeC ₆ H ₄	0	0	2	0	0	2	-	-	-
<i>p</i> -MeOC ₆ H ₄	0	0	2	0	0	2	-	-	-
<i>p</i> -ClC ₆ H ₄	0	0	2	0	0	2	-	-	-

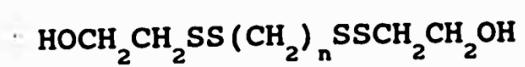
Table 36. *In vitro* test results for ArCH₂SSC $\begin{matrix} \text{NH}_2 \\ \text{NH}_2 \end{matrix}$ Cl⁻

Ar	(1)			(2)			(3)		
	10	100	1000	10	100	1000	10	100	1000
C ₆ H ₄	0	0	4	0	0	4	-	-	-
<i>o</i> -MeC ₆ H ₄	0	1	4	0	0	4	-	-	-
<i>p</i> -ClC ₆ H ₄	0	0	4	0	0	4	-	-	-
<i>p</i> -MeC ₆ H ₄	0	1	4	0	0	4	-	-	-
<i>p</i> -MeOC ₆ H ₄	0	0	4	0	0	4	-	-	-

Table 37. *In vitro* test results for PhthNSSCH₂Ar

Ar	(1)			(2)			(3)		
	10	100	1000	10	100	1000	10	100	1000
C ₆ H ₄	0	1	2	0	1	2	-	-	-
<i>o</i> -ClC ₆ H ₄	0	1	2	0	2	2	-	-	-
<i>p</i> -MeC ₆ H ₄	0	1	2	0	0	2	-	-	-
<i>p</i> -MeOC ₆ H ₄	2	2	4	0	2	4	-	-	-

Table 38. *In vitro* test results for



n	(1)			(2)			(3)		
	10	100	1000	10	100	1000	10	100	1000
2	1	2	4	1	2	4	1	1	4
3	1	2	4	1	2	4	1	2	4
4	2	2	4	1	3	4	1	2	4

Table 39 *In vitro* test results for Guazatine/Imazalil and Phenylmercury acetate

	(1)			(2)			(3)		
	10	100	1000	10	100	1000	10	100	1000
Guazatine/ Imazalil	3	3	4	3	3	4	3	3	4
Phenylmercury acetate	2	3	4	2	3	4	2	3	4

3.2 Performance of the compounds tested

All the compounds of the type $\text{ArCH}_2(\text{S})_n\text{CH}_2\text{CH}_2\text{OH}$ controlled the fungi *F.culmorum*, *F.oxysporum*, and *G graminis* at 1000 ppm. However, at lower concentrations of 100 ppm and 10 ppm, the level of control varied only slightly with changes in the value of *n* and there was generally decrease in activity at the lower concentrations.

For unsymmetrical trisulphides (Table 31) the presence of substituents in either the *ortho* or *para* position of the benzene ring of the compounds led to an increase in activity. Electron donating groups led to more activity than electron withdrawing groups.

For unsymmetrical tetrasulphides (Table 32) the *para* chloro compound was the most active and this was difficult

to explain in the light of the above observations for the unsymmetrical analogues. When compared with the unsymmetrical trisulphides, they showed slightly lower activity.

Unsymmetrical disulphides (Table 33) were less able to control *F.culmorum* at 10 ppm when compared with other classes of compound of the same general type. The *p*-fluoro compound however showed some promise in that it was able to control this fungus at this concentration (48%I). All the compounds in this class were able to show moderately good control of the other two fungi and no distinct substituent activity relationship was generally noticed.

Unsymmetrical monosulphides tested (Table 34) were particular good for the control of *F.culmorum* but were not as good for the control of *F.oxysporum* and *G.graminis*. Also, in this class of compound, there is no distinct dependence of activity on the substituents in the benzene ring, irrespective of their being electron donating or withdrawing.

From the results obtained for all the compounds of the various classes, there was no evidence that the number of sulphur atoms in each compound contributed significantly to fungicidal activity. It was shown that monosulphides were as good as their trisulphide analogues for the control of *F.culmorum* and were even found to be better than the disulphides for the control of this fungus. When compared with guazatine/imazalil and phenyl mercury acetate which are

well known fungicides, some of these compounds showed good promise as potential fungicides because the level of activity observed was comparable to that of these standard fungicides.

The symmetrical compounds ($\text{ArCH}_2\text{SSSCH}_2\text{Ar}$) tested, (Table 35) showed poor activity even at 1000 ppm for the control of *F.culmorum* and *F.oxysporum*. This may indicate that the hydroxyethyl group may play an important part in the fungicidal activity of the unsymmetrical oligosulphides discussed above.

The benzylthioisothiuronium chlorides tested (Table 36), were only able to control the fungal growth of the organisms at 1000 ppm, hence they do not show any promise of practical application. Variation of the substituents on the benzene ring of these compounds does not lead to any appreciable change in activity.

The phthalimido disulphides tested (Table 37) do not show good activity even at 1000 ppm except for the *p*-methoxy compound that was able to give >80% control of *F.culmorum* and *F.oxysporum* at this concentration.

The compounds $\text{HOCH}_2\text{CH}_2\text{SS}(\text{CH}_2)_n\text{SSCH}_2\text{CH}_2\text{OH}$ (Table 38) showed some activity and were able to control the three fungi but they were not as effective as compounds of the general type: $\text{ArCH}_2(\text{S})_n\text{CH}_2\text{CH}_2\text{OH}$.

3.3 Glasshouse screening of compounds

On the basis of the results obtained from the *in vitro* testing of the compounds, five of these compounds (ET1, ET2, ET3, ET4, and ET5) were selected for *in vivo* screening. The glasshouse screening of the compounds was carried out at the Department of Plant Science, Scottish Agricultural College Auchincruive. They were screened against five fungi and the results obtained are presented in Tables 40, 41, 42, 43 and 44. ET1 to ET5 are as defined below.

ET1 = 4-fluorobenzyl 2-hydroxyethyl disulphide

ET2 = 4-methoxybenzyl 2-hydroxyethyl trisulphide

ET3 = 2-chlorobenzyl 2-hydroxyethyl disulphide

ET4 = 4-methoxybenzyl 2-hydroxyethyl disulphide

ET5 = 4-methoxybenzyl 2-hydroxyethyl monosulphide

Table 40. Post-inoculation treatments against *Erysiphe graminis* on barley seedlings

Treatment	Percentage leaf area infected ^a		
	Assessment One	Assessment Two	Assessment Three
Control	15.74±0.684	26.78±1.188	41.17±1.802
ET1	3.92±0.282	9.24±0.851	13.28±1.087
ET2	4.70±0.270	10.13±0.604	10.96±0.729
ET3	2.72±0.449	6.76±0.820	10.50±1.094
ET4	2.13±0.215	6.60±0.716	10.40±0.709
ET5	2.67±0.211	7.45±0.462	10.28±0.701

^aAssessments One, Two, and Three were carried out 6, 8 and 10 days (post-inoculation) respectively.

Table 41. Post-inoculation treatments against *Botrytis fabae* on bean seedlings

Treatment	Percentage leaf area infected ^a	
	Assessment One	Assessment Two
Control	3.50±0.58	5.55±0.86
ET1	2.29±0.57	3.29±0.61
ET2	5.14±0.74	7.43±1.16
ET3	6.31±0.97	11.94±1.76
ET4	6.38±1.46	9.50±2.44
ET5	3.25±0.62	5.06±1.15

^aAssessments One and Two were carried out 6 and 8 days (post-inoculation) respectively.

Table 42. Post-inoculation treatments against *Podosphaera leucotricha* on apple seedlings

Treatment	Mean Disease Score ^{a,b}		
	Assessment One	Assessment Two	Assessment Three
Control	2.0	2.0	2.5
ET1	0.2	1.0	1.0
ET2	0.5	1.0	1.0
ET3	0.2	1.0	1.0
ET4	0.5	0.5	0.5
ET5	1.5	2.0	2.0

^aAssessments One, Two and Three were carried out 13, 15 and 17 days (post-inoculation) respectively.

^bApples were assessed using the following infection key;

- 0 = No infection
- 1 = A few isolated spores
- 2 = <50% infection
- 3 = >50% infection

Table 43. Post-inoculation treatments against *Uromyces viciae-fabae* on bean seedlings

Treatment	Percentage leaf area infected ^a	
	Assessment One	Assessment Two
Control	8.06 \pm 1.24	13.25 \pm 2.43
ET1	7.93 \pm 1.49	7.64 \pm 1.38
ET2	4.79 \pm 0.49	6.31 \pm 0.96
ET3	5.50 \pm 0.87	9.33 \pm 1.45
ET4	7.19 \pm 1.42	10.88 \pm 1.75
ET5	4.75 \pm 1.47	3.86 \pm 1.03

^aAssessments One and Two were carried out 15 and 19 days (post-inoculation) respectively.

Table 44. Effect of compounds on infection of potato leaf discs by the blight fungus *Phytophthora infestans*

Treatment	Disease Score ^{a,b}
Control	3
ET1	1
ET2	3
ET3	3
ET4	2
ET5	1

^aDisease infection was examined after 4 days.

^bPotatoes were assessed using the following key:

- 1 = a few isolated sporophores
- 2 = < 50% infection
- 3 = > 50% infection

The glasshouse comparisons of the compounds are presented in Figures 15, 16 and 17.

Performance of the compounds

All compounds were tested at a concentration of 0.33%. At higher concentration, all compounds were phytotoxic causing leaf damage.

Overall, 2-fluorobenzyl 2-hydroxyethyl disulphide (ET1)

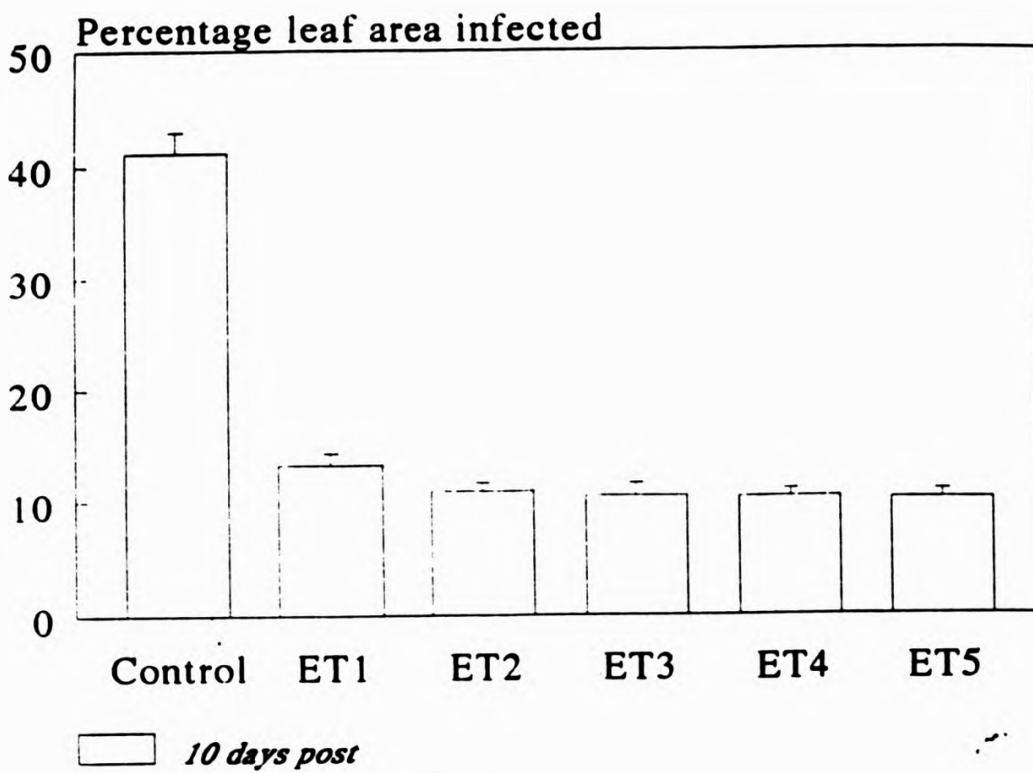


Figure 15 Glasshouse comparison of compounds
Post-inoc treatments vs *E. graminis*

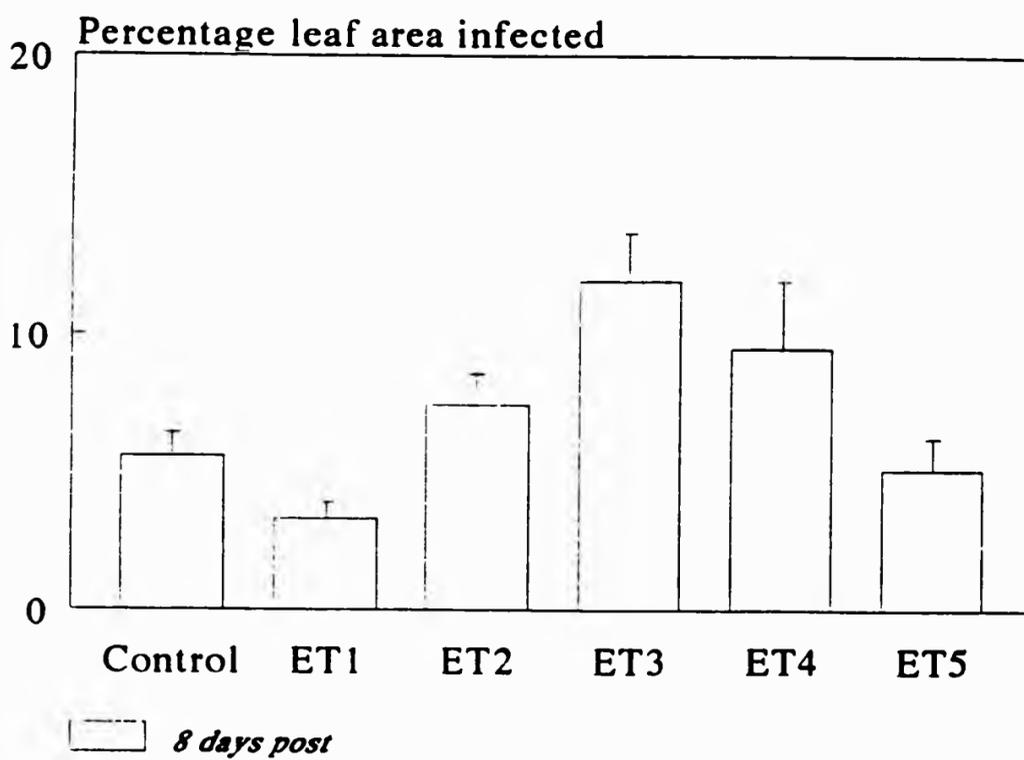


Figure 16 Glasshouse comparison of compounds
Post-inoc treatments vs *B. fabae*

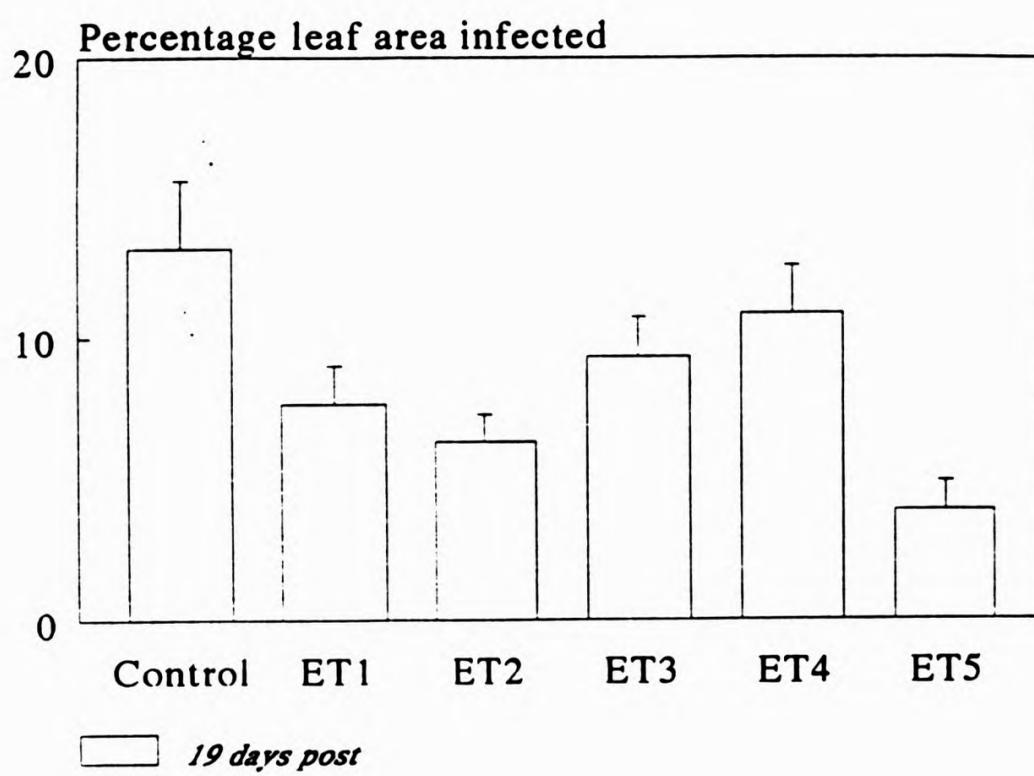


Figure 17 Glasshouse comparison of compounds
Post-inoc treatments vs *U. viciae-fabae*



gave the greatest spectrum of disease control, reducing infection in all host-pathogen systems examined. Greatest disease control was observed against barley powdery mildew, chocolate spot on broad bean and blight on potato. 4-Methoxybenzyl 2-hydroxyethyl disulphide (ET4) gave best control of apple powdery mildew, while 4-methoxybenzyl 2-hydroxyethyl monosulphide (ET5) gave best control of bean rust and also provided some control of potato blight.

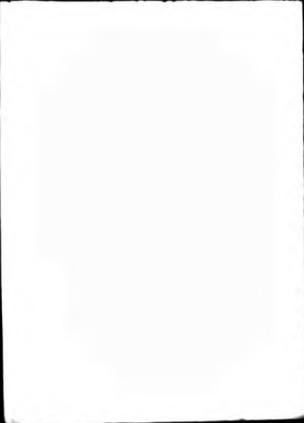
CHAPTER FOUR

EXPERIMENTAL

List of Reagents and their Suppliers

<u>Reagents</u>	<u>Supplier</u>
Acetic acid	BDH
Activated Charcoal	BDH
Allyl mercaptan	Aldrich
Benzyl bromide	Aldrich
Benzyl mercaptan	Aldrich
Calcium chloride	BDH
Carbon tetrachloride	BDH
2-Chlorobenzyl mercaptan	Lancaster Synthesis
4-Chlorobenzyl mercaptan	Lancaster Synthesis
2-Chloroethanol	Aldrich
3-Chloroperoxybenzoic acid	Aldrich
Dichloromethane	BDH
Diethyl ether (anhydrous)	BDH
1,2-dimercaptoethane	Lancaster Synthesis
1,3-dimercaptopropane	Lancaster Synthesis
1,4-dimercaptobutane	Lancaster Synthesis
Dimethylamine	Aldrich
Dimethylformamide	BDH
Di-n-butylamine	BDH
Ethanol	BDH
Furfuryl alcohol	Aldrich
2-Furfuryl mercaptan	Lancaster Synthesis
Guazatine/Imazalil	Murphy Chemical Co.
n-Hexane	Aldrich

Hydrochloric acid (concentrated)	BDH
Hydrogen peroxide (27.5 wt.% solution)	Aldrich
Iodine	Aldrich
Magnesium sulphate (anhydrous)	Aldrich
Methanol	BDH
2-Mercaptoethanol	Aldrich
2-Mercaptobenzimidazole	Lancaster Synthesis
2-Mercaptobenzothiazole	Lancaster Synthesis
2-Methylbenzyl mercaptan	Lancaster Synthesis
4-Methylbenzyl mercaptan	Lancaster Synthesis
4-Methoxybenzyl mercaptan	Lancaster Synthesis
Molecular Sieves (type 4A)	E. Merck
Murganic RPB	Murphy Chemical Co.
Peracetic acid	Aldrich
Petroleum ether	BDH
Phthalimide	Aldrich
Potassium bromide	Aldrich
Potassium carbonate (anhydrous)	BDH
Potassium ethyl xanthate	Aldrich
Potassium phthalimide	Aldrich
o-Phenylenediamine	Aldrich
Saboround Dextrose Agar	Oxoid
Silica gel	Merck
Sodium bisulphite	BDH
Sodium chloride	BDH
Sodium disulphide nonahydrate	Aldrich
Sodium hydroxide	BDH



Sodium hydrogen carbonate	BDH
Sodium thiosulphate pentahydrate	BDH
Sulphur	BDH
Sulphur dichloride	Aldrich
Sulphur monochloride	Aldrich
Thioacetic acid	Aldrich
Thiourea	Aldrich
Toluene	BDH
Triethyl phosphate	Aldrich
Trichloromethylsulphenyl chloride	Aldrich

4.1 Purification of starting materials, reagents and solvents.

Most reagents involved in this work were used without further purification; however sulphur monochloride was purified by distillation prior to use. It was distilled over sulphur and the fraction collected at 138-139 °C at atmospheric pressure. Similarly, sulphur dichloride was purified by distillation and the fraction collected at 58-60 °C.

Solvents were dried as follows:

- (a) Dimethylformamide was dried over molecular sieves (E. Merck type 4 A).
- (b) Toluene and diethyl ether were dried over sodium wire.

4.2 Analytical methods

4.2.1 Carbon, hydrogen, nitrogen and sulphur analysis

All analyses for carbon, hydrogen, nitrogen and sulphur were carried out in the Department of Applied Chemistry (University of North London) using a Carlo Erba 1106 Elemental Analyser.

4.2.2 Nuclear magnetic resonance spectroscopy

Routine ^1H nmr spectra were obtained using a Perkin-Elmer R 12B continuous wave spectrometer at a field of 60 MHz, and on a Bruker WP80 instrument at 80 Mz. Higher field ^1H nmr and ^{13}C nmr were recorded on a Bruker AM250 Fourier transform spectrometer at 250.13 MHz and 62.89 MHz respectively. Chemical shifts for ^1H and ^{13}C nmr spectra are given relative to the internal standard tetramethylsilane (TMS).

4.2.3 Mass spectrometry

Low resolution electron impact (E.I.) mass spectra were recorded in the Department of Applied Chemistry (University of North London) using a KRATOS 'PROFILE' high resolution mass spectrometer which is a double-focussing sector field instrument.

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4.3 Preparation of intermediates and reagents

4.3.1 2-Mercaptobenzimidazole

A mixture of *o*-phenylenediamine (16.2 g, 0.15 mol), potassium ethyl xanthate (26.4 g, 0.165 mol), ethanol (300 cm³) and water (45 cm³) in a 500 cm³ round bottom flask was heated under reflux for 13 h. Activated charcoal (6.0 g) was added to the mixture cautiously, and the mixture was heated at reflux temperature for an additional 10 minutes, after which the charcoal was removed by filtration. The filtrate was heated to 60-70 °C, and warm tap water (150 cm³) was added followed by the addition of acetic acid (12.5 cm³) in water (25 cm³) with vigorous stirring. The desired product separated out as off-white crystals and the mixture was kept in the refrigerator overnight to effect complete crystallization. The product was collected in a Büchner funnel, dried at 40 °C for 2 days, and recrystallized from methanol to give 2-mercaptobenzimidazole (10.50 g, 68%) as a white crystalline solid; (Found: C, 55.88; H, 3.93; N, 18.00; S, 21.32. Calc. for C₇H₆N₂S: C, 55.98; H, 4.03; N, 18.67; S, 21.27%), m.p. 301-303 °C (lit.¹⁷¹ 303-304 °C).

4.3.2 2-Furfurylmercaptan¹⁷²

Thiourea (19.0 g, 0.25 mol) was placed in a 250 cm³ round-bottomed flask. Water (25 cm³) and concentrated hydrochloric acid (12.5 cm³) were added. The solid was dissolved by gentle heating and the solution obtained was

cooled to 30 °C. Furfuryl alcohol (21.7 cm³, 0.25 mol) was then added to the solution. The ensuing reaction, which comenced spontaneously within a few minutes, was strongly exothermic and the flask was cooled under the tap so as to keep the temperature near 60 °C. When the reaction subsided cooling was discontinued and the dark green solution was allowed to stand at room temperature for 12 h. Sodium hydroxide (11.25 g, 0.28 mol) in water (25 cm³) was added to the reaction mixture and immediately a heavy brown oil separated consisting of S-2-furfurylisoithiourea which had already partially decomposed to 2-furfurylmercaptan. The flask was quickly fitted with a steam inlet tube and condenser, and steam distillation was carried out as long as the distillate contained oily drops. The mercaptan was separated from the aqueous phase, dried over calcium chloride and filtered through a glass-wool plug to give 2-furfuryl mercaptan (10.10 g, 40%) as a light yellow liquid; tlc (3:1 ether/DCM on silica) gave a single spot, R_f 0.63; (Found: C, 52.48; H, 5.30; S, 28.16. Calc. for C₅H₆OS: C, 52.60; H, 5.31; S, 28.08%); δ_H (CDCl₃) 1.90 (SH, t, 1H, ³J_{HCSH} = 5 Hz), 3.73 (CH₂, d, 2H), 6.29-6.78 (furyl-H, m, 1H), 7.32 (furyl-H, m, 2H); δ_C (CDCl₃) 20.98 (HSCH₂), 106.27 (furylC-3), 110.48 (furylC-4), 141.95 (furylC-2), 153.52 (furylC-1); MS: m/z (%), 114 (M⁺, 2), 81 (100).

4.3.3 Trichloromethylthiosulphenyl chloride¹⁶⁴

A mixture of trichloromethylsulphenyl chloride (17.0 g, 0.09 mol), sulphur (4.0 g, 0.12 mol) and triethyl phosphate (0.47 cm³, 0.003 mol) was heated under reflux for 7 h at 140-150 °C. The resultant material was filtered and the filtrate was fractionally distilled to give trichloromethylthiosulphenyl chloride (8.50 g, 50%) as a yellow viscous oil; (Found: C, 5.62; S, 29.34. Calc. for CCl₃S₂: C, 5.51; S, 29.55%); b.p. 60-65 °C at 3.0 mmHg (lit.¹⁶⁴ b.p. 63-66 °C at 2.5 mmHg); MS: m/z (%), 218 (M⁺, 16), 186 (21), 154 (15).

4.4 N,N-Thiobisphthalimide

Phthalimide (14.72 g, 0.10 mol) was dissolved in anhydrous dimethylformamide (80 cm³) (dried over molecular sieve type 4A). Sulphur monochloride (8.08 cm³, 0.10 mol) was added dropwise (10 min) under nitrogen. After about 20 minutes, a precipitate appeared and the resultant yellow mixture was stirred for an additional 20 h at 28 °C. A white crystalline solid which formed was collected by filtration, dried, and recrystallized from dichloromethane/carbon tetrachloride (3:1) to give N,N-thiobisphthalimide (14.46 g, 89%) as a white crystalline solid (Found: C, 59.23; H, 2.45; N, 8.69; S, 9.79. Calc. for C₁₆H₈N₂O₄S: C, 59.26; H, 2.49; N, 8.64; S, 9.89%); m.p. 321-323 °C (lit.¹⁵⁷ m.p. 315-317 °C). The i.r spectrum (KBr disc) exhibited no -NH₂, =NH or -COOH bands.

4.5.1 Preparation of S-(4-methylbenzylthio)isothiuronium chloride

A mixture of 4-methylbenzyl mercaptan (10.48 g, 0.076 mol), thiourea (6.82 g, 0.089 mol), hydrochloric acid (12.06 cm³), water (12.06 cm³) and ethanol (180 cm³) was kept at 0-10 °C by means of an ice-salt bath while hydrogen peroxide (9.65 g) was added dropwise with vigorous stirring for a period of 1 h. The stirring was continued for an additional 2 h. Dithioformamidine hydrochloride which was formed was filtered off and the solvent was removed from the filtrate by rotary evaporation to give a solid residue which was then dissolved in a small amount of ethanol. This solution was diluted with ether to give a white solid which was recrystallized from ethanol-ether solvent system, and dried to give the desired S-(4-methylbenzylthio)isothiuronium chloride (13.30 g, 71%) as a white crystalline solid; (Found: C, 43.54; H, 5.49; N, 11.25; S, 25.80. Calc. for C₉H₁₃ClN₂S₂: C, 43.44; H, 5.28; N, 11.26; S, 25.77%); m.p. 158-159 °C (lit¹⁴⁴. m.p. 157-159 °C).

A similar method was used in the preparation of the following compounds.

4.5.2 S-(4-chlorobenzylthio)isothiuronium chloride

4-Chlorobenzyl mercaptan (17.45 g, 0.11 mol), thiourea (10.05 g, 0.13 mol), concentrated hydrochloric acid and hydrogen peroxide (14.0 g) gave S-(4-chlorobenzylthio)isoth-

iouronium chloride (19.26 g, 65%) as a white crystalline solid; (Found: C, 35.56; H, 3.62; N, 10.56; S, 23.72. Calc. for $C_8H_{10}Cl_2N_2S_2$: C, 35.67; H, 3.75; N, 10.40; S, 23.81%); m.p. 153-154 °C (lit.¹⁴⁴ m.p. 150-152 °C).

4.5.3 S-(2-Methylbenzylthio)isothiuronium chloride

2-Methylbenzyl mercaptan (10.48 g, 0.076 mol), thiourea (6.82 g, 0.089 mol), concentrated hydrochloric acid (12.06 cm³) and hydrogen peroxide (9.65 g) gave S-(2-methylbenzylthio)isothiuronium chloride (14.26 g, 76%) as a white crystalline solid; (Found: C, 43.51; H, 5.36; N, 11.36; S, 25.87. Calc. for $C_9H_{12}ClN_2S_2$: C, 43.44; H, 5.28; N, 11.26; S, 25.77%); m.p. 162-163 °C (lit.¹⁴⁴ m.p. 161-163 °C).

4.5.4 S-(2-Chlorobenzylthio)isothiuronium chloride

2-Chlorobenzyl mercaptan (9.72 g, 0.06 mol), thiourea (5.53 g, 0.07 mol), concentrated hydrochloric acid (9.54 cm³) and hydrogen peroxide (7.6 g) gave S-(2-chlorobenzylthio)isothiuronium chloride (18.53 g, 71%) as a white crystalline solid, (Found: C, 35.84; H, 3.61; N, 10.52; S, 23.69. Calc. for $C_8H_9ClN_2S_2$: C, 35.67; H, 3.75; N, 10.40; S, 23.81%); m.p. 153-154 (lit.¹⁴⁴ m.p. 155-156 °C)

4.5.5 S-(4-methoxybenzylthio)isothiuronium chloride

4-Methoxybenzyl mercaptan (10.62, 0.069 mol), thiourea (6.17 g, 0.081 mol), concentrated hydrochloric acid (11.0 cm³) and hydrogen peroxide (9.38 g) gave S-(4-methoxybenzylthio)isothiuronium chloride (14.29 g, 78%) as a white crystalline solid; (Found: C, 40.05; H, 4.65; N, 10.53; S, 24.13. Calc. for C₉H₁₂ClN₂OS₂: C, 40.81; H, 4.96; N, 10.58; S, 24.21%); m.p. 155-156 °C (lit.¹⁴⁴ m.p. 153-155 °C).

4.5.6 S-(2-Hydroxyethylthio)isothiuronium chloride

2-Mercaptoethanol (7.80 cm³, 0.11 mol), thiourea (10.50 g, 0.13 mol), concentrated hydrochloric acid (17.5 cm³), and hydrogen peroxide (14.0 g) gave S-(2-hydroxyethylthio)isothiuronium chloride (17.65 g, 85%) as a white crystalline solid; (Found: C, 19.07; H, 4.82; N, 14.93; S, 33.89. Calc. for C₃H₉ClN₂OS₂: C, 19.09; H, 4.82; N, 14.86; S, 33.93%); m.p. 105-106 °C (lit.¹⁴⁴ m.p. 106-107 °C).

4.5.7 S-Benzylthioisothiuronium chloride

Benzyl mercaptan (12.9 cm³, 0.11 mol), thiourea (10.05 g, 0.13 mol), concentrated hydrochloric acid (17.5 cm³) and hydrogen peroxide (14.0 g) gave S-benzylthioisothiuronium chloride (19.12 g, 74%) as a white crystalline solid; (Found: C, 40.98; H, 4.83; N, 11.96; S, 27.10. Calc. for C₈H₁₁ClN₂S₂: C, 40.91; H, 4.73; N, 11.94; S, 27.27%); m.p. 147-149 °C (lit.¹⁴⁴ m.p. 145-148 °C).

4.5.8 Allylthioisothiuronium chloride

Allyl mercaptan (8.93 cm³, 0.11 mol), thiourea (10.05 g, 0.13 mol), concentrated hydrochloric acid (17.5 cm³) and hydrogen peroxide (14.0 g) gave allylthioisothiuronium chloride (11.03 g, 54%) as a white solid; (Found: C, 25.82; H, 4.84; N, 15.14; S, 34.46. C₄H₉ClN₂S₂ requires: C, 26.01; H, 4.92; N, 15.17; S, 34.71%); m.p. 137-139 °C.

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4.6.1 Preparation of benzyl 2-hydroxyethyl disulphide¹⁶¹

Step A

Benzyl bromide (12.0 cm³, 0.10 mol) in methanol (120 cm³) was put into a three-necked round bottom flask equipped with a condenser, a 100 cm³ dropping funnel and a mechanical stirrer. Water was added slowly with stirring until a slight turbidity developed. The stirred mixture was heated to reflux and sodium thiosulphate pentahydrate (31.0 g, 0.125 mol) in water (25 cm³) was added over 30 minutes. The slightly yellow solution was heated for an additional 4 h and allowed to cool to room temperature. The alcohol was removed by rotary evaporation, the remaining milky solution was diluted with water (120 cm³) and extracted twice with hexane (2 x 80 cm³). The organic layer was discarded and the aqueous solution of the crude thiosulphate was cooled to 0 °C and stored in the refrigerator overnight.

Step B

Into a 250 cm³ two-necked round bottom flask fitted with a dropping funnel and a gas inlet tube under an atmosphere of nitrogen was added sodium hydroxide (4.0 g, 0.1 mol) in water (10 cm³). Mercaptoethanol (7.8 cm³, 0.1 mol) was added dropwise over a 2 h period with rapid stirring at room temperature. The thiolate solution, containing HOCH₂CH₂SNa,

became viscous toward the end of the addition and was diluted with water (3 cm³), and cooled to 0 °C.

Step C

The cooled thiolate solution in B above was quantitatively transferred into a dropping funnel fitted to a three-necked flask equipped with a mechanical stirrer and a thermometer. The crude thiosulphate solution obtained in step A above was put into this flask and cooled to 0 °C with the aid of an ice-salt bath. The cold thiolate solution was added rapidly with vigorous stirring during 3 minutes followed by aqueous saturated sodium chloride (20 cm³) and the mixture was warmed to 5 °C. Stirring was stopped 15 minutes after the start of addition of sodium chloride. The crude disulphide which separated out as an oil was removed and the aqueous layer was extracted twice with diethyl ether (2 x 100 cm³). The extracts were combined with the oil, washed twice with water (2 x 100 cm³), dried over granular calcium chloride and filtered through a glass wool plug. Solvent was removed by rotary evaporation. Total removal of solvent was carried out under reduced pressure by collecting the material in a flask fitted for shaking. This gave benzyl 2-hydroxyethyl disulphide¹²¹ (2.91 g, 40%) as a yellow oil; tlc 3:1 (ether/DCM on silica) gave a single spot, R_f 0.63; (Found: C, 53.87; H, 6.36; S, 32.86. Calc. for C₉H₁₂OS₂: C, 53.97; H, 6.05; S, 31.96%); δ_H (CDCl₃) 2.22 (OH, s, 1H), 2.51

(SCH₂CH₂OH, t, 2H, ³J_{HCCH} = 6 Hz), 3.73 (HOCH₂CH₂, t, 2H, ³J_{HCCH} = 6 Hz), 3.93 (ArCH₂, s, 2H), 7.25 (Ar-H, m, 5H); δ_c (CDCl₃) 40.61 (SCH₂CH₂), 41.09 (ArCH₂S), 60.03 (HOCH₂CH₂), 126.90 (ArC-4), 127.47 (ArC-3,5), 129.24 (ArC-2,6), 137.24 (ArC-1). Trace amount of HOCH₂CH₂SSCH₂CH₂OH (3%) was formed as impurity, δ_H (CDCl₃) 2.76 (HOCH₂CH₂SSCH₂CH₂, t, 0.28, ³J_{HCCH} = 5 Hz), 3.92 (HOCH₂CH₂SSCH₂CH₂, t, .29, ³J_{HCCH} = 5 Hz); δ_c (CDCl₃) 43.34 (CH₂CH₂SSCH₂CH₂), 64.93 (CH₂CH₂SSCH₂CH₂OH).

Similar procedures were used in the preparation of the following compounds.

4.6.2 2-Furfuryl 2-hydroxyethyl disulphide

2-Choroethanol (2.9 cm³, 0.043 mol), sodium thiosulphate pentahydrate (10.67 g, 0.043 mol), sodium hydroxide (1.72 g, 0.043 mol) and 2-furfuryl mercaptan (5 g, 0.043 mol) gave 2-furfuryl 2-hydroxyethyl disulphide¹²¹ (5.84 g, 71%) as a dark brown oil; tlc 4:1 (pet ether/DCM) gave one single spot R_f 0.51; (Found: C, 44.07; H, 5.39; S, 33.46. Calc. for C₇H₁₀O₂S₂: C, 44.21; H, 5.30; S, 33.65%); δ_H (CDCl₃) 2.56 (SCH₂CH₂OH, t, 2H, ³J_{HCCH} = 6 Hz), 2.86 (OH, s, 1H), 3.72 (SCH₂CH₂OH, t, 2H, J_{HCCH} = 6 Hz), 3.91 (ArCH₂, s, 2H), 6.20-6.33 (Ar-H, m, 2H), 7.36-7.38 (Ar-H, m, 1H); δ_c (CDCl₃) 35.47 (SCH₂CH₂), 35.65 (Ar-CH₂), 60.00 (HOCH₂), 108.96 (furyl C-3), 110.74 (furyl C-2), 142.42 (furyl C-4), 150.07 (furyl C-1); MS: m/z (%), 190 (M⁺, 3), 158 (2), 125 (7), 81

(100). Trace amount of furfuryl disulphide (4%) was formed as impurity, δ_{H} (CDCl_3) 3.66 ($\text{ArCH}_2\text{SSCH}_2\text{Ar}$, s, 0.3H); δ_{C} (CDCl_3) 40.88 ($\text{ArCH}_2\text{SSCH}_2\text{Ar}$), (Ar = 2-furfuryl).

4.6.3 2-Benzimidazolyl 2-hydroxyethyl disulphide

2-Chloroethanol (2.9 cm^3 , 0.043 mol), sodium thiosulphate pentahydrate (10.67 g, 0.043 mol), sodium hydroxide (1.72 g, 0.043 mol) and 2-mercaptobenzimidazole (6.46 g, 0.043 mol) gave 2-benzimidazolyl 2-hydroxyethyl disulphide (8.76 g, 65%) as a white crystalline solid; (Found: C, 47.54; H, 4.39; N, 12.38; S, 28.33. $\text{C}_9\text{H}_{10}\text{N}_2\text{OS}_2$ requires: C, 47.76; H, 4.46; N, 12.32; S, 28.23%); m.p. 147-148 $^{\circ}\text{C}$; δ_{H} (CDCl_3) 3.16 ($\text{SCH}_2\text{CH}_2\text{OH}$, t, 2H, $^3J_{\text{HCCH}} = 5$ Hz), 3.97 ($\text{HOCH}_2\text{CH}_2\text{S}$, t, 2H, $^3J_{\text{HCCH}} = 5$ Hz), 4.73 (OH, s, 1H), 7.31-7.44 (Ar-H, m, 1H), 7.76 (Ar-H, m, 3H); δ_{C} (CDCl_3) 42.85 (SCH_2CH_2), 60.01 (HOCH_2), 122.15 (NCS), 124.68 (ArC-4), 126.56 (ArC-3), 136.47 (ArC-2,5), 155.42 (ArC-1); MS: m/z (%), 226 (M^+ , 2), 194 (10), 168 (11), 136 (23), 104 (100).

4.7.1 Preparation of dibenzyl disulphide

Benzyl bromide (12.0 cm^3 , 0.1 mol), sodium thiosulphate pentahydrate (24.82 g, 0.1 mol) in water (25 cm^3) and ethanol (20 cm^3) were mixed and heated under reflux for 23 h while maintaining the bath temperature at 98-100 $^{\circ}\text{C}$. Iodine (12.69 g, 0.1 mol) was added to the hot mixture, followed by

the addition of sodium bisulphite to remove excess of iodine and the crude product which separated was removed. The aqueous layer was extracted twice with ether (2 x 25 cm³) and the ether extracts were combined with the crude product. The total was extracted three times with water (3 x 50 cm³), the ethereal layer was separated and dried over anhydrous magnesium sulphate, and the ether was removed under reduced pressure to give a solid which was recrystallized from methanol to give dibenzyl disulphide (11.52 g, 62%) as a white crystalline solid; (Found: C, 67.89; H, 5.83; S, 25.80. Calc. for C₁₄H₁₄S₂: C, 68.26; H, 5.74; S, 25.99%); m.p. 71-72 °C (lit.¹⁷³ m.p. 71 °C); δ_{H} (CDCl₃) 3.56 (Ar-CH₂, s, 4H), 7.28 (Ar-H, m, 10H); δ_{C} (CDCl₃) 43.18 (ArCH₂), 127.38 (ArC-1), 128.43 (ArC-3,5), 129.38 (ArC-2,6), 137.31 (ArC-4); MS: m/z (%), 246 (M⁺, 60), 214 (2), 155 (19), 123 (13), 91 (100).

4.7.2 Preparation of acetyl benzyl disulphide

Benzylthioisothiuronium chloride (2.11 g, 0.008 mol) in water (32 cm³) was added dropwise to an ice-cold solution of thioacetic acid (0.71 cm³, 0.008 mol) in aqueous potassium carbonate (30 cm³, 4%) with vigorous stirring. Stirring was continued for an additional 20 minutes after which a white solid separated, which was collected, washed with several portions of water and left to dry overnight. Recrystallization of this solid from petroleum ether, b.p.

40-60 °C, gave acetyl benzyl disulphide (1.43 g, 90%) as a white crystalline solid; (Found: C, 54.51; H, 5.04; S, 32.50. Calc. for C₉H₁₀OS₂: C, 54.52; H, 5.09; S, 32.32%); m.p. 56-57 °C (lit.¹⁴⁴ m.p. 55-57 °C); δ_H (CDCl₃) 2.31 (CH₃, s, 3H), 3.91 (Ar-CH₂, s, 2H), 7.29 (Ar-H, m, 5H); δ_C (CDCl₃) 28.70 (CH₃), 42.97 (ArCH₂), 127.85 (ArC-1), 128.64 (ArC-3,5), 129.50 (ArC-2,6), 136.14 (ArC-4), 195.08 (C=O); MS: m/z (%), M (198, 50), 156 (12), 123 (43), 91(80), 43 (100).

4.8.1 Preparation of 2-chlorobenzyl phthalimido disulphide

A mixture of *N,N'*-thiobisphthalimide (11.49 g, 0.035 mol) and 2-chlorobenzyl mercaptan (4.6 cm³, 0.035 mol) was refluxed in toluene (150 cm³) for 4 h. On cooling to room temperature, phthalimide separated out as a solid and was filtered off. The filtrate was evaporated under reduced pressure to give a solid product which was filtered and allowed to dry in air overnight. Twice recrystallization of this material from ethanol afforded 2-chlorobenzyl phthalimido disulphide (10.55 g, 90%) as a needle-like white crystalline solid; (Found: C, 53.71; H, 2.96; N, 4.18; S, 19.10. C₁₅H₁₀ClNO₂S₂ requires: C, 53.65; H, 3.01; N, 4.17; S, 19.08%); m.p. 148-149 °C; δ_H (CDCl₃) 4.32 (Ar-CH₂, s, 2H), 7.23 (Ar-H, m, 4H), 7.84 (Ar-H, m, 4H); δ_C 43.13 (Ar-CH₂S), 124.07 (ArC-1), 126.82 (ArC-3), 129.70, (ArC-2),

126.7 (ArC-5), 129.6 (ArC-6), 131.9 (ArC-4), 132.21 (ArC-3',4'), 134.09 (ArC-2',5'), 134.83 (ArC-1',6'), 167.82 (C=O); MS: m/z (%), 335 (M⁺, 1), 270 (19), 210 (18), 178 (16), 157 (8) 147 (37), 125 (92), 76 (21).

Similar procedures were used to prepare the following compounds.

4.8.2 4-Methylbenzyl phthalimido disulphide

N,N'-Thiobisphthalimide (12.98 g, 0.04 mol) and 4-methylbenzyl mercaptan (5.53 g, 0.04 mol) gave 4-methylbenzyl phthalimido disulphide (11.22 g, 89%) as needle-like white crystals; m.p. 131-132 °C; (Found: C, 60.89; H, 4.25; N, 8.67; S, 20.21. $C_{16}H_{13}NO_2S_2$ requires: C, 60.94; H, 4.16; N, 8.89; S, 20.33; δ_H (CDCl₃) 2.30 (CH₃, s, 3H), 4.30 (ArCH₂S, s, 2H), 7.25 (Ar-H, m, 4H), 7.85 (Ar-H, m, 4H); δ_C 21.17 (CH₃), 45.21 (Ar-CH₂S), 124.03 (ArC-3,5), 129.32 (ArC-2,6), 129.35 (ArC-1), 132.25 (ArC-4), 133.35 (ArC-3',4'), 134.77 (ArC-2',5'), 137.43 (ArC-1',6'), 169.06 (C=O); MS: m/z (%), 315 (M⁺, 13), 250 (12), 194 (4), 178 (2) (14), 147 (21), 137 (21), 105 (100), 76 (23).

4.8.3 4-Chlorobenzyl phthalimido disulphide

N,N'-Thiobisphthalimide (16.24 g, 0.05 mol) and 4-chlorobenzyl mercaptan (6.6 cm³, 0.05 mol) gave 4-chlorobenzyl phthalimido disulphide (15.95 g, 95%); as needle-like white crystals; (Found: C, 53.69; H, 2.99; N, 4.17; S, 19.20.

$C_{15}H_{10}NClO_2S_2$ requires: C, 53.65; H, 3.01; N, 4.17; S, 19.08%; m.p. 153-154 °C; δ_H ($CDCl_3$) 4.38 (Ar- CH_2S , s, 2H), 7.25 (Ar-H, m, 4H), 7.85 (Ar-H, m, 4H); δ_C ($CDCl_3$) 43.48 (Ar- CH_2S), 124.21 (ArC-1), 126.79 (ArC-3,5), 129.67 (ArC-2,6), 131.26 (ArC-4), 132.18 (ArC-3',4'), 134.48 (ArC-2',5'), 135.08 (ArC-1',6'), 169.57 (C=O); MS: m/z (%), 335 (M^+ , 2), 270 (16), 210 (20), 178 (18), 157 (12), 147 (36), 125 (94), 76 (18).

4.8.4 Benzyl phthalimido disulphide

N,N'-Thiobisphthalimide (4.06 g, 0.0126 mol) and benzyl mercaptan (1.45 cm³, 0.0125 mol) gave benzyl phthalimido disulphide (3.25, 86%) as needle-like white crystals; (Found: C, 59.73; H, 3.66; N, 4.80; S, 21.23. Calc. for $C_{15}H_{11}NO_2S_2$: C, 59.75; H, 3.68; N, 4.65; S, 21.27%); m.p. 135-137 °C (lit.¹⁵⁹ m.p. 134-136 °C); δ_H ($CDCl_3$) 4.30 (Ar CH_2S , s, 2H), 7.25 (Ar-H, m, 5H), 7.85 (Ar-H, m, 4H); δ_C ($CDCl_3$) 42.56 (Ar- CH_2S), 125.11 (ArC-1), 127.32 (ArC-3,5), 130.02 (ArC-2,6), 131.78 (ArC-4), 133.25 (ArC-3',4'), 134.65 (ArC-2',5'), 135.33 (ArC-1',6'), 169.47 (C=O); MS: m/z (%), 301 (M^+ , 24), 236 (46), 210 (22), 178 (22), 147 (38), 123 (43), 104 (55), 76 (15), 91 (100).

4.8.5 2-Methylbenzyl phthalimido disulphide

N,N'-Thiobisphthalimide (12.98 g, 0.04 mol) and 2-methylbenzyl mercaptan (5.53 g, 0.04 mol) gave 2-methylbenzyl phthalimido disulphide (10.89 g, 85%) as needle-like white

crystals; (Found: C, 60.76; H, 4.21; N, 8.89; S, 20.21. $C_{16}H_{13}NO_2S_2$ requires: C, 60.94; H, 4.16; N, 8.89; S, 20.33%); m.p. 147-148 °C; δ_H (CDCl₃) 2.33 (CH₃, s, 3H), 4.37 (ArCH₂S, s, 2H), 7.25 (Ar-H, m, 4H), 7.85 (Ar-H, m, 4H); δ_C (CDCl₃) 20.98 (CH₃), 45.67 (ArCH₂S), 124.47 (ArC-1), 129.12 (ArC-3), 128.90 (ArC-5), 129.46 (ArC-6), 130.11 (ArC-2), 132.36 (ArC-1), 133.37 (ArC-3',4'), 134.68 (ArC-2',5'), 138.01 (ArC-1',6'), 167.98 (C=O); MS: m/z (%), 315 (M⁺, 10), 250 (13), 194 (25), 178 (12), 147 (21), 137 (26), 105 (100), 76 (16).

4.8.6 4-Methoxybenzyl phthalimido disulphide

N,N'-Thiobisphthalimide (16.24 g, 0.5 mol) and 4-methoxybenzyl mercaptan (7.7 g, 0.05 mol) gave 4-methoxybenzyl phthalimido disulphide (14.08 g, 85%) as a crystalline white solid; (Found: C, 58.06; H, 3.97; N, 4.26; S, 19.40. $C_{16}H_{13}NO_3S_2$ requires: C, 58.00; H, 3.96; N, 4.23; S, 19.36%); m.p. 148-149 °C; δ_H (CDCl₃) 3.78 (CH₃O, s, 3H), 4.30 (Ar-CH₂, s, 2H), 6.85 (Ar-H, m, 2H), 7.35 (Ar-H, m, 2H), 7.85 (Ar-H, m, 4H); δ_C (CDCl₃) 25.78 (CH₃O), 45.29 (ArCH₂S), 125.75 (ArC-3,5), 130.32 (ArC-2,6), 113.72 (ArC-1), 158.34 (ArC-4), 134.37 (ArC-3',4'), 135.03 (ArC-2',5'), 138.58 (ArC-1',6'), 167.64 (C=O); MS: m/z (%), 331 (M⁺, 12), 266 (14), 210 (24), 178 (13), 153 (27), 147 (16), 121 (100), 76 (28).

4.8.7 2-Hydroxyethyl phthalimido disulphide

N,N'-Thiobisphthalimide (12.18 g, 0.0375 mol) and mercaptoethanol (2.64 cm³, 0.0375 mol) gave 2-hydroxyethyl phthalimido disulphide (7.18 g, 76%) as a crystalline white solid; (Found: C, 47.05; H, 3.51; N, 5.72; S, 25.10. C₁₀H₉NO₃S₂ requires: C, 47.06; H, 3.56; N, 5.49; S, 25.13%); m.p. 214-216 °C; δ_H (CDCl₃) 2.59 (OH, s, 1H), 2.89 (HOCH₂CH₂S, t, 2H, ³J_{HCCH} = 5 Hz), 3.79 (HOCH₂CH₂S, t, 2H, ³J_{HCCH} = 5 Hz), 7.28 (Ar-H, m, 4H); δ_C (CDCl₃) 41.37 (SCH₂CH₂), 42.86 (ArCH₂S), 60.14 (HOCH₂) 133.76 (ArC-3,4), 134.96 (ArC-2,5), 138.16 (ArC-1,6); MS: m/z (%), 255 (M⁺, 23), 211 (14), 179 (41), 147 (76), 130 (61), 104 (89), 76 (100).

4.8.8 Trichloromethyl phthalimido disulphide

A mixture of potassium phthalimide (2.70 g, 0.0146 mol) in water (29 cm³) and ice (29 g) was stirred vigorously while trichloromethylthiosulphenyl chloride (3.36 g, 0.0154 mol) in hexane (30 cm³) was being added over a 15 minute period. The separated solid was filtered, washed with several portions of water, and air-dried to give trichloromethyl phthalimido disulphide (3.05 g, 66%) as a white solid; (Found: C, 32.95; H, 1.27; N, 4.22, S, 19.40. Calc. for C₉H₄Cl₃NO₂S₂: C, 32.89; H, 1.23; N, 4.26; S, 19.48; m.p. 129-130 °C (lit.¹⁶⁵ m.p. 130-132°C); δ_H (CDCl₃) 7.31 (Ar-H, m, 4H); δ_C (CDCl₃) 132.32 (ArC-3,4), 134.03 (ArC-2,5), 136.87 (ArC-1,6); MS: m/z (%), 316 (M⁺, 48), 284 (11), 252 (19) 146 (26), 106 (27).

4.9 Preparation of Symmetrical Trisulphides

4.9.1 Di-(4-methoxybenzyl) trisulphide

A solution of dimethylamine (6.77 g, 0.060 mol) was added to a stirred solution of S-(4-methoxybenzylthio)isothiuronium chloride (7.92 g, 0.030 mol) in methanol (37.5 cm³). After 35 minutes of the addition, a white solid separated out and the stirring was continued for an additional 2 h. The solid that formed was filtered off, washed with several portions of methanol and recrystallized twice from ethanol to give di-(4-methoxybenzyl) trisulphide (7.50 g, 74%) as needle-like white crystals; (Found: C, 56.80; H, 5.33; S, 29.20. Calc. for C₁₆H₁₈O₂S₃: C, 56.77; H, 5.37; S, 28.40%); m.p. 172-173 °C (lit.¹⁴⁴ m.p. 171-173 °C); δ_{H} (CDCl₃) 2.38 (CH₃O, s, 6H), 4.06 (ArCH₂S, s, 4H), 7.20 (Ar-H, m, 8H); δ_{C} (CDCl₃) 42.61 (ArCH₂S), 55.24 (CH₃O), 113.51 (ArC-1), 128.43 (ArC-3,5), 130.58 (ArC-2,6), 159.06 (ArC-4); MS: m/z (%), 338 (M⁺, 11), 306 (1), 273 (29), 153 (58), 138 (4), 121 (41), 109 (8).

Similar procedures were used to prepare the following compounds.

4.9.2 Di-(2-chlorobenzyl) trisulphide

Dimethylamine (6.77 g, 0.060 mol) and S-(2-chlorobenzylthio)isothiuronium chloride (8.08 g, 0.030 mol) gave di-(2-chlorobenzyl) trisulphide (7.65 g, 74%) as needle-like

white crystals; (Found: C, 48.26; H, 3.39; S, 27.50. Calc. for $C_{14}H_{12}Cl_2S_3$: C, 48.41; H, 3.49; S, 27.68%); m.p. 75-76 °C (lit.¹⁴⁴ m.p. 75 °C); δ_H (CDCl₃) 4.14 (ArCH₂S, s, 4H), 7.35 (Ar-H, m, 8H); δ_C 40.48 (ArCH₂S), 126.75 (ArC-1), 129.05 (ArC-3), 129.78 (ArC-5), 131.70 (ArC-2), 134.25 (ArC-6), 134.28 (ArC-4); MS: m/z (%), 347 (M⁺, 9), 314 (1), 281 (12), 157 (7), 125 (100).

4.9.3 Di-(4-methylbenzyl) trisulphide

Dimethylamine (6.77 g, 0.060 mol) and S-(4-methylbenzylthio) isothiuronium chloride (7.46 g, 0.030 mol) gave di-(4-methylbenzyl) trisulphide (4.35 g, 72%) as needle-like white crystals; (Found: C, 61.90; H, 6.17; S, 31.16. Calc. for $C_{16}H_{18}S_3$: C, 62.10; H, 5.93; S, 31.38%); m.p. 54-55 °C (lit.¹⁴⁴ m.p. 55-57 °C); δ_H (CDCl₃) 2.32 (CH₃, s, 6H), 4.01 (ArCH₂S, s, 4H), 7.27 (Ar-H, m, 8H); δ_C (CDCl₃) 21.17 (CH₃), 42.89 (ArCH₂S), 129.32 (ArC-1), 128.83 (ArC-3,5), 133.37 (ArC-2,6), 137.32 (ArC-4); MS: m/z (%), 306 (M⁺, 2), 274 (1), 241 (12), 137 (5), 105 (100).

4.9.4 Di-(4-chlorobenzyl) trisulphide

Dimethylamine (6.77 g, 0.060 mol) and S-(4-chlorobenzylthio) isothiuronium chloride (8.08 g, 0.030 mol) gave di-(4-chlorobenzyl) trisulphide (7.79 g, 75%) as a white flaky solid; (Found: C, 48.51; H, 3.51; S, 27.55. Calc. for $C_{14}H_{12}Cl_2S_3$: C, 48.41; H, 3.49; S, 27.68%); m.p. 81-82 °C (lit.¹⁴⁴ m.p. 82-83 °C); δ_H (CDCl₃) 3.97 (ArCH₂S, s, 4H),

7.27 (Ar-H, m, 8H); δ_c (CDCl₃) 42.25 (ArCH₂S), 128.76 (ArC-1), 130.73 (ArC-3,5), 133.49 (ArC-2,6), 134.96 (ArC-4); MS: m/z (%), 347 (M⁺, 4), 314 (1), 281 (13), 157 (11), 125 (100).

4.9.5 Di-(2-methylbenzyl) trisulphide

Dimethylamine (6.77 g, 0.030 mol) and S-(2-methylbenzylthio) isothiuronium chloride (3.98 g, 0.015 mol) gave di-(2-methylbenzyl) trisulphide (2.42 g, 76%) as a flaky white solid; (Found: C, 61.96; H, 5.74; S, 31.30. Calc for C₁₆H₁₈S₃: C, 62.69; H, 5.93; S, 31.38%); m.p. 48-49 °C (lit.¹⁴⁴ m.p. 47-49 °C); δ_H (CDCl₃) 3.78 (CH₃, s, 6H), 4.00 (ArCH₂S, s, 4H), 7.23 (Ar-H, m, 8H); δ_c 19.33 (CH₃), 41.16 (ArCH₂S), 126.05 (ArC-1), 127.97 (ArC-3), 134.02 (ArC-5), 130.62 (ArC-2), 136.96 (ArC-6), 137.52 (ArC-4); MS: m/z (%), 306 (M⁺, 17); 274 (1), 241 (43), 137 (17), 105 (100).

4.9.6 Dibenzyl trisulphide

Dimethylamine (4.51 g, 0.040 mol) and benzylthioisothiuronium chloride (5.00 g, 0.020 mol) gave dibenzyl trisulphide (3.34 g, 61%) as needle-like white crystals; (Found: C, 60.58; H, 5.14; S, 34.28. Calc. for C₁₄H₁₄S₃: C, 60.41; H, 5.08; S, 34.53%); m.p. 50-51 °C (lit.¹⁴⁴ m.p. 48.5-49.5 °C); δ_H (CDCl₃) 4.02 (ArCH₂S, s, 4H), 7.30 (Ar-H, m, 10H); δ_c (CDCl₃) 43.11 (ArCH₂S), 127.56 (ArC-1), 128.60 (ArC-3,5), 129.43 (ArC-2,6), 136.50 (ArC-4); MS: m/z (%), 278 (M⁺, 8), 277 ([M-1]⁺, 31), 246 (12), 213 (54), 181 (7), 155 (1), 123

(36), 91 (100).

4.9.7 Preparation of di-(2-hydroxyethyl) trisulphide¹⁷⁴

A solution of sodium trisulphide was prepared by dissolving sulphur (6.40 g, 0.20 mol) in a solution of sodium sulphide nonahydrate (24.02 g, 0.10 mol) in water (32.5 cm³). To the red solution was added ethylene chlorohydrin (13.4 cm³, 0.20 mol) over a 1 h period. Heat was evolved and the flask was cooled with ice-water. The crude product began to separate when about two thirds of the chlorohydrin had been added. The resultant mixture was stirred for an additional 4 h, and the oily crude product was obtained by the removal of water and unreacted chlorohydrin through rotary evaporation at reduced pressure. This material was then fractionally distilled and di-(2-hydroxyethyl) trisulphide was obtained as a yellow oil; (Found: C, 25.74; H, 5.42; S, 51.59. Calc. for C₄H₁₀O₂S₃: C, 25.80; H, 5.44; S, 51.57%); b.p. 80-85 °C at 1 mmHg; δ_{H} (CDCl₃) 1.51 (OH, t, 2H, $^3J_{\text{HOCH}} = 8$ Hz), 2.69 (CH₂SSSCH₂, dt, 4H, $^3J_{\text{HCCH}} = 6$ Hz), 3.74 (HOCH₂, t, 4H, $^3J_{\text{HCCH}} = 6$ Hz); MS: m/z (%), 186 (M⁺, 6), 90 (14), 58 (27), 45 (100).

4.10 Preparation of Unsymmetrical Trisulphides

4.10.1 4-Methoxybenzyl 2-hydroxyethyl trisulphide^{115,121}

A mixture of 4-methoxybenzyl phthalimido disulphide (6.63 g, 0.02 mol) and 2-mercaptoethanol (1.4 cm³, 0.02 mol) in toluene (200 cm³) was heated under reflux for 150 h. The reaction mixture was allowed to cool to room temperature and the solid which crystallized out was filtered off to give phthalimide (2.85 g, 82%), m.p. 234-235 °C. Toluene was removed by rotary evaporation of the filtrate and the crude product was chromatographed on silica gel and first eluted with petroleum ether which removed trace amount of di-(4-methoxybenzyl) trisulphide that was formed. The desired product was then eluted with dichloromethane as eluent. The eluted solution, on rotary evaporation followed by the total removal of solvent, gave 4-methoxybenzyl 2-hydroxyethyl trisulphide (3.77 g, 72%) as a light yellow oil; tlc (1:1 CH₂Cl₂/CCl₄ on silica) gave a single spot, R_f 0.48; (Found: C, 45.67; H, 5.36; S, 36.70. Calc. for C₁₀H₁₄O₂S₃: C, 45.77; H, 5.39; S, 36.55%); δ_H (CDCl₃) 2.41 (OH, s, 1H), 2.83 (SCH₂CH₂OH, t, 2H, ³J_{HCC} = 6 Hz), 3.57 (HOCH₂CH₂S, t, 2H, ³J_{HCC} = 6 Hz) 4.01 (ArCH₂, s, 2H), 4.82 (CH₃O, s, 3H), 7.29 (Ar-H, m, 4H); δ_C (CDCl₃) 41.32 (SCH₂CH₂), 42.32 (ArCH₂S), 60.04 (HOCH₂CH₂S), 64.54 127.20 (ArC-1), 127.63 (ArC-3,5), 130.03 (ArC-2,6), 138.14 (ArC-4); MS: m/z (%), 262 (M⁺, 6), 198 (3), 186 (7), 121 (29). Trace amount of 4-methoxybenzyl trisulphide (3%) was formed as

impurity δ_{H} (CDCl_3) 3.57 ($\text{ArCH}_2\text{SSSCH}_2\text{Ar}$, s, 0.4H); δ_{C} (CDCl_3) 43.13 ($\text{ArCH}_2\text{SSSCH}_2\text{Ar}$); MS: m/z (%), 338 (M^+ , 6).

Similar procedure was used to prepare the following compound.

4.10.2 Benzyl 2-hydroxyethyl trisulphide^{115,121}

Benzyl phthalimido disulphide (6.02 g, 0.02 mole) and 2-mercaptoethanol (1.4 cm^3 , 0.02 mol) gave benzyl 2-hydroxyethyl trisulphide (2.68 g, 24%) as a yellow oil; tlc (3:1 ether/DCM on silica) gave a single spot, R_f 0.61; (Found: C, 46.40; H, 5.28; S, 41.61. Calc. for $\text{C}_9\text{H}_{12}\text{OS}_3$: C, 46.51; H, 5.21; S, 41.39%); δ_{H} (CDCl_3) 2.15 (OH, s, 1H), 2.96 ($\text{SCH}_2\text{CH}_2\text{OH}$, t, 2H, $^3J_{\text{HCCH}} = 6$ Hz), 3.91 ($\text{HOCH}_2\text{CH}_2\text{S}$, t, 2H, $^3J_{\text{HCCH}} = 6$ Hz), 4.02 (ArCH_2S , s, 2H), 7.38 (Ar-H, m, 10H); δ_{C} (CDCl_3) 41.40 (SCH_2CH_2), 43.01 59.57 (HOCH_2S), 127.51 (ArC-1), 128.63 (ArC-3,5), 129.38 (ArC-2,6), 136.45 (ArC-4); MS: m/z (%), 232 (M^+ , 10), 200, (23), 153 (4), 121 (100). Trace amount of dibenzyl trisulphide (4%) was formed as impurity, δ_{H} (CDCl_3) 4.07 ($\text{ArCH}_2\text{SSSCH}_2\text{Ar}$, s, 0.3H), δ_{C} (CDCl_3) 43.01 ($\text{ArCH}_2\text{SSSCH}_2\text{Ar}$); MS: m/z (%), 246 (M^+ , 10).

4.11 Preparation of Unsymmetrical Trisulphides

4.11.1 Preparation of 4-methylbenzyl 2-hydroxyethyl trisulphide

Twice distilled sulphur dichloride (3.19 g, 0.031 mol) in absolute ether (20 cm³) was added to a mixture of 2-hydroxyethyl mercaptan (2.65 g, 0.031 mol) and 4-methylbenzyl mercaptan (4.70 g, 0.034 mol) and the reaction mixture was maintained between 0-4 °C with an ice/salt bath. After the addition of sulphur dichloride, the reaction mixture was allowed to reach room temperature and the stirring was continued for an additional 24 h. The mixture was diluted with dichloromethane (500 cm³), a 10-fold dilution, and extracted with 3 portions of water (3 x 100 cm³). The organic layer was removed and dried with anhydrous magnesium sulphate, and the solvent was then removed by rotary evaporation to give a light yellow clear oil. This liquid was chromatographed on a silica gel column with light petroleum ether (b.p. 40-60 °C) as the first eluting solvent. This solvent was able to remove the symmetrical trisulphide di-(4-methylbenzyl) trisulphide, which is the major impurity. The column was then eluted with petroleum ether/dichloromethane (4:1) until no spot due to the symmetrical compound was observed in the tlc. Finally the desired compound was eluted with dichloromethane, followed by the removal of solvent by rotary evaporation. Total removal of solvent was carried out under reduced pressure by collecting the material in a flask fitted for shaking. This

gave 4-methylbenzyl 2-hydroxyethyl trisulphide (2.3 g, 38%) as a clear light yellow oil; tlc (2:1 ether/DCM on silica) gave a single spot with R_f 0.62; (Found: C, 48.83; H, 5.78; S, 39.00. $C_{10}H_{14}OS_3$ requires: C, 48.73; H, 5.74; S, 39.03%); δ_H ($CDCl_3$) 2.31 (CH_3 , s, 3H), 2.64 (OH, s, 1H), 2.93 (SCH_2CH_2OH , t, 2H, $^3J_{HCCH} = 6$ Hz), 3.86 ($HOCH_2CH_2S$, t, 2H, $^3J_{HCCH} = 6$ Hz), 4.04 ($ArCH_2$, s, 2H), 7.17 (Ar-H, m, 4H); δ_C ($CDCl_3$) 21.12 (CH_3), 41.29 (SCH_2CH_2), 42.86 ($Ar-CH_2S$), 59.68 ($HOCH_2$), 127.03 (ArC-1), 129.27 (ArC-2,6), 133.13 (ArC-3,5), 137.34 (ArC-4); MS: m/z(%) 246 (M^+ , 2), 214 (2), 181 (7), 137 (10), 105 (100), 45 (65).

Similar procedures were used in the preparation of the following compounds.

4.11.2 2-Chlorobenzyl 2-hydroxyethyl trisulphide

2-Chlorobenzyl mercaptan (5.19 cm^3 , 0.040 mol), sulphur dichloride (2.81 cm^3 , 0.037 mol), and 2-mercaptoethanol (2.80 cm^3 , 0.040 mol) gave 2-chlorobenzyl 2-hydroxyethyl trisulphide (3.62 g, 36.7%) as a clear light yellow oil; tlc (2:1 ether/DCM on silica) gave a single spot, R_f 0.59; (Found: C, 40.40; H, 4.20; S, 36.20. $C_9H_{11}ClOS_3$ requires: C, 40.51; H, 4.16; S, 36.02%); δ_H ($CDCl_3$) 2.41 (OH, s, 1H), 2.97 (SCH_2CH_2OH , t, 2H, $^3J_{HCCH} = 6$ Hz), 3.91 ($HOCH_2CH_2S$, t, 2H, $^3J_{HCCH} = 6$ Hz), 4.19 ($Ar-CH_2$, s, 2H), 7.23-7.33 (Ar-H, m, 2H), 7.33 (Ar-H, m, 2H); δ_C ($CDCl_3$) 40.58 (SCH_2CH_2), 41.46 ($Ar-CH_2$), 59.56 ($HOCH_2$), 125.89 (ArC-1), 126.68 (ArC-3), 127.1 (ArC-5), 129.80 (ArC-6), 131.70 (ArC-2),

133.96 (ArC-4); MS: m/z(%) 266 (M⁺, 2), 234 (2), 201 (1), 157 (3), 125 (17), 45 (59).

4.11.3 Benzyl 2-hydroxyethyl trisulphide^{115,121}

Benzyl mercaptan (5.87 cm³, 0.050 mol), sulphur dichloride (3.49 cm³, 0.046 mol) and mercaptoethanol (3.51 cm³, 0.050 mol) gave benzyl 2-hydroxyethyl trisulphide (2.87 g, 26.9%) as a light yellow clear oil; tlc (2:1 ether/DCM on silica) gave a single spot, R_f 0.68; (Found: C, 46.33; H, 5.24; S, 41.50. Calc. for C₉H₁₂OS₃: C, 46.51; H, 5.21; S, 41.51%); δ_H (CDCl₃) 2.57 (OH, s, 1H), 2.92 (SCH₂CH₂OH, t, 2H, ³J_{HCCH} = 6 Hz), 3.85 (HOCH₂CH₂S, t, 2H, ³J_{HCCH} = 6 Hz), 4.07 (Ar-CH₂, s, 2H), 7.03 (Ar-H, m, 5H); δ_C (CDCl₃) 41.28 (SCH₂CH₂), 42.97 (Ar-CH₂S), 59.61 (HOCH₂), 127.62 (ArC-1), 128.61 (ArC-3,5), 129.40 (ArC-2,6), 136.24 (ArC-4); MS: m/z (%), 232 (M⁺, 3), 200 (4), 167 (14), 124 (23), 91 (100), 45 (68).

4.11.4 2-Methylbenzyl 2-hydroxyethyl trisulphide

2-Methylbenzyl mercaptan (5.81 cm³, 0.043m mol), sulphur dichloride (3.04 cm³, 0.040 mol) and 2-mercaptoethanol (3.01 cm³, 0.043 mol) gave 2-methylbenzyl 2-hydroxyethyl trisulphide (3.25 g, 37%) as a light yellow clear oil; tlc (2:1 ether/DCM on silica) gave a single spot, R_f 0.52; (Found: C, 48.76; H, 5.72; S, 38.80. C₁₀H₁₄OS₃ requires: C, 48.73; H, 5.74; S, 39.03%); δ_H (CDCl₃) 2.38 (CH₃, s, 3H), 2.41 (OH, s, 1H), 2.94 (SCH₂CH₂OH, t, 2H, ³J_{HCCH} = 6 Hz), 3.87 (HOCH₂CH₂S, t, 2H, ³J_{HCCH} = 6 Hz), 4.11 (Ar-CH₂, s, 2H), 7.16 (Ar-H, m, 4H); δ_C (CDCl₃) 22.25 (CH₃), 41.38 (SCH₂CH₂),

42.98 (Ar-CH₂), 60.01 (HOCH₂), 127.16 (ArC-1), 128.54 (ArC-2), 129.38 (ArC-6), 133.24 (ArC-3), 133.8 (ArC-5), 137.39 (ArC-4); MS: m/z (%), 246 (M⁺, 2), 214 (3), 181 (3), 137 (3); 105 (100), 45 (58).

4.11.5 4-Chlorobenzyl 2-hydroxyethyl trisulphide

4-Chlorobenzyl mercaptan (6.33 cm³, 0.048 mol), sulphur dichloride (3.34 cm³, 0.044 mol) and 2-mercaptoethanol (3.36 cm³, 0.048 mol) gave 4-chlorobenzyl 2-hydroxyethyl trisulphide (3.25 g, 33%) as a light yellow clear oil; tlc (2:1 ether/DCM on silica) gave a single spot, R_f 0.65; (Found: C, 40.27; H, 4.29; S, 36.36. C₉H₁₁ClOS₃ requires: C, 40.51; H, 4.16; S, 36.02%); δ_H (CDCl₃) 2.40 (OH, s, 1H); 2.97 (SCH₂CH₂OH, t, 2H, ³J_{HCCH} = 6 Hz), 3.89 (HOCH₂CH₂S, t, 2H, ³J_{HCCH} = 6 Hz), 4.04 (Ar-CH₂, s, 2H), 7.28 (Ar-H, m, 4H); δ_C (CDCl₃) 40.31 (SCH₂CH₂), 41.39 (Ar-CH₂S), 59.52 (HOCH₂), 126.59 (ArC-1), 129.78 (ArC-3,5), 131.65 (ArC-2,6), 133.84 (ArC-4); MS: m/z (%) 266 (M⁺, 2), 234 (1), 201 (2), 157 (1), 125 (23), 45 (62).

4.11.6 4-Methoxybenzyl 2-hydroxyethyl trisulphide^{115,121}

4-Methoxybenzyl mercaptan (6.69 cm³, 0.048 mol), sulphur dichloride (3.34 cm³, 0.044 mol) and 2-mercaptoethanol (3.37 cm³, 0.048 mol) gave 4-methoxybenzyl 2-hydroxyethyl trisulphide (4.02 g, 35%) as a light yellow clear oil; tlc (2:1 ether/DCM on silica) gave a single spot, R_f 0.57; (Found: C, 45.82; H, 5.36; S, 36.80. Calc. for C₁₀H₁₄O₂S₃: C, 45.76; H, 5.39; S, 36.65%); δ_H (CDCl₃) 2.40 (OH, s, 1H),

2.88 ($\text{SCH}_2\text{CH}_2\text{OH}$, t, 2H, $^3J_{\text{HCCH}} = 6$ Hz), 3.92 ($\text{HOCH}_2\text{CH}_2\text{S}$, t, 2H, $^3J_{\text{HCCH}} = 6$ Hz), 3.87 (CH_3O , s, 3H), 4.01 (Ar- CH_2 , s, 2H) 7.35 (Ar-H, m, 4H); δ_c (CDCl_3) 41.32 (SCH_2CH_2), 42.96 (Ar- CH_2), 55.11 (CH_3O), 59.16 (HOCH_2), 114.19 (ArC-1), 129.54 (ArC-3,5), 132.78 (ArC-2,6), 158.89 (ArC-4); MS: m/z (%), 262 (M^+ , 2), 197 (4), 186 (3), 153 (2), 121 (29), 45 (53).

4.11.7 2-Furfuryl 2-hydroxyethyl trisulphide^{115,121}

2-Furfuryl mercaptan (4.64 cm³, 0.046 mol), sulphur dichloride (3.26 cm³, 0.043 mol) and 2-mercaptoethanol (3.28 cm³, 0.046 mol) gave 2-furfuryl 2-hydroxyethyl trisulphide (3.22 g, 34%) as a yellow oil (which turned dark on exposure to light after about 24 h); tlc (3:1 ether/DCM on silica) gave a single spot, R_f 0.46; (Found: C, 38.17; H, 4.78; S, 43.40. Calc. for $\text{C}_7\text{H}_{10}\text{O}_2\text{S}_3$: C, 37.81; H, 4.54; S, 43.26%); δ_H (CDCl_3) 2.52 (OH, s, 1H), 2.98 ($\text{SCH}_2\text{CH}_2\text{OH}$, t, 2H, $^3J_{\text{HCCH}} = 7$ Hz), 3.90 ($\text{HOCH}_2\text{CH}_2\text{S}$, t, 2H, $^3J_{\text{HCCH}} = 7$ Hz), 4.09 (Ar- CH_2 , s, 2H), 6.33 (Ar-H, m, 2H), 7.40 (Ar-H, m, 1H); δ_c CDCl_3 35.32 (SCH_2CH_2), 41.69 (Ar- CH_2), 59.62 (HOCH_2), 109.50 (furylC-3), 110.66 (furylC-4), 142.73 (furylC-5), 149.20 (furylC-2); MS: m/z (%), 222 (M^+ , 2); 186 (1), 157 (1), 118 (1), 81 (100), 45 (49).

4.12 Preparation of Unsymmetrical Tetrasulphides

4.12.1 Preparation of 2-methylbenzyl 2-hydroxyethyl tetrasulphide

Twice distilled sulphur monochloride (2.48 cm³, 0.031 mol) in absolute ether was added to a stirred mixture of 2-methylbenzyl mercaptan (4.59 cm³, 0.034 mol) and 2-mercaptoethanol (2.38 cm³, 0.034 mol) in ether (25 cm³), and the reaction mixture was maintained between 0-4 °C with an ice salt bath. After the addition of sulphur monochloride, the mixture was allowed to reach room temperature and the stirring was continued for an additional 4 h. The mixture was diluted with dichloromethane (500 cm³), a 10-fold dilution, and extracted with 3 portions of water (100 cm³). The organic layer was removed and dried with anhydrous magnesium sulphate, followed by the removal of solvent by rotary evaporation to give a deep yellow clear oil. The oil was chromatographed on a silica gel column with light petroleum ether, b.p. 40-60 °C, as the first eluting solvent. This solvent was able to remove the symmetrical tetrasulphide, bis(2-methylbenzyl) tetrasulphide, which is the major impurity. The column was then eluted with petroleum ether/dichloromethane (4:1) until no spot due to residual symmetrical tetrasulphide was observed in the tlc. Finally, the desired compound was eluted with dichloromethane, followed by the removal of solvent by rotary evaporation. Total removal of solvent was achieved under reduced pressure by collecting the compound in a flask

fitted for shaking to give 2-methylbenzyl 2-hydroxyethyl tetrasulphide (5.58 g, 53%) as a deep yellow clear oil; tlc (2:1 ether/DCM on silica) gave a single spot, R_f 0.59; (Found: C, 43.20; H, 5.14; S, 45.80. $C_{10}H_{14}OS_4$ requires: C, 43.17; H, 5.07; S, 46.00%); δ_H ($CDCl_3$) 2.21 (OH, s, 1H), 2.40 (CH_3 , s, 3H), 3.06 (SCH_2CH_2OH , t, 2H, $^3J_{HCCH} = 6$ Hz), 3.91 ($HOCH_2CH_2S$, t, 2H, $^3J_{HCCH} = 6$), 4.18 (Ar- CH_2 , s, 2H), 7.18 (Ar-H, m, 4H); δ_C ($CDCl_3$) 19.53 (CH_3), 41.76 (SCH_2CH_2), 42.83 (Ar- CH_2), 60.04 ($HOCH_2$), 126.14 (ArC-1), 128.31 (ArC-3), 127.9 (ArC-5), 130.85 (ArC-2), 130.2 (ArC-6), 137.06 (ArC-4); MS: m/z (%) 278 (M^+ , 2), 214 (9), 186 (2), 137 (4), 105 (100), 45 (60).

Similar procedures were used in the preparation of the following compounds.

4.12.2 Benzyl 2-hydroxyethyl tetrasulphide^{115,121}

Benzyl mercaptan (6.33 cm³, 0.054 mol), sulphur monochloride (3.94 cm³, 0.049 mol) and 2-mercaptoethanol (3.78 cm³, 0.054 mol) gave benzyl 2-hydroxyethyl tetrasulphide (5.28 g, 37%) as a deep yellow oil; tlc (2:1 ether/DCM on silica) gave a single spot, R_f 0.64; (Found: C, 40.71; H, 4.54; S, 48.60. Calc. for $C_9H_{12}OS_4$: C, 40.74; H, 4.58; S, 48.56); δ_H ($CDCl_3$) 2.30 (OH, s, 1H), 3.05 (SCH_2CH_2OH , t, 2H, $^3J_{HCCH} = 6$ Hz), 3.90 ($HOCH_2CH_2S$, t, 2H, $^3J_{HCCH} = 6$ Hz); 4.15 (Ar- CH_2 , s, 2H); 7.32 (Ar-H, m, 5H); δ_C $CDCl_3$ 41.65 (SCH_2CH_2), 43.31 (Ar- CH_2S), 59.80 ($HOCH_2$), 127.67 (ArC-1), 128.67 (ArC-3,5), 129.43 (ArC-2,6), 135.99 (ArC-4); MS: m/z (%), 264 (M^+ , 2),

200 (11), 167 (3), 123 (5), 91 (100), 45 (53).

4.12.3 4-Methoxybenzyl 2-hydroxyethyl tetrasulphide

4-Methoxybenzyl mercaptan (4.73 cm³, 0.043 mol), sulphur monochloride (2.48 cm³, 0.031 mol) and 2-mercaptoethanol (2.38 cm³, 0.034 mol) gave 4-methoxybenzyl 2-hydroxyethyl tetrasulphide (4.49 g, 45%) as a deep yellow oil; tlc (2:1 ether/DCM on silica) gave a single spot, R_f 0.53; (Found: C, 40.83; H, 4.78; S, 43.30. C₁₀H₁₄O₂S₄ requires: C, 40.82; H, 4.80; S, 43.50%); δ_H (CDCl₃) 2.61 (OH, s, 1H); 3.05 (SCH₂CH₂OH, t, 2H, ³J_{HCC} = 6 Hz), 3.77 (CH₃O, s, 3H), 3.92 (HOCH₂CH₂S, t, 2H, ³J_{HCC} = 6 Hz); 4.12 (Ar-CH₂, s, 2H), 6.87 (Ar-H, m, 2H), 7.22 (Ar-H, m, 2H); δ_C (CDCl₃) 41.62 (SCH₂CH₂), 43.07 (Ar-CH₂S), 55.23 (CH₃O), 59.79 (HOCH₂), 114.50 (ArC-1), 130.63 (ArC-3,5), 131.3 (ArC-2,6), 159.06 (ArC-1); MS: m/z (%), 294 (M⁺, 2), 230 (8), 198 (5), 153 (5), 121 (100), 45 (62).

4.12.4 4-Chlorobenzyl 2-hydroxyethyl tetrasulphide

4-Chlorobenzyl mercaptan (5.72 cm³, 0.044 mol), sulphur monochloride (3.21 cm³, 0.040 mol) and 2-mercaptoethanol (3.08 cm³, 0.044 mol) gave 4-chlorobenzyl 2-hydroxyethyl tetrasulphide (5.24 g, 40%) as a deep yellow oil; tlc (2:1 ether/DCM on silica) gave a single spot, R_f 0.61; (Found: C, 36.23; H, 3.69; S, 42.79. C₉H₁₁ClOS₄ requires: C, 36.19; H, 3.71; S, 42.85%); δ_H (CDCl₃) 2.13 (OH, s, 1H), 3.07 (SCH₂CH₂OH, t, 2H, ³J_{HCC} = 6 Hz), 3.92 (HOCH₂CH₂S, t, 2H, ³J_{HCC} = 6 Hz), 4.11 (Ar-CH₂, s, 2H), 7.29 (Ar-H, m, 4H); δ_C

(CDCl₃) 41.71 (SCH₂CH₂), 43.39 (Ar-CH₂), 59.60 (HOCH₂), 126.47 (ArC-1), 128.51 (ArC-3,5), 130.76 (ArC-2,6), 134.63 (ArC-4); MS: m/z (%), 298 (M⁺, 3), 266 (8), 234 (3), 201 (5), 157 (4), 125 (100), 45 (59).

4.12.5 4-Methylbenzyl 2-hydroxyethyl tetrasulphide

4-Methylbenzyl mercaptan (5.13 cm³, 0.038 mol), sulphur monochloride (2.77 cm³, 0.035 mol) and 2-mercaptoethanol (2.66 cm³, 0.038 mol) gave 4-methylbenzyl 2-hydroxyethyl tetrasulphide (4.65 g, 44%) as a deep yellow oil; tlc (2:1 ether/DCM on silica) gave a single spot, R_f 0.61; (Found: C, 43.28; H, 4.98; S, 45.76. C₁₀H₁₄OS₄ requires: C, 43.17; H, 5.07; S, 46.00%); δ_H (CDCl₃) 2.33 (OH, s, 1H), 2.38 (CH₃, s, 3H), 3.05 (SCH₂CH₂OH, t, 2H, ³J_{HCC} = 6 Hz), 3.90 (HOCH₂CH₂S, t, 2H, ³J_{HCC} = 6 Hz), 4.12 (Ar-CH₂, s, 2H), 7.19 (Ar-H, m, 4H); δ_C (CDCl₃) 19.29 (CH₃), 41.70 (SCH₂CH₂), 42.79 (Ar-CH₂S), 59.99 (HOCH₂), 126.09 (ArC-1), 128.20 (ArC-3,5), 130.69 (ArC-2,6), 136.94 (ArC-4); MS: m/z (%), 278 (M⁺, 2); 214 (11); 186 (3); 137 (5); 105 (100), 45 (49).

4.12.6 2-Furfuryl 2-hydroxyethyl tetrasulphide

2-Furfuryl mercaptan (4.64 cm³, 0.046 mol), sulphur monochloride (3.36 cm³, 0.043 mol) and 2-mercaptoethanol (3.28 cm³, 0.046 mol) gave 2-furfuryl 2-hydroxyethyl tetrasulphide (3.68 g, 31%) as a deep yellow oil (which turned dark on exposure to light after 24 h); tlc (3:1 ether/DCM gave a single spot, R_f 0.42; (Found: C, 32.96; H, 3.86; S, 50.29. C₇H₁₀O₂S₄ requires: C, 33.08; H, 3.97; S, 50.36%); δ_H

(CDCl₃) 2.57 (OH, s, 1H), 2.99 (SCH₂CH₂OH, t, 2H, ³J_{HCCH} = 7 Hz), 3.92 (HOCH₂CH₂S, t, 2H, ³J_{HCCH} = 7 Hz), 4.11 (ArCH₂, s, 2H), 6.39 (Ar-H, m, 2H), 7.47 (Ar-H, m, 1H); δ_c (CDCl₃) 35.38 (SCH₂CH₂), 41.83 (ArCH₂), 60.01 (HOCH₂), 109.65 (furylC-3), 111.02 (furylC-4), 143.02 (furylC-5) 149.57 (furylC-2); MS: m/z (%), 254 (M⁺, 4), 222 (5), 190 (9), 158 (3), 113 (6), 81 (100), 45 (47).

4.13 Preparation of Unsymmetrical Disulphides

4.13.1 Preparation of 2-chlorobenzyl 2-hydroxyethyl disulphide

To a solution of 2-chlorobenzyl mercaptan (6.05 cm³, 0.046 mol) and 2-hydroxyethylthioisothiuronium chloride (9.40 g, 0.049 mol) in methanol (100 cm³) was added a solution of sodium hydrogen carbonate (6.00 g, 0.071 mol) in water (100 cm³) with vigorous stirring in an ice/salt bath. Stirring was continued for 2 h after which an oil separated out. This was extracted with dichloromethane and the organic layer was collected, washed three times with water (3 x 150 cm³) and dried with anhydrous magnesium sulphate. The oil was chromatographed on a silica gel column with light petroleum ether as the eluting solvent. This solvent was able to remove any trace of symmetrical trisulphide that was formed. The column was further eluted with petroleum

ether/dichlorometane (4:1) until no spot due to the symmetrical trisulphide was observed in the tlc. The desired product was finally eluted with dichloromethane, followed by the removal of solvent by rotary evaporation. Total removal of the solvent was achieved under reduced pressure by collecting the compound in a flask fitted for shaking to give 2-chlorobenzyl 2-hydroxyethyl disulphide as a clear light yellow oil; tlc (2:1 ether/DCM on silica) gave a single spot R_f 0.63; (Found: C, 46.43; H, 4.87; S, 28.00. $C_9H_{11}ClOS_2$ requires: C, 46.05; H, 4.73; S, 27.26%); δ_H ($CDCl_3$) 2.54 (SCH_2CH_2OH , t, 2H, $^3J_{HCCH} = 6$ Hz), 2.80 (OH, s, 1H), 3.71 ($HOCH_2CH_2S$, t, 2H, $^3J_{HCCH} = 6$ Hz), 3.99 ($ArCH_2$, s, 2H), 7.17 (Ar-H); δ_C ($CDCl_3$) 40.78 (SCH_2CH_2), 40.93 ($Ar-CH_2S$), 60.06 ($HOCH_2$), 126.70 (ArC-1), 129.71 (ArC-2), 133.91 (ArC-5), 131.41 (ArC-6), 134.03 (ArC-3), 134.73 (ArC-4); MS: m/z (%), 234 (M^+ , 5), 202 (1), 157 (3), 125 (100), 45 (53).

Similar procedures were used in the preparation of the following compounds.

4.13.2 4-Methoxybenzyl 2-hydroxyethyl disulphide

2-Hydroxyethylthioisothiuronium chloride (9.40 g, 0.0498 mol), 4-methoxybenzyl mercaptan (6.10 cm^3 , 0.0465 mol) and sodium hydrogen carbonate (6.40 g, 0.0714 mol) gave 4-methoxybenzyl 2-hydroxyethyl disulphide (6.2 g, 58%), as a white crystalline solid; tlc (2:1 ether/DCM on silica) gave a single spot, R_f 0.57; (Found: C, 52.13; H, 6.15; S, 27.42.

$C_{10}H_{14}O_2S_2$ requires: C, 52.16; H, 6.13; S, 27.83%); m.p. 89-91 °C; δ_H ($CDCl_3$) 2.47 (OH, s, 1H), 2.54 (SCH_2CH_2OH , t, 2H, $^3J_{HCC} = 6$ Hz), 3.74 ($HOCH_2CH_2S$, t, 2H, $^3J_{HCC} = 6$ Hz), 3.77 (CH_3O , s, 3H), 3.85 (Ar- CH_2 , s, 2H), 6.86-7.21 (Ar-H, m, 4H); δ_C ($CDCl_3$) 40.79 (SCH_2CH_2), 42.74 (Ar- CH_2S), 55.21 (CH_3O), 60.15 ($HOCH_2$), 113.85 (ArC-1), 129.21 (ArC-3,5), 130.41 (ArC-2,6), 158.99 (ArC-4); MS: m/z (%), 230 (M^+ , 2), 198 (1) 153 (3), 121 (100), 45 (46).

4.13.3 2-Methylbenzyl 2-hydroxyethyl disulphide^{115,121}

2-Hydroxyethylthioisothiuronium chloride (9.40 g, 0.0498 mol), 2-methylbenzyl mercaptan (6.28 cm³, 0.0465 mol) and sodium hydrogen carbonate (6.00 g, 0.0714 mol) gave 2 methylbenzyl 2-hydroxyethyl disulphide (6.47 g, 65%) as a clear light yellow oil; tlc (2:1 ether/DCM on silica) gave a single spot, R_f 0.62; (Found: C, 56.14; H, 6.59; S, 29.89. Calc. for $C_{10}H_{14}OS_2$: C, 56.04; H, 6.60; S, 29.89%); δ_H ($CDCl_3$) 2.38 (CH_3 , s, 3H), 2.48 (SCH_2CH_2S , t, 2H, $^3J_{HCC} = 6$ Hz), 2.49 (OH, s, 1H), 3.67 ($HOCH_2CH_2S$, t, 2H, $^3J_{HCC} = 6$ Hz), 3.91 (Ar CH_2 , s, 2H), 7.15 (Ar-H, m, 4H); δ_C ($CDCl_3$) 19.21 (CH_3), 40.79 (SCH_2CH_2), 41.42 (Ar CH_2), 60.03 ($HOCH_2$), 125.91 (ArC-1), 127.79 (ArC-2), 130.49 (ArC-6), 134.67 (ArC-3), 134.12 (ArC-5), 136.68 (ArC-4); MS: m/z (%), 214 (M^+ , 4), 182 (2), 137 (6), 105 (100), 45 (48).

4.13.4 Benzyl 2-hydroxyethyl disulphide^{115,121}

2-Hydroxyethylthioisothiuronium chloride (9.40 g, 0.0498 mol), benzyl mercaptan (5.6 cm³, 0.048 mol) and sodium

hydrogen carbonate (6.00 g, 0.0714 mol) gave benzyl 2-hydroxyethyl disulphide (5.86 g, 63%) as a clear light yellow oil; tlc (2:1 ether/DCM on silica) gave a single spot, R_f 0.70; (Found: C, 54.04; H, 5.97; S, 32.20. Calc for $C_9H_{12}OS_2$: C, 53.99; H, 6.04; S, 31.97%); δ_H ($CDCl_3$) 2.34 (OH, s, 1H), 2.49 (SCH_2CH_2OH , t, 2H, $^3J_{HCCH} = 6$ Hz), 3.68 ($HOCH_2CH_2S$, t, 2H, $^3J_{HCCH} = 6$ Hz), 3.88 (Ar- CH_2 , s, 2H), 7.30 (Ar-H, m, 5H); δ_C ($CDCl_3$) 40.74 (SCH_2CH_2), 43.30 (Ar CH_2S), 60.13 ($HOCH_2$), 127.53 (ArC-1), 128.77 (ArC-3,5), 129.29 (ArC-2,6), 137.14 (ArC-4); MS: m/z (%), 200 (8), 168(2), 153 (1), 123 (2), 91 (100), 45 (56).

4.13.5 4-Chlorobenzyl 2-hydroxyethyl disulphide

2-Hydroxyethylthioisothiuronium chloride (9.40 g, 0.0498 mol), 4-chlorobenzyl mercaptan (6.05 cm³, 0.0465 mol) and sodium hydrogen carbonate (6.00 g, 0.071 mol) gave 4-chlorobenzyl 2-hydroxyethyl disulphide (6.95 g, 64%) as a clear light yellow oil; tlc (2:1 ether/DCM on silica) gave a single spot, R_f 0.59; (Found: C, 46.13; H, 4.67; S, 27.10. C₉H₁₁ClOS₂ requires: C, 46.05; H, 4.73; S, 27.31%); δ_H (CDCl₃) 2.36 (OH, s, 1H), 2.56 (SCH₂CH₂OH, t, 2H, ³J_{HCC} = 6 Hz), 3.73 (HOCH₂CH₂S, t, 2H, ³J_{HCC} = 6 Hz), 3.84 (Ar-CH₂, s, 2H), 7.27 (Ar-H, m, 4H); δ_C (CDCl₃) 40.91 (SCH₂CH₂), 42.58 (Ar-CH₂), 60.16 (HOCH₂), 128.69 (ArC-1), 130.58 (ArC-3,5), 133.37 (ArC-2,6), 135.75 (ArC-4); MS: m/z (%), 234 (M⁺, 2); 202 (1), 167 (1), 157 (2), 125 (100), 45 (43).

4.13.6 4-Methylbenzyl 2-hydroxyethyl disulphide^{115,121}

2-Hydroxyethylthioisothiuronium chloride (9.40 g, 0.0498 mol), 4-methylbenzyl mercaptan (6.28 cm³, 0.0465 mol) and sodium hydrogen carbonate (6.00 g, 0.071 mol) gave 4-methylbenzyl 2-hydroxyethyl disulphide (5.98 g, 60%) as a clear light yellow oil; tlc (2:1 ether/DCM on silica) gave a single spot, R_f 0.59; (Found: C, 56.11; H, 6.68; S, 29.84. Calc. for C₁₀H₁₄OS₂: C, 56.04; H, 6.60; S, 29.89%); δ_H (CDCl₃) 2.31 (CH₃, s, 1H) 2.49 (OH, s, 1H), 2.53 (SCH₂CH₂OH, t, 2H, ³J_{HCC} = 6 Hz), 3.69 (HOCH₂CH₂S, t, 2H, ³J_{HCC} = 6 Hz), 3.84 (Ar-CH₂, s, 2H), 7.17 (Ar-H, m, 4H); δ_C (CDCl₃), 21.12 (CH₃), 40.76 (SCH₂CH₂), 43.17 (ArCH₂S), 60.13 (HOCH₂), 129.14 (ArC-1), 129.22 (ArC-3,5), 133.99 (ArC-2,6), 137.21

(ArC-4); MS: m/z (%), 214 (M⁺, 5), 182 (3), 137 (8), 105 (100).

4.13.7 Propane-1,3-bis(2-hydroxyethyl disulphide)

S-2-Hydroxyethylthioisothiuronium chloride (5.36 g, 0.028 mol), 1,3-dimercaptopropane (1.43 cm³, 0.014 mol) and sodium hydrogen carbonate (3.41 g, 0.041 mol) gave propane-1,3-bis(2-hydroxyethyl disulphide) (4.85 g, 66%) as a white amorphous solid; tlc (3:1 ether/DCM on silica) gave a single spot, R_f 0.49; (Found: C, 32.31; H, 6.18; S, 49.00. C₇H₁₆O₂S₄ requires: C, 32.31; H, 6.20; S, 49.17); m.p. 46-47 °C; δ_H (CDCl₃) 2.12 (SCH₂CH₂CH₂S, q, 2H), 2.87 (HOCH₂CH₂, dt, 8H, ³J_{HCCH} = 6 Hz), 3.11 (OH, s, 2H), 3.87 (HOCH₂, t, 4H, ³J_{HCCH} = 6 Hz); δ_C (CDCl₃) 28.14 (SCH₂CH₂CH₂S), 36.98 (SCH₂CH₂CH₂S), 41.13 (HOCH₂CH₂S), 60.14 (HOCH₂); MS: m/z (%), 260 (M⁺, 3), 183 (78), 154 (9), 139 (4), 109 (70), 45 (100).

4.13.8 Ethane-1,2-bis(2-hydroxyethyl disulphide)

S-2-Hydroxyethylthioisothiuronium chloride (5.36 g, 0.028 mol), 1,2-dimercaptoethanol (0.014 mol) and sodium hydrogen carbonate (3.41 g, 0.041 mol) gave ethane-1,2-bis-(2-hydroxyethyl disulphide) as a white powder solid, tlc (3:1 ether/DCM on silica) gave a single spot R_f 0.53; (Found: C, 29.27; H, 5.73; S, 51.99. C₆H₁₄O₂S₄ requires: C, 29.26; H, 5.74; S, 52.04%); m.p. 38-39 °C; δ_H (CDCl₃) 2.32 (SCH₂CH₂S, t, 4H, ³J_{HCCH} = 6 Hz), 2.68 (HOCH₂CH₂, t, 4H, ³J_{HCCH} = 6 Hz), 2.96 (OH, s, 2H), 3.84 (HOCH₂, t, 4H, ³J_{HCCH} = 6 Hz);

δ_c (CDCl₃) 38.23 (SCH₂CH₂S), 40.89 (HOCH₂CH₂S), 60.16 (HOCH₂); MS: m/z (%), 246 (M⁺, 5), 197 (7), 165 (4), 137 (8), 109 (65), 45 (100).

4.13.9 Butane-1,4-bis(2-hydroxyethyl disulphide)

S-2-Hydroxyethylthioisothiuronium chloride (5.36, 0.028 mol), 1,4-dimercaptobutanol (0.014 mol) and sodium hydrogen carbonate (3.41 g, 0.041 mol) gave butane-1,4-bis(2-hydroxyethyl disulphide) as a white amorphous solid, tlc (3:1 ether/DCM on silica) gave a single spot R_f 0.56; (Found: C, 35.03; H, 6.62; S, 46.67. C₈H₁₈O₂S₄ requires: C, 35.09; H, 6.70; S, 46.61%); m.p. 54-56 °C; δ_H (CDCl₃) 1.82 (SCH₂CH₂CH₂CH₂S, q, 4H), 2.71 (OH, s, 2H), 2.74 (SCH₂CH₂CH₂CH₂S, t, 4H, ³J_{HCCH} = 6 Hz), 2.86 (HOCH₂CH₂S, t, 4H, ³J_{HCCH} = 6 Hz), 3.87 (HOCH₂, t, 4H, ³J_{HCCH} = 6 Hz); δ_c (CDCl₃) 27.72 (SCH₂CH₂CH₂CH₂S), 38.37 (SCH₂CH₂CH₂CH₂S), 41.09 (HOCH₂CH₂S), 60.26 (HOCH₂); MS: m/z (%), 274 (M⁺, 2), 197 (78), 168 (8), 139 (2), 109 (65), 45 (100).

4.13.10 Benzothiazol-2-yl 2-hydroxyethyl disulphide

S-2-Hydroxyethylthioisothiuronium chloride (9.40 g, 0.0498 mol), 2-mercaptobenzothiazole (7.78 g, 0.0465 mol) and sodium hydrogen carbonate (6.00 g, 0.0714 mol) gave benzothiazol-2-yl 2-hydroxyethyl disulphide as a light yellow powder solid; tlc (2:1 ether/DCM on silica) gave a single spot, R_f 0.58; (Found: C, 44.36; H, 3.84; S, 39.52. C₉H₉NOS₃ requires: C, 44.41; H, 3.73; S, 39.52); m.p.

187-188 °C; δ_H (CDCl₃) 3.07 (SCH₂CH₂OH, t, 2H, $^3J_{\text{HCCH}} = 5$ Hz), 3.89 (HOCH₂CH₂S, t, 2H, $^3J_{\text{HCCH}} = 5$ Hz), 4.68 (OH, s, 1H), 7.27-7.45 (Ar-H, m, 1H), 7.71-7.99 (Ar-H, m, 2H); δ_C (CDCl₃) 42.62 (SCH₂CH₂), 59.13 (HOCH₂), 121.21 (SCS), 124.94 (ArC-2), 126.46 (ArC-3,4), 135.82 (ArC-5), 153.37 (ArC-6), 170.93 (ArC-1); MS: m/z (%), 243 (M⁺, 8), 211 (4), 188 (1), 104 (2), 45 (100).

4.13.11 Prop-2-enyl 2-hydroxyethyl disulphide

S-2-Hydroxyethylthioisothiuronium chloride (9.40 g, 0.0498 mol), allyl mercaptan (3.7 cm³, 0.0465 mol), and sodium hydrogen carbonate (6.00 g, 0.0714 mol) gave *pro-2-enyl 2-hydroxyethyl disulphide* (4.75 g, 68%) as a deep yellow oil; tlc (3:1 ether/DCM on silica) gave a single spot, R_f 0.63; (Found: C, 39.92; H, 6.70; S, 42.57; C₅H₁₀OS₂ requires: C, 39.99; H, 6.72; S, 42.62%); δ_H (CDCl₃) 2.69 (OH, s, 1H), 2.84 (SCH₂CH₂OH, t, 2H, $^3J_{\text{HCCH}} = 6$ Hz), 3.34 (CHCH₂, d, 2H), 3.84 (HOCH₂CH₂, t, 2H, $^3J_{\text{HCCH}} = 6$ Hz), 5.19 (H₂C=CH, m, 2H), 5.86 (H₂C=CH, m, 1H); δ_C (CDCl₃) 41.22 (SCH₂CH₂), 42.06 (CHCH₂S), 60.21 (HOCH₂), 118.76 (CHCH₂), 133.25 (H₂C=CH); MS: m/z (%), 150 (M⁺, 54), 118 (8), 106 (35), 73 (32), 45 (100).

4.13.12 2-Fluorobenzyl 2-hydroxyethyl disulphide^{115,121}

S-2-Hydroxyethylthioisothiuronium chloride (9.40 g, 0.0498 mol), 2-fluorobenzyl mercaptan (6.61 g, 0.0465 mol) and sodium hydrogen carbonate (6.00 g, 0.0714 mol) gave 2-fluorobenzyl 2-hydroxyethyl disulphide (6.59 g, 65%) as a

yellow oil; tlc (3:1 ether/DCM on silica) gave a single spot, R_f 0.59; (Found: C, 49.49; H, 5.04; S, 29.10. Calc. for $C_9H_{11}FOS_2$: C, 49.55; H, 5.08; S, 29.33%); δ_H ($CDCl_3$) 2.41 (OH, s, 1H), 2.54 (SCH_2CH_2OH , t, 2H, $^3J_{HCCH} = 6$ Hz), 3.73 ($HOCH_2CH_2S$, t, 2H, $^3J_{HCCH} = 6$ Hz), 3.86 ($ArCH_2S$, s, 2H), 6.96-7.00 (Ar-H, m, 2H), 7.03-7.31 (Ar-H, m, 2H); δ_C ($CDCl_3$) 40.83 (SCH_2CH_2), 42.50 ($ArCH_2S$), 60.13 ($HOCH_2CH_2S$), 115.63 (ArC-1), 130.94 (ArC-3,5), 133.01 (ArC-2,6), 160.26 (ArC-4); MS: m/z (%) 218 (M^+ , 9), 186 (2), 141 (4), 139 (1), 121 (1), 109 (100), 45 (56).

4.14 Preparation of Unsymmetrical Monosulphides

4.14.1 Preparation of 2-chlorobenzyl 2-hydroxyethyl monosulphide^{175,176}

2-Chlorobenzyl mercaptan (11.7 cm³, 0.090 mol) was added to a solution of sodium hydroxide (3.60 g, 0.090 mol) in water (10 cm³) diluted with ethanol (100 cm³). No attempt was made to isolate the mercaptide. 2-Chloroethanol (6.04 cm³, 0.090 mol) was added to the above mixture with cooling in an ice-salt bath and vigorous stirring. The mixture was heated under reflux for 4 h and allowed to cool. It was then diluted with water and the crude product separated out as an oil. The oil was washed with water in order to remove any remaining sodium chloride and extracted with dichloromethane. The dichloromethane layer was extracted

with three portions of water (3 x 100 cm³) and dried over magnesium sulphate, followed by the removal of the solvent by rotary evaporation under reduced pressure. The crude product was chromatographed on a silica gel column with light petroleum ether (b.p 40-60⁰) as the first eluting solvent. The desired product was eluted with dichloromethane, followed by the removal of solvent by rotary evaporation. Total removal of solvent was carried out under reduced pressure by collecting the material in a flask fitted for shaking. This gave 2-chlorobenzyl 2-hydroxyethyl monosulphide (12.4 g, 68%) as a yellow oil; tlc (3:1 ether/DCM on silica) gave a single spot, R_f 0.72; (Found: C, 53.36; H, 5.53; S, 15.90. Calc. for C₉H₁₁ClOS: C, 53.33; H, 5.49; S, 15.79%); δ_H (CDCl₃) 2.64 (SCH₂CH₂OH, t, 2H, ³J_{HCCH} = 6 Hz), 3.06 (OH, s, 1H), 3.68 (HOCH₂CH₂S, t, ³J_{HCCH} = 6 Hz), 3.81 (ArCH₂, s, 2H), 7.17-7.32 (Ar-H, m, 4H); δ_C (CDCl₃) 33.25 (SCH₂CH₂), 34.39 (Ar-CH₂S), 60.53 (HOCH₂), 126.85 (ArC-1), 129.71 (ArC-2), 130.73 (ArC-6), 133.81 (ArC-3), 133.2 (ArC-5), 135.84 (ArC-4); MS: m/z (%), 202 (M⁺, 10), 157 (9), 125 (100), 45 (61).

Similar procedures were used in the preparation of the following compounds.

4.14.2 2-Methylbenzyl 2-hydroxyethyl monosulphide^{175,176}
2-Methylbenzyl mercaptan (10.9 cm³, 0.080 mol), 2-chloroethanol (5.4 cm³, 0.080 mol) and sodium hydroxide (3.22 g, 0.080 mol) gave 2-methylbenzyl 2-hydroxyethyl monosulphide

(9.0 g, 62%) as a yellow oil; tlc (3:1 ether/DCM on silica) gave a single spot, R_f 0.68; (Found : C, 65.80, H, 7.70; S, 17.80. Calc. for $C_{10}H_{14}OS$: C, 65.80; H, 7.67; S, 17.59%); δ_H ($CDCl_3$) 2.38 (CH_3 , s, 3H), 2.61 (OH, s, 1H), 2.68 (SCH_2CH_2OH , t, 2H, $^3J_{HCCH} = 6$ Hz), 3.66 ($HOCH_2CH_2S$, t, 2H, $^3J_{HCCH} = 6$ Hz), 3.71 (Ar- CH_2 , s, 2H), 7.15 (Ar-H, m, 4H); δ_C ($CDCl_3$) 19.13 (CH_3), 33.81 (SCH_2CH_2), 34.54 (Ar- CH_2S), 60.44 ($HOCH_2$), 125.86 (ArC-1), 127.44 (ArC-2), 129.63 (ArC-6), 135.63 (ArC-3), 135.0 (ArC-5), 136.63 (ArC-4); MS: m/z (%), 182 (M^+ , 49), 137 (6), 105 (100), 45 (48).

4.14.3 4-Methoxybenzyl 2-hydroxyethyl monosulphide^{175,176}
4-Methoxybenzyl mercaptan (13.9 cm³, 0.100 mol), 2-chloroethanol (6.71 cm³, 0.100 mol); and sodium hydroxide (4.0 g, 0.100 mol) gave 4-methoxybenzyl 2-hydroxyethyl monosulphide (13.3 g, 67%) as a yellow oil; tlc (3:1 ether/DCM on silica) gave a single spot, R_f 0.69; (Found: C, 60.84; H, 7.11; S, 15.90. Calc. for $C_{10}H_{14}O_2S$: C, 60.58; H, 7.12; S, 16.14); δ_H ($CDCl_3$) 2.58 (OH, s, 1H), 2.60 (SCH_2CH_2OH , t, 2H, $^3J_{HCCH} = 6$ Hz), 3.67 ($HOCH_2CH_2S$, t, 2H, $^3J_{HCCH} = 6$ Hz), 3.78 (CH_3O , s, 1H), 3.87 (Ar- CH_2 , s, 2H), 6.82 (Ar-H, m, 2H), 7.20 (Ar-H, m, 2H); δ_C ($CDCl_3$) 34.19 (SCH_2CH_2), 35.10 (Ar CH_2S), 55.25 (CH_3O), 60.26 ($HOCH_2$), 113.98 (ArC-1), 129.92 (ArC-3,5), 135.33 (ArC-2,6), 158.69 (ArC-4); MS: m/z (%), 198 (M^+ , 30), 153 (3), 121 (100), 45 (47).

4.14.4 Benzyl 2-hydroxyethyl monosulphide^{175,176}

Benzyl mercaptan (8.80 cm³, 0.075 mol), 2-chloroethanol (5.0 cm³, 0.075 mol) and sodium hydroxide (3.00 g, 0.075 mol) gave benzyl 2-hydroxyethyl monosulphide (7.4 g, 59%) as a yellow oil; tlc (3:1 ether/DCM on silica) gave a single spot, R_f 0.73; (Found: C, 64.17; H, 7.20; S, 18.80. Calc. for C₉H₁₂OS: C, 64.26; H, 7.21; S, 19.02); δ_H (CDCl₃) 2.55 (SCH₂CH₂OH, t, 2H, ³J_{HCCH} = 6 Hz), 2.88 (OH, s, 1H), 3.63 (HOCH₂CH₂S, t, 2H, ³J_{HCCH} = 6 Hz), 3.67 (ArCH₂, s, 2H), 7.27 (Ar-H, m, 5H); δ_C (CDCl₃) 33.78 (SCH₂CH₂), 35.28 (Ar-CH₂S), 60.22 (HOCH₂), 128.57 (ArC-1), 129.24 (ArC-3,5), 130.11 (ArC-2,6), 131.47 (ArC-4); MS: m/z (%), 168 (M⁺, 27), 123 (22), 91 (100), 45 (54).

4.14.5 4-Chlorobenzyl 2-hydroxyethyl monosulphide^{175,176}

4-Chlorobenzyl mercaptan (11.0 cm³, 0.085 mol), 2-chloroethanol (5.71 cm³, 0.085 mol), and sodium hydroxide (3.40 g, 0.085 mol) gave 4-chlorobenzyl 2-hydroxyethyl monosulphide (13.2 g, 73%) as a yellow oil; tlc (3:1 ether/DCM on silica) gave a single spot, R_f 0.69; (Found: C, 53.29; H, 5.46; S, 15.84. Calc. for C₉H₁₁ClOS: C, 53.33; H, 5.49; S, 15.79%); δ_H (CDCl₃) 2.66 (SCH₂CH₂OH, t, 2H, ³J_{HCCH} = 6 Hz), 3.04 (OH, s, 1H), 3.69 (HOCH₂CH₂S, t, 2H, ³J_{HCCH} = 6 Hz), 3.79 (ArCH₂, s, 2H), 7.19-7.35 (Ar-H, m, 4H); δ_C (CDCl₃) 33.46 (SCH₂CH₂), 34.75 (Ar-CH₂S), 60.42 (HOCH₂), 128.68 (ArC-1), 129.38 (ArC-3,5), 132.13 (ArC-2,6), 134.89 (ArC-4); MS: m/z (%), 202 (M⁺, 12), 157 (9), 125 (100), 45 (50).

4.14.6 4-Methylbenzyl 2-hydroxyethyl monosulphide^{175,176}
4-Methylbenzyl mercaptan (9.1 cm³, 0.067 mol), 2-chloroethanol (4.5 cm³, 0.067 mol), and sodium hydroxide (2.68 g, 0.067 mol) gave 4-methylbenzyl 2-hydroxyethyl monosulphide (7.3 g, 60%) as a yellow oil; tlc (3:1 ether/DCM on silica) gave a single spot, R_f 0.70; (Found: C, 65.78; H, 7.74; S, 17.63. Calc. for C₁₀H₁₄OS: C, 65.80; H, 7.67; S, 17.59%); δ_H (CDCl₃) 2.31 (CH₃, s, 3H), 2.59 (OH, s 1H), 2.61 (SCH₂CH₂OH, t, 2H, ³J_{HCC} = 6 Hz), 3.64 (HOCH₂CH₂S, t, 2H, ³J_{HCC} = 6 Hz), 3.66 (Ar-CH₂, s, 2H), 7.16 (Ar-H, m, 4H); δ_C (CDCl₃) 21.06 (CH₃), 34.19 (SCH₂CH₂), 35.41 (ArCH₂S), 60.24 (HOCH₂), 128.72 (ArC-1), 129.25 (ArC-3,5), 134.94 (ArC-2,6), 136.77 (ArC-4); MS: m/z (%), 182 (M⁺, 42), 137 (5), 105 (100), 45 (54).

4.15 Attempted preparation of 4-methoxybenzyl 2-hydroxyethoxy disulphide via the oxidation of 4-methoxybenzyl 2-hydroxyethyl disulphide

To a solution of 4-methoxybenzyl 2-hydroxyethyl disulphide (5.86 g, 0.0255 mol) in methanol (75 cm³) was added a solution of perchlorobenzoic acid (4.51 g, 0.026 mol) in methanol (100 cm³) at 0-10 °C. The reaction was slightly exothermic and stirring was continued at this temperature for a further 2 h. The resultant mixture was worked up in the usual manner (Section 2.8.1) to give a light yellow oil that changed to brown on standing. (Found: C, 53.10; H,

4.12; S, 23.12. Calc. for $C_{10}H_{14}O_3S_2$: C, 48.75; H, 5.74; S,
26.03.

4.16 Biological screening experiments

4.16.1 In vitro screening of compounds

After a couple of trials that involved cultivation of the fungi *Fusarium culmorum*, *Fusarium oxysporum* and *Gaeumannomyces graminis* in different nutrients, it was found that the most suitable was Saboround Dextrose Agar (SDA). Therefore these fungi were cultivated in this nutrient for all screening experiments.

A solution of the chemical to be tested (1000 ppm) in SDA medium was prepared by dissolving 0.2 g in acetone (20 cm³), followed by the addition of distilled water (80 cm³) at 60 °C. This mixture was then added to sterilized SDA solution containing agar (13 g) in water (100 cm³). (Sterilization of the SDA solution had been previously carried out by placing it in an autoclave at 121 °C and leaving it at this temperature for 15 minutes). Dilution of the 1000 ppm solution (20 cm³) by addition to a solution containing SDA (13 g) in water (180 cm³), gave a 100 ppm solution. Similarly, a 10 ppm solution was prepared by adding 20 cm³ of the 100 ppm solution to a solution containing SDA (13 g) in water (180 cm³). A control solution was similarly prepared containing SDA (13 g) in water (200 cm³). Also, solutions containing (a) guazatine/imazalil, and (b) phenyl mercury acetate at various concentrations of active ingredient (1000 ppm, 100 ppm, 10 ppm) were prepared as standards.

The solutions were poured in Petri dishes and allowed to cool. Each plate was then inoculated with a 5 mm agar plug containing actively growing fungus. All plates were kept inside a sterilized incubator, maintained at 25 °C. The growth diameter of the fungal spore was measured every three days until there was complete growth on the control dish, i.e. until all the surface of the plate was covered with fungal spore (approximate diameter, 86 cm³).

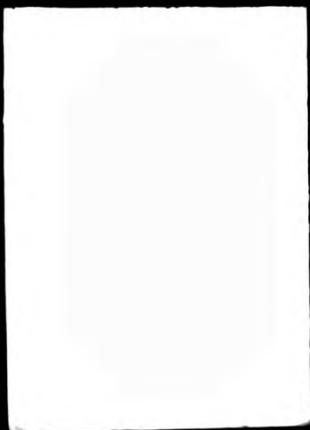
4.17 Glasshouse screening of compounds

4.17.1 Post-inoculation treatments against *Erysiphe graminis* on barley seedlings

The samples (0.1 cm³) were dispersed in acetone (5 cm³) and then added to distilled water (25 cm³) to give 0.33% solution. Tween 20 (30 µl) was added to give a 0.1% solution. Seedlings were inoculated at the second leaf stage and sprayed three days later. The percentage powdery mildew infection on the second leaves was assessed using standard area diagrams 6, 8 and 10 days post-inoculation (Figure 15).

4.17.2 Post-inoculation treatments against *Botrytis fabae* on bean seedlings

The samples (0.1 cm³) were dispersed in acetone (5 cm³) and then added to distilled water (25 cm³) to give 0.33%



solution. Tween 20 (30 μ l) was added to give a 0.1% solution. Seedlings were inoculated at the third leaf stage and sprayed three days later. The percentage chocolate spot infection on the third leaves was assessed using standard area diagrams 6 and 8 days post-inoculation (Figure 16).

4.17.3 Post-inoculation treatment against *Podosphaera leucotricha* on apple seedlings

The samples (0.1 cm^3) were dispersed in acetone (5 cm^3) and then added to distilled water (25 cm^3) to give 0.33% solution. Tween 20 (30 μ l) was added to give a 0.1% solution. Seedlings were inoculated at the fourth stage and sprayed three days later. The percentage powdery mildew infection on the fourth leaves was assessed using standard area diagrams 13, 15 and 17 days post-inoculation.

4.17.4 Post-inoculation treatments against *Uromyces viciae-fabae* on bean seedlings

The samples (0.1 cm^3) were dispersed in acetone (5 cm^3) and then added to distilled water (25 cm^3) to give 0.33% solution. Tween 20 (30 μ l) was added to give a 0.1% solution. Seedlings were inoculated at the third leaf stage and sprayed three days later. The percentage rust infection on the third leaves was assessed using standard area diagrams 15 and 19 days post-inoculation (Figure 17).

4.17.5 Effects of compounds on infection of potato leaf discs by the blight fungus *Phytophthora infestans*

Leaf discs were floated on distilled water containing 0.33% of the compound to be tested, in a glass Petri dish. Thereafter, a droplet containing a suspension of sporangiospores was placed onto the leaf disc, and the Petri dishes placed in a controlled environment room for 4 days. Leaf discs were then examined for blight infection.

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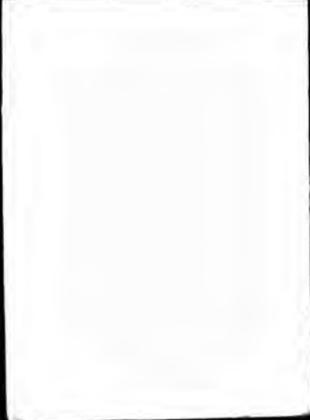
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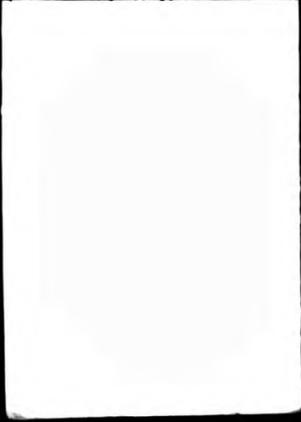
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