

A Thesis entitled

STUDIES ON THE SYNTHESIS AND STEREOCHEMISTRY
OF CYCLIC THIOCARBONATES AND
RELATED COMPOUNDS

submitted by

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in partial fulfilment of the requirements for the

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ABSTRACT

The literature on dithiols has been reviewed, with emphasis on the stereochemistry of vicinal dithiols.

In part I, the syntheses of several substituted cyclic carbonates and thiocarbonates are described, and the reactions of these compounds with metal alkyl xanthates to give, in most cases, the cyclic trithiocarbonates are also reported. The mechanisms of these reactions are discussed in the context of previous work in this field, which is briefly reviewed.

Four substituted ethylene thiocarbonates were prepared, two from cis-2,3-epoxybutane, and two (in optically active form) from L-(+)-dimethyl tartrate.

A potential route to meso- or DL-butane-2,3-diol from trans-1,4-dibromobut-2-ene was developed. The synthesis of the complete series of bis(benzyloxymethyl)ethylene thiocarbonates is reported, the trans-compounds from cis-2-butene-1,4-diol, and the cis-compounds from trans-1,4-dibromobut-2-ene.

The syntheses of cis-4,5-cyclohexano-1,3-oxathiolan-2-thione and cis-4,5-cyclohexano-1,3-dithiolan-2-one are described, and the reactions of these compounds and also of cis- and trans-2-mercaptocyclohexanol and of cis-cyclohexane-1,2-dithiol with xanthate are also reported. Cyclohexene sulphide was obtained from trans-4,5-cyclohexano-1,3-oxathiolan-2-one by heating it with base, thus proving the intermediacy of the episulphide in the xanthate mechanism.

The preparation of three decalin trithiocarbonates from a cis- and trans- Δ^2 -octalin mixture via the dithiols is described.

In part II, the investigation of a potential route to dithiols via trans-2-(phenyliminocarbamoylthio)cyclohexyl acetate is described. Treatment with base unexpectedly gave trans-2-phenylimino-4,5-cyclohexano-1,3-dithiolan, an authentic sample of which was prepared via the trithiocarbonate methyl iodide salt. The results from the corresponding cis-series are also reported.

ACKNOWLEDGEMENTS

I would like to express my gratitude to Professor L.N. Owen for his constant encouragement and advice throughout the course of this work.

I would also like to thank all my colleagues in the department, especially those in the Armstrong Laboratory, Costas (for his early morning companionship), Derek (for the beer and the squash) and Tony (for his sub-stores).

Thanks are also due to Mr. K.I. Jones and Mr. R.H. Woodbridge of the Microanalytical Laboratory, to Mrs. J. Lee for the mass spectral data and Mrs. B. Day of the Organic Stores.

Finally, I would like to thank Maria del Carmen Serrano for typing the manuscript inspite of the writing.

*"We continue to overlook the fact that
work has become a leisure activity"*

Mark Abrams.

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INTRODUCTORY
REVIEW

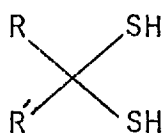
DITHIOLS

Ethane dithiol was prepared in 1840 by Ludwig and Weidman¹ by treating ethylene chloride with an alcoholic hydrogen sulphide/potassium sulphide solution in the absence of air, and several metal salts were prepared from the dithiol. The treatment of a dihalide with an alkali metal hydrogen sulphide remains one of the easiest methods for preparing simple dithiols. An upsurge of interest in dithiols occurred towards the end of the Second World War, when it was discovered that they were effective antidotes for arsenicals; more recently, considerable interest is being shown in their biochemical properties. Dithiols have been reviewed by Owen²; Reid³ and Patai⁴ have sections on dithiols, and Field⁵ has discussed them in his review of recent synthetic organic sulphur chemistry.

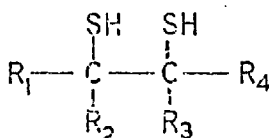
Dithiols can be broadly classified into three main types:

- (a) acyclic aliphatic,
- (b) cyclic aliphatic,
- (c) aromatic.

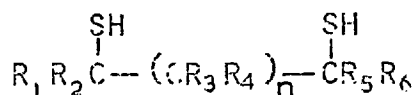
The aliphatic dithiols can be further divided into gem di-(1), vicinal di-(2) and α,ω di-(3).



(1)



(2)



(3)

$n > 0$; $\text{R}_3 \text{R}_4$ usually H

PREPARATION OF DITHIOLS

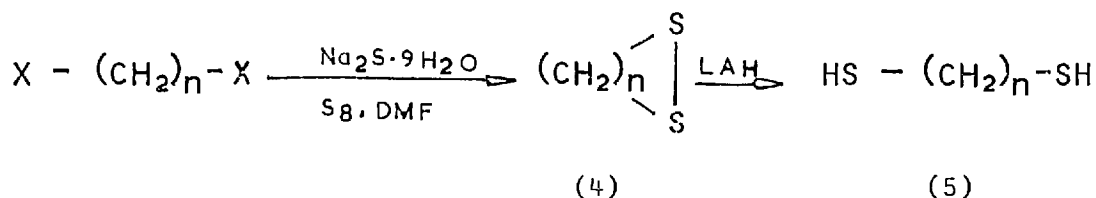
Wardell⁶ has reviewed the preparative methods for thiols, and in theory, any one of these methods can be applied to dithiols, but in

practice, there are often problems due to neighbouring group effects, as discussed by Owen².

I. From dihalides

(a) by direct displacement

Hall and Reid⁷ prepared the series of α,ω dithiols $\text{HS}(\text{CH}_2)_n\text{SH}$ up to $n = 12$ from the corresponding dibromides by treatment with ethanolic sodium hydrogen sulphide, but found very poor yields for $n = 4,5$ due to preferential intramolecular displacement of the second bromide ion to give the cyclic sulphide. Halide displacement is the oldest method,¹ and a generalisation of this method, with aryl or alkyl substituents, was reported⁸, giving seven examples. Vicinal dithiols have been synthesised by Pavlic et al.⁹ from the dibromide by treatment with sodium hydrogen sulphide and hydrogen, sulphide under pressure. These authors found this method failed for dimercaptopropionic acid, dimercaptosuccinic ester, and 2,3-dimercapto-*tert*-butanol, the major reaction being elimination of the halogen acid or reduction of the dihalide by the thiulating agent. Putrun'kin¹⁰ described the preparation of a series of dithiol sulphonates from the unsaturated sulphonate by bromination, followed by displacement by SH^- , and obtained the thiol in high purity via the lead salt. Disodium disulphide (Na_2S_2) has also been used as the thiulating agent for the preparation of ethane dithiol from the dibromide in 74% yield¹¹. More recently, Eliel et al.¹² reported a stereoselective synthesis which is particularly suited to the preparation of sterically hindered thiols, or of a particular diastereomer. This involved conversion of a dihalide or disulphonate ester to a di- (N) or polysulphide by displacement with disulphide ion, followed by lithium aluminium hydride reduction to the dithiol (5). In particular, 2-methyl-2,4-dibromopropane was converted to the dithiol in respectable yield.

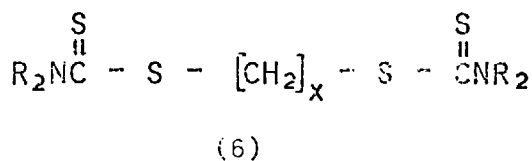


(b) via dithiolacetates

Pavlic¹³ modified the dihalide route by displacing the halogens with thiolacetic acid, followed by hydrolysis of the dithiolacetate, to give vicinal dimercaptocarboxylic acids. The route via the thiolacetate is often more convenient than preparing the dithiol directly. It has been used to prepare the β -glucoside of 2,3-dimercaptopropanol,¹⁴ the 2,3-dimercaptopropyl ethers of glycerol (α and β) and glycollic acid¹⁵, dithiol derivatives of polyhydric alcohols,^{16,17} and polymethoxydithiols.¹⁸ The methane sulphonates (lower yields)¹⁹, or the *p*-toluene sulphonates^{19,20} have also been treated with potassium thiolacetate, instead of the dibromide¹⁴⁻¹⁸, to give the dithiolacetate.

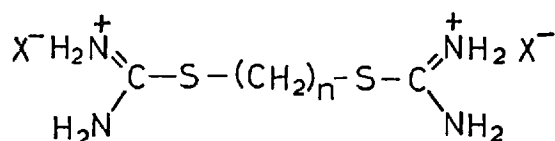
(c) via dithiourethanes

Braun²¹ treated diiodides with dithiocarbamates to give the bisdithiourethane (6), which on alkaline hydrolysis yielded the dithiol.



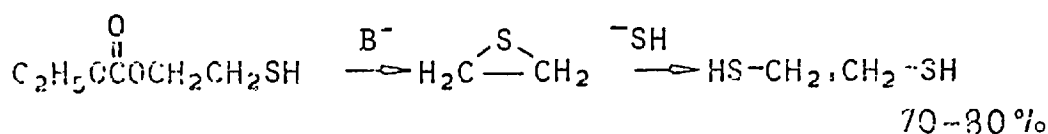
(d) via diisothiuronium salts

Polymethylene dithiols up to dodecane were prepared by alkaline hydrolysis of the corresponding diisothiuronium dihydrohalide salts (7)²², which were previously prepared from the dihalide by treatment with thiourea in ethanol.²³



(7)

Cossar et al.²⁴ have developed an improved route for simple dithiols that eliminated intermediate handling stages. The diisothiuronium salt was prepared in a high boiling solvent, and then cleaved with a high boiling amine, the dithiol being distilled off. Yields of $\text{HS}(\text{CH}_2)_n\text{SH}$ were 58, 78 and 80% for $n = 3, 4$ and 5 respectively. Ethane dithiol could not be prepared by this method due to opening of the intermediate episulphide to give other products; instead, these authors prepared it by reaction of ethyl 2-mercaptoethyl carbonate (8) with ammonium hydrogen sulphide.

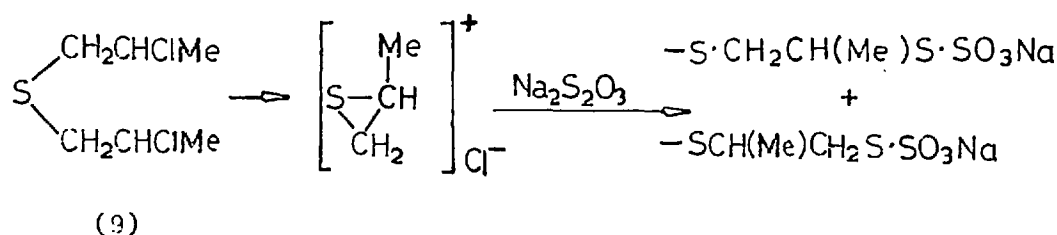


(8)

Hall and Reid⁷ used the isothiuronium route to prepare the α,ω dithiols where $n = 4, 5$ after direct displacement gave mostly the cyclic sulphides.

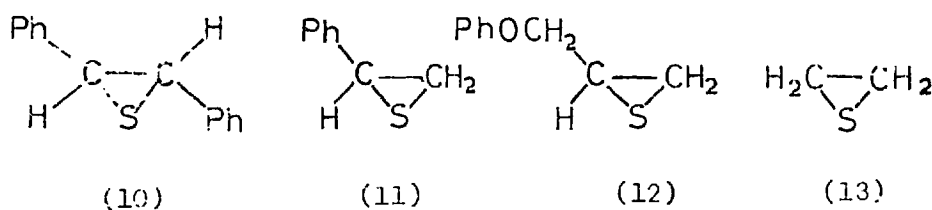
(e) via Bunte salts

Di-2-chloropropyl sulphide (9) was treated with sodium thiosulphate to give a mixture of Bunte salts, formed because of cyclic sulphonium ion participation.²⁵ Subsequent hydrogenation over a cobalt pentasulphide catalyst gave a good yield of the corresponding isomeric dithiols, bis-1-methyl-2-mercaptoethyl sulphide and bis-2-methyl-2-mercaptoethyl sulphide, together with a little pentane-1,2-dithiol and possibly some 1-methyl-2-mercaptoethyl 2-methyl-2-mercaptoethyl sulphide.



II From episulphides

Meade and Woodward²⁶ first described the opening of ethylene sulphide with hydrogen sulphide to give ethane dithiol in 50% yield, and suggested this as a new route to vicinal dithiols, since the episulphides are normally readily available from the epoxides. Culvenor²⁷ prepared cyclopentane- and cyclohexane-1,2-dithiol by opening the appropriate episulphide with SH^- . Recently, the sulphurating properties of the sulphurated hydride NaBH_2S_3 have been used to convert episulphides to dithiols²⁸, although substituents can interfere. An intermediate polysulphide is first formed, which on reduction with lithium aluminium hydride gives the dithiol. Episulphide (10) gave only trans-stilbene, (11) and (12) gave the 1,2-dithiols in 65% and 53% yields respectively, and (13) gave only polymeric material.

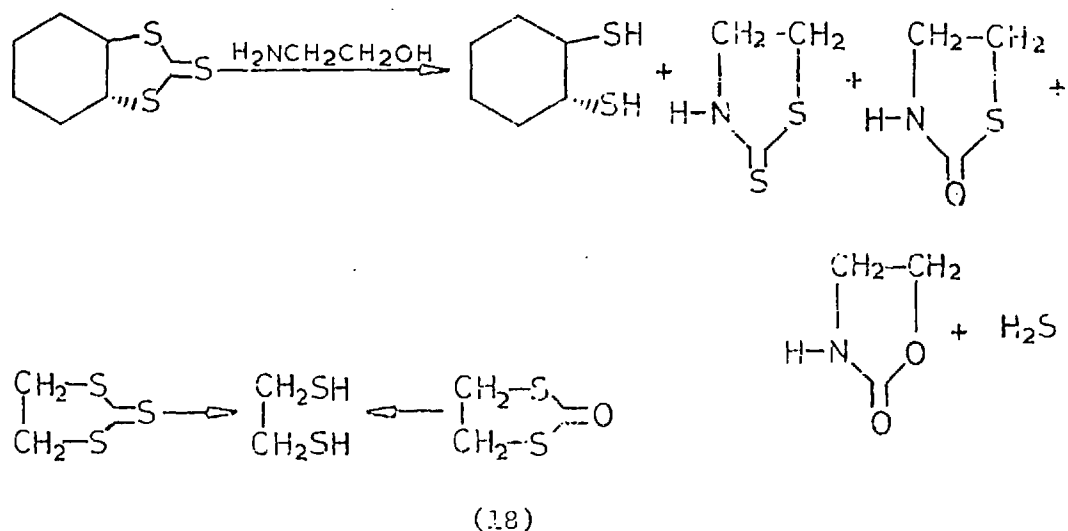


III Reaction of unsaturated carbon-carbon bonds and thiolacetic acid

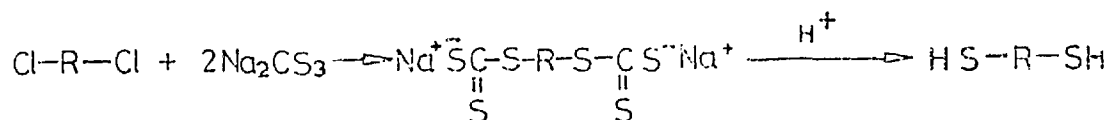
Addition of thiolacetic acid to monosubstituted acetylene occurs "abnormally" to give a mixture of mono- and 1,2-di- adducts²⁹. Treatment

IV From trithiocarbonates

Cyclic trithiocarbonates have been reduced by lithium aluminium hydride^{27,33,34,35} or hydrolysed^{36,37} to the corresponding 1,2-dithiol. Culvenor and Davies³⁶ found problems due to the low solubility of cyclohexene trithiocarbonate in ethanol, although propylene and isobutylene trithiocarbonates were hydrolysed readily under alkaline conditions. 2-Aminoethanol has been used as the hydrolysing agent³⁷, and gave cyclohexane-1,2-dithiol (75%), ethane dithiol (80%) and also ethane dithiol (79%) from 1,3-dithiolan-2-one (18).

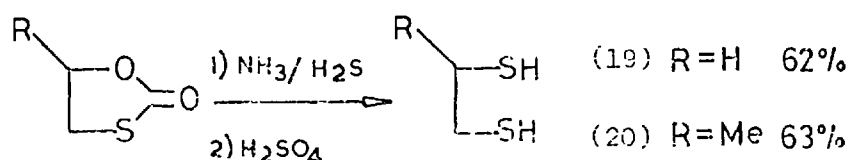


Alkylene dihalides, on treatment with sodium trithiocarbonate give the ditritthiocarbonate salts, which on acidification lose carbon disulphide to give the dithiol³⁸.

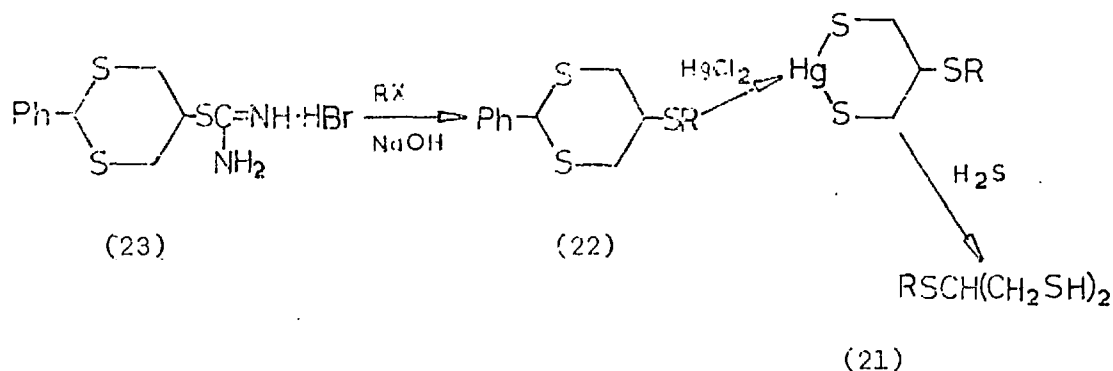


V Miscellaneous preparations

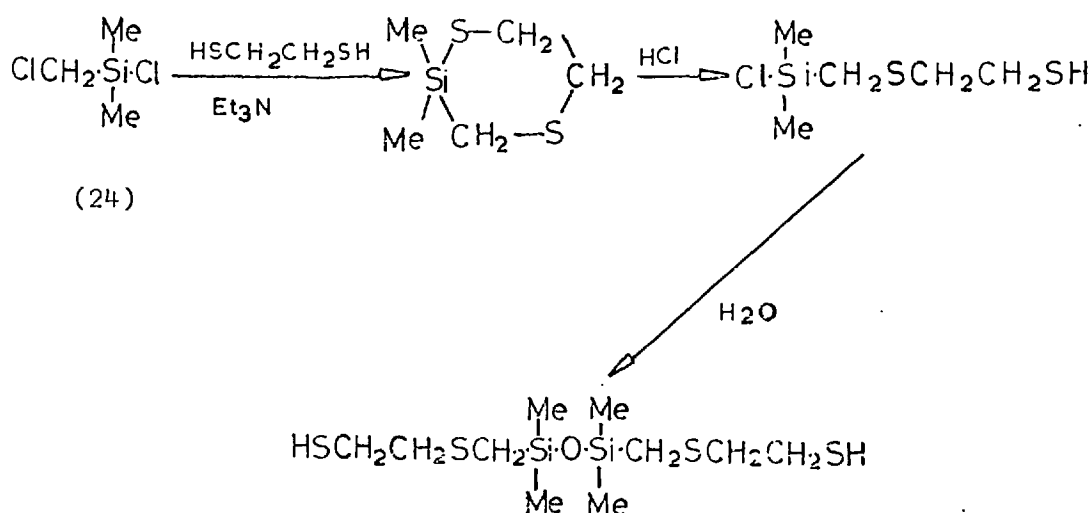
Pflugfelder^{39,40} described a surprising preparation of ethane dithiol (19) and propane-1,2-dithiol (20) from the corresponding 1,3-oxathiolan-2-ones. The patent³⁹ suggests this is a general method, and quoted the following examples:



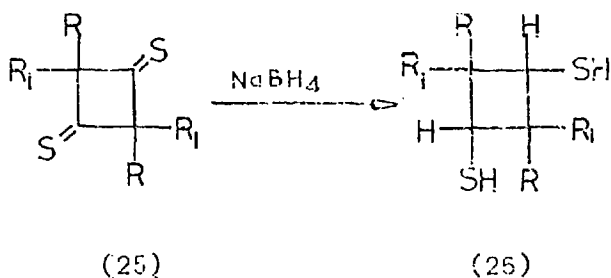
1,3-Dimercaptoisopropyl derivatives (21) were synthesised from the dithiane (22), where R is alkyl or mercaptoalkyl⁴¹. In the latter case, these were prepared from dithiane (23) by reaction with RX, such as chloroacetic acid. Treatment of the dithiane with mercury II chloride opened the ring; the salt was then treated with hydrogen sulphide to give the free thiol.



Wieber and Schmidt⁴² prepared interesting silicon containing dithiols from monochlorotrimethylchlorosilane (24) using ethane dithiol, and also propane dithiol.



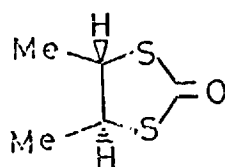
A South African patent⁴³ describes the reaction of cis,cis-1,5-cyclooctadiene with thiol acetic acid to give the bithiolacetate, which on hydrolysis gave 1,4(or 5)-cyclooctane dithiol. The substituted cyclobutane-1,3-dithione (25) has been reduced to the dithiol (26)⁴⁴.



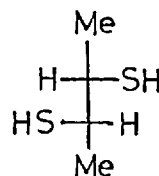
STEREOCHEMISTRY OF VICINAL DITHIOLS

The principles which apply to the stereochemistry of vicinal dithiols and of vicinal diols are similar. Thus in symmetrical acyclic systems, the terms meso and racemic may be applicable, whilst alicyclic dithiols can exist in cis or trans forms. Very few optically active vicinal dithiols are known. L-(+)-2,3-butane dithiol was synthesised from D-(-)-2,3-butanediol by Corey and Mitra⁴⁵. The diol was converted to the D-(+)-di-p-toluene sulphonate which was reacted with potassium thiocyanate

to give the L-(+)-dithiocyanate. Treatment of this with hydrogen iodide and phosphorus gave the L(-)-dithiocarbonate (27), which was reduced by lithium aluminium hydride to give the L-(+)-dithiol (28).



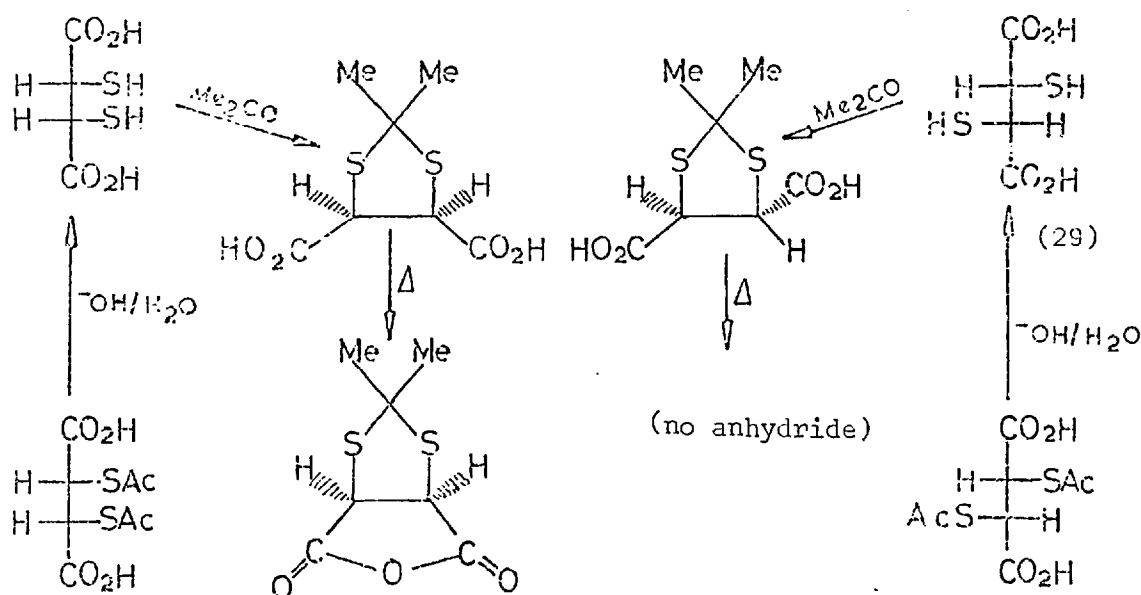
(27)



(28)

Anisuzzaman and Owen⁴⁶ prepared (R) and (S)-2,3-dimercaptopropanol.

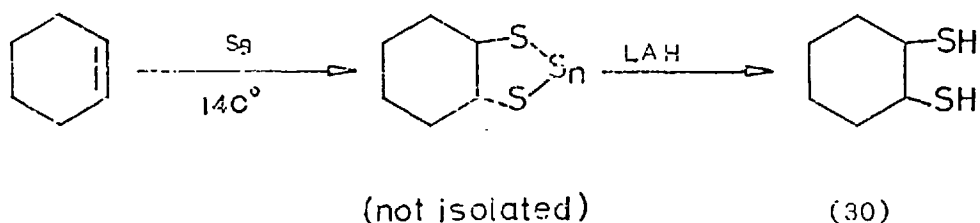
Gerecke et al.⁴⁷ prepared a mixture of meso- and DL-2,3-dimercapto-succinic acid by the method of Owen and Sultanbawa³⁰, which was fractionally crystallised to give the two isomers; the less soluble and higher melting was assigned to be the meso form, and this was proved chemically as follows:



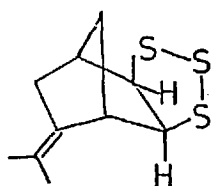
The DL form (29) was resolved into the (+) and (-) optically active isomers, via the brucine salt, thus proving the configuration of the

more soluble, lower melting form to be DL.

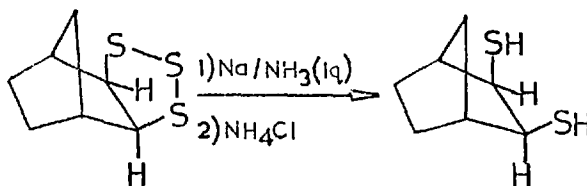
Very few preparations of alicyclic cis-dithiols have been described in the literature, the earliest being that of Bateman et al.⁴⁸ in which excess of a cyclic olefin was treated with sulphur at 140°, and the crude product subsequently reduced. No details were given for cyclohexane dithiol but its trithiocarbonate was prepared and found to be different from the known trans isomer, thus identifying the dithiol as cis (30). Other authors gave details, and recorded a yield of 12%⁴⁹.



The effect of zinc oxide on this reaction has been studied⁵⁰, its presence increasing the reaction rate but resulting in mainly trans addition of sulphur; in its absence, a radical chain mechanism gives low rates of cis addition. The disadvantages of this type of reaction are that yields are low, and an excess of the olefin is required. A modification of this reaction involving "activated" sulphur resulted in selective and stereospecific sulphuration of certain olefins in 80 - 90% yields⁵¹. Bicyclo[2.2.1]hept-2-ene and 5-ethylidenebicyclo[2.2.1]hept-2-ene were treated with a slurry of sulphur in dimethylformamide, "activated" by treatment with ammonia at 35°, to give the trithioderivatives (31) and (32) in 80% and 71% yields respectively. The trithio compound (31) was reduced by sodium in liquid ammonia to the dithiol (33); a conversion of olefin to dithiol of 60% (based on sulphur) but, unfortunately, excess olefin is still required.



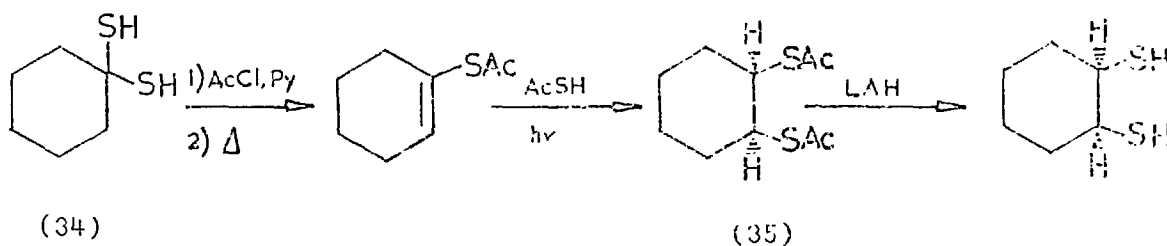
(32)



(31)

(33)

An interesting stereoselective conversion of cyclohexane 1,1-dithiol (34) into cis-cyclohexane 1,2-dithiol has been reported⁵². The intermediate bithiolacetate was a mixture of the cis- (35), 84%, and trans-, 16%, isomers, but was inseparable. The isomeric dithiols were, however, separated by distillation to give the cis-dithiol in 41% yield from the bithiolacetate. cis-Cyclopentane-1,2-dithiol (86%) was prepared in a similar manner.

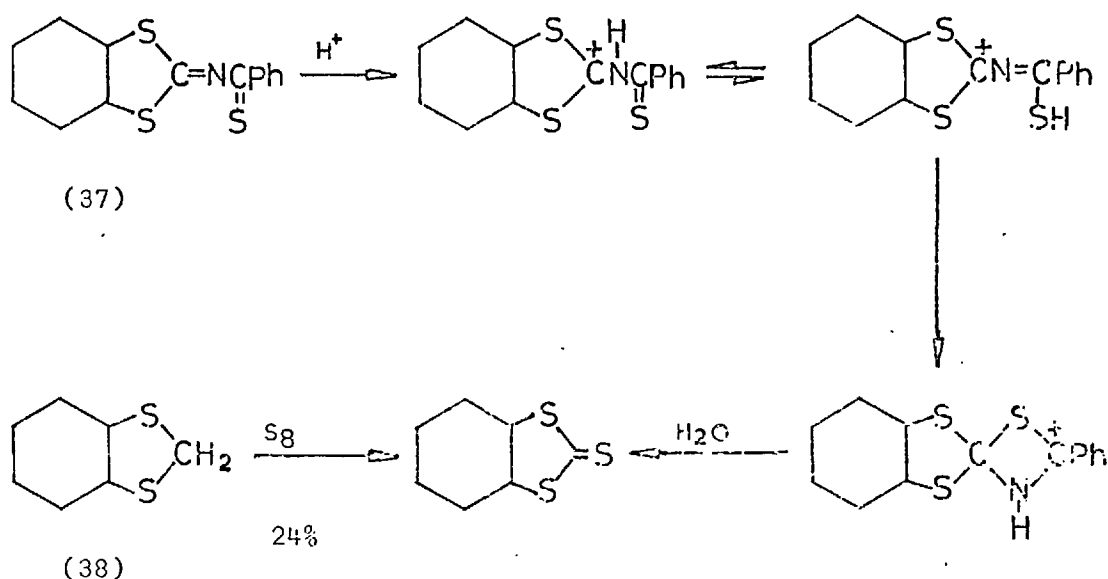


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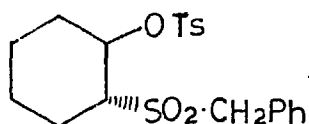
(35)

A common route to dithiols involves reduction of the trithiocarbonate, but most reported preparations of cis-cyclohexene trithiocarbonate (36) involve reaction of the dithiol itself^{48,49}. A general, and novel, synthesis was reported by Okazaki *et al.*⁵³ Cyclohexene was photolysed with 5-phenyl-1,2,4-dithiazole-3-thione to give the 1,3-cycloaddition product (37), which was then hydrolysed to give the cis-trithiocarbonate. The 1,3-cycloaddition products were obtained from cyclopentene, cyclohexene and cyclooctene in 64, 62 and 60% yields. Although these authors

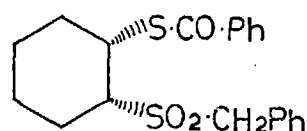
did not reduce the trithiocarbonates, it is one of two recorded syntheses of a cis-trithiocarbonate that does not use the cis-dithiol as starting material. Böhme and Müller⁴⁹ prepared cis-cyclohexene trithiocarbonate from the 1,3-dithian (38), which was prepared from cyclohexene.



Ali *et al.*⁵⁴ have developed a potential general route to cis-dithiols. The preparation of a cis-dithiol by intermolecular displacement on a trans-2-(alkylthio)cyclohexyl toluene-*p*-sulphonate is unlikely to proceed, neighbouring group participation leading, through an intermediate epim-sulphonium ion, to the trans-dithiol. These workers accordingly prepared trans-2-benzylsulphonylcyclohexyl toluene-*p*-sulphonate (39) and converted it into cis-2-(benzylthio)cyclohexyl benzyl sulphone (40) with potassium thiobenzoate. Lithium aluminium hydride reduction unfortunately failed to reduce the sulphone function, but the synthesis still remains as a potential route to cis-dithiols.



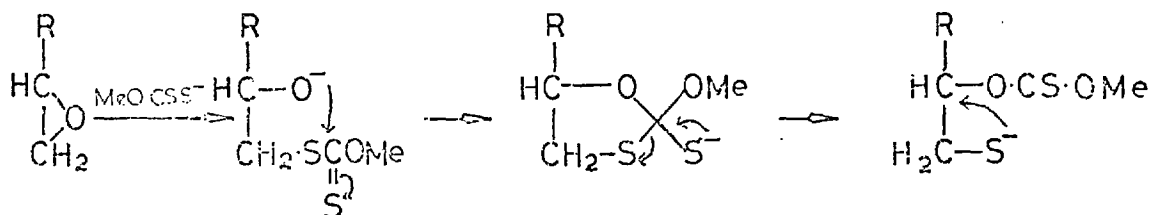
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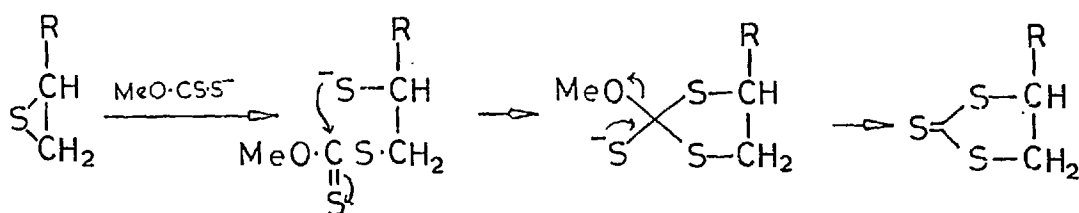


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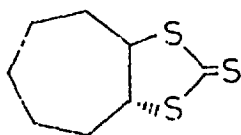
Alicyclic trans-dithiols are much more readily available than the corresponding cis-isomers. They can be prepared directly by opening of episulphide with SH^{27} , by reduction of trithiocarbonates³⁴, and by base hydrolysis of trithiocarbonates^{36,37}. trans-Cyclohexane-1,2-dithiol has been prepared in highest yield (90%) by the reduction of the trithiocarbonate³⁴. Reduction of trans-1,2-dithiocyanatocyclohexane to give the episulphide, also gave the dithiol (10%) as a byproduct⁵⁵. Other trans-1,2-dithiols prepared by reduction of trithiocarbonates include derivatives of cyclopentane³⁴, tetralin³³, and cyclohex-4-ene³³.

trans-Cyclohexene trithiocarbonate has been prepared by reaction of *O*-alkyl xanthate salts with epoxide⁵⁶ and episulphide⁵⁶. The mechanism for the formation of trithiocarbonates from epoxides via episulphides was first outlined by Culvenor et al.⁵⁶, but the stereochemical aspects were first correctly formulated by Creighton and Owen⁵⁷ in their work on terminal sugar epoxides, the reaction proceeding via the episulphide with an overall inversion of configuration as shown below:

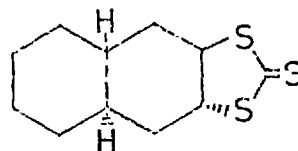




A polar solvent is essential for the formation of trithiocarbonates; trans-cyclohexene trithiocarbonate was obtained in only 3.5% yield from the epoxide using CS_2 and a tertiary amine under pressure⁵⁸. A polar solvent assists the opening of the intermediate episulphide. Other cyclic trithiocarbonates prepared from the corresponding epoxides are those based on cycloheptane (41)⁵⁹ and trans-decalin (42)⁵⁴.

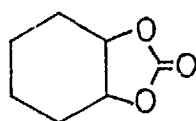


(41)

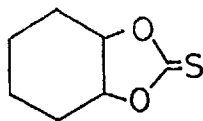


(42)

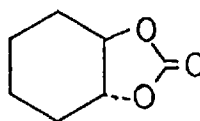
trans-Cyclohexene trithiocarbonate has also been prepared by the action of O-alkyl xanthate salts on thiocarbonates (43)-(48)⁵⁹ and (49)⁶⁰, although only (47)-(49) gave a high yield. The mechanisms of trithiocarbonate formation from these compounds will be discussed in the results section. Other preparations of trans-cyclohexene trithiocarbonate were from 2-(2,4-dinitrophenylthio)cyclohexanol (50)⁶¹, trans-2-chlorocyclohexanol⁵⁵ and from trans-2-chlorocyclohexane thiol²⁷.



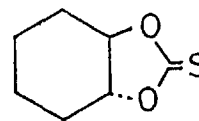
(43)



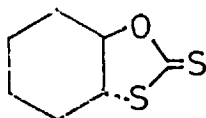
(44)



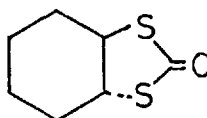
(45)



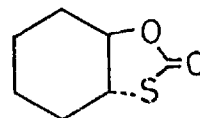
(46)



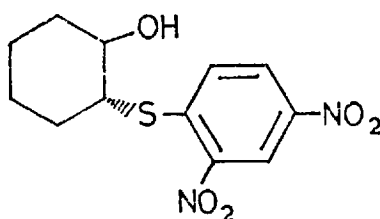
(47)



(48)

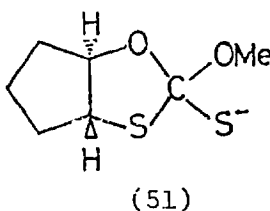


(49)



(50)

Iqbal and Owen³⁴ found cyclopentene trithiocarbonate to be readily available from the episulphide, but the epoxide only gave trans-2-mercaptocyclopentanol, because the necessary intermediate for trithiocarbonate formation (51) contains two trans-fused five membered rings, and is not formed because of strain. 3,4-Epoxytetrahydrofuran, 3,4-epoxytetrahydrothiophene and 1,2-epoxyindane similarly failed to give trithiocarbonates³³.



PREPARATION OF GEM DITHIOLS

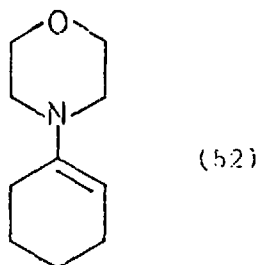
(a) from ketones and aldehydes

This route was first used by Cairns et al.⁶² who treated aldehydes and ketones with hydrogen sulphide under pressure, and confirmed the structures by the following reactions:

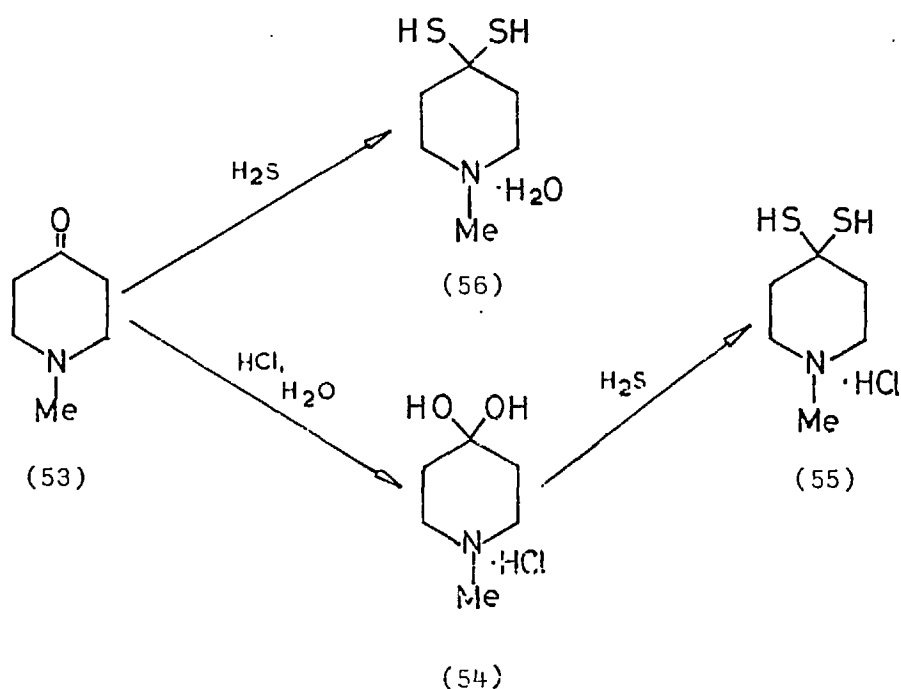


Certain aldehydes give good yields under pressure, but other carbonyl compounds require pressures of 7,500 - 8,500 atmospheres. A modification of this method⁶³ gave the first crystalline gem dithiol, 2,2-dimercapto-1,3-diphenyl propane, by the combined action of hydrogen chloride and hydrogen sulphide on dibenzyl ketone at atmospheric pressure. Previously, these conditions had been reported as giving thiones, which then trimerized⁶⁴, probably due to alkaline work up. Campaigne and Edwards⁶⁵ found the reaction to be less general than might be expected; only three out of twelve alkyl ketones giving a gem dithiol. One of these was 1,3-di-p-chloro-phenyl-2-propanone; 2-indanone gave the trithione, others, for example 1,1-diphenyl-2-propanone, the α,β -unsaturated sulphide, phenyl-2-indanone the enethiol and 1,3-di-p-nitrophenyl-2-propanone did not react. About

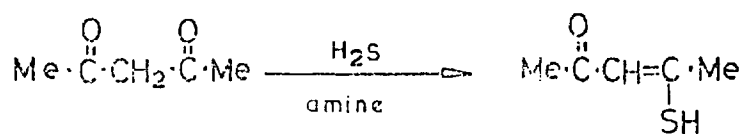
the same time, Magnusson⁶⁶ found several ketones that give trimers of the thione or did not react under these conditions. Fluorinated or chlorinated aldehydes and ketones which gave stable gem diols were found to give the gem hydroxythiol on treatment with hydrogen sulphide⁶⁷. 1,3-Dichloro-1,1,3,3-tetrafluoro-2-mercapto-2-propanol was prepared from sym-dichlorotetrafluoro acetone in 81% yield at 80°, but in lower yield at room temperature. Cyclopentanone and cyclohexanone were converted to the 1,1-dithiols by hydrogen sulphide in a polar solvent with morpholine as a catalyst⁶⁸. The conversion of 1-morpholinocyclohexene (52) to cyclohexane 1,1-dithiol by hydrogen sulphide⁶⁹, suggests that where catalysis is by a primary or secondary amine, the conversion of ketones to gem dithiols proceeds via the enamine.



A search for 1-methyl pyridines having a sulphur functional group in the 4 position, for use as potential antiradiation compounds led to the treatment of 1-methyl-4-piperidone (53) with hydrogen chloride and hydrogen sulphide, and gave the trimer of the corresponding thioketone.⁷⁰ Conversion of the starting material (53) to the gem diol hydrochloride (54), followed by reaction with hydrogen sulphide in isopropyl alcohol gave the desired dithiol as the hydrochloride salt (55). The dithiol hydrate (56) was obtained by reaction of (53) with hydrogen sulphide in isopropyl alcohol.

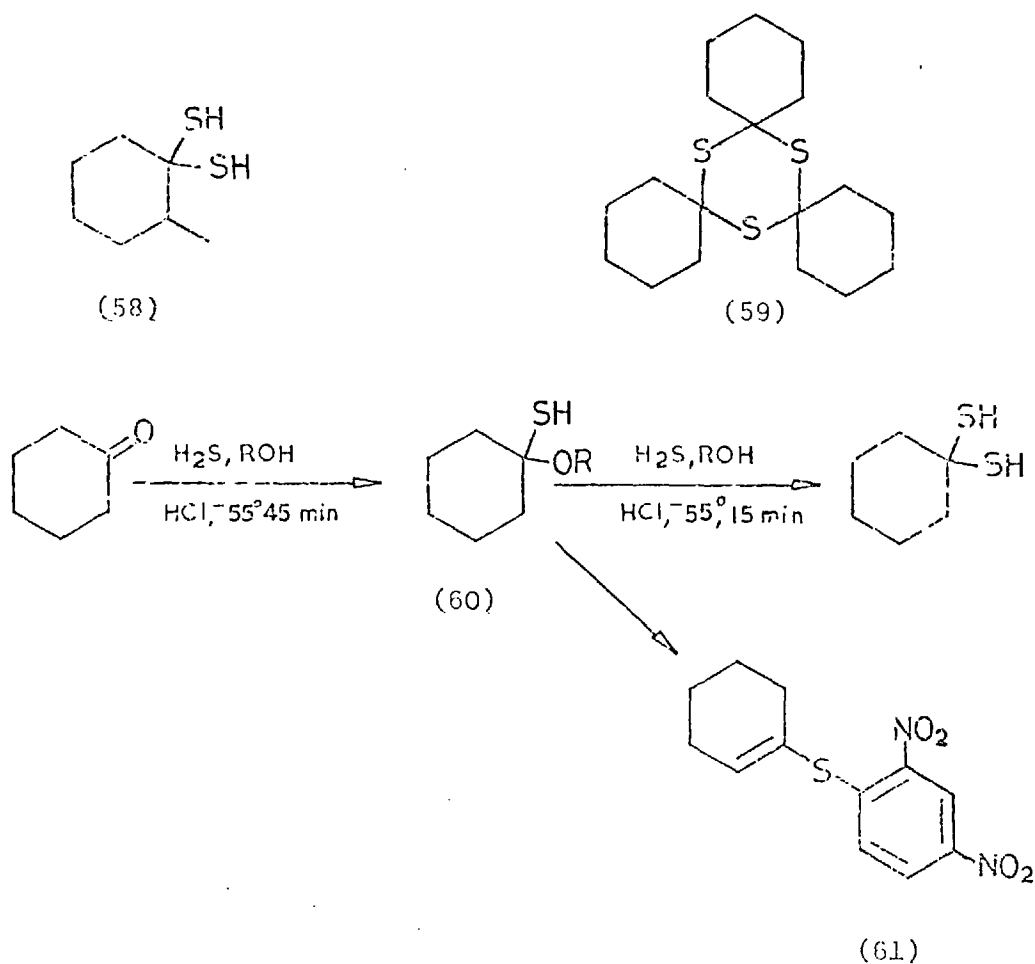


The base catalysed reaction of ketones with hydrogen sulphide has been evaluated on the basis of the effects of different amines and solvent systems⁷¹. Thiones are sometimes isolated as the sole product, or as a byproduct, and are usually formed by elimination of hydrogen sulphide from the dithiol on distillation. From monoketones, the yields are generally low, with the exception of cyclic ketones. Ammonia, and primary and secondary amines, were found to be suitable general catalysts, but a tertiary amine, triethylamine, gave no, or poor yields, even with cyclohexanone; the partial success was attributed in this case to the known complex between triethylamine and cyclohexanone. 1,3-Diketones were found to give the mono-thioketones, for example, 2-mercapto-2-pentane-4-one (57) was formed from acetyl acetone.



(57)

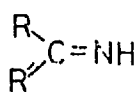
It was also found that 1,2-diketones were reduced quantitatively to the monoketone by hydrogen sulphide, but with an amine present, the hydroxy ketone is formed. The cycle of gem dithiol to thioketone to gem dithiol has been confirmed in the case of cyclohexane 1,1-dithiol. Heating eliminates hydrogen sulphide to give the thione and the gem dithiol can be regenerated by adding hydrogen sulphide⁷². A more thorough study of the conversion of ketones to gem dithiols with hydrogen sulphide has been made⁷³. 1-Methyl cyclohexanone in ethanol at 0°C gave the 1,1-dithiol (58) but cyclohexanone gave the trimer (59). At -55°C, cyclohexanone also gave the dithiol, the reaction proceeding via the intermediate alkoxy thiol (60), which was proved by isolating the 2,4-dinitrochlorobenzene derivative (61).



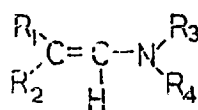
Bleische and Mayer⁷⁴ have studied the acid catalysed conversion of aliphatic ketones and β -ketoacids to the corresponding gem dithiols with hydrogen sulphide at atmospheric pressure.

(b) from enamines and ketimines

Ketimines (62) and enamines (63) can usually be prepared from the parent ketones, and provide a potentially useful route to gem dithiols when the parent ketone fails to react.

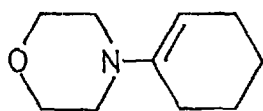


(62)

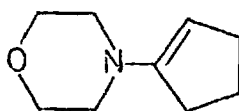


(63)

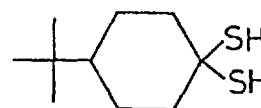
Nomura and Takeuchi⁷⁵ first described the treatment of enamines with hydrogen sulphide, and reported the products to be thioketones. This reaction was later found to give gem dithiols^{68,69}. Simple aliphatic ketones can be converted to gem dithiols via the ketimine, but sterically hindered ketones, such as dicyclohexyl ketone, do not give ketimines.⁷⁶ Generally, treatment of the ketimine with hydrogen sulphide at temperatures between -40° and 0° , followed by acidification, gives the gem dithiol, sometimes in good yield⁷⁷. Magnusson⁷⁶ prepared 2,2-dimercapto-3,3-dimethyl butane, which has a melting point of 200° by this route. The conditions of Nomura and Takeuchi⁷⁵ were used on 1-morpholine cyclohexane (52) and 1-morpholino cyclopentane (64) and gave the gem dithiol in both cases⁶⁹. It was suggested that this is the best route for the preparation of gem dithiols, even though 3-morpholino- Δ^2 -cholestene gave the trithione⁶⁹, this last reaction being ascribed to a change in solvent. Enamines were found to give similar results, and the substituted cyclohexane 1,1-dithiol (65) has been prepared by this route⁷⁸.



(52)



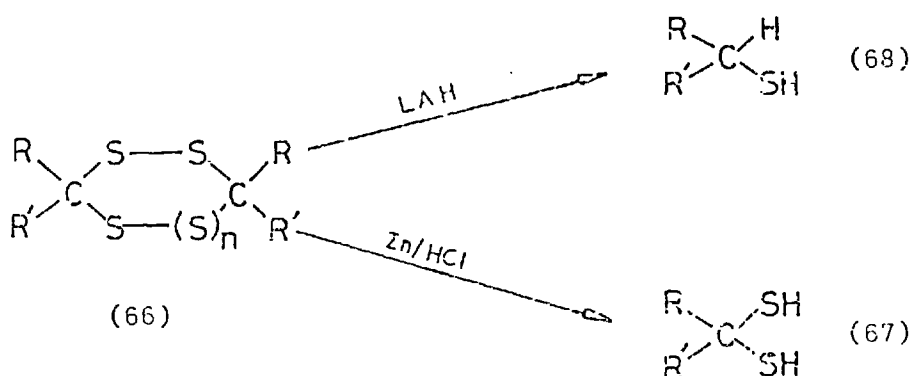
(64)



(65)

(c) preparation via thiane rings

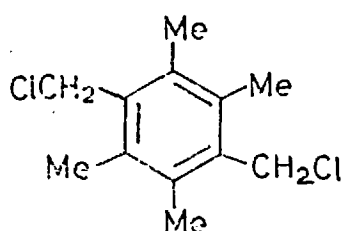
Tetra and pentathiane rings (66) (prepared from ketones by reaction with ammonium polysulphide⁷⁴) have been reduced to gem dithiols (67) with zinc and hydrochloric acid but lithium aluminium hydride gave the monothiol (68)⁸⁰.



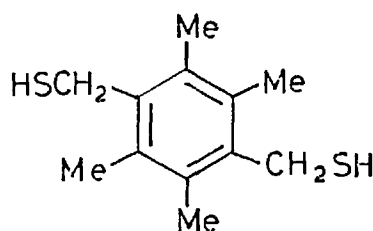
AROMATIC DITHIOLS

The preparation of aromatic dithiols is not necessarily straight forward, due to the activating or deactivating effect of substituents already present. Thiolation on the substituent groups themselves is straight forward. Bis(mercaptomethyl) compounds are prepared from the corresponding bis(halomethyl) compounds by treatment with two moles of a thio compound, such as thiourea, dithiocarbamates, xanthate, and the

mercapto compound obtained by hydrolysis or ammonolysis⁸¹. Bis(chloromethyl)durene (69) was converted to bis(mercaptomethyl)durene (70) via the dithiuronium compound.



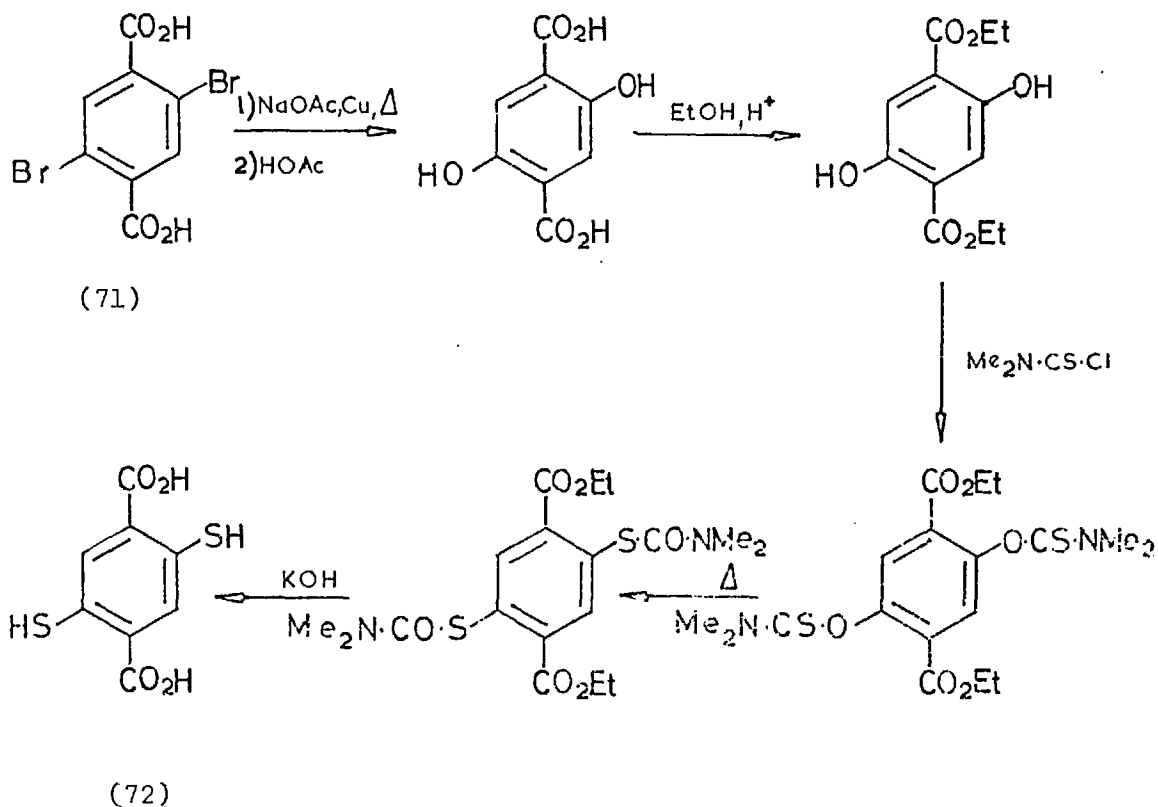
(69)



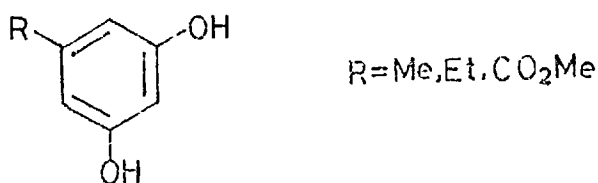
(70)

Generally, aromatic dithiols can be prepared by reduction of disulphonyl chlorides⁸², and by dealkylation of bis(alkyl) thiobenzenes with sodium in liquid ammonia⁸³. In the second method, the thioether is prepared from the aromatic dibromo compound, and is especially useful if the dibromide is more accessible than the corresponding sulphonic acid or sulphonyl chloride. One method for the preparation of the thioethers involves reaction of the dibromides with cuprous mercaptides⁸⁴.

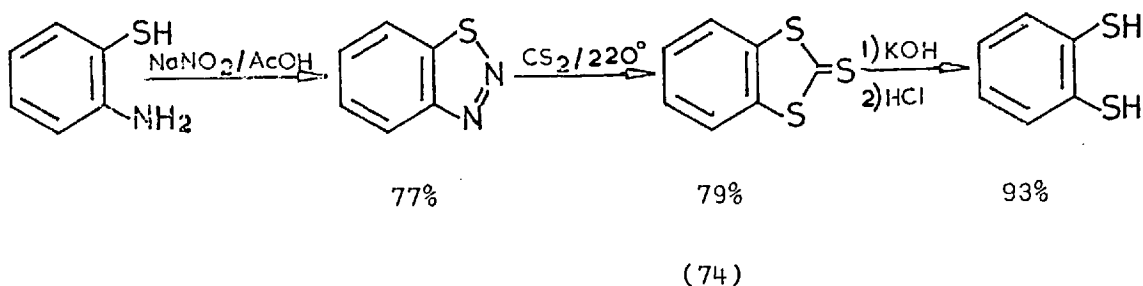
Some aryl halides can undergo direct nucleophilic replacement of halogen, but these reactions only proceed if strong electron withdrawing groups are present in the compound. Thus the best route for the preparation of 2,5-dimercapto phthalic acid was found to be as shown in the scheme⁸⁵ (direct conversion of (71) to (72) with copper and potassium hydrogen sulphide gave an impure product). This was an evaluative study to find the best route for a bifunctional system. This scheme also illustrates the conversion of phenols using dialkylthiocarbamoyl chloride, and a modified Newman-Kwart rearrangement.



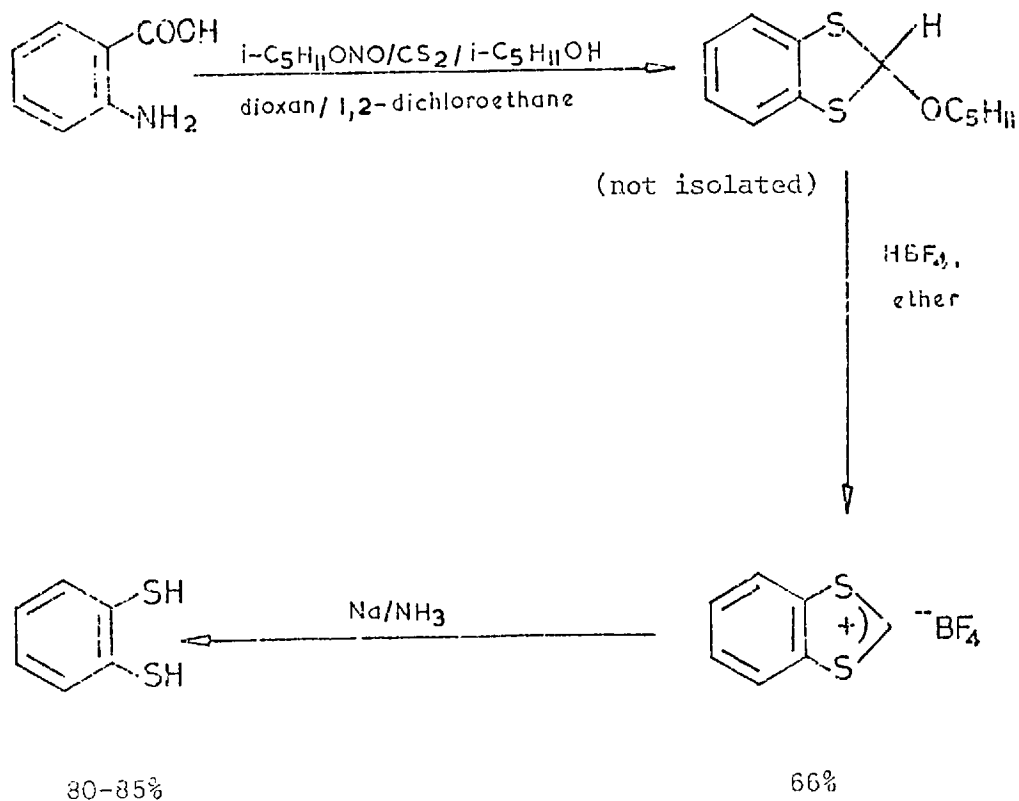
Diamines can be converted, via the diazonium salt, with thiourea to the corresponding dimercapto compounds⁸⁶. Thiophenol has been converted to 1,4-dimercaptobenzene via the sulphonyl chloride in low (22%) yield⁸⁷. Kurth *et al.*⁸⁸ prepared three substituted mercapto benzenes from substituted resorcin (73) via the *Q*-aryl thiocarbamates, which were converted to the *S*-aryl thiocarbamates, and hydrolysed to give the dithiols.



Benzene-1,2-dithiol has been conveniently synthesised via the trithiocarbonate (74)⁸⁹:-

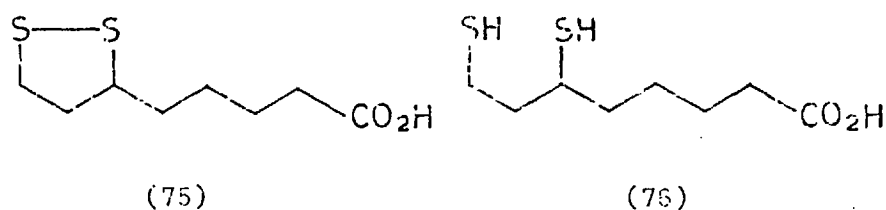


More recently, anthranilic acid has been converted to benzene-1,2-dithiol via the tetrafluoroborate salt⁹⁰:-



BIOCHEMISTRY OF DITHIOLS

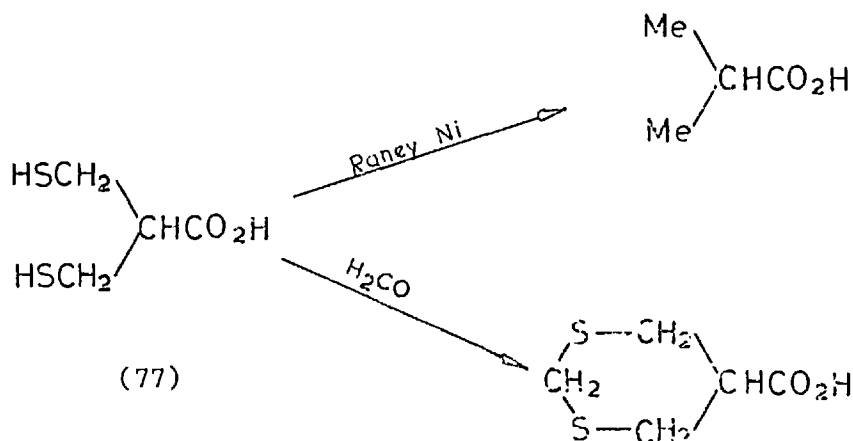
Macromolecular dithiols are relatively common in nature, an example being thioredoxin, a dithiol protein, which was isolated from Baker's yeast⁹¹, and functions in the transport of electrons from reduced nicotinamide adenine dinucleotide phosphate (NADPH) to ribonucleotides in the biosynthesis of 2'-deoxyribonucleotides. By contrast, very few low molecular weight dithiols have been discovered. The best known of these is dihydrolipoic acid (76), the reduced form of α -lipoic acid (75)^{92,93}.



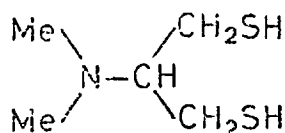
This disulphide-dithiol cofactor is covalently bound to one of the enzymes in a multienzyme system which catalyses oxidative decarboxylation of α -keto acids.⁹³ As its reduced form (76), it exists as a constrained dithiol system, which readily undergoes oxidation to an intramolecular disulphide. This transformation is the key to the use of dithiols in biological systems, the oxidation potential of such a process being much lower than comparable intermolecular processes, for example, cysteine to cystine. α -Lipoic acid was first isolated by Reed *et al.*⁹⁴, and the structure of the oxidised form (75) was established by Bullock *et al.*⁹⁵

2,2'-Dimercaptoisobutyric acid (77) was isolated from asparagus

by Jansen⁹⁶, who proved the structure by Raney nickel desulphurisation, and by reaction with formaldehyde. The dithiol acid was synthesised from the 2,2'-diiodocompound via the dithiolacetate⁹⁷.



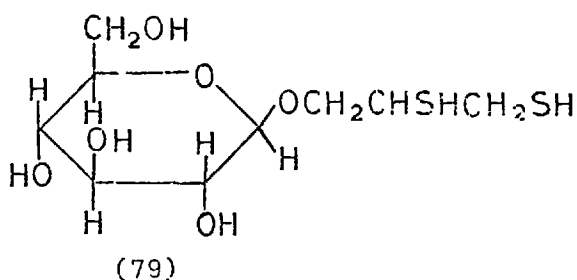
More recently the structure of 2-dimethylaminopropane-1,3-dithiol (dihydroneisostoxin) (78), isolated from marine anellid, was determined⁹⁸; the first synthesis was of its oxalate by Hagiwara *et al.*⁹⁹.



(78)

The recognition of dithiol centres in proteins¹⁰⁰ led to the development of 2,3-dimercaptopropanol (British Anti Lewisite, BAL) as an antidote for arsenic poisoning¹⁰¹. Cyclic dithioarsenites are much more stable than acyclic analogues derived from monothiols, and this formed the basis of the chemotherapeutic use of BAL to remove arsenic from the body, since

the dithiol abstracts the metal from the less stable compounds formed between it and the protein thiols. The O-glucoside (BAL-intrav)(79) was found to be particularly effective¹⁴; it was less toxic than BAL, and could be administered intravenously, being water soluble.

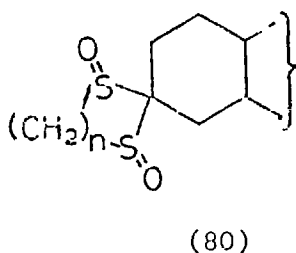


Almost any dithiol will complex with arsenic, and other metals, more efficiently than a monothiol but in chemotherapeutic applications, many dithiols are very toxic in their own right. A major application of dithiols in biochemical studies has been their use in protecting protein thiols from disulphide formation. Cleland¹⁰² developed the use of dithiothreitol (Cleland's reagent), and its isomer, dithioerythritol, in this field. Dithiothreitol has a very low redox potential, -0.33 volts at pH 7, and is capable of not only maintaining thiols in the reduced state, but also of reducing disulphides quantitatively. The other advantages are that it is water soluble, not readily air oxidised, and has little odour. Since the original report, this reagent has grown more and more popular, and there are now numerous recorded instances of its use in biochemical studies.

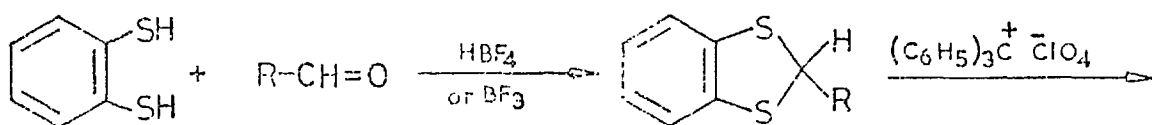
The use of dithiols in biochemistry has commercial applications; a patent¹⁰³ describes the use of 1,4-dimercapto-2,3-butane diol as the reducing agent in human hair waving preparations.

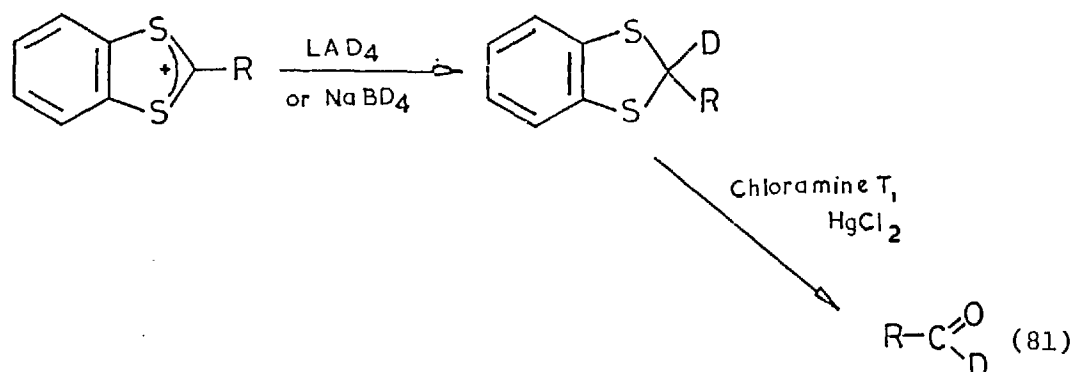
USES OF DITHIOLS

Propane-1,3-dithiol and ethane-1,2-dithiol have often been used to form dithioacetals, and this area has been reviewed¹⁰⁴. These dithioacetals are used as a carbonyl protection group, for the reduction of carbonyl groups, as a methylene blocking group, and as intermediates in the preparation of complex hydrocarbons, olefins, aldehydes and ketones. Steroidal dithiol acetals have been converted back to the ketone via the disulphoxide (80)¹⁰⁵, which is hydrolysed to the ketone by aqueous base.



There are many instances of specific dithiols being used in synthesis; one interesting example is the use of benzene-1,2-dithiol in the synthesis of aromatic and aliphatic 1-deuterioaldehydes (81)¹⁰⁶:-



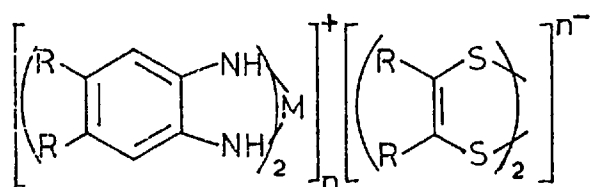


Industrially, polymercaptans have potential uses, and have been prepared by reaction of dithiols with polymethylene dihalides¹⁰⁷, polyepoxides¹⁰⁸, acetylenes under free radical conditions^{109,110} and bis(sulphenylthiocarbamates).¹¹¹ The reaction of polydimercaptans with halo-hydrins or cyclic oxides¹¹², and oxidative coupling of dithiols^{113,114} also give polymers. Another application has been the use of dithiols as cross linking agents in the vulcanisation of rubber¹¹⁵.

Mention has already been made of the reaction of 2,3-dimercapto-propanol with arsenicals, but it has long been known that dithiols form complexes with many metals, ethane dithiol being first isolated as its lead complex.¹ An early study¹¹⁶ isolated dithiol complexes of metals such as iron, lead, and tin, and subsequent workers realised the analytical applications of such complexes. Toluene-3,4-dithiol, which can be stored as its zinc complex (treatment with dilute acid or base releasing the free thiol), was developed as a general analytical reagent for qualitative analysis of metals such as copper, cobalt, bismuth, thallium and antimony¹¹⁷⁻¹²¹. Hoyer *et al.*¹²² have recently reviewed the use of unsaturated 1,2-dithiolato ligands as analytical reagents for the photometric determination of transition metals in trace amounts.

The tremendous growth in the ligand chemistry of transition metals has resulted in the discovery of some potentially useful complexes.

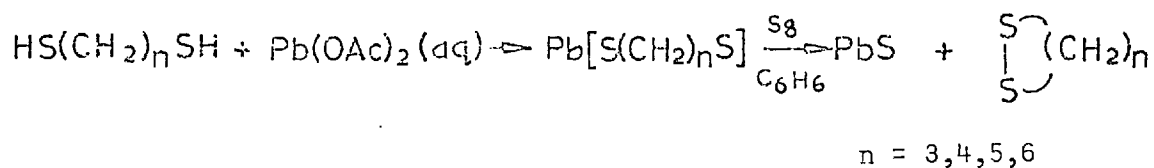
For example, Miles and Wilson¹²³ found certain metal salts of the general type shown below (82) to be semiconducting, one of the best in this respect being tris(O-phenylenediamine) nickel bis(ethenedithiolato) nickelate.



(82)

Generally, in complex studies, the dithiolato ligands are unsaturated, for example toluene dithiol and maleonitrile dithiol, the reason for this being that electron transfer reactions are facilitated. Recent studies include the dithiolato complexes of molybdenum and tungsten¹²⁴, and complexes of indium with bidentate sulphur ligands¹²⁵. Uri¹²⁶ reported the development of new α -dithiodiketone chelates, particularly bis(stilbene-dithiolate) nickel as antioxidants that combine in a unique way the properties of free radical acceptors, peroxide decomposers, and u.v. stabilisers.

Finally, lead complexes of dithiols have been used in the preparation of cyclic sulphides¹²⁷:-



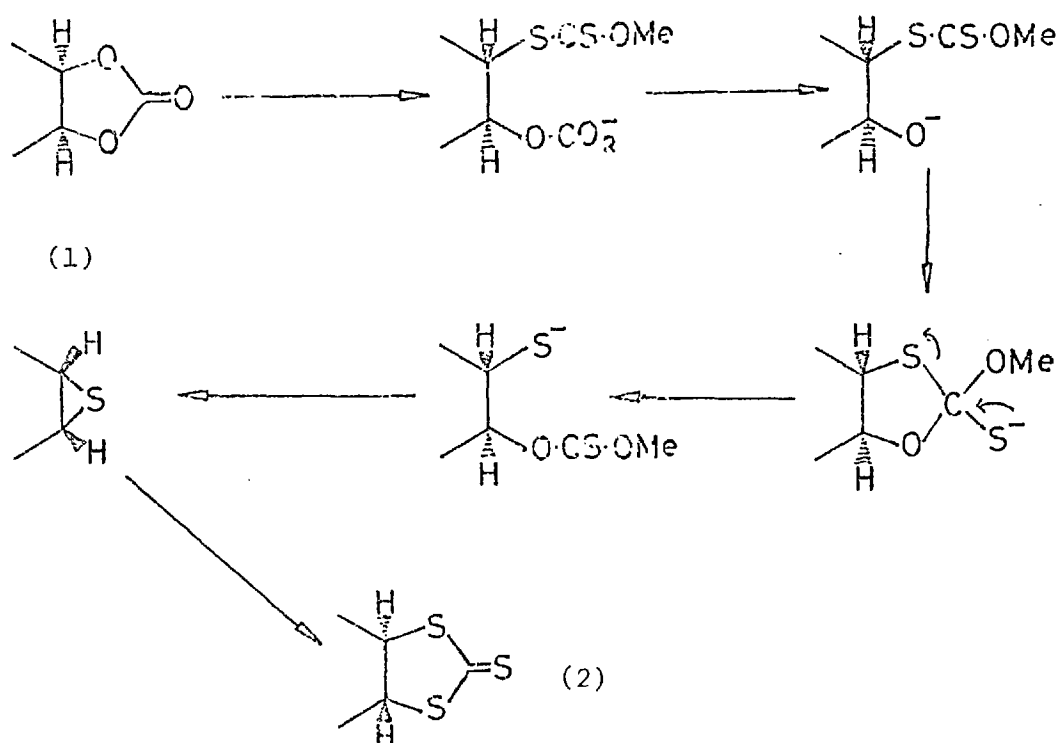
The advantage of this method is that the two sulphur atoms are held close together, and polysulphide formation is eliminated.

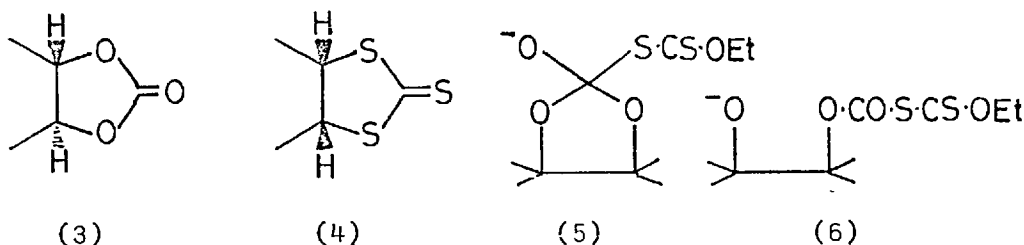
DISCUSSION
AND RESULTS

PART 1 THE SYNTHESIS OF SOME CYCLIC THIOCARBONATES AND THEIR REACTION
WITH POTASSIUM METHYL XANTHATE

INTRODUCTION

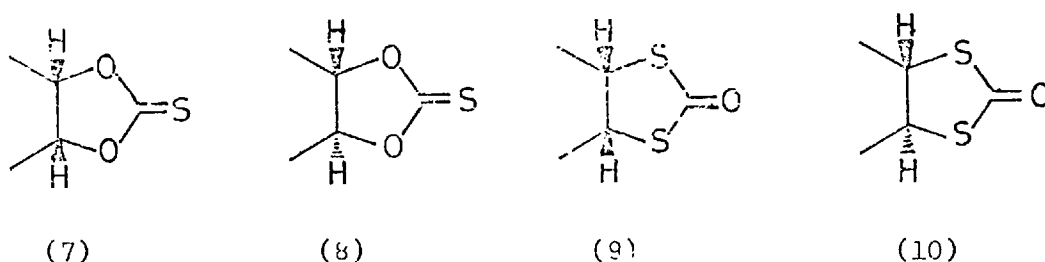
Kardouche and Owen⁵⁹ have obtained cyclic trithiocarbonates from cyclic carbonates and thiocarbonates, prepared from 1,2-diols, by reaction with *O*-alkyl xanthate salts. The *cis*-butane carbonate (1) afforded the *trans*-trithiocarbonate (2) in 18% yield, in accord with the expectation that attack by xanthate would initially give the *cis*-episulphide, as shown below; the subsequent reaction of this compound proceeds with inversion of configuration at one carbon atom, as shown by Creighton and Owen⁵⁷. The DL-carbonate (3) was found to give the *cis*-trithiocarbonate (4) in 34% yield, by the same mechanism.





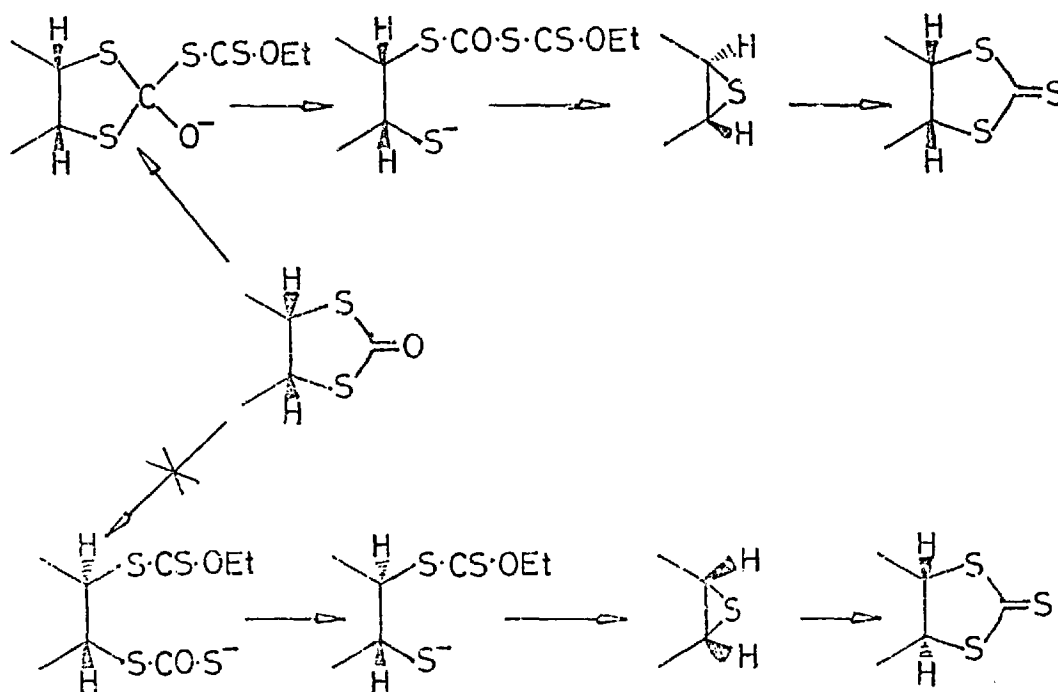
The low yields of trithiocarbonates obtained from (1) and (3) were ascribed by these workers to competitive attack on the carbonyl group, which leads to intermediates of types (5) and (6). The mixed anhydride (6) is probably easily solvolysed to give the diol, and this leads to loss of substrate.

In order to confirm this view, cis- and trans-4,5-dimethyl-1,3-dioxolan-2-thione, (7) and (8), were prepared, and as expected, because of the lower nucleophilic susceptibility of the thiocarbonyl group, the yields of trithiocarbonate were higher.



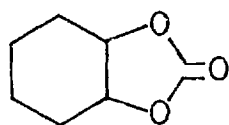
The dithiocarbonates (9) and (10) gave back the parent trithiocarbonate in almost quantitative yield on reaction with xanthate. Attack at the alkyl position, with inversion of configuration, followed by loss of carbonyl sulphide and cyclisation, would lead to the trithiocarbonate of opposite configuration; Kardouche and Owen therefore concluded that fission of the carbon-sulphur bond must be difficult, and

is overshadowed by attack on the carbonyl group, which leads to the tri-thiocarbonate of the observed configuration:

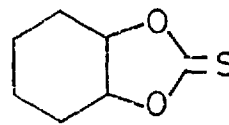


These authors also reacted cis-4,5-cyclohexano-1,3-dioxolan-2-one (11) and cis-4,5-cyclohexano-1,3-dioxolan-2-thione (12) with xanthate, and both were found to give the trans-trithiocarbonate in 29% and 60% yield respectively; the stereochemical result being the same as that observed with the cis-carbonate (1) and the cis-thiocarbonate (7). The corresponding trans-compounds (13) and (14) also gave the trans-trithiocarbonate, but in low yield; this must be formed by a different mechanism since the normal mechanism (attack at the "alkyl" position) would require the formation of the non-existent trans-1,2-epithiocyclohexane. Attack at the alkyl position would, therefore, be non-productive of the cis-trithiocarbonate, and the formation of the trans-trithiocarbonate must arise from attack at the carbonyl or thiocarbonyl group to give intermediates similar to (6) which amongst other reactions can form some

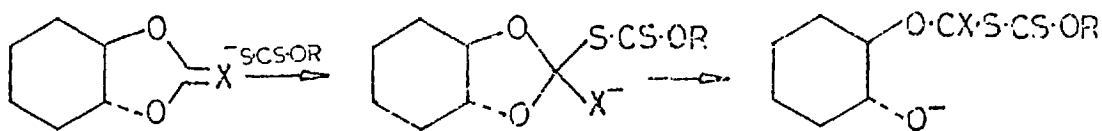
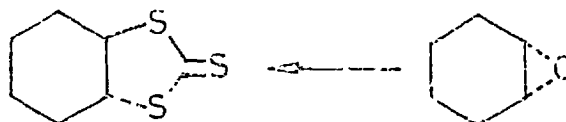
1,2-epoxycyclohexane and hence the trans-trithiocarbonate. This mechanism was supported by the lower yield from the thiocarbonyl compound (13), 5%, compared with 12% from the carbonyl compound (14).



(11)

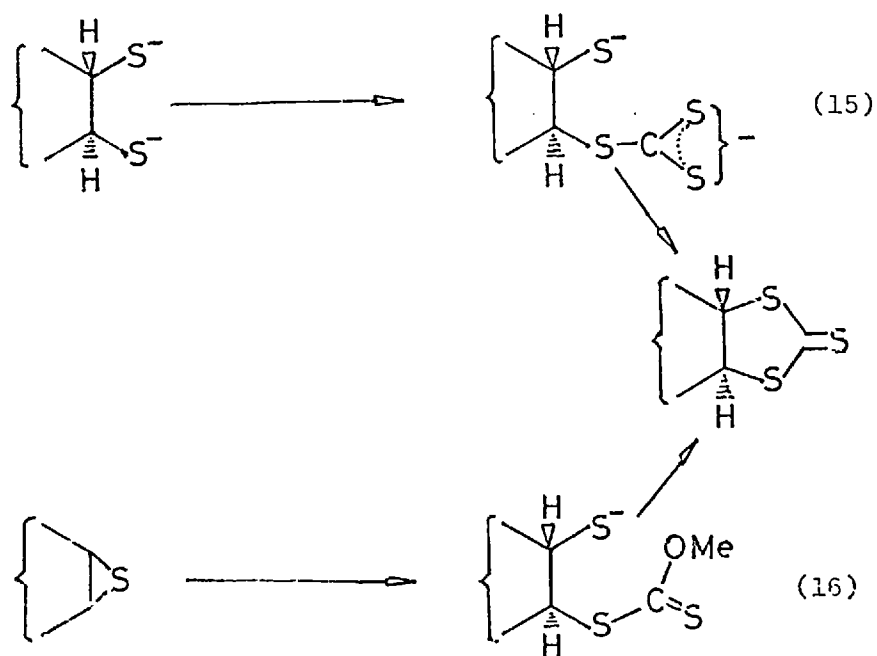


(12)

(13) $X = S$ (14) $X = O$ 

Kardouche¹²⁸ has discussed the above mechanism much more thoroughly and has considered the alternative pathways in greater detail.

Kyaw and Owen³³ suggested a mechanism for the reaction of dithiols with sodium methyl xanthate, which proceeds by way of intermediates of type (15). In contrast, the reaction of the episulphide leads to intermediates of type (16).



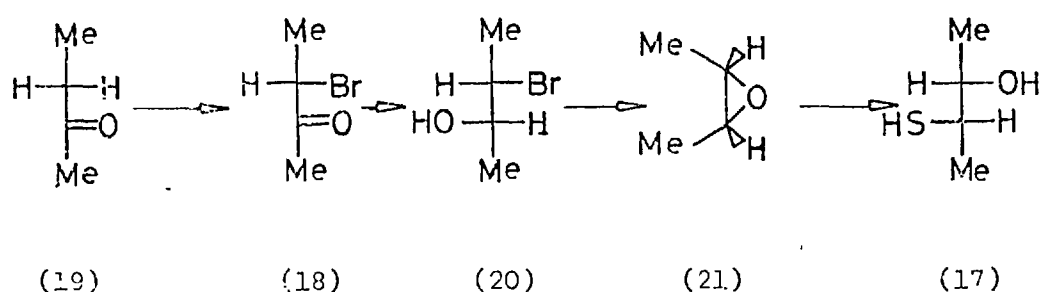
Nucleophilic attack will occur much more readily in intermediate (16), but these authors found the relative ease of attack was not critical when the highly strained trans-function has to be formed between two five-membered rings, cyclopentene sulphide giving the trans-trithiocarbonate, and trans-cyclopentane-1,2-dithiol failing to do so, even after prolonged heating.

In the present investigation, the mechanism of formation of cyclic trithiocarbonates from cyclic carbonates and thiocarbonates has been investigated further by the synthesis, and reaction with xanthate, of a wider variety of thiocarbonates, hydroxythiols and dithiols.

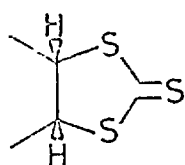
Synthesis of trans-4,5-dimethyl-1,3-oxathiolan-2-thione, trans-4,5-dimethyl-1,3-oxathiolan-2-one, (4S,5R)-4,5-dimethyl-1,3-oxathiolan-2-thione and (4S,5R)-4,5-dimethyl-1,3-oxathiolan-2-one, and their reactions with potassium methyl xanthate

The following reactions leading to DL-threo-3-mercaptobutan-2-ol

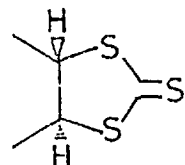
(17) were carried out. Methyl 1-bromoethyl ketone (18) was prepared by brominating methyl ethyl ketone (19), according to the procedure of Catch *et al.*¹²⁹; borohydride reduction of the bromoketone gave DL-threo-3-bromobutan-2-ol (20). Treatment of the bromohydrin (20) with potassium hydroxide gave cis-2,3-epoxybutane (21), which was opened with hydrogen sulphide, by the method of Price and Kirk¹³⁰, to give the hydroxythiol (17).



Reaction of the hydroxythiol (17) with sodium ethyl xanthate gave a mixture of cis-4,5-dimethyl-1,3-dithiolan-2-thione (4), and the trans-isomer (2).



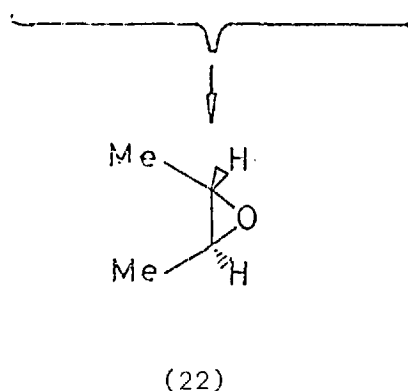
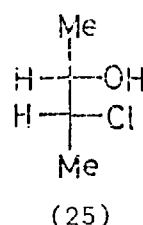
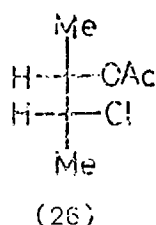
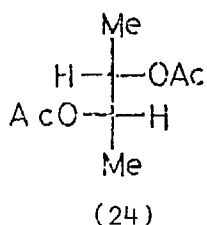
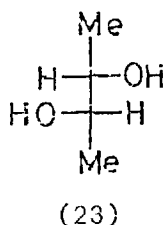
(4)



(2)

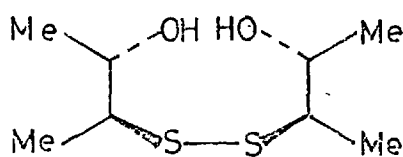
At this stage, it was realised that the cis-epoxide was not stereochemically pure, and gas-liquid chromatography showed different samples of the epoxide to contain between 20% and 40% of trans-2,3-epoxybutane (22).

A sample of the trans-epoxide was prepared from an authentic sample of DL-butane-2,3-diol (23). The diol was converted to DL-2,3-diacetoxy butane (24) by the method of Lucas and Garner¹³¹, which on treatment with hydrochloric acid and hydrogen chloride gave the expected product, DL-erythro-3-chlorobutan-2-ol (25)¹³¹, and also DL-erythro-3-chloro-2-acetoxy butane (26). Reaction of a mixture of (25) and (26) with potassium hydroxide gave the trans-epoxide. Gas-liquid chromatography showed this trans-epoxide to contain 5% of the cis-isomer, and confirmed the impurity in the original cis-epoxide to be the trans-isomer (2 metre, 15% Carbowax column, 100°; retention times: cis- 63 and trans- 57 seconds). Gas-liquid chromatography of the bromohydrin formed in the borohydride reduction showed the presence of at least 20% of the erythro-isomer.



A sample of the cis-epoxide (98% pure, by g.l.c.) was obtained from the mixed epoxides by fractional distillation through a 30 cm column packed

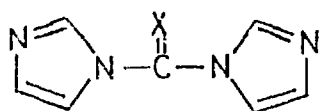
with helices, and employing a very high reflux ratio, one drop of distillate being collected every seventy seconds. The cis-epoxide was opened with hydrogen sulphide to give the pure hydroxythiol (17), and also a quantity of meso- (27), and DL-trans, trans-3,3'-dithiobis(butan-2-ol), which was formed by oxidation during work up. The disulphide structure (rather than a monosulphide formed by opening of the cis-epoxide by the hydroxythiol) was confirmed by its mass spectrum.



(27)

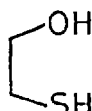
Cyclic carbonates and thiocarbonates have usually been prepared by reaction of diols, hydroxythiols, and dithiols with phosgene and with thiophosgene, although ethyl carbonate has also been used to prepare cyclic carbonates¹²⁸. Generally, the yields from these reactions are reasonable (50-60%), although cis-2-mercaptocyclohexanol failed to react with thiophosgene¹²⁸. Corey and Winter¹³² used N,N-thiocarbonyldiimidazole (28) as an alternative to thiophosgene in the synthesis of five-membered ring thiocarbonates. Early in this work, the reactions of phosgene and thiophosgene with the stereochemically impure hydroxythiol (17) were studied, but these reagents were found to be inconvenient to use, and accordingly it was decided to use the diimidazole reagent (28) instead. 2-Mercaptoethanol (29) was chosen as a model compound, and gave 1,3-oxathiolan-2-thione (30) in 84% yield. Jones and Andreades¹³³ reported the synthesis of (30) from the lead salt of the hydroxythiol and thiophosgene in 46% yield, but also found that all fractions contained 5% of the isomer, 1,3-dithiolan-

-2-one (31). In the preparation involving the diimidazole reagent, no peak was detectable at 1672 cm^{-1} in the infra-red spectrum, indicating a high degree of purity.

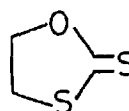


(28) X = S

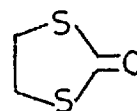
(32) X = O



(29)



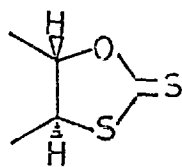
(30)



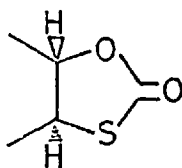
(31)

The preparation of N,N'-carbonyldiimidazole (32) was reported by Staab¹³⁴, but an attempt to repeat this failed, presumably because (32) is more sensitive to moisture, and it was therefore concluded that selective oxidation of the thiocarbonyl compounds would prove to be an adequate route to carbonyl compounds, as first described by Challenger et al.¹³⁵ for the oxidation of trithiocarbonates, and found to give high yields by other workers^{136, 137}. N,N'-carbonyldiimidazole is now commercially available, and its use in the synthesis of cyclic carbonates from diols has been reported recently to give high yields¹³⁸, and it is probable that this now represents the best synthetic route for such compounds.

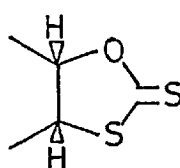
The pure hydroxythiol (17) was treated with the diimidazole reagent (28) to give trans-4,5-dimethyl-1,3-oxathiolan-2-thione (33) in 93% yield; reaction of this with mercuric acetate gave trans-4,5-dimethyl-1,3-oxathiolan-2-one (34) in 60% yield, an overall conversion of 56% from the hydroxythiol.



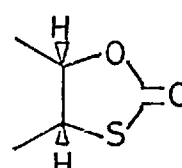
(33)



(34)



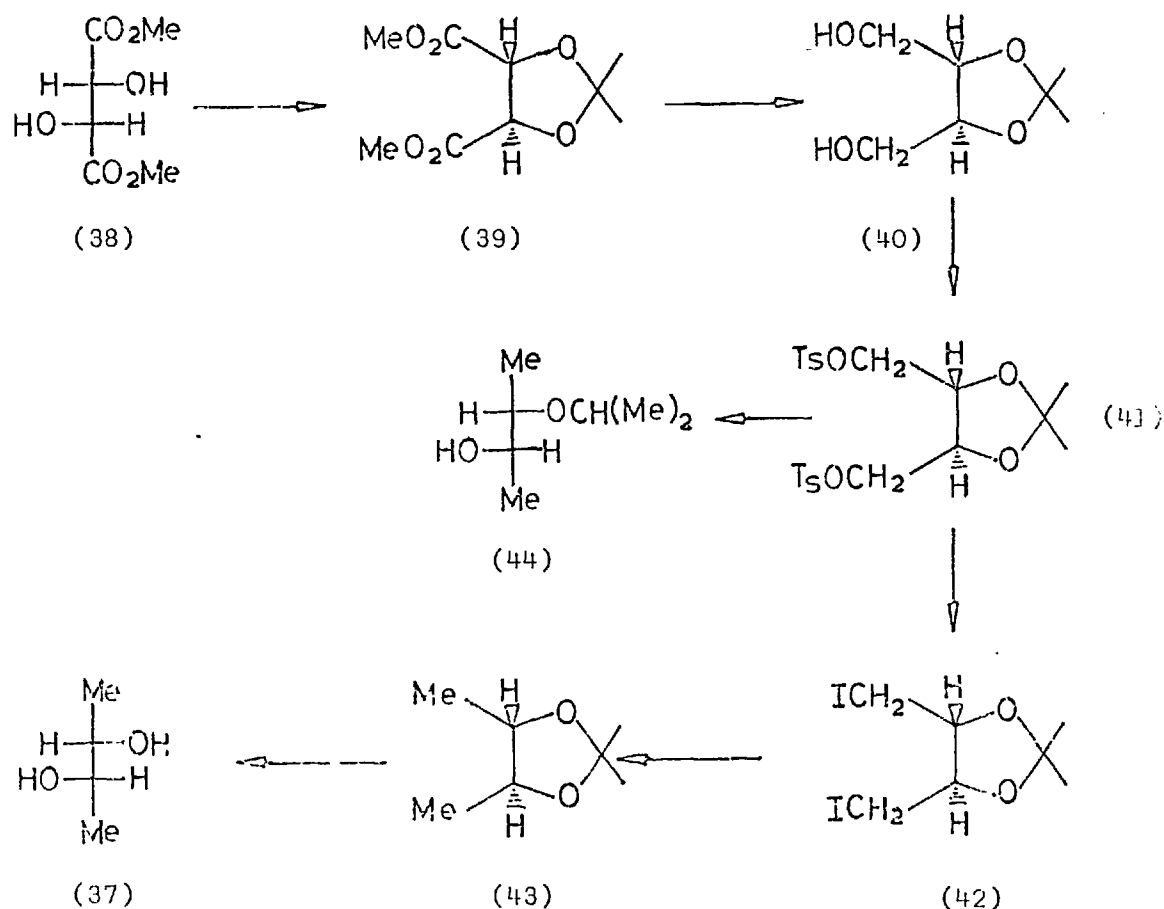
(35)



(36)

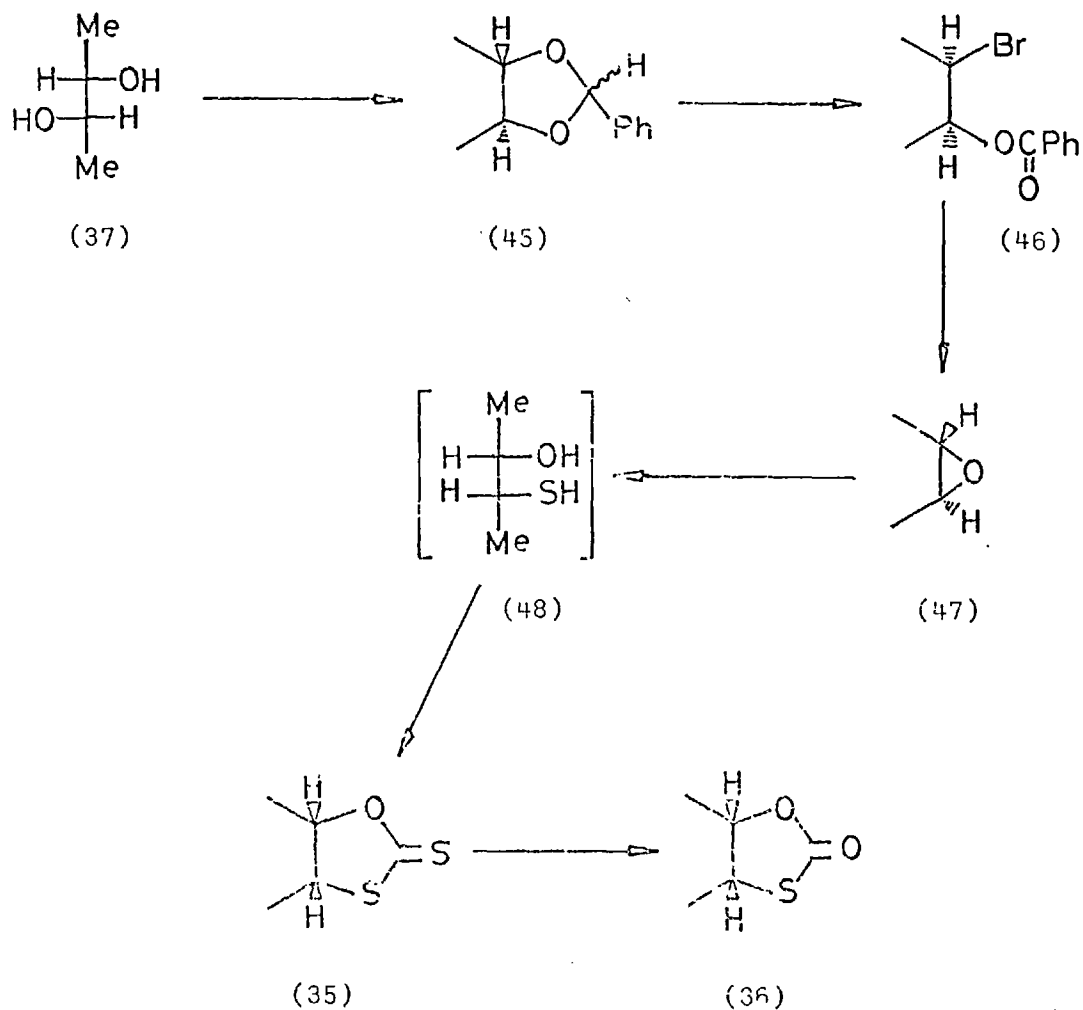
The two cis-thiocarbonates, (35) and (36) were synthesised in optically active forms, (4S,5R)-4,5-dimethyl-1,3-oxathiolan-2-thione and (4S,5R)-4,5-dimethyl-1,3-oxathiolan-2-one respectively, from L-(+)-butane-2,3-diol (37), which was prepared from L-(+)-dimethyl tartrate (38). The tartrate was converted to L-(-)-dimethyl-2,3-O-isopropylidene tartrate (39) by reaction with 2,2-dimethoxypropane using the method of Carmack and Kelley¹³⁹; reduction of this, following the procedure of Feit¹⁴⁰, gave L-(+)-2,3-O-isopropylidenethreitol (40). The optically active threitol was converted to the butane diol (37) by following the route used by Rubin et al.¹⁴¹, proceeding via the ditosylate (41) and the diiodide (42). It had been originally hoped that the ditosylate (41) would be reduced by lithium aluminium hydride to give L-O-isopropylidenebutane-2,3-diol (43) directly, but this reaction in fact gave L-(+)-2-isopropoxybutan-3-ol (44), a compound which has been reported as a derivative of butane-2,3-diol which had been prepared by fermentation of sucrose¹⁴². Rubin et al.¹⁴¹ reported that Raney nickel reduction of the diiodide to give O-isopropylidenebutane-2,3-diol gave a product which contained water as the main impurity, and which was difficult to remove. In view of this it was decided to use methanol as the solvent, and potassium acetate as a base to remove the hydrogen iodide produced. The expected product (43), however, formed an azeotrope with methanol, and during

fractional distillation the isopropylidene function was lost, and the diol (37) itself was isolated in 47% yield.



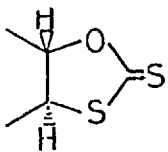
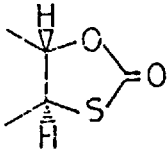
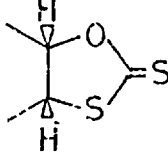
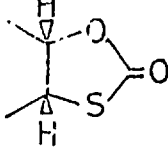
The diol (37) was converted to L-(+)-2-phenyl-4,5-dimethyl-1,3-dioxolane (45) by the method of Gagnaire and Robert¹⁴³; treatment of this with *N*-bromosuccinimide in carbon tetrachloride, as described by Seeley and McElwee¹⁴⁴, gave (2R, 3S)-2-bromo-3-benzyloxy butane (46), which on reaction with potassium hydroxide gave the trans-epoxide, (2S,3S)-2,3-epoxybutane (47). The crude epoxide was examined by gas-liquid chromatography, and was found to contain less than 2% of the cis-isomer, together with some other impurity, probably ethylene glycol. The crude epoxide was opened immediately with hydrogen sulphide to give the hydroxythiol (48), which was not isolated, but reacted with the diimidazole reagent to give the thiocarbonate (35) in 11.5% yield, based on the epoxide. Reaction

of (35) with mercuric acetate gave the thiocarbonate (36) in 58% yield. The yield from this last step was almost certainly low because of the scale of the reaction.



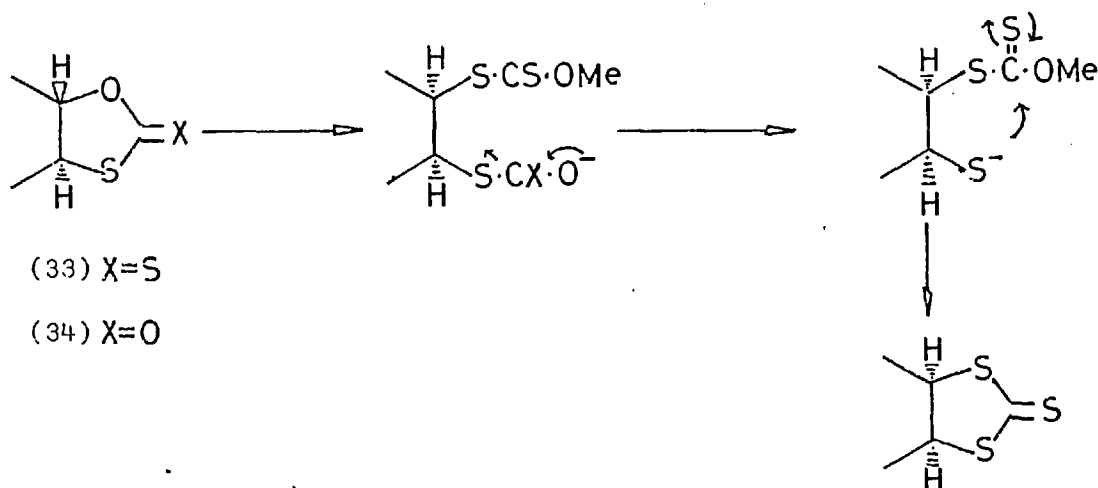
The reactions of the four thiocarbonates (33)-(36) with potassium methyl xanthate were carried out in sealed tubes at 64-66° for four days. The trithiocarbonates formed, and the yields, are summarised in Table I.

Table I

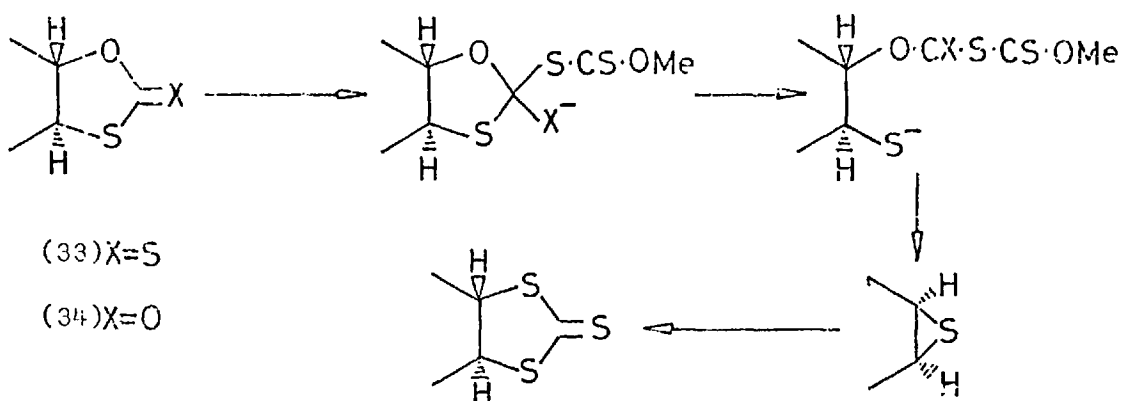
Thiocarbonate	Trithiocarbonate formed	Yield
(33) 	trans	81%
(34) 	trans	76%
(35) 	cis	46%
(36) 	cis	86%

Reactions of this type had previously been carried out¹²⁸ without taking any precautions to exclude air. Early in the present work, they were carried out in the same way, and were found to give low yields, or in the case of (35), no trithiocarbonate at all. The sealed tube method not only allows the reaction to be carried out on a small scale, but gives good yields, almost certainly because oxygen is excluded from the system by methanol vapour when the tube is sealed. The above four reactions all proceeded with retention of configuration, the products being confirmed as pure isomers by p.m.r. spectroscopy for (33), (34) and (36), and by melting points and mixed melting points for all four. It is likely that the lower yield (46%) from (35) is a spurious result; if (33) and (34) give comparable yields, within the errors imposed by the small scale, (35) should give a similar yield to that from (36).

For the trans-compounds (33) and (34), attack at the ring-oxygen site would lead, via loss of carbonyl sulphide and cyclisation, to the trithiocarbonate of opposite configuration:



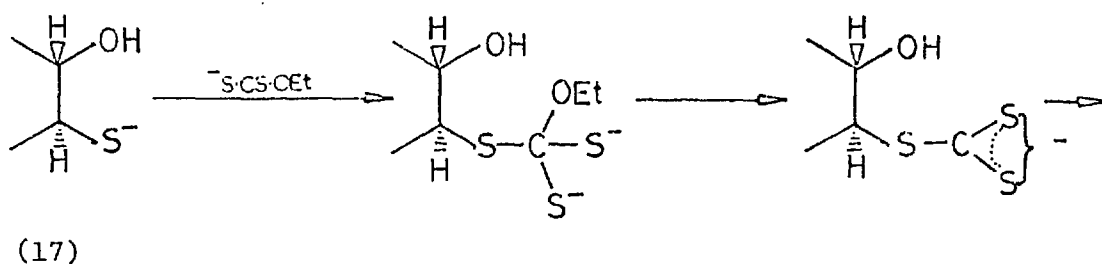
As previously discussed, Kardouche and Owen⁵⁹ concluded that fission of the carbon-sulphur bond is difficult, and is overshadowed by other mechanisms in the case of the dithiol carbonates (9) and (10), and therefore for (33) and (34), the only likely source of trithiocarbonate is via attack on the carbonyl or thiocarbonyl group:

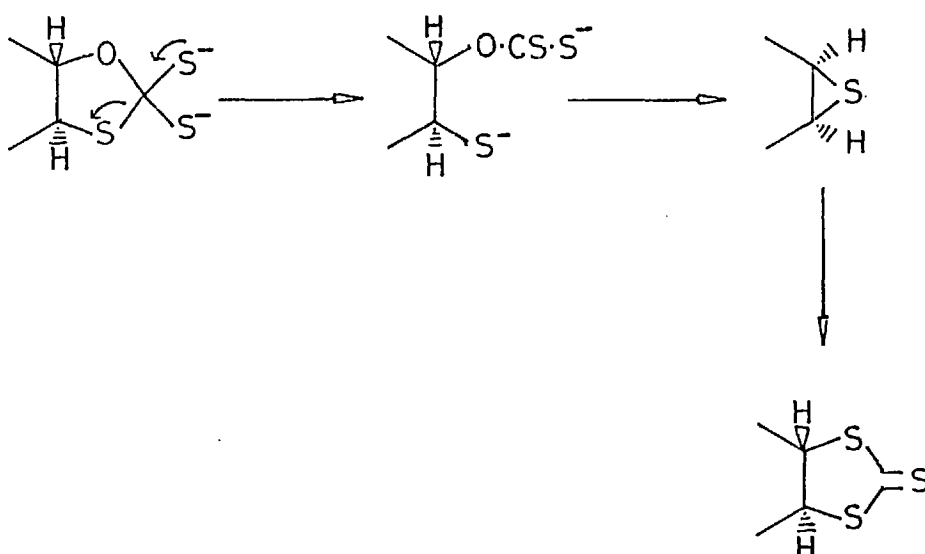


The trans-thiocarbonate (8) gave a higher yield of trithiocarbonate than the trans-carbonate (3) because the lower susceptibility of the thiocarbonyl group to nucleophilic attack reduced the likelihood of non-productive competitive attack on the thiocarbonyl group⁵⁹. It would

therefore be expected that (33) and (35) would give an appreciable quantity of the trithiocarbonate of opposite configuration, arising from attack at the ring-oxygen site, but this was not the case. The reason for this behaviour must be that, as only one site is available for attack at the ring, instead of two as in (8) and (3), the probability of successful attack is lower anyway; also, the thiocarbonyl group probably does not differ in its nucleophilic susceptibility from the carbonyl group as much as expected. This difference produced an effect in the yields from (3) and (8), but in the case of (33) and (34), it appears not to play an important role in the reaction mechanism.

DL-threo-3-Mercaptobutan-2-ol (17) was reacted with sodium ethyl xanthate to give the trans-trithiocarbonate in low yield. It was previously mentioned (p 45) that a mixture of the isomeric hydroxythiols gave a mixture of the cis- and trans-trithiocarbonates on reaction with xanthate, and although the reaction was not actually carried out, it is expected that the erythro-hydroxythiol (48) would give the cis-trithiocarbonate. Hydroxyl functions are very poor leaving groups, and the hydroxythiols must react by attack of thiol on xanthate, as proposed by Kyaw and Owen³³ for the reaction of dithiols. Inversion of configuration occurs when the episulphide intermediate is formed, followed by a second when this is opened by xanthate, resulting in an overall retention of configuration.

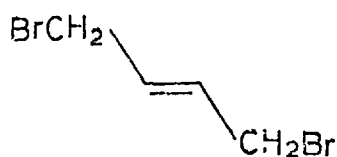




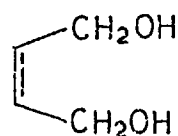
The reaction of (17) was carried out under aerobic conditions, and the low yield is almost certainly caused by sulphide formation, although no specific attempts were made to isolate such products.

Synthesis of *cis*- and *trans*-bis(benzyloxymethyl)ethylene carbonates and thiocarbonates and their reaction with potassium methyl xanthate

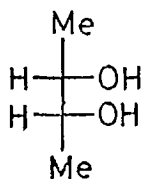
The original purpose of this part of the present investigation was to prepare a stereochemically pure butane-2,3-diol from *trans*-1,4-dibromo-2-butene (49). A potential route for the preparation of either *meso*- (50) or DL-butane-2,3-diol (23) from either the *trans*-olefin (49) or *cis*-2-butene-1,4-diol (51) was developed, *cis*- (52) and *trans*-1,4-Dibenzyl-oxy-2,3-epoxybutane (53) were prepared, and the carbonates and thiocarbonates synthesised from these.



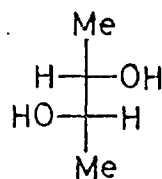
(49)



(51)

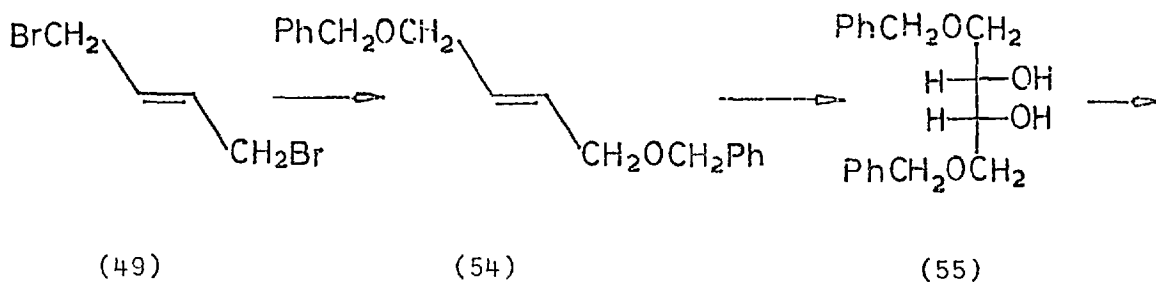


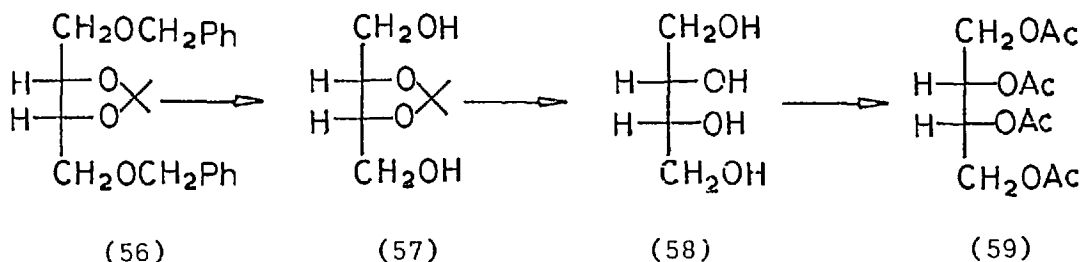
(50)



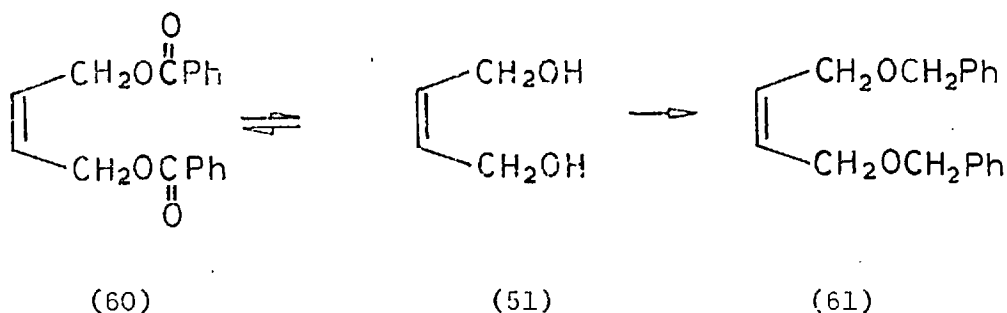
(23)

The trans-olefin (49) was converted to trans-1,4-dibenzzyloxy-2-butene (54) by the procedure of Kiss and Sirchman¹⁴⁵ using sodium and benzyl alcohol; reaction of this olefin with performic acid, following the method used by Roebuck and Adkins¹⁴⁶ on cyclohexene, gave meso-1,4-dibenzzyloxybutane-2,3-diol (55) in 75% yield. Treatment of this diol with 2,2-dimethoxypropane gave meso-1,4-dibenzzyloxy-2,3-O-isopropylidene-butane-2,3-diol (56) in 52% yield, which on reduction using a palladium-charcoal catalyst, yielded 2,3-O-isopropylidene-erythritol (57). Compound (57) was not isolated, but was converted to erythritol (58), for identification purposes, by stirring with acid ion-exchange resin. The isopropylidene compound (57) could be converted through to meso-butane-2,3-diol by the route previously described for the preparation of L-(+)-butane-2,3-diol (37), i.e. via the di-p-toluenesulphonate, the diiodide, and reduction, followed by removal of the isopropylidene function. Erythritol was converted to its tetra acetate (59) for comparison with an authentic sample.





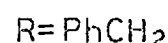
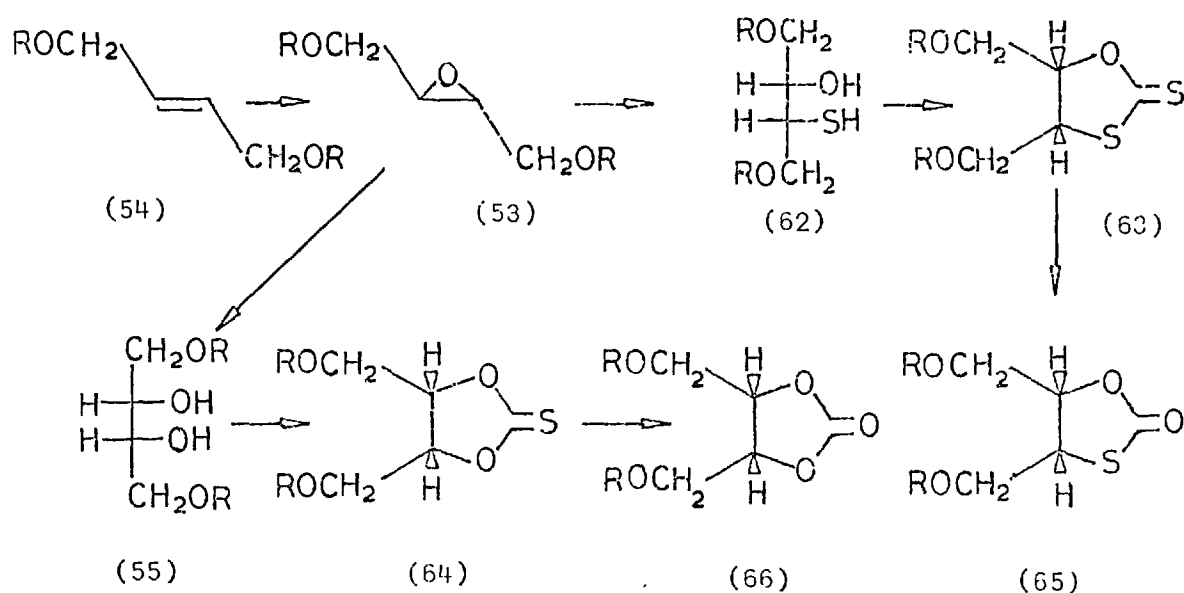
Treatment of the olefin (54) with permanganate, after the method of Clarke and Owen¹⁴⁷, gave the DL-isomer of (55); subsequent reaction of this in the manner outlined above would give DL-butane-2,3-diol. cis-2-Butene-1,4-diol (51), purified via its dibenzoate (60), was converted to cis-1,4-dibenzoyloxy-2-butene (61) by stirring with benzyl bromide and powdered potassium hydroxide; reaction of this olefin with performic acid would ultimately lead to DL-butane-2,3-diol, and treatment with permanganate would lead to the meso-diol.

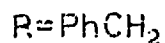
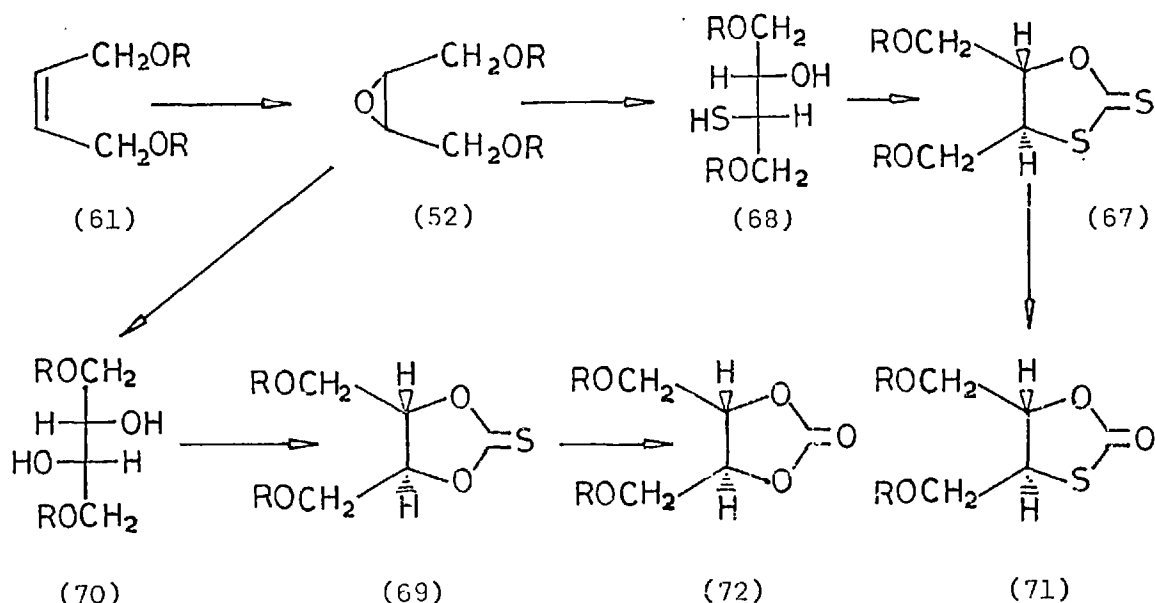


The trans-dibenzoyloxy olefin (54) was reacted with m-chloroperbenzoic acid to give the known¹⁴⁵ trans-1,4-dibenzoyloxy-2,3-epoxybutane (53). The corresponding cis-epoxide (52) was prepared from the cis-olefin (61)

using the same reagent, except that carrying out the reaction in refluxing ether was more successful than at room temperature, very little olefin remaining as impurity after one day in the first case. The trans-epoxide (53) was opened with hydrogen sulphide to give 1,4-di-O-benzyl-2-thioerythritol (62), which was not isolated but treated with thiocarbonyldiimidazole to give cis-4,5-bis(benzyloxymethyl)-1,3-oxathiolan-2-thione (63). The meso-diol (55), which was also prepared by acid catalysed hydrolysis of the trans-epoxide (53), on treatment with thiocarbonyldiimidazole gave cis-4,5-bis(benzyloxymethyl)-1,3-dioxolan-2-thione (64). Reaction of (63) and (64) with mercuric acetate gave cis-4,5-bis(benzyloxymethyl)-1,3-oxathiolan-2-one (65) and cis-4,5-bis(benzyloxymethyl)-1,3-dioxolan-2-one (66) respectively.

The same sequence of reactions on the cis-epoxide (52) led to trans-4,5-bis(benzyloxymethyl)-1,3-oxathiolan-2-thione (67) via 1,4-di-O-benzyl-2-thiothreitol (68), trans-4,5-bis(benzyloxymethyl)-1,3-dioxolan-2-thione (69) via DL-1,4-dibenzyloxybutane-2,3-diol (70), trans-4,5-bis(benzyloxymethyl)-1,3-oxathiolan-2-one (71) and trans-4,5-bis(benzyloxymethyl)-1,3-dioxolan-2-one (72).





Reaction of the trans-epoxide (53) with sodium methyl xanthate produced some surprising results. At the reflux temperature, no trithiocarbonate was isolated, but at lower temperatures, cis-4,5-bis(benzyloxymethyl)-1,3-dithiolan-2-thione (73) was isolated in varying yields. These results are summarised in Table II.

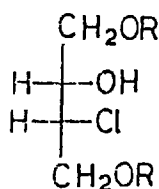
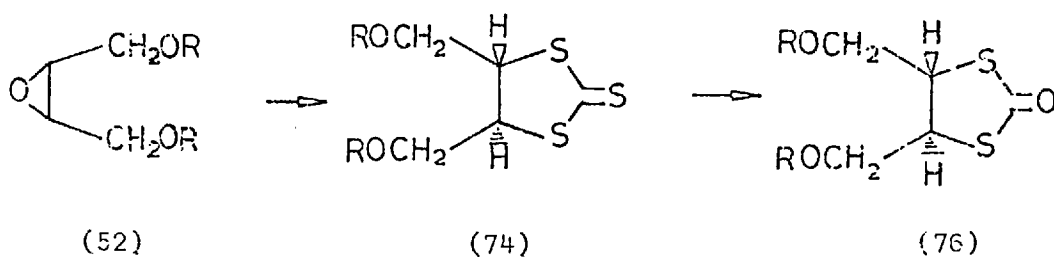
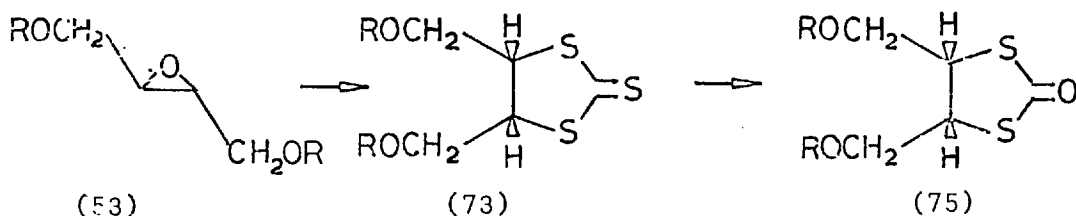
Table II

Temperature	20°	31°	40°	49°	64.5°	60-63° *
% Yield	11	34	51	50	0	52

* Sealed tube, potassium methyl xanthate.

The trithiocarbonate (73) was itself reacted with potassium methyl xanthate at the reflux temperature, and no starting material was recovered. In the case of the reaction of the epoxide in a sealed tube, it is probable that at the moment of sealing, most of the oxygen in the tube has been excluded by methanol vapour, and it is therefore probable that at higher

temperatures oxygen plays a significant part in the destruction of the trithiocarbonate. Reaction of the cis-epoxide (52) with potassium methyl xanthate in a sealed tube gave trans-4,5-bis(benzyloxymethyl)-1,3-dithiolan-2-thione (74) in 79% yield; under aerobic conditions the yields obtained were 76% at 45°, and 3% at the reflux temperature. The cis- and trans-trithiocarbonates (73) and (74) were treated with mercuric acetate to give cis-4,5-bis(benzyloxymethyl)-1,3-dithiolan-2-one (75) and trans-4,5-bis(benzyloxymethyl)-1,3-dithiolan-2-one (76) respectively.



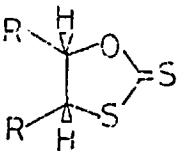
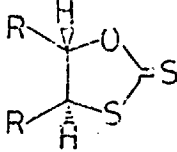
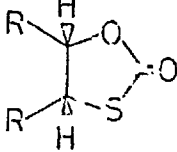
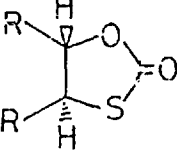
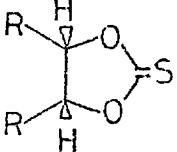
(77)

R = PhCH₂

Reaction of the trans-epoxide (53) with dilute hydrochloric acid gave the erythro-chlorohydrin (77), and traces of the meso-diol (55).

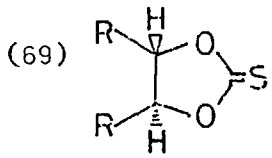
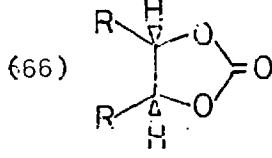
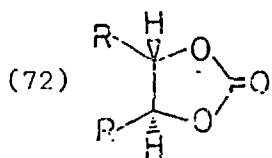
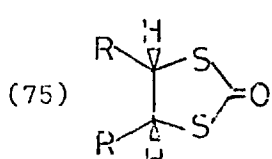
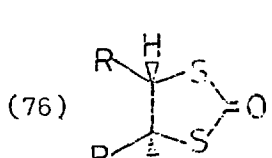
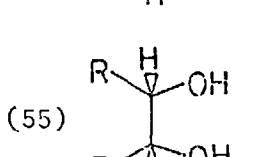
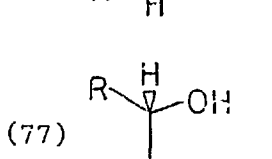
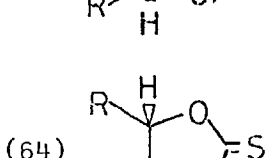
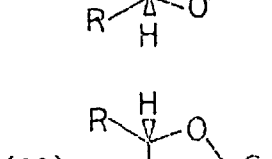
The reactions of the ten thiocarbonates and carbonates, (63)-(67), (69), (71), (72), (75) and (76), the chlorohydrin (77) and the meso-diol (55) with potassium methyl xanthate were carried out at the reflux temperature in sealed tubes. In addition, the reactions of the cis- and trans-thiocarbonates (64) and (69) with potassium methyl xanthate were carried out under aerobic conditions at 43°. The results of all these reactions are summarised in Table III.

Table III

Starting material	Temp.	Time (days)	Trithio-carbonate	Yield	Other products
(63) 	64-66°	4	cis	77%	
(67) 	64-66°	4	trans	90%	
(65) 	64-66°	4	cis	87%	
(71) 	64-66°	4	trans	94%	
(64) 	64-66°	4	trans	trace	

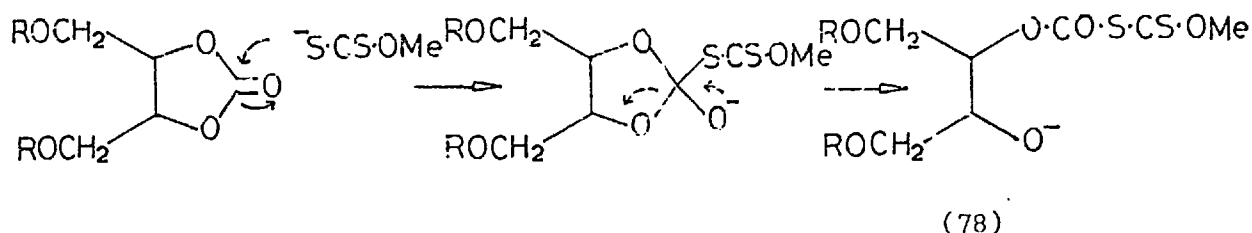
R = PhCH₂OCH₂

Table III/continued

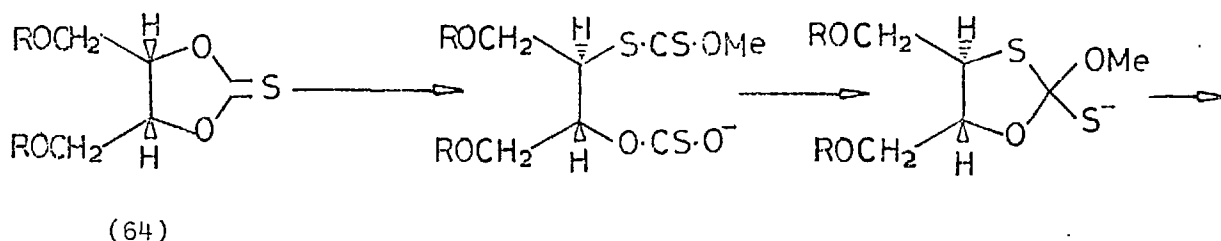
Starting material	Temp.	Time (days)	Trithio-carbonate	Yield	Other products
(69) 	64-66°	4	cis	trace	DL-diol (70)
(66) 	64-66°	4	-	-	meso-diol (55)
(72) 	64-66°	4	-	-	DL-diol (70)
(75) 	64-66°	4	cis	76%	
(76) 	64-66°	4	trans	71%	
(55) 	64-66°	4	-	-	recovered (55)
(77) 	64-66°	4	cis	46%	
(64) 	43°	13	-	-	cis-carbonate (66)
(69) 	43°	16	-	-	DL-diol (70)

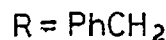
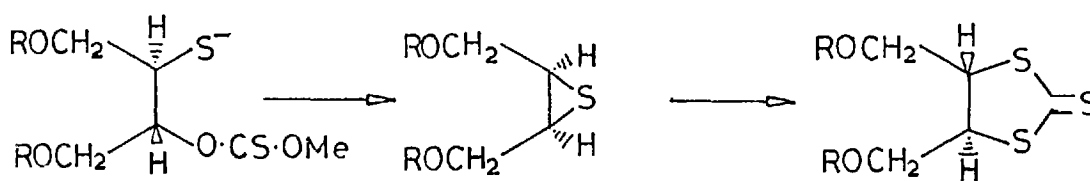
R = PhCH₂OCH₂

Both carbonates, (66) and (72), gave no trithiocarbonate, the major product being the corresponding diol. The corresponding butane carbonates (1) and (3), gave the trithiocarbonates by attack of xanthate at the alkyl oxygen site, the low yields being ascribed to non-productive competitive attack on the carbonyl group⁵⁹. In the case of (66) and (72), there are increased steric effects at the alkyl oxygen site, and the net result is for the majority of attack to occur on the carbonyl group, attack at the alkyl oxygen site not being detected, and the diols are formed by solvolysis of intermediates such as (78).

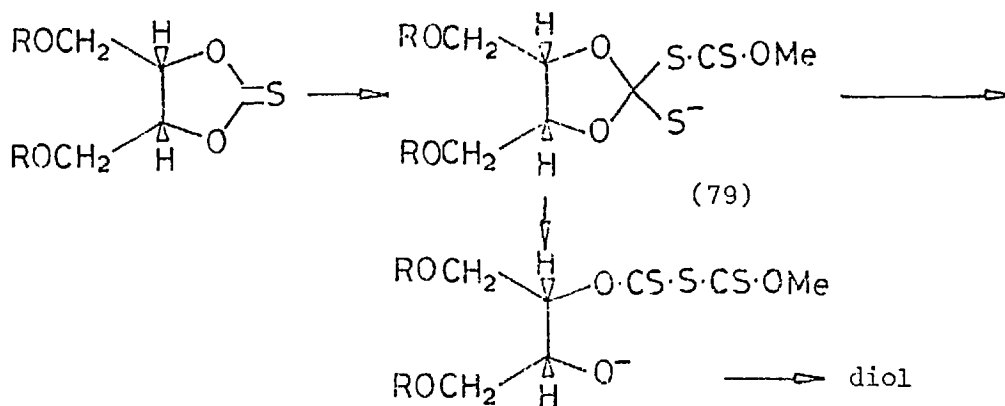


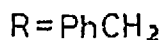
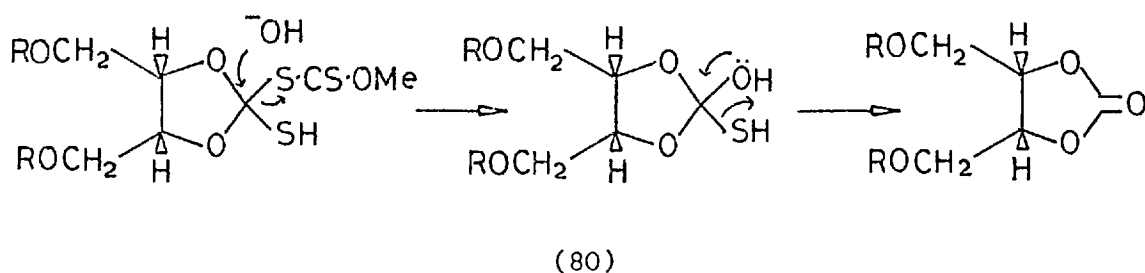
In the sealed tube reactions, the two monothiocarbonates (64) and (69) both gave traces of the trithiocarbonate of opposite configuration. This can be explained by the lower susceptibility of the thiocarbonyl group to nucleophilic attack resulting in a higher rate of attack at the alkyl oxygen site, as is the case in the corresponding butane compounds, resulting in a detectable quantity of trithiocarbonate, although the major products were again the diols.



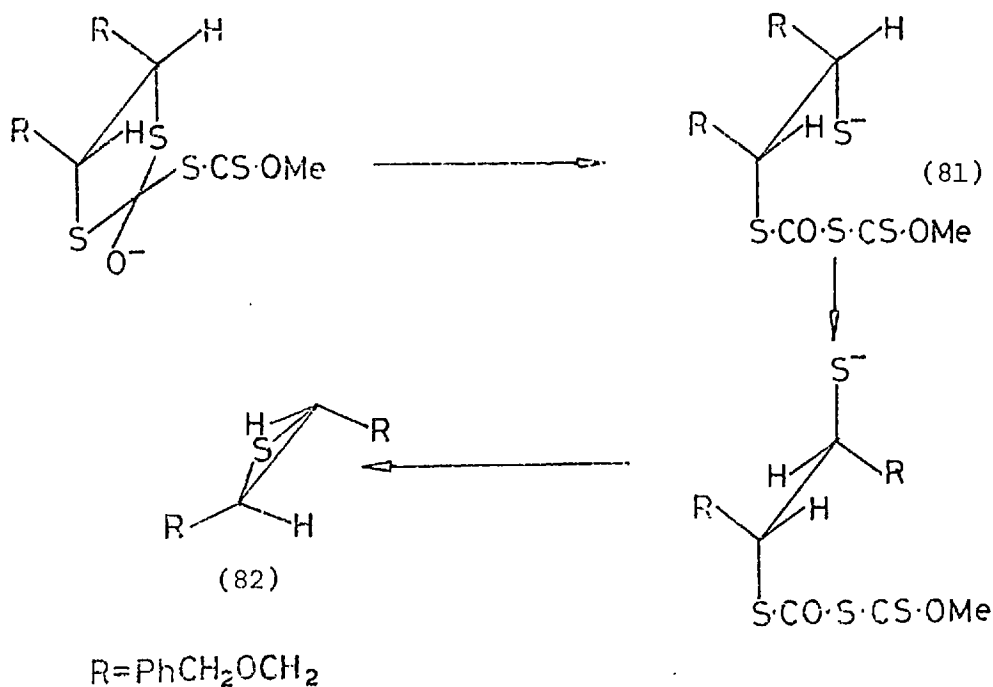


In the reaction carried out at 43° , the cis-thiocarbonate (64) gave, most surprisingly, the cis-carbonate (66) in 75% yield; in a repeat experiment, a lower yield of carbonate, and the meso-diol were obtained. The trans-thiocarbonate (69) gave the expected DL-diol as the major product. The likely mechanism for the formation of (66) involves attack of xanthate on the thiocarbonyl group to give intermediate (79), which at 43° does not react further, except perhaps to be partly solvolysed to the diol, until the reaction is worked up (dilution with water, and extraction with dichloromethane), when the hemithioacetal (80) is formed, which eliminates hydrogen sulphide to give the carbonate. It is suspected that some of the intermediates in this reaction were isolated by chromatography; two bands having a higher R.F. than the carbonate were found on attempted repurification to give further small quantities of the carbonate.





As expected, the two dithiocarbonates (75) and (76) reacted to give trithiocarbonate with retention of configuration. The mechanism of this reaction must be the same as in the corresponding butane compounds; the only difference is that the yields from (75) and (76) are substantially less than theoretical. The most probable explanation is that the bulkiness of the substituent groups reduces the rate of episulphide formation, and therefore increases the degree of solvolysis that occurs, and hence reduces the yield of trithiocarbonate, i.e. the step from (81) to (82) occurs more slowly than the butane equivalent.



The two other dithiocarbonates (63) and (67), and the monothiocarbonates (65) and (71) all reacted to give trithiocarbonates, with retention of configuration, in high yield. The mechanisms for the formation of trithiocarbonates from these compounds is the same as that previously discussed for the corresponding butane thiocarbonates, involving attack on the carbonyl or thiocarbonyl group, and therefore the presence of bulky substituent groups will not affect the mechanism of reaction, other than perhaps increasing slightly the solvolysis of intermediates.

The meso-diol (55) was also treated with xanthate, and as expected no trithiocarbonate was isolated, only starting material being isolated from the reaction. The erythro-chlorohydrin (77) gave the cis-trithiocarbonate in 46% yield, which is a relatively high yield from a chlorohydrin.

The reaction of these substituted thiocarbonates with xanthate has provided further insights into the mechanisms of such reactions, and of special interest has been the effect of bulky substituents on attack at the alkyl oxygen site. The isolation of diols from various reactions has been facilitated by their crystalline nature; they are almost certainly formed in the butane carbonate reactions, but the isolation, and especially the characterisation of small quantities of liquid diols present difficulties.

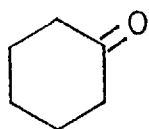
Synthesis of some cyclohexanethiocarbonates and related compounds and their reactions with xanthate

As mentioned in the introduction (p 42), Kardouche and Owen⁵⁹, and also Meloy⁶⁰, have described the reactions of some cyclohexanethiocarbonates and carbonates with xanthate to give the trans-trithiocarbonate. It was pointed out that for steric reasons, the trans-compounds must react by a different mechanism from that of the butane thiocarbonates, and in

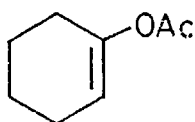
order to elucidate this further, some of the previously unknown cyclohexanethiocarbonates were synthesised, and their reactions with potassium methyl xanthate studied. Other aspects of the possible mechanisms were studied and the reactions of some hydroxythiols and dithiols with xanthate were also carried out.

cis-2-Mercaptocyclohexanol (83) was prepared from cyclohexanone (84) via cyclohexenyl acetate (85) and cis-diacetyl-2-mercaptocyclohexanol (86). The preparation of the diacetate (86) presented unexpected difficulties.

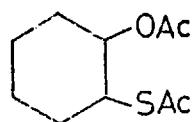
Behringer and Kley¹⁴⁸ found activation of the cyclohexenyl acetate with oxygen to be necessary before reaction with the thiolacetic acid; Meloy⁶⁰ added a trace of acetic acid and reported the reaction to proceed satisfactorily. These methods, and the use of an old sample of (85), failed in the present work until eventually a reasonable yield was obtained. This behaviour suggests the reaction is a radical one and it is possible that the use of a radical initiator would eliminate irregularities in the yield. In contrast, Goodman et al.¹⁴⁹ found the reaction of cyclopentenyl acetate with thiolacetic acid to proceed smoothly, and in good yield, without any prior activation. The hydroxythiol (83) was obtained from the diacetate by the method described by Meloy⁶⁰ using methanolic hydrogen chloride.



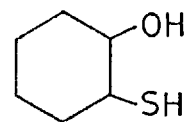
(84)



(85)

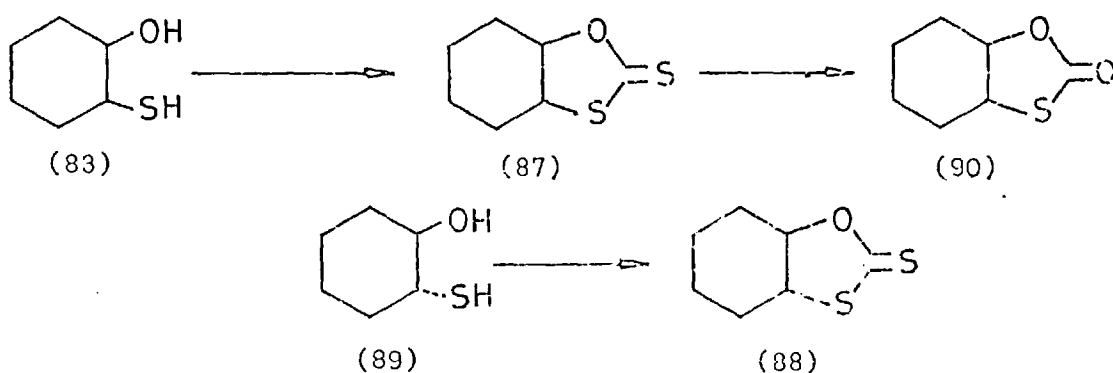


(86)

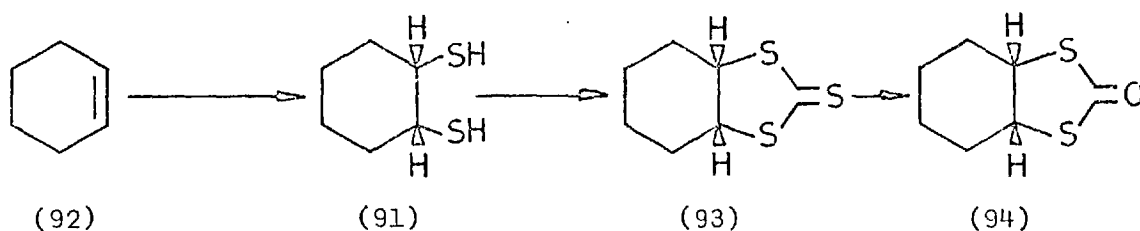


(83)

Treatment of the hydroxythiol (83) with thiocarbonyldiimidazole gave cis-4,5-cyclohexano-1,3-oxathiolan-2-thione (87) in good yield; Kardouche¹²⁸ was unable to prepare (87) from (83) using thiophosgene as the reagent. trans-4,5-Cyclohexano-1,3-oxathiolan-2-thione (88) was similarly prepared from trans-2-mercaptocyclohexanol (89). Treatment of the dithiocarbonate (87) with mercuric acetate gave cis-4,5-cyclohexano-1,3-oxathiolan-2-one (90); in this reaction, decomposition was the main result, only 19% of the desired product being isolated at the second attempt. This was the only thiocarbonylthiocarbonate to do this in the present work; normally yields in excess of 80% were obtained.



cis-Cyclohexane-1,2-dithiol (91) was prepared by the method of Bate-man *et al.*⁴⁸ by reacting an excess of cyclohexene (92) with sulphur at 140°, and reducing the resulting trisulphide with lithium aluminium hydride. The cis-trithiocarbonate (93) was prepared from the dithiol by reaction with thiocarbonyldiimidazole; treatment of (93) with mercuric acetate gave cis-4,5-cyclohexano-1,3-dithiolan-2-one (94).



In the present work, the reactions of thiocarbonates (87), (90) and (94), hydroxythiols (83) and (89), and the cis-dithiol (91) with O-methyl xanthate were carried out. The action of xanthate on trithio-carbonate (95) was also studied. The results of these reactions, and the reactions of the other cyclohexanethiocarbonates with O-alkyl xanthates already reported in the literature are summarised in Table IV. All reactions were carried out under reflux conditions, and no precautions were taken to exclude air, except where stated.

Table IV

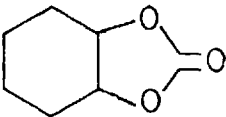
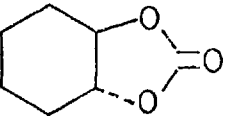
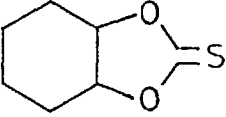
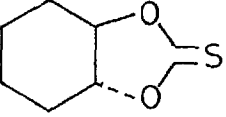
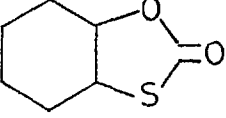
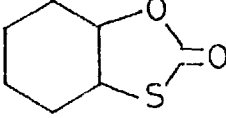
Starting material	Trithio-carbonate formed	Yield	Solvent	Reflux (days)	Reference
(11) 	trans	29%	EtOH	1	59
(14) 	trans	12%	EtOH	4	59
(12) 	trans	60%	EtOH	4	59
(13) 	trans	5%	EtOH	4	59
(90) 	trans	v. small	MeOH	8 hrs	60
(90) 	trans ?	trace	MeOH	4	-

Table IV/continued

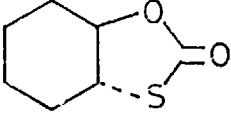
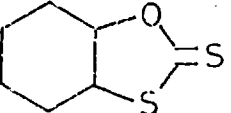
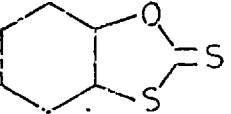
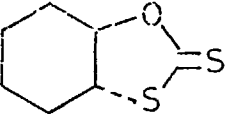
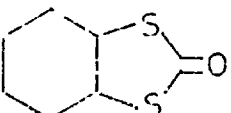
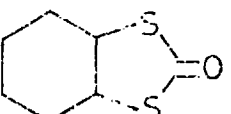
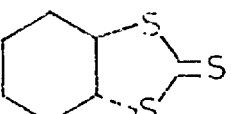
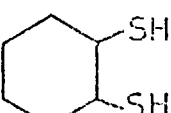
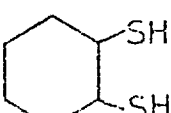
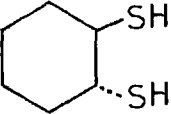
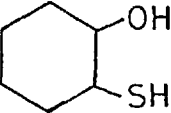
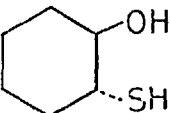
Starting material	Trithio-carbonate formed	Yield	Solvent	Reflux (days)	Reference
(96) 	trans	100%	MeOH	6 hrs	60
(87) 	trans	9%	MeOH	1	-
(87) 	trans	17%*	MeOH	4	-
(88) 	trans	100%	EtOH	1	128
(94) 	cis	48%	MeOH	4	-
(97) 	trans	97%	EtOH	4	59
(95) 	trans	92%	MeOH	4	-
(91) 	cis	81%	MeOH	3 $\frac{3}{4}$	-
(91) 	cis	95%	H ₂ O	1 $\frac{1}{2}$	49

Table IV/continued

Starting material	Trithio-carbonate formed	Yield	Solvent	Reflux (days)	Reference
(98) 	trans	65%	MeOH	4**	33
(83) 	trans	14%	MeOH	4 $\frac{3}{4}$	-
(89) 	trans	54%	MeOH	4	-

* sealed tube

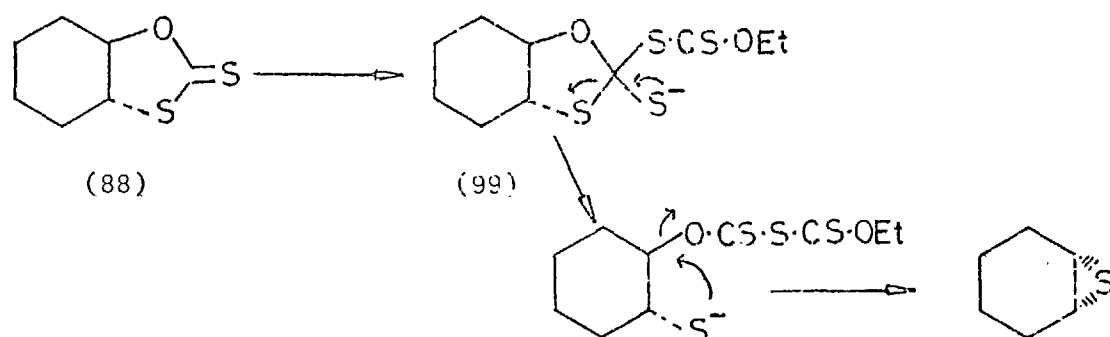
** room temperature

Kardouche¹²⁸ attempted to isomerise the cis- and trans-thiocarbonates (12) and (13) to (90) and (96) with potassium iodide, according to the method used by Jones and Andreades¹³³ on 1,3-oxathiolan-2-thione; isomerisation could have been a possible mechanistic route for those compounds. In the present work, the isomerisation of the trans-dithiocarbonate (88) to (97) was attempted, but heating in carbon tetrachloride, or in refluxing ethanol, or treatment with sodium ethoxide in refluxing ethanol produced no change. These compounds must therefore react as they are; isomerisation before reaction cannot occur to any significant extent. The reaction of the trans-trithiocarbonate (95) with xanthate was carried out in order to confirm the stability of this compound under reflux conditions. Unlike cis-4,5-bis(benzyloxymethyl)-1,3-dithiolan-2-thione (73) (p 59), the trithiocarbonate was essentially recovered, thus precluding any loss of yield by the destruction of the product. The reaction of cyclohexanol with xanthate although it could not possibly give any trithiocarbonate, gave very little extractable material, thus proving that hydroxy groups

are not displaced by O-alkyl xanthates. This was also supported by the recovery of meso-1,4-dibenzoyloxybutane-2,3-diol when it was treated with xanthate in a sealed tube, as previously mentioned (p 66).

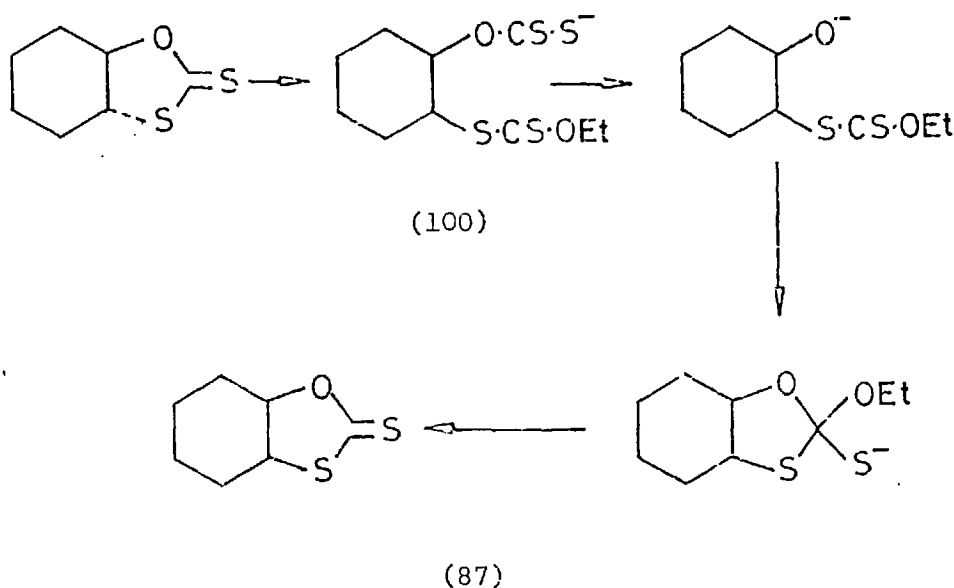
In the various schemes shown below, on going steps only are shown; in principle at least, all steps are reversible. In general, it has been assumed that if there is a choice, collapse of an intermediate leads to the formation of a thioanion in preference to an oxyanion. Kardouche and Owen⁵⁹ concluded that fission of carbon-sulphur bonds was difficult, and therefore, these bonds have generally been assumed to remain unbroken, or once formed are not opened again.

Kardouche¹²⁸ suggested the most likely mechanism for the reaction of dithiocarbonate (88) involved attack on the thiocarbonyl group to give the cyclic intermediate (99), followed by formation of the cyclohexene sulphide, which is converted to the trans-trithiocarbonate.



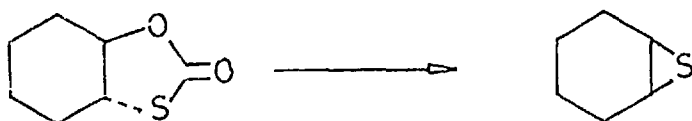
The alternative mechanism involved breaking the carbon-sulphur bond to give the cis-intermediate (100) (breaking the carbon-oxygen bond would lead to the cis-trithiocarbonate) which would lead to the isomeric cis-dithiocarbonate (87) from which the trans-trithiocarbonate might be formed by attack on the carbon-oxygen bond. Kardouche ruled this second mechanism out on the grounds that it required fission of a carbon-sulphur

bond in preference to fission of a carbon-oxygen bond in the first stage, but the reverse choice in a later stage. In the present work (87) was found to give the trans-trithiocarbonate in only 9% yield under the same conditions. The 100% yield of trans-trithiocarbonate from (88) effectively rules out the second pathway.

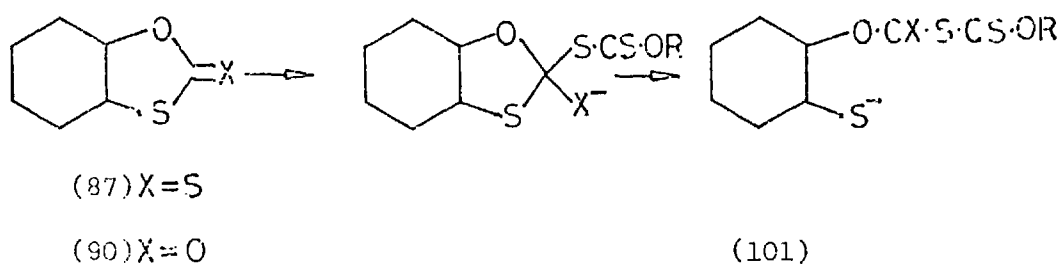


Meloy⁶⁰ obtained 100% yield of trans-trithiocarbonate from the monothiocarbonate (96) and this must be formed by the same mechanism as in the case of (88), i.e. via the episulphide. The involvement of the episulphide as an intermediate was confirmed by heating (96) with sodium carbonate; traces of episulphide were detected (nasal analysis), although because of its relatively high boiling point, most of the episulphide was presumably converted to polymeric products. Miles and Owen¹⁵⁰ reported the formation of cyclohexene sulphide from trans-2-mercaptocyclohexyl acetate in 70% yield by steam distillation with aqueous sodium carbonate under reduced pressure. Attack at the ring site of (96) could also occur,

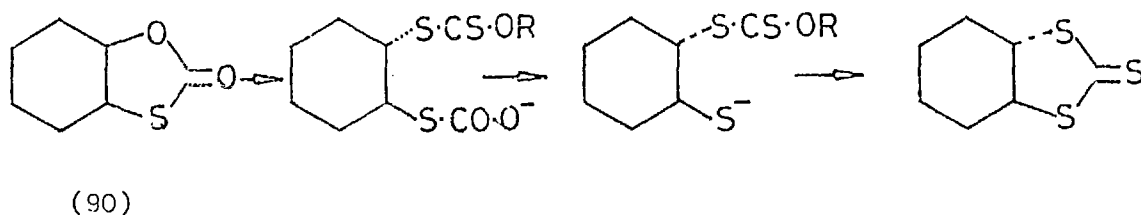
but the reaction via the episulphide is probably fast, and therefore no cis-trithiocarbonate is detected in the product.



For the two corresponding cis-compounds, the mechanism must be different; the stereochemistry of the intermediate (101) cannot allow episulphide formation.



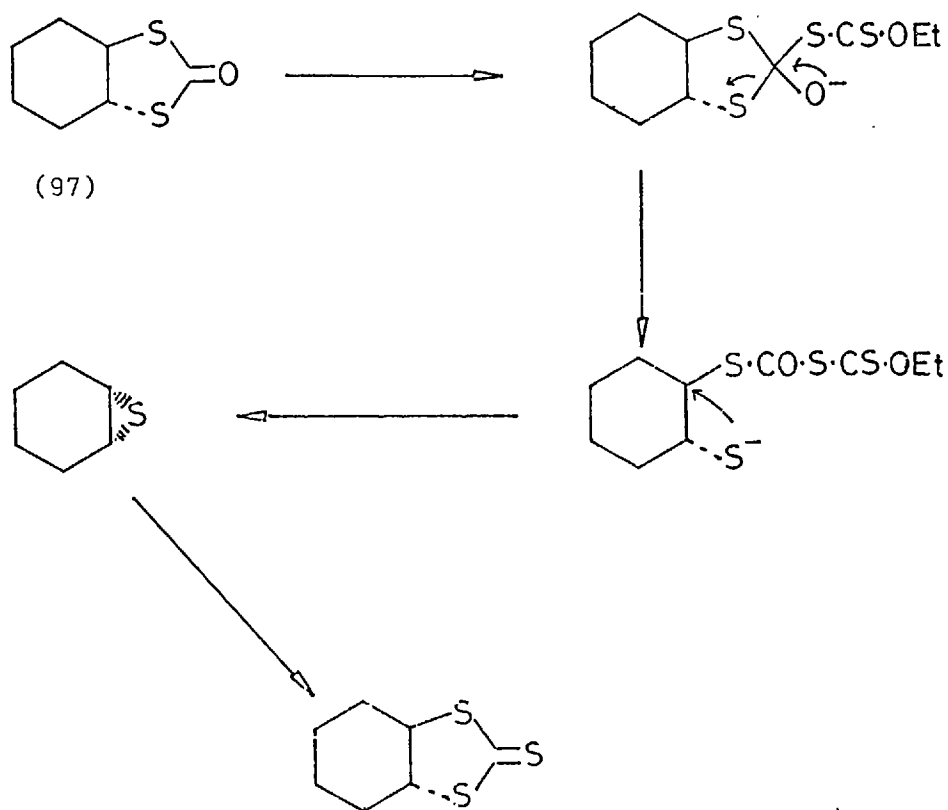
Attack at the carbonyl group in (90), or the thiocarbonyl group in (87) would therefore lead to loss of substrate due to solvolysis of intermediate (101). If attack at the ring site was important, the yield would have been high, because the reaction pathway is short.



Melay⁶⁰ described the yield of trans-trithiocarbonate from (90) as "very small". This could have arisen from the presence of a small amount of trans-thiocarbonate (96); this reaction was repeated in the present work and a similar result was obtained even though the reaction time was four days rather than six hours.

The yield of trans-trithiocarbonate from the cis-thiocarbonyl compound (87) was 9% under the normal reflux conditions, but in a sealed tube reaction the yield was 17% based on consumed starting material. This result illustrates two important aspects of these mechanisms. The first is that in the absence of air, intermediate (101) which is in equilibrium with starting material, is not all destroyed by further reaction. Secondly, the only possible route for trithiocarbonate formation must be via attack on the ring oxygen site and although this must occur very slowly (the non-consumption of all the starting material illustrates this) there is now no fast competitive episulphide formation to overshadow it. The other possibility to be considered was the existence of at least 10% of the trans-isomer in the cis-2-mercaptocyclohexanol used to prepare both thiocarbonates (87) and (90). This was ruled out on two counts; firstly, (90) did not give 10% of the trithiocarbonate, and secondly, a 100 Mhz p.m.r. spectrum run on the cis-2-mercaptocyclohexanol showed no peaks due to the trans-isomer, whereas an artificial mixture containing about 30% trans-isomer did so. This does not rule out the presence of a little of the trans-isomer, but as far as thiocarbonate (87) is concerned, the part played in the trithiocarbonate formation is negligible.

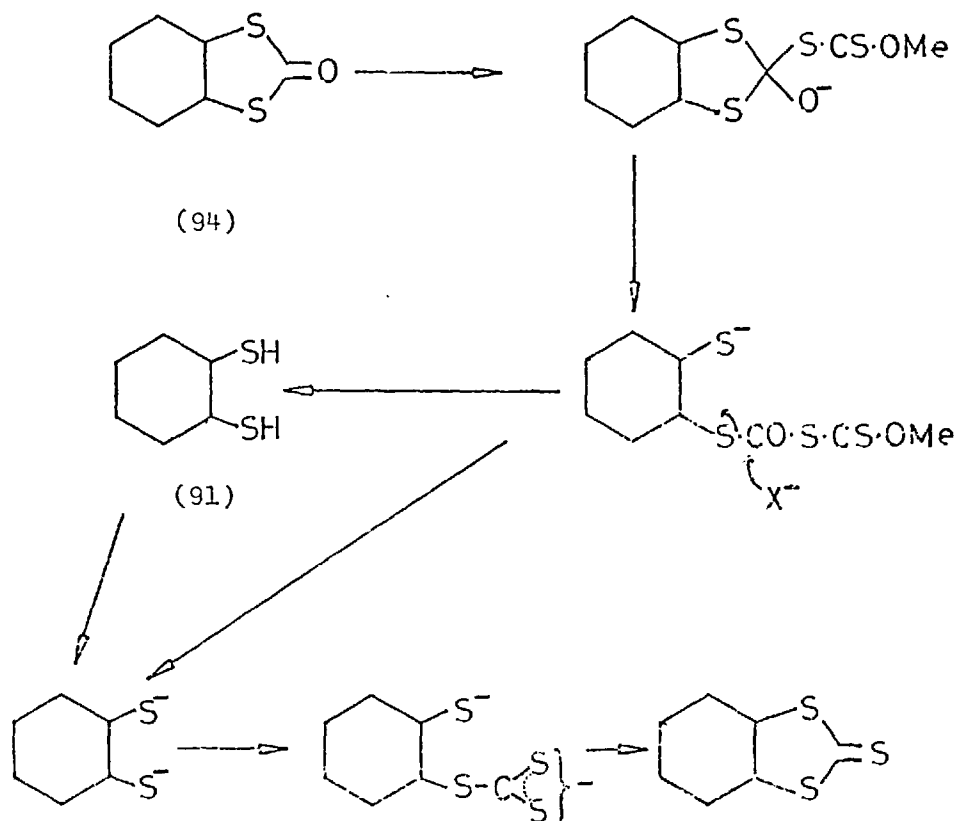
The trans-dithiol carbonate (97) was reported by Kardouche and Owen⁵⁹ to give the trans-trithiocarbonate almost quantitatively. By analogy with the butane compounds, this proceeds by attack on the carbonyl group and via the episulphide¹²⁸:



(Breaking of the carbon-sulphur bonds, which has been ruled out by Kardouche and Owen⁵⁹, would lead to the cis-trithiocarbonate.)

The cis-isomer, which gave a 40% yield of cis-trithiocarbonate, must proceed by a different mechanism since the one illustrated above would require the formation of the non-existent trans-episulphide. The only possible way for cis-trithiocarbonate to form must be by way of the thioanion (102) which is then solvolysed to give the dithiol or give the dithioanion directly. The mechanism from then on is as proposed by Kyaw and Owen³³. The lower yield compared with the trans-isomer must be due to the longer mechanistic pathway and consequently loss of substrate by

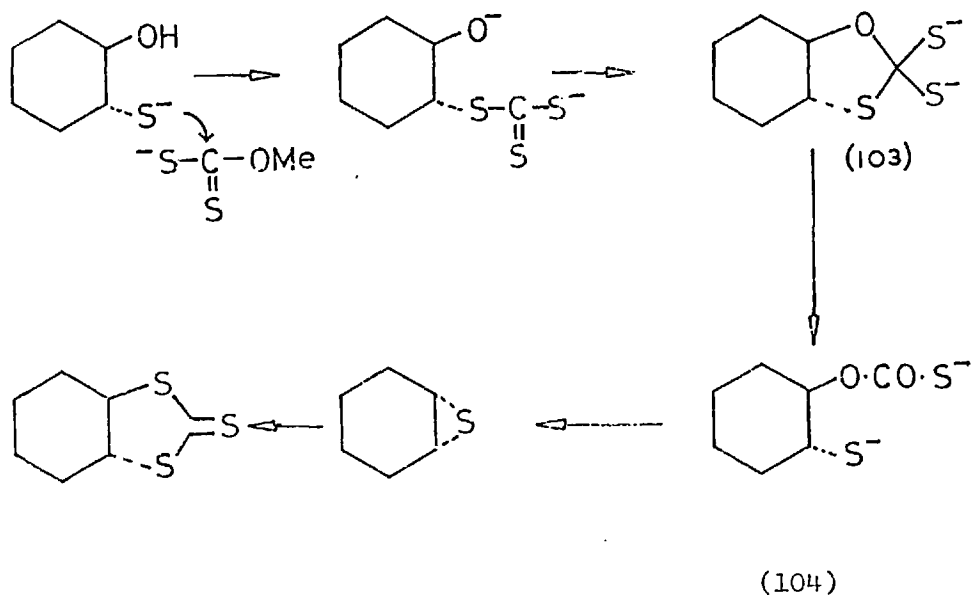
solvolysis followed by disulphide formation.



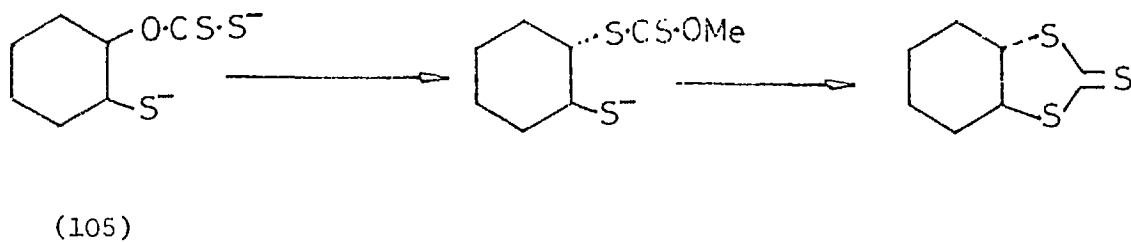
As expected, the cis-lithiol (91) gave a higher yield (81%) of cis-trithiocarbonate than the cis-dithiolcarbonate (94).

The two hydroxythiols (83) and (89) both gave the trans-trithiocarbonate. The possibility of displacement of hydroxyl group playing a significant part in the mechanism was ruled out when cyclohexanol failed to react with xanthate. Breaking of the carbon-sulphur bond having been ruled out in several mechanisms previously discussed, the mechanism of reaction must involve attack of thioanion on xanthate itself, followed by cyclisation to give intermediate (103). For the trans-hydroxythiol, this

can collapse to give (104), which has the correct stereochemistry for episulphide formation, and hence yield the trans-trithiocarbonate.



In the case of the cis-compound (83), the intermediate (105) corresponding to (104) has the wrong stereochemistry for episulphide formation. The trans-trithiocarbonate must, therefore, be formed by displacement of the O-CS_2^- group and cyclisation:



A relatively low yield of trans-trithiocarbonate (14%) was obtained from (83); this must be caused by side reactions (possibly air oxidation). Whereas (104) would react very rapidly to give the episulphide, further attack of xanthate on (105) must be a slow process. Although recovery of unused starting material was not attempted due to isolation problems, it is possible that unconsumed cis-hydroxythiol remains at the end of the reaction,

Finally, two of the reactions listed in table IV gave a further viewpoint to the mechanisms of formation of trithiocarbonates from thiocarbonates. The reaction of the trans-hydroxythiol (89) was carried out in the normal way, and after extraction of the product the aqueous residues were left for one week and then re-extracted to yield a further 1 mg of trithiocarbonate. As this represented 0.3% of the yield, this result is not too significant. However, when the trans-trithiocarbonate (95) itself was reacted with xanthate only 76% of the starting material was recovered on normal work-up; one day later a further 16% was extracted from the aqueous layer. This result suggests that some of the trithiocarbonate was present in the final reaction mixture as a water soluble anion, and this only came out of solution when the concentration of the free trithiocarbonate was reduced. Several thiocarbonates have been reported to give the trans-trithiocarbonate in 100% yield; it is, therefore, uncertain how important this result is, especially as previous workers have never reported re-extraction of aqueous residues after some time has passed.

In conclusion, some general tendencies in the reactions of cyclohexanethiocarbonates with xanthate can be outlined:

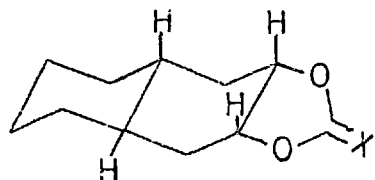
- (1) Once a carbon-sulphur bond is formed in a reaction, it appears not to be broken unless doing so results in the formation of the episulphide. Similarly, carbon-sulphur bonds in the starting materials

are not broken.

- (2) The carbonyl group is attacked in preference to the two ring oxygen sites.
- (3) If only one ring oxygen site is available, attack proceeds mainly at the carbonyl or thiocarbonyl group.
- (4) The longer the mechanistic pathway, the lower the final yield of trithiocarbonate because of solvolysis of intermediates.

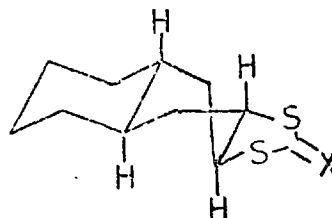
Studies on the Synthesis of Decalin Thiocarbonates

The decalin system is of especial interest in the thiocarbonate field because it is conformationally less flexible than the cyclohexane ring. Kardouche and Owen⁵⁹ have reported the preparation of the cyclic carbonate (106) and thiocarbonate (107) from trans-decalin-2 α ,3 α -diol, but trans-decalin-2 α ,3 β -diol failed to give the corresponding trans-fused esters. However, the trans-decalin-2 β ,3 α -trithiocarbonate (108) and the dithiocarbonate (109) were prepared by these authors from the 2,3-epoxide. In the present work, the preparation of some other decalin thiocarbonates was attempted.



(106) X=O

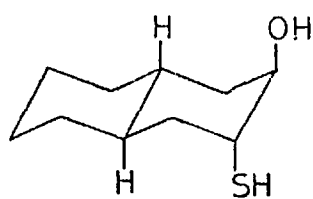
(107) X=S



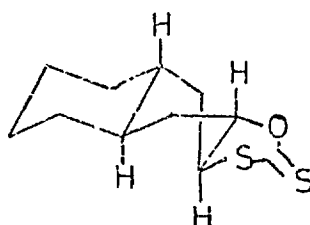
(108) X=S

(109) X=O

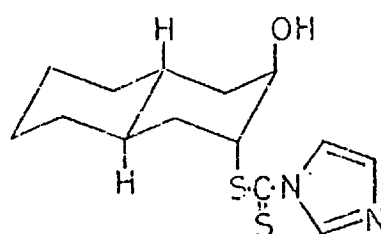
Following the success of thiocarbonyldiimidazole in preparing cis-4,5-cyclohexano-1,3-oxathiolan-2-thione, it was hoped that the reagent would prove as useful in preparing 2 β ,3 α -(thiocarbonyloxythio)-trans-decalin (110) from 2 β -hydroxy-3 α -mercapto-trans-decalin (111). Treatment of the hydroxythiol with the reagent at room temperature, in refluxing chloroform, and in refluxing xylene all failed to give the desired product. This result is not too surprising; the desired product would require the cyclohexane ring involved to assume a boat conformation and corresponds with the failure of trans-decalin-2 β ,3 α -diol to react with thiophosgene⁵⁹. In each of the three attempts, several products were isolated and p.m.r. spectra indicated that all contained the imidazole group. Only one of these products was both stable enough and present in sufficient quantity to be fully characterised and was identified as 2 β -hydroxy-3 α -(imidazolyl-1-thiocarbonylthio)-trans-decalin (112). The instability of some of the other products suggests the presence of free thiol groups; repurification on t.l.c. would therefore result in some disulphide formation.



(111)



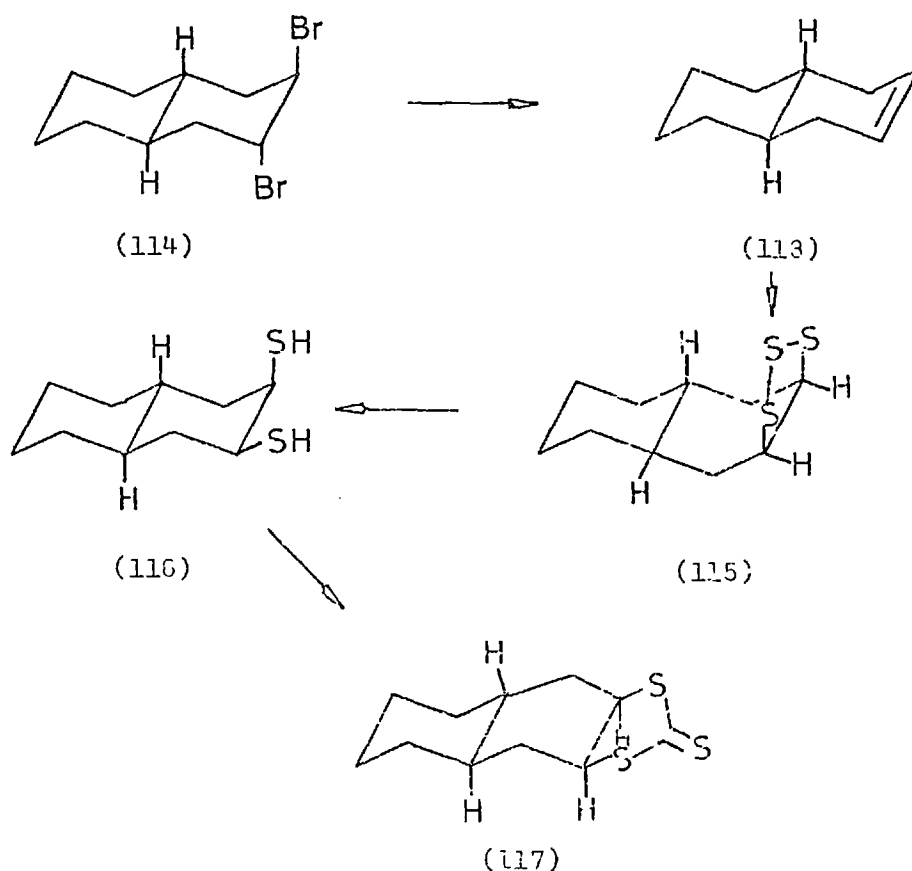
(110)



(112)

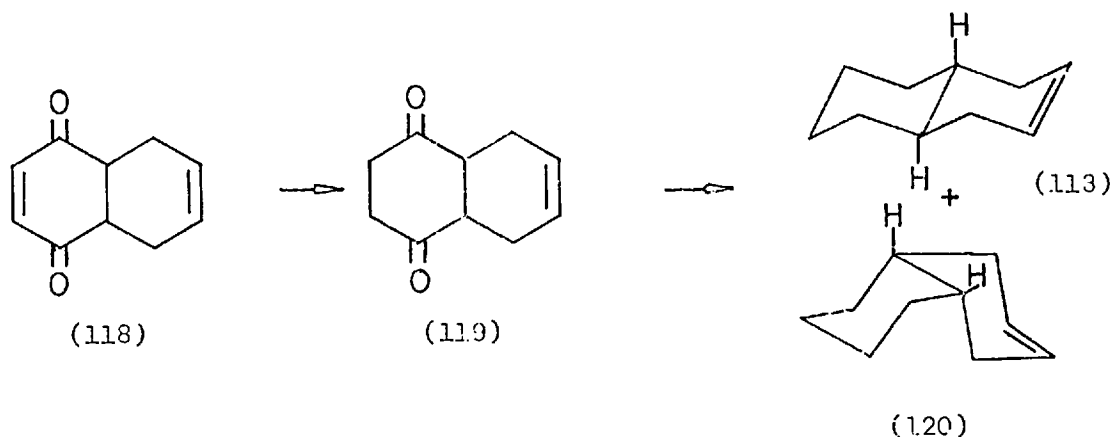
trans- Δ^2 -Octalin (113), prepared by reaction of trans- Δ^2 -octalin dibromide (114) with zinc dust according to the method of Johnson *et al*¹⁵¹ was reacted with activated sulphur using the method of Shields and Kurtz⁵¹, to give the trithiocompound (115). A small quantity of this product was retained for characterisation; however, on repurification it appeared to throw out sulphur. The crude trithiocompound was reduced with lithium

aluminium hydride to give the dithiol (116), which was immediately treated with thiocarbonyldiimidazole to give the crude trithiocarbonate (117).

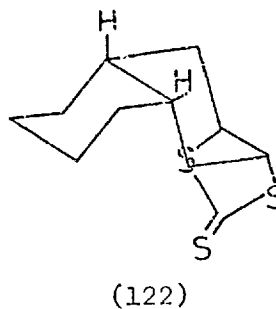
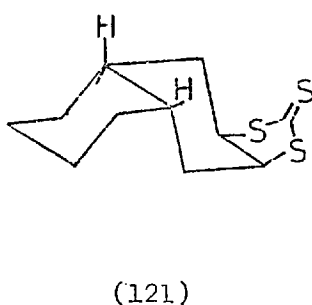


The crude trithiocarbonate was purified by t.l.c. and found to consist of three major yellow components. Two of these were definitely identified as decalin trithiocarbonates whilst the third had only a melting point recorded. Although at first sight surprising, this result has a logical explanation. trans- Δ^2 -Octalin was prepared by the route of Johnson *et al.*,¹⁵¹ who condensed butadiene with *p*-benzoquinone to give (118), which on zinc dust reduction gave (119). Previous preparations had involved isomerisation of (119) to its trans-isomer with base, a process which had been assumed to be complete but in fact led to impure trans- Δ^2 -octalin. Johnson *et al.*,¹⁵¹ allowed the isomerisation to occur during the Huang-Minlon reduction of (119) to give a mixture of (113) and its

cis-isomer (120). Purification via the dibromide gave pure trans- Δ^2 -octalin.



In the present work, the residues from a purification by this method were used as source material. Repeated recrystallisation of this residue gave a sample with melting point 60-62° (lit.,¹⁵¹ 84-85.5°), and it had been hoped that the amount of impurity present was small. The presence of substantial quantities of the cis- Δ^2 -octalin therefore led to the formation of two other trithiocarbonates (121) and (122).

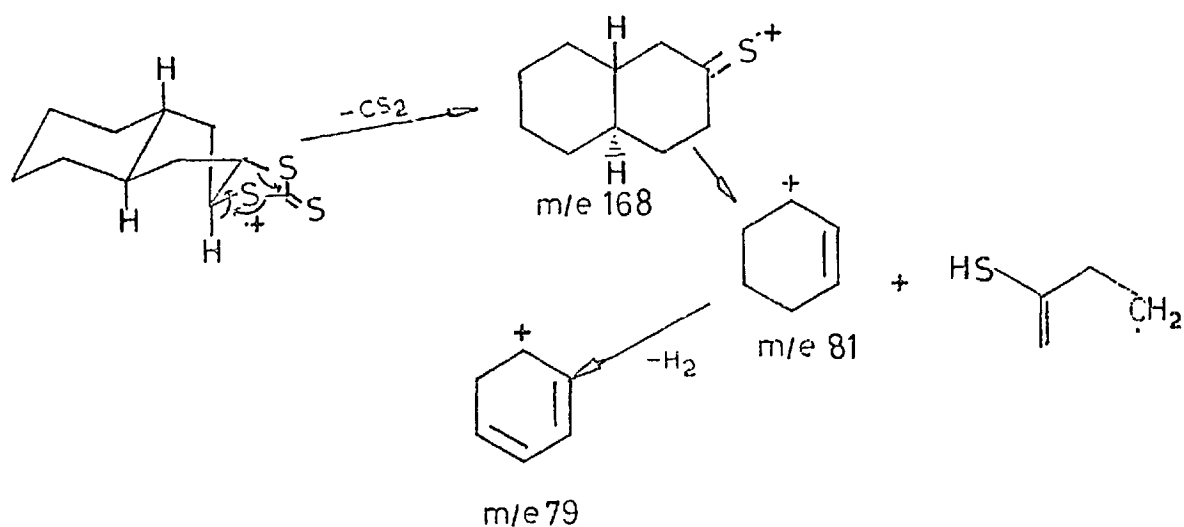


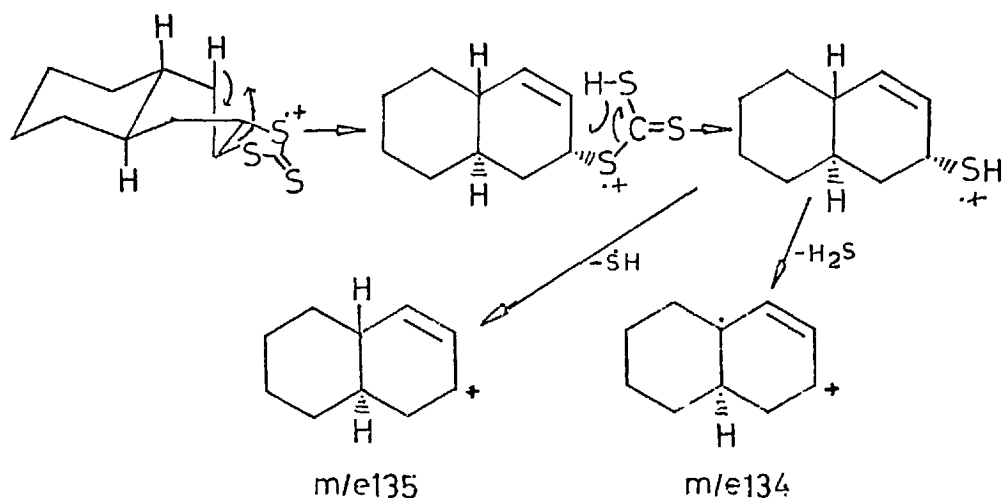
The low resolution mass spectra of compounds (117) and (121) or (122) were recorded and the relative abundances of the different ions are given in table V, along with those reported for compound (108)¹²⁸.

Table V

Compound (121/122)		(117)	(108)		(121/122)	(117)	(108)
m/e				m/e			
244 (M^+)	100	100	100	94	29	26	13
168	13	-	4	93	21	28	25
139	12	-	-	92	21	24	23
135	40	60	43	91	23	37	25
134	30	44	36	81	16	22	19
121	13	31	61	79	28	39	30
119	9	-	9	77	11	19	-
105	-	10	-	76	-	13	14
99	-	-	11	67	32	53	43
96	-	-	16	55	-	19	20
95	21	33	73	41	15	46	34

The structures assigned to the two trithiocarbonates (121) or (122) and (117) were based on the fragmentation patterns. Kardouche¹²⁸ suggested the following mechanisms to account for the peaks in the mass spectrum of (108):



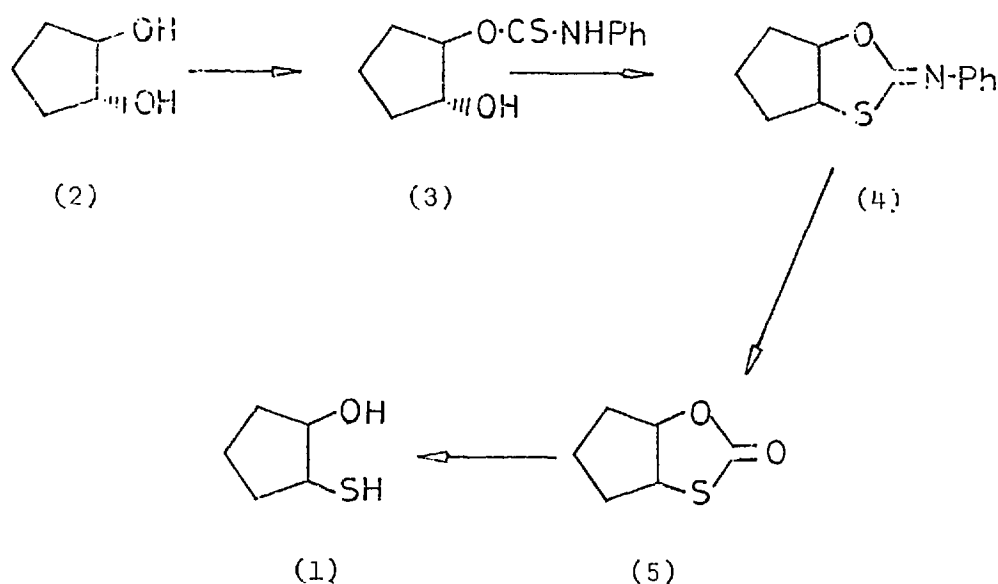


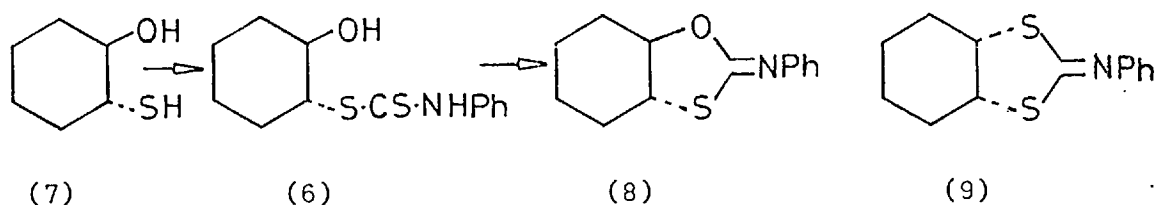
For the trans-2 β ,3 α -trithiocarbonate (108), the cyclohexane ring is in the skew-boat conformation. Similarly in the cis-2 β ,3 β -trithiocarbonate (121), the second ring is in the boat conformation, whereas in the trans-2 β ,3 β -trithiocarbonate (117) the chair form of the cyclohexane ring is only slightly distorted. The effect of these conformations show in the mass spectra. The peak at m/e 168 is present in all three spectra but in the case of (117) it is very small. This suggests that the major fragmentation is by the second pathway resulting in larger m/e 135 and 134 peaks than in the other two spectra and this can only be explained on the basis of ring strain, (117) being the least strained trithiocarbonate. Both (121) (or (122)) and (108) have slightly more strained conformations and their fragmentation patterns correspond reasonably well.

The preparation of these trithiocarbonates has demonstrated the usefulness of the olefin-sulphur method for preparing cis-dithiols and especially its application to limited quantities of olefin. The failure to prepare the dithiocarbonate (110) has illustrated the greater degree of rigidity in the decalin system and the limitations it imposes on thiocarbonate preparations.

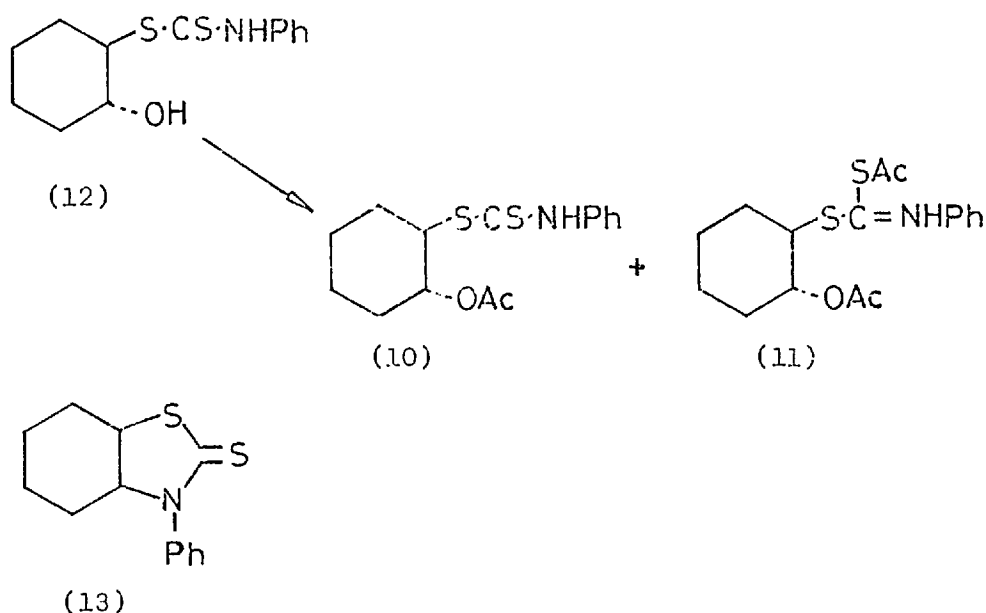
PART 2 STUDIES ON A POTENTIAL ROUTE TO CIS DITHIOLS

There is no method at present available for the stereospecific synthesis of alicyclic cis-dithiols in good yields. Goodman et al.¹⁴⁹ reported the synthesis of cis-2-mercaptocyclopentanol (1) from trans-cyclopentane-1,2-diol (2) via the mono(phenylthiourethane) (3) which gave the phenylimino compound (4) on treatment with thionyl chloride; hydrolysis of (4) gave the thiocarbonate (5) which was reduced to the hydroxythiol. Ali et al.⁵⁴ prepared the phenyldithiourethane (6) from trans-2-mercaptocyclohexanol (7) but this gave the monothio compound (8) on treatment with thionyl chloride instead of the hoped for cis-dithio compound (9). In the present work, the reactions of ^{the acetate of} (6) and its cis-isomer with base were studied and authentic samples of (9) and its trans-isomer were prepared.

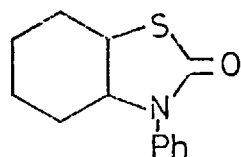




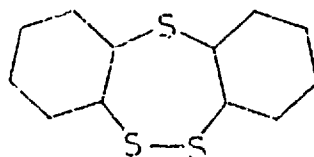
trans-2-(Phenylthiocarbamoylthio)cyclohexyl acetate (10) and trans-2-[[acetylthio](phenylimino)-methylthio]cyclohexyl acetate (11) were prepared from trans-2-(phenylthiocarbamoylthio)cyclohexanol (12) by reaction with acetic anhydride in pyridine by the method of Ali *et al.*⁵⁴ Owen¹⁵² described the treatment of (10) with warm ethanolic potassium hydroxide solution to give a cyclisation product which was expected to have the structure (9) or (13). If (9) were formed, this would be a potential route to cis-dithiols. This reaction was repeated in the present work, and the same product was obtained from the diacetate (11).



Goodman *et al.*¹⁴⁹ hydrolysed the phenylimino compound (4) by heating it with 50% acetic acid at 80° for four hours, and it was expected that the cyclisation product, if it had structure (9) would be similarly hydrolysed. Under the same conditions, the cyclisation product was recovered, and it was concluded that structure (13) was the correct one. Reaction of (13) with mercuric acetate was expected to give the carbonyl compound (14) but repeated reactions only once gave a product with a carbonyl stretch in the infra-red spectrum. This was later identified as an adduct between mercuric acetate and the sulphide (15) on the evidence of the mass spectrum and analysis. These adducts are well known and mercuric acetate has been used to separate mixtures of sulphides.¹⁵³



(14)

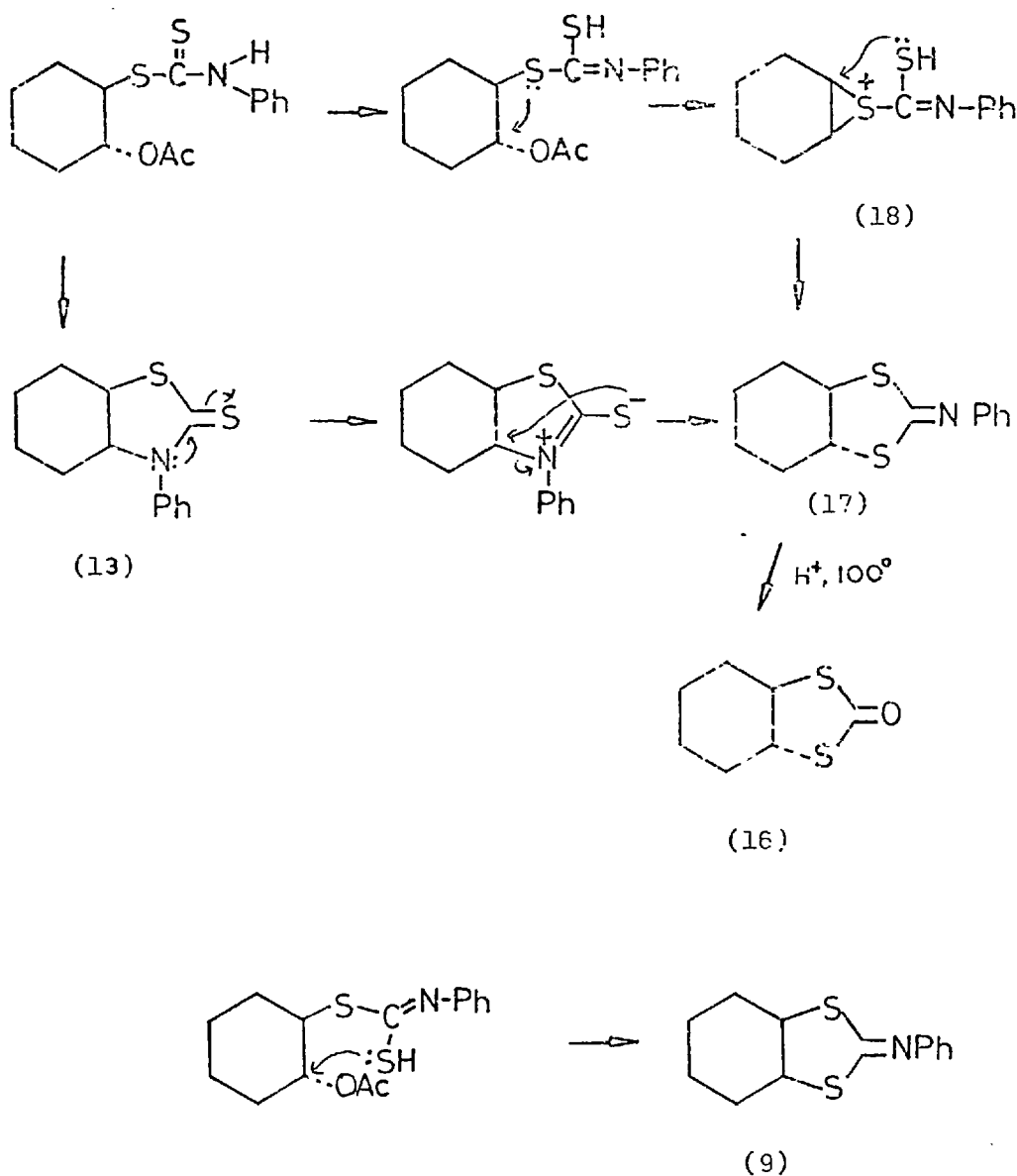


(15)

It was now decided to repeat the hydrolysis of the cyclisation product under more vigorous conditions. Reaction with a mixture of hydrochloric and acetic acids at 100° for three days gave trans-4,5-cyclohexano-1,3-dithiolan-2-one (16) in 83% yield. This indicated that the cyclisation product was in fact trans-2-phenylimino-4,5-cyclohexano-1,3-dithiolan (17), a surprising stereochemical result which was substantiated by an independent synthesis described later.

Two possible mechanisms can be proposed and these are outlined below. In both cases, the loss of acetate occurs rapidly, to give the sulphonium ion intermediate (18) in the one case and (13) in the other. Rearrangement

of (13) to the observed product is unlikely to occur readily, whilst intramolecular opening of (18) would rapidly give the observed product. The possibility arises in the sulphonium ion route that alternative displacement of acetate to give (9) could also occur. It is probable however, that under the conditions used, this second possibility does not arise and the sulphonium ion mechanism is more likely as it would give the correct product fairly rapidly.



The yellow diacetate (11) reacts in the same way, after deacetylation (loss of yellow colouration occurs very rapidly on addition of base).

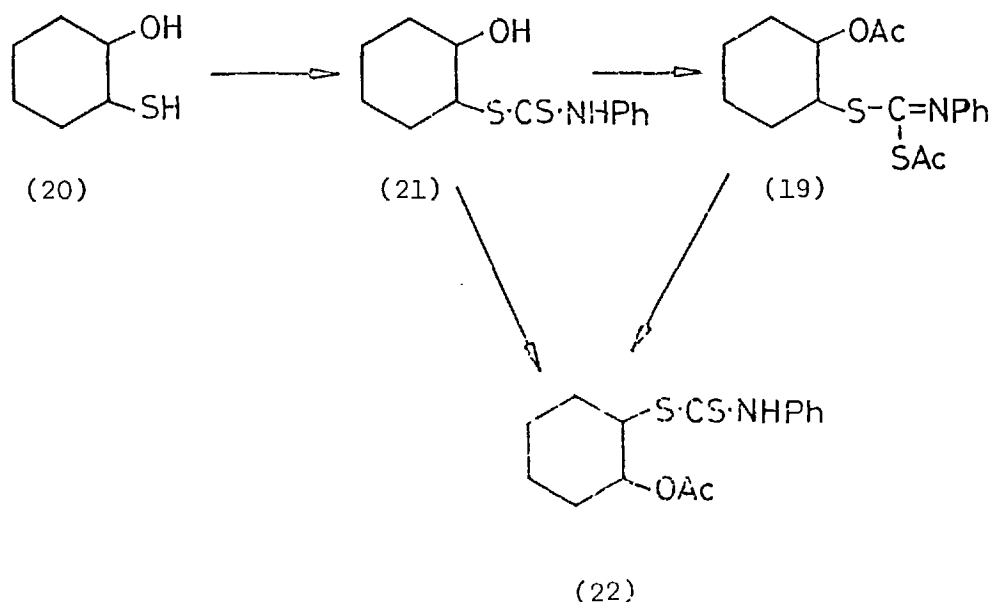
In order to try and obtain (9) from the cyclisation reaction a variety of other conditions were employed and these are summarised in Table VI. When these reactions gave a cyclisation product it was identified as (17) on the basis of spectral and melting point information.

Table VI

Starting material	Conditions	Cyclisation product	Recovered starting material	Other products
(10)	DMSO, 100°, 2 hrs		yes	traces
(10)	DMSO, 95°, 3 days	39%	yes	-
(10)	KOAc, EtOH, 12 hrs	-	yes	-
(10)	KOAc, EtOH, 50°, 3 days	-	yes	traces
(10)	KOAc, EtOH, reflux, "	-	-	phenylthiourethane
(10)	$\bar{\text{S}}$.CS.OMe, room temp., 2 days	-	yes	(not identified)
(10)	$\bar{\text{S}}$.CS.OMe, reflux, 4 days	-	-	Ph.NH.CO.OMe and Ph.NH.CS.OMe
(11)	DMSO, 80-90°, 1day	-	-	many

The formation of the trans-product (17) from the trans-phenylthiourethane made it important to study the cis series. cis-2-[(Acetylthio)(phenylimino)-methylthio]cyclohexyl acetate (19) was prepared by the procedure described by Ali et al.⁵⁴ for the trans-compound. cis-2-Mercapto-cyclohexanol (20) was treated with phenylisothiocyanate to give cis-2-(phenylthiocarbamoylthio)cyclohexanol (21) which on reaction with (excess) acetic anhydride gave the diacetate (19). Use of less than the required amount of acetic anhydride in this reaction gave cis-2-(phenylthiocarbamoylthio)cyclohexyl acetate (22), which was also obtained from (19) by

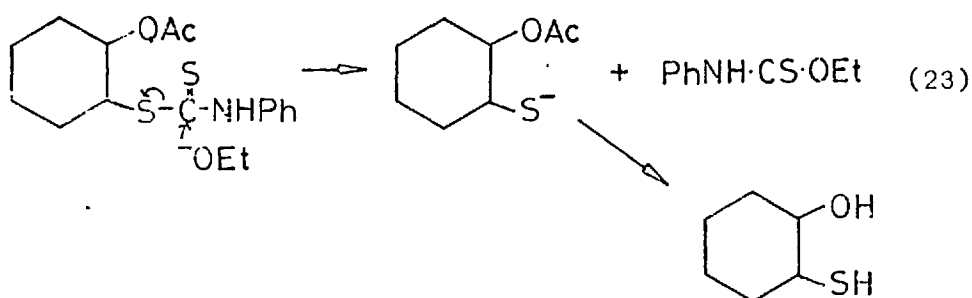
partial deacetylation using dilute hydrochloric acid.



The monoacetate (22) was found to have a wide melting point range; the same effect was observed in both samples. At first the presence of some trans-isomer in the hydroxythiol (20) was suspected but the p.m.r. experiment reported on p 75 suggested this was not so. Also, slow crystallisation of (22) gave a sample with melting point range 105-110°; but on recrystallisation this fell to 88-94°. It was, therefore, concluded that this compound was dimorphous.

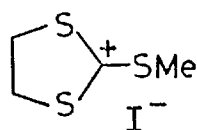
Treatment of the cis-monoacetate (22) with base under the conditions of Owen¹⁵² gave phenylthiourethane (23) in 37% yield, and also the hydroxy compound (21). The cis-diacetate (19) behaved in a similar manner. Rapid deacetylation (loss of colour) occurred on addition of base and on work up, phenylthiourethane was obtained in 72% yield along with traces of the hydroxy compound (21) and other products. This deacetylation and

decomposition of the cis-compounds is not entirely unexpected. The stereochemistry is unfavourable for cyclisation and if loss of the O-acetyl group occurs as fast as the S-acetyl group is lost from (19), very little - if any - cyclisation could take place. In the case of the trans-compound, cyclisation occurs readily and normally faster than the competitive deacetylation.

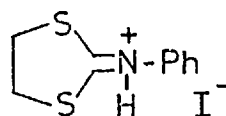


In view of the unexpected result of the cyclisation in the trans-series it was considered desirable to synthesise both the cis- and the trans-phenylimino compounds by an independent route. Mayer and Schaefer¹⁵⁴ reported the preparation of the methyl iodide salt of ethylene trithiocarbonate (24) which on treatment with aniline yielded the amine salt (25). In the present work, under the same conditions trans-cyclohexene trithiocarbonate failed to give any methyl iodide salt, but the use of dichloromethane instead of nitromethane gave reasonable quantities of trans-4,5-cyclohexano-1,3-dithiolan-2-thione methyl iodide (26). Analysis figures for this compound indicated the presence of four additional methyl iodide molecules of crystallisation, which explained the low yield, and also the failure of (26) to recrystallise from ethanol or any other solvent. In most cases, recrystallisation attempts resulted in precipitation of the trithiocarbonate. Treatment of the salt (26) with aniline, followed by immediate base hydrolysis gave trans-4,5-cyclohexano-2-phenylimino-1,3-dithiolan (17), which was identical in every respect with samples prepared by base

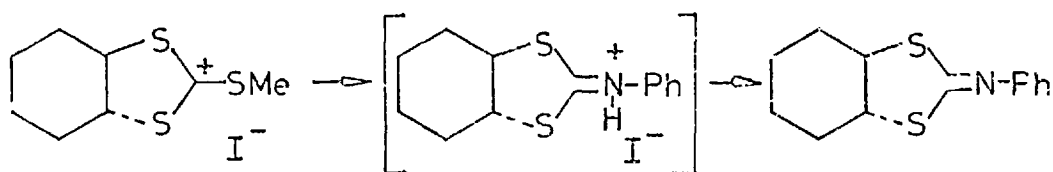
cyclisation of the monoacetate (10).



(24)



(25)

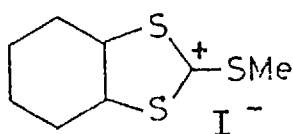


(26)

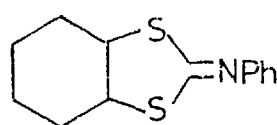
(17)

4,5-cyclohexano

A sample of cis-2-phenylimino-1,3-dithiolan (9) was prepared by the same route from cis-cyclohexene trithiocarbonate via the cis-methyl iodide salt which was shown by analysis to also contain methyl iodide molecules of crystallisation. The amine salt was again not isolated, but hydrolysed directly to the final product.



(28)



(9)

Jones¹⁵⁵ has reported the preparation of (9) in good yield from cis-cyclohexane-1,2-dithiol and phenyl isothiocyanate. This preparation was repeated in the present work, but was found to give a poor yield of the expected product, along with a little (5%) of cis-cyclohexene trithiocarbonate and substantial quantities of diphenyl thiourea. The good yield reported by Jones is probably normal for this reaction since ethane dithiol has been reported to react with phenyl isothiocyanate to give 2-phenylimino-1,3-dithiolan in 80% yield.¹⁵⁶ The majority of the diphenyl thiourea formed had the correct melting point¹⁵⁷ 154-155° but a small sample had a melting point of 167-168.5°. This sample had the correct M⁺ ion in the mass spectrum, the only possibilities are that it is either a different crystalline form or that it is a dimer. The phenylimino compound (9) is formed in this reaction by displacement of ⁻SH from the isothiocyanate; the trithiocarbonate is presumably formed by displacement of PhNH⁻ followed by cyclisation.

As a final part of this work, the mass spectra of two different samples of both the cis-phenylimino compound (9) and the trans-isomer (17) were run. One sample of each (9a) and (17a) was prepared by the methyl iodide salt route; the other cis-sample (9b) was that prepared from the cis-dithiol by Jones and the second trans-sample (17b) was that made by base cyclisation of the monoacetate (10). The details of these spectra are summarised in table VII; all peaks with relative abundancies of less than 5% have been omitted.

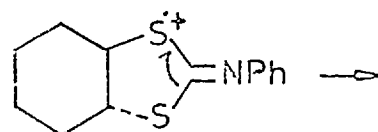
Table VII

Sample	9a	9b	17a	17b
Temperature	30°	70°	30°	30°
m/e	Relative abundancies			
249	35	45	70	17
194	11	5	-	-

Table VII/continued...

167	-	-	10	9
149	17	-	-	-
146	27	29	-	-
135	24	31	95	100
114	-	-	31	34
105	8	-	-	-
103	5	5	-	-
97	-	-	5	-
93	-	7	-	-
91	12	-	-	-
85	-	-	-	6
81	100	100	100	83
80	11	9	66	66
77	38	35	34	35

The two samples of each isomer have basically the same spectrum, but there are differences between the two isomers. The cis-compound (9) shows a relatively strong peak at m/e 146 that the trans-samples do not show; on the other hand the trans-compound (17) exhibits a strong peak at m/e 114 that is not shown by the cis-compound. The other differences are that the trans-spectra show stronger peaks at m/e 135 and m/e 80. These could be explained by the following fragmentation patterns, shown below for the trans-compound (17).



EXPERIMENTAL

EXPERIMENTAL SECTION

Bracketed numerals, preceeded by the letter "N", refer to the page number in the laboratory notebooks. Where the experiment has been repeated, the yield quoted refers to the first page number given.

Infra-red spectra were recorded on Perkin-Elmer 700 or 157G instruments. P.m.r. spectra were determined in deuteriochloroform solution on a Varian T-60 machine using tetramethylsilane as an internal reference. Optical rotations were determined on a Perkin-Elmer 141 polarimeter in a 1 dm tube, and Mass Spectra were determined on an A.E.I. M.S. 9 instrument. Melting points were determined on a Kofler block and are uncorrected.

The adsorbent for thin layer chromatography (t.l.c.) was Kieselgel CF₂₅₄ (E. Merck Ltd.). The developing solvent used was dichloromethane, unless otherwise specified. Organic solutions were dried over magnesium sulphate, unless otherwise stated, and solvents were removed under reduced pressure. Petroleum refers to the fraction b.p. 40-60°.

Abbreviations

G.l.c. : Gas-liquid chromatography

T.H.F. : Tetrahydrofuran

D.M.F. : N,N-dimethylformamide

In p.m.r. spectra : s (singlet), m (multiplet), d (doublet), dd (double doublet), t (triplet), q (quartet).

PART 1 THE SYNTHESIS OF SOME CYCLIC THIOCARBONATES AND THEIR REACTION
WITH POTASSIUM METHYL XANTHATE

The following general procedures were employed in this part of the present work.

(i) Reactions with xanthate

These reactions were carried out, generally under reflux conditions with the reagents described in each case. Work up consisted of cooling the reaction mixture, diluting with water, extracting with dichloromethane, drying the combined extracts, and concentrating under reduced pressure to give the crude product. Normally, purification by t.l.c., with dichloromethane as the developing solvent, unless otherwise stated, gave the pure product.

(ii) Reactions with N,N'-thiocarbonyldiimidazole

After the reaction was complete, the reaction mixture was washed with water, dilute hydrochloric acid, water again, then dried and concentrated to give the crude product. T.l.c., with dichloromethane as the developing solvent, unless otherwise stated, gave the pure product.

(iii) Reactions with mercuric acetate

A mixture of the starting material, glacial acetic acid, and mercuric acetate was stirred at 40-50° for 40-50 minutes, cooled, diluted with dichloromethane, and filtered. The filtrate was evaporated to dryness, water added, and the mixture extracted with dichloromethane. The combined extracts were washed with sodium bicarbonate solution, dried, concentrated, and the residue purified by t.l.c., with dichloromethane as the developing solvent, unless otherwise stated, to give the pure product.

Synthesis of trans-4,5-dimethyl-1,3-oxathiolan-2-thione, trans-4,5-dimethyl-1,3-oxathiolan-2-one, (4S,5R)-4,5-dimethyl-1,3-oxathiolan-2-thione and (4S,5R)-4,5-dimethyl-1,3-oxathiolan-2-one, and their reactions with potassium methyl xanthate.

Methyl 1-bromoethyl ketone (N 169, 3, 11, 55, 57, 111, 123)

This compound was prepared by the method of Catch *et al.*¹²⁹ Bromine (610 g) was added dropwise to a stirred mixture of methyl ethyl ketone (473 g), water (950 g) and potassium chlorate (114 g). The heavy layer of crude products was distilled under reduced pressure to remove unreacted ketone. Redistillation of the crude product through a packed column under nitrogen gave methyl 1-bromoethyl ketone (434 g; 44%), b.p. 78-82° at 125 mmHg (lit.,¹²⁹ 70° at 70 mmHg).

DL-threo-3-Bromobutan-2-ol (N 57, 7, 15, 23, 49, 113, 125, 171)

The procedure described by Kardouche¹²⁸ was followed. Potassium borohydride (28.8 g) in water (400 ml) was added dropwise to a stirred mixture of methyl 1-bromoethyl ketone (190 g) and methanol (400 ml), and the temperature kept below 20°. After the addition was complete, the mixture was left at room temperature for 30 minutes and then neutralised with dilute sulphuric acid. The reaction mixture was saturated with sodium chloride and extracted with ether. The combined extracts were dried, concentrated and distilled under reduced pressure to give the title product (125.7 g; 63%), b.p. 56-58° at 14 mmHg (lit.,¹⁵⁸ 50° at 13 mmHg). (G.l.c., 15% carbowax on chromosorb W, 2 metre, 180°, showed the presence of the erythro-isomer).

cis-2,3-Epoxybutane (N 57, 21, 29, 39, 115, 127, 175)

DL-threo-3-Bromobutan-2-ol (125.7 g) was added dropwise to a stirred solution of potassium hydroxide (202 g) in water (95 ml) at 90-95°. The crude product distilled over at ~ 60° (57.7 g; 98%) and was redistilled to give the pure epoxide, the fraction boiling at 58-60.5° being collected (lit.,¹⁵⁹ 59.9-60.4°).

G.l.c. analysis (15% carbowax on chromosorb W, 2 metre column, 100°) showed the above epoxide to contain a substantial amount of the trans-epoxide (retention times: cis- 63 and trans- 57 seconds).

DL-threo- and erythro-3-Mercaptobutan-2-ol (N 31, 25, 43, 47, 51, 55, 59, 71, 131)

The procedure used by Price and Kirk¹³⁰ was followed. A mixture of cis- and trans-2,3-epoxybutane was added dropwise to a stirred solution of potassium hydroxide (4.8 g) in ethanol (63 ml) saturated with hydrogen sulphide at 0°. After the addition was complete, the mixture was left at 0° for 30 minutes, and then overnight at room temperature. The reaction mixture was acidified with dilute sulphuric acid after diluting with water (100 ml), extracted with dichloromethane (3 x 50 ml), the combined extracts washed with sodium bicarbonate solution, dried and concentrated. Distillation of the residue gave the title product (4.5 g; 51%), b.p. 65-66° at 22 mmHg (lit.,¹³⁰ 73.5-74.0° at 31 mmHg).

cis- and trans-4,5-Dimethyl-1,3-dithiolan-2-thione from DL-threo- and erythro-3-mercaptobutan-2-ol (N 61).

The mixed 3-mercaptobutan-2-ols (0.7 g) and a mixture of carbon disulphide added to a solution of sodium (1.15 g) in ethanol (70 ml) were refluxed for 53 hours. Work up according to the general procedure, t.l.c.

(ether/petroleum (1:2)), and fractional crystallisation gave trans- and (cis- + trans)-4,5-dimethyl-1,3-dithiolan-2-thione, 70 mg and 160 mg respectively (230 mg; 23%), trans- m.p. 34-41°, depresses m.p. of authentic cis-isomer to below room temperature (21°), τ : trans- 5.83 (2H, m), 8.43 (6H, d, Me); cis- + trans- 5.83 + 5.50 (2H, m), 8.43 and 8.50 (6H, m, Me) (lit.,¹²⁸ trans- 5.87 (2H, m), 8.39 (6H, d) cis- 5.50 (2H, m), 8.48 (6H, d)).

DL-2,3-Diacetoxybutane (N 95, 146)

The procedure described by Lucas and Garner¹³¹ was followed. DL-Butane-2,3-diol (supplied by Professor Owen, 6.7 g) and dry pyridine (30.0 g) were stirred together and acetic anhydride (16.9 g) added slowly, the temperature of the reaction mixture being maintained below 40°. Stirring was continued overnight, and distillation under reduced pressure gave DL-2,3-diacetoxybutane (8.0 g; 62%) b.p. 89-92° at 17 mmHg (lit.,¹³¹ 82.1-82.2° at 10 mmHg). A further quantity was crystallised from the undistilled residue and recrystallised from ether (1.63 g; 13%) m.p. 32-35°.

DL-erythro-3-Chlorobutan-2-ol (N 101, 149)

The method of Lucas and Gould¹⁶⁰ was used. DL-2,3-diacetoxybutane (9.0 g) was dissolved in concentrated hydrochloric acid (13 ml). Dry hydrogen chloride gas was passed into the stirred solution at -10° until 4.98 g had been added. The mixture was left for four days then poured onto sodium bicarbonate (24.0 g) with stirring. The mixture was filtered, the solid washed with ether and the aqueous layer extracted with ether (total volume 250 ml). The combined extracts were washed with sodium bicarbonate solution, dried, and concentrated. Distillation gave the title product (2.28 g; 41%) b.p. 70-74° at 61 mmHg (lit.,¹⁶⁰ 70-72.5° at

30 mmHg), and DL-erythro-3-chloro-2-acetoxybutane (1.15 g; 15%) b.p. 86-87° at 32 mmHg (lit., ¹⁶⁰ 70-72.5° at 30 mmHg).

trans-2,3-Epoxybutane (N 105)

A solution of potassium hydroxide (8.5 g) in water (4.5 ml) was heated to 90-100° and a mixture of DL-erythro-3-chlorobutan-2-ol (2.02 g) and DL-erythro-3-chloro-2-acetoxybutane (0.84 g) was added dropwise and the crude product (0.67 g; 39%) distilled over at ~ 60°. The crude product was redistilled and a middle fraction collected to give a small sample of pure (95% by g.l.c.) trans-2,3-epoxybutane.

cis-2,3-Epoxybutane (N 127)

Pure (98% by g.l.c.) cis-2,3-epoxybutane was obtained from the mixed epoxides by fractional distillation through a 30 cm column packed with helices and employing a high reflux ratio which gave early fractions rich in trans-epoxide and left a residue of the pure cis-epoxide.

DL-threo-3-Mercaptobutan-2-ol (N 129, 159)

This compound was prepared in the same way as previously described for the mixed isomers from cis-2,3-epoxybutane (6.0 g). Work up and distillation gave the title product (2.69 g; 31%) b.p. 66.5-67° at 24 mmHg, $\nu_{\text{max.}}$: 3380 (OH), 2560 (SH), 1167 and 930 cm^{-1} (film) and a mixture of meso- and DL-trans, trans-3,3'-dithiobis(butan-2-ol) b.p. 122° at 0.6 mmHg, $\nu_{\text{max.}}$: 3360 (OH), 1102, 992 and 920 cm^{-1} (film), τ : 5.82-6.58 (2H, m), 6.75-7.55 (2H, m), 7.15-7.82 (2H, m, OH, exch.), 8.72 (12H, m, Me), m/e 210 (M^+ , 100), 174 (22), 133 (18), 120 (69), 105 (33), 89 (40), 88 (29), 87 (53), 81 (33).

N,N'-Thiocarbonyldiimidazole (N 467, 73, 83, 156, 166, 191, 408)

The method described by Staab and Walther¹⁶¹ was followed. Thiophosgene (12.3 g) in dry benzene (80 ml) was added dropwise to a stirred mixture of imidazole (29.0 g) and dry dichloromethane (200 ml) at room temperature. Stirring was continued for one hour after the addition was complete; the mixture was filtered, the solid material washed with a little dichloromethane and the filtrate concentrated under reduced pressure to give the crude product (17.7 g; 93%). The reagent was normally used in the crude state, but a portion was recrystallised from dichloromethane/petroleum to give the pure product, m.p. 97-99° (lit.,¹⁶¹ 105-106°).

1-3-Oxathiolan-2-thione (N 89, 81, 83)

A solution of N,N'-thiocarbonyldiimidazole (3.0 g) in dry dichloromethane (60 ml) was added to a mixture of 2-mercaptoethanol (1.0 g) and pyridine (6.0 g) in dry dichloromethane (30 ml) and the whole stirred for 2 days. Usual work up gave the title compound (1.65 g, 84%) (oil), $\nu_{\max}$: 1380, 1280, 1072, 1018, 933, and 752 cm^{-1} (film).

trans-4,5-Dimethyl-1,3-oxathiolan-2-thione (N 129, 145, 151)

N,N'-Thiocarbonyldiimidazole (2.1 g) in dry dichloromethane (32 ml) was added dropwise to a stirred mixture of DL-threo-3-mercaptobutan-2-ol (1.0 g), pyridine (6.2 g) and dry dichloromethane (25 ml) and stirring continued overnight. Usual work up gave trans-4,5-dimethyl-1,3-oxathiolan-2-thione (1.51 g; 94%), (oil), $\nu_{\max}$: 1388, 1340, 1203, 1083, and 907 cm^{-1} (film), τ : 4.83-5.53 (1H, m), 5.80-6.47 (1H, m), 8.45 (6H, t, Me) (Found: C, 40.84; H, 5.59; S, 43.43. $\text{C}_5\text{H}_8\text{OS}_2$ requires C, 40.53; H, 5.44; S, 43.28%).

trans-4,5-Dimethyl-1,3-oxathiolan-2-one (N 131, 151, 165)

A mixture of trans-4,5-dimethyl-1,3-oxathiolan-2-thione (0.34 g) and glacial acetic acid (1.8 ml) was reacted with mercuric acetate (1.8 g) according to the general procedure. T.l.c. (petroleum/ether (4:1)) gave pure trans-4,5-dimethyl-1,3-oxathiolan-2-one (0.20 g; 66%) (oil), $\nu_{\max}$: 1723, 1345, 1255, 958 and 751 cm^{-1} (film), τ : 5.33-5.87 (1H, m), 5.97-6.63 (1H, m), 8.52 (6H, d, Me) (Found: C, 45.56; H, 6.07; S, 24.24. $\text{C}_5\text{H}_8\text{O}_2\text{S}$ requires C, 45.43; H, 6.10; S, 24.26%).

L-(-)-2,3-O-Isopropylidene dimethyl tartrate (N 293, 249, 271, 451)

The method of Carmack and Kelley¹³⁹ was followed. (+)-Dimethyl tartrate (Koch-Light, 5.0 g), *p*-toluenesulphonic acid (100 mg), 2,2-dimethoxypropane (3.5 g) and dry benzene (11 ml) were refluxed together overnight. The lower boiling fractions, including the benzene-methanol azeotrope were removed by distillation through a Vigreux column. The catalyst was neutralised with sodium carbonate and the reaction mixture distilled under vacuum to give the title compound (5.8 g; 94%), b.p. 100° at 0.5 mmHg (lit.,¹³⁹ 82-90° at 0.02 mmHg), $[\alpha]_{\text{D}}^{21} = 44.2^\circ$ ($c = 5.45$, CHCl_3) (lit.,¹³⁹ $[\alpha]_{\text{D}}^{20} = 49.4$ (neat liquid)).

L-(+)-2,3-O-Isopropylidenethreitol (N 305, 253, 480)

The procedure described by Feit¹⁴⁰ was used. A suspension of lithium aluminium hydride (10 g) in dry ether (120 ml) was refluxed with stirring for 30 minutes. A solution of L-(-)-2,3-O-isopropylidene dimethyl tartrate (26.3 g) in ether (120 ml) was added dropwise. After the addition was complete, refluxing was continued for a further 2½ hours. After cooling to 0°, ethyl acetate (~ 70 ml), followed by water (10 ml), sodium hydroxide

solution (4N, 10 ml) and water again (10 ml) were cautiously added. The solid material was filtered off, and thoroughly extracted with ether (Soxhlet). The combined ether solutions were dried, and concentrated under reduced pressure. Distillation under vacuum gave the title product (16.0 g, 82%), b.p. 96-98° at 0.3 mmHg (lit.,¹⁴⁰ 96-96.5 at 0.5 mmHg, m.p. 49.5-51°), $[\alpha]_D^{23.0} + 5.2$ (c = 4.99, CHCl₃) (lit.,¹⁴⁰ $[\alpha]_D^{20} + 4.1$ (c = 5, CHCl₃)).

L-(-)-1,4-Ditosyl-2,3-O-isopropylidenethreitol (N 259, 313, 481)

The conditions of Rubin et al.¹⁴¹ were used. L-(+)-2,3-O-Isopropylidenethreitol (13.17 g) in pyridine (86 ml) was cooled to -10°, and recrystallised *p*-toluenesulphonyl chloride (33.0 g) was added in one portion. The flask was shaken until the mixture was almost homogeneous when violent shaking produced a precipitate. The mixture was left overnight at 0°. Water (200 ml) was added, and the reaction again left overnight at 0°. The solid was filtered off and washed with 90% ethanol. Recrystallisation from ethanol gave pure L-(-)-1,4-ditosyl-2,3-O-isopropylidenethreitol (34.1 g; 89%), m.p. 90.5-91.5° (lit.,¹⁴¹ 90-92°), $[\alpha]_D^{23.0} - 10.6$ (c = 5.27, CHCl₃) (lit.,¹³⁹ $[\alpha]_D^{24} - 12.4$ (c = 5, CHCl₃)).

L-(+)-2-Isopropoxybutan-3-ol (N 267)

The procedure reported by Schmid and Karrer¹⁶² for the reduction of a sugar tosylate was followed. L-(-)-1,4-Ditosyl-2,3-O-isopropylidene-threitol (30 g) was dissolved in excess dry benzene and the solution concentrated to 35 ml. Ether (120 ml) and lithium aluminium hydride (5.2 g) were added, and the mixture refluxed overnight. A further quantity (2.5 g) of the hydride was added and refluxing continued for a further

24 hours. The reaction mixture was cooled to 0° , ethyl acetate and then water cautiously added followed by sodium hydroxide solution and then more water. The solid material was filtered off, washed with ether; the combined ether solutions were dried, concentrated and distilled to give L-(+)-2-isopropoxybutan-3-ol (4.5 g; 54%), b.p. $140-141^{\circ}$, $n_D^{21.5}$ 1.4129, $[\alpha]_D^{24} + 68.9$ ($c = 4.85$, CHCl_3), ν_{max} : 3425 (OH), 1118 and 940 cm^{-1} (film), τ : 6.00-7.08 (3H, m), 6.27 (1H, m, OH, exch.), 8.88 (12H, m).

L-(-)-1,4-Dideoxy-1,4-diiodo-2,3-O-isopropylidenethreitol (N 314, 279, 482)

The method of Rubin et al.¹⁴¹ was used. L-(-)-1,4-ditosyl-2,3-O-isopropylidenethreitol (43.4 g), sodium iodide (65.0 g), and acetone (200 ml) were refluxed together for $5\frac{1}{2}$ hours. Sodium p-toluenesulphonate was removed by filtration and washed with acetone. The filtrate and washings were combined, concentrated, mixed with water (250 ml) and extracted with dichloromethane (1 x 100, 2 x 50 ml). The combined extracts were washed with thiosulphate solution (0.1 N, 50 ml), then water (1 x 100, 1 x 60 ml), dried and concentrated to give the crude product (35.0 g; 99%). Distillation of the crude product under vacuum gave the pure title product (25.2 g; 73%), b.p. 108° at 0.78 mmHg (lit.,¹⁴¹ $80-82^{\circ}$ at 0.05 mmHg), $[\alpha]_D^{24.0} - 16.9$ ($c = 8.28$, MeOH) (lit.,¹⁴¹ for D isomer, $[\alpha]_D + 17.5^{\circ}$ ($c = 8.5$, MeOH)).

L-(+)-Butane-2,3-diol (N 331)

Potassium acetate (16.0 g) in dry methanol (100 ml) was added to a solution of L-(-)-1,4-dideoxy-1,4-diiodo-2,3-O-isopropylidenethreitol (22.4 g) in methanol (100 ml). Raney nickel (~ 7 g) was added and the mixture hydrogenated at atmospheric pressure. When approximately the theoretical uptake had been reached (2610 ml), the reaction mixture was

filtered to remove the catalyst and distilled. This distillate was fractionally distilled through a 40 cm Vigreux column to remove most of the methanol. The residual solution was diluted with ether (150 ml), molecular sieve (4A, 150 g) added, and the mixture left for 1 week. The molecular sieve was removed by filtration, washed with ether and the combined ether solutions concentrated and then distilled under reduced pressure to give L-(+)-butane-2,3-diol (2.46 g; 47%) b.p. 84-86° at 15 mmHg (lit.,¹⁴¹ $\sim$ 170°), $[\alpha]_D^{23.0} + 19.8$ (c = 3.8, CHCl₃) (lit.,¹⁴¹ $[\alpha]^{25} + 12.4$).

L-(+)-2-Phenyl-4,5-dimethyl-1,3-dioxolan (N 400)

The procedure of Gagnaire and Robert¹⁴³ was followed. L-(+)-Butane-2,3-diol (2.19 g), benzaldehyde (5.1 g) and sulphuric acid (N, 2 drops) were stirred together at 95° for 16 hours. The reaction mixture was cooled, diluted with ether (15 ml), washed with saturated aqueous sodium bicarbonate and the aqueous layer extracted with ether (10 ml). The combined ether solutions were washed with a solution of sodium metabisulphite (4.0 g) in water (10 ml), and the aqueous layer again extracted with ether. The combined ether solutions were dried, concentrated under reduced pressure and distilled under vacuum to give L-(+)-2-phenyl-4,5-dimethyl-1,3-dioxolan (3.74 g; 86%), b.p. 55-56° at 0.13 mmHg (lit.,¹⁴³ 119° at 19 mmHg), $[\alpha]_D^{24.5} + 32.0$ (c = 4.87, CHCl₃), $\nu_{\max}$: 1495, 1233, 970 and 775 cm⁻¹ (film), τ : 2.6 (5H, m, Ph), 4.02 (1H, s), 6.18 (2H, m), 8.67 (6H, m, Me).

(2R,3S)-2-Bromo-3-benzoyloxybutane (N 401)

The method described by Seeley and McElwee¹⁴⁴ was used. L-(+)-2-Phenyl-4,5-dimethyl-1,3-dioxolan (3.53 g) was added dropwise to a slurry

of N-bromosuccinimide (3.60 g) in carbon tetrachloride (41 ml) cooled in an ice bath. The mixture was stirred in the dark for 1 day at room temperature, filtered, the filtrate washed with saturated aqueous bicarbonate solution (20 ml), dried (sodium sulphate) and concentrated under reduced pressure to give the crude title product (5.47 g; 107%).

(2S,3S)-trans-2,3-Epoxybutane (N 433)

Crude (2R,3S)-2-bromo-3-benzoyloxybutane (5.12 g), sodium hydroxide (1.9 g) and ethylene glycol (14.2 ml) were slowly heated to 140° and the volatile products collected. G.l.c. (2 metre column, 15% carbowax on chromosorb W, 100°) showed these to consist of a little ethylene glycol, less than 2% of the cis-epoxide and (2S,3S)-trans-2,3-epoxybutane (0.54 g; 37%), τ : 7.28 (2H, m), 8.70 (6H, d, Me).

(2S, 3R)-3-Mercaptobutan-2-ol (N 435)

This was prepared as previously described for the mixed isomers (p 101) from (2S,3S)-trans-2,3-epoxybutane (0.49 g) to give the crude product (124 mg; 17%).

(4S,5R)-4,5-Dimethyl-1,3-oxathiolan-2-thione (N 436)

Crude (2S,3R)-3-mercaptobutan-2-ol (124 mg), pyridine (0.76 g), and dry dichloromethane (3.1 ml) were stirred together at room temperature and a solution of N,N'-thiocarbonyldiimidazole (0.25 g) in dry dichloromethane (4 ml) added over 4 minutes. Stirring was continued overnight at room temperature. Usual work up gave (4S,5R)-4,5-dimethyl-1,3-oxathiolan-2-thione (116 mg; 67%), (oil) $\nu_{\max}$: 1144, 894 and 750 cm^{-1} (film) τ 4.45-5.15 (1H, m), 5.72-6.32 (1H, m), 8.51 (6H, t, Me) (Found: C, 40.58; H, 5.20; S, 43.43. $\text{C}_5\text{H}_8\text{OS}_2$ requires C, 40.53; H, 5.44; S, 43.28%).

(4S,5R)-4,5-Dimethyl-1,3-oxathiolan-2-one (N 461)

(4S,5R)-4,5-Dimethyl-1,3-oxathiolan-2-thione (57 mg) in glacial acetic acid (2.5 ml) was reacted with mercuric acetate (245 mg) according to the general procedure to give (4S, 5R)-4,5-dimethyl-1,3-oxathiolan-2-one (29 mg; 57%) (oil), $\nu_{\max}$: 1730, 1190, 1106 and 953 cm^{-1} (film), τ : 4.83-5.43 (1H, m), 5.73-6.47 (1H, m), 8.57 (6H, dd, Me) (Found: C, 45.84; H, 6.11; S, 22.76. $\text{C}_5\text{H}_8\text{O}_2\text{S}$ requires C, 45.43; H, 6.10; S, 24.26%).

trans-4,5-Dimethyl-1,3-dithiolan-2-thione from trans-4,5-dimethyl-1,3-oxathiolan-2-thione (N 462)

Carbon disulphide (0.53 ml) was added to a solution of potassium hydroxide (0.335 g) in dry methanol (5.7 ml) and 0.9 ml of this mixture was added to the starting material (23.5 mg) in a glass tube which was sealed and heated at 64-66° for 4 days. Usual work up gave trans-4,5-dimethyl-1,3-dithiolan-2-thione (21 mg, 81%) which was crystallised from ether/petroleum and recrystallised from petroleum (b.p. 60-80°), m.p. 39-41°, m.m.p. with authentic sample 33-43°, τ : 5.90 (2H, m), 8.43 (6H, d, Me), (lit.,¹²⁸ 5.37 (2H, m), 8.39 (6H, deformed d)).

trans-4,5-Dimethyl-1,3-dithiolan-2-thione from trans-4,5-dimethyl-1,3-oxathiolan-2-one (N 464)

Carbon disulphide (0.53 ml) was added to a solution of potassium hydroxide (0.330 g) in dry methanol (5.5 ml) and 0.56 ml of this mixture added to the starting material (9.0 mg) in a glass tube which was sealed and heated at 64-66° for 4 days. Usual work up gave trans-4,5-dimethyl-1,3-dithiolan-2-thione (10.2 mg; 76%), which was crystallised and recrystallised from petroleum (b.p. 60-80°), m.p. 40.5-42°, m.m.p. with an authentic sample 40.5-42°, τ : 5.85 (2H, m), 8.38 (6H, d, Me) (lit.,¹²⁸

5.87 (2H, m), 8.39 (6H, deformed d)).

cis-4,5-Dimethyl-1,3-dithiolan-2-thione from (4S,5R)-4,5-dimethyl-1,3-oxathiolan-2-thione (N 457)

Carbon disulphide (0.53 ml) was added to a solution of potassium hydroxide (0.330 g) in dry methanol (5.7 ml) and 0.56 ml of this mixture added to the starting material (11.3 mg) in a glass tube which was sealed and heated at 64-66° for 4 days. Usual work up gave cis-4,5-dimethyl-1,3-dithiolan-2-thione (5.7 mg; 46%) which was crystallised from ether/petroleum m.p. 41-42°, m.m.p. with trans-isomer < 22°.

cis-4,5-Dimethyl-1,3-dithiolan-2-thione from (4S,5R)-4,5-dimethyl-1,3-oxathiolan-2-one (N 463)

Carbon disulphide (0.53 ml) was added to a solution of potassium hydroxide (0.335 g) in dry methanol (5.7 ml) and 0.28 ml of this mixture added to the starting material (5.0 mg) in a glass tube, which was sealed and heated at 64-66° for 4 days. Usual work up and t.l.c. (dichloromethane/petroleum (3:1)) gave cis-4,5-dimethyl-1,3-dithiolan-2-thione (4.8 mg; 87%) which was recrystallised from petroleum (b.p. 60-80°) m.p. 40.5-42°, m.m.p. with trans-isomer < 22.5°, τ : 5.58 (2H, m), 8.52 (6H, d, Me) (lit.¹²⁸, 5.50 (2H, m), 8.48 (6H, deformed d)).

trans-4,5-Dimethyl-1,3-dithiolan-2-thione from DL-threo-3-mercaptoputan-2-ol (N 133)

Carbon disulphide (5 g) was added to a solution of sodium (1.15 g) in ethanol (25 g), the mixture added to the starting material (0.6 g) and the whole refluxed for 7 days. Usual work up gave trans-4,5-dimethyl-1,3-dithiolan-2-thione (29.4 mg; 3%) m.p. 41.5-42°, m.m.p. with an

authentic sample 39.5-41.5°, τ : 5.87 (2H, m), 8.41 (6H, d, Me) (lit.¹²⁸, 5.87 (2H, m), 8.39 (6H, deformed d)).

Synthesis of cis- and trans-bis(benzyloxymethyl)ethylene carbonates and thiocarbonates, and their reaction with potassium methyl xanthate

trans-1,4-Dibenzyloxy-2-butene (N 357, 251, 277, 315)

The procedure of Kiss and Sirchman¹⁴⁵ was followed. Sodium (2.3 g) was dissolved in benzyl alcohol (120 ml), the solution diluted with dioxan (30 ml) and trans-1,4-dibromo-2-butene (supplied by Professor Owen, 10.7 g) added. After 10 minutes, the reaction mixture was heated on a steam bath for 3 hours. Solid material was filtered off, the dioxan removed under reduced pressure and the residue distilled under vacuum to give the title product (12.1 g; 90%), b.p. 160-161° at 0.5 mmHg (lit.¹⁴⁵, 203-205° at 5 mmHg), n_D^{27} 1.5469 (lit.¹⁴⁵, n_D^{20} 1.5519).

Meso-1,4-Dibenzyloxybutane-2,3-diol (i) (N 485, 483)

The method used by Roebuck and Adkins¹⁴⁶ on cyclohexene was employed. Hydrogen peroxide (30%, 4.3 ml) was added to formic acid (90%, 18.4 ml), and trans-1,4-dibenzyloxy-2-butene (8.0 g) added with stirring. When a uniform emulsion had formed, the reaction mixture was heated to 50° and stirred at 40° overnight. A small quantity of aqueous sodium metabisulfite solution was added, and the water and formic acid removed under reduced pressure. A solution of sodium hydroxide (2.7 g) in water (5.3 ml) was added so that the temperature remained below 45°. The reaction mixture was diluted with water (25 ml) and extracted with dichloromethane (60 ml). The extracts were washed with dilute hydrochloric acid, then

with aqueous sodium bicarbonate solution, dried, and concentrated to dryness under reduced pressure. The crude product was recrystallised from ether/petroleum to give pure meso-1,4-dibenzyloxybutane-2,3-diol (6.75 g; 75%) m.p. 57.5-58.5° (lit.,¹⁶³ 56-57°).

meso-1,4-Dibenzyloxy-O-isopropylidenebutane-2,3-diol (N 489)

meso-1,4-Dibenzyloxybutane-2,3-diol (5.0 g), p-toluenesulphonic acid monohydrate (0.2 g), 2,2-dimethoxypropane (3.0 g) and dry benzene (12 ml) were refluxed together for 5 hours, the benzene-methanol azeotrope being slowly removed from the top of a small column. The reaction mixture was cooled, the catalyst neutralised with sodium carbonate (0.3 g), excess dimethoxypropane and benzene removed under reduced pressure and the residue distilled to give meso-1,4-dibenzyloxy-O-isopropylidenebutane-2,3-diol (2.9 g; 51%), b.p. 184-186° at 0.75 mmHg, $\nu_{\max}$: 1227, 1111, 957 and 917 cm^{-1} (film), τ : 2.7 (10H, s, Ph), 5.47 (4H, s), 5.4-5.77 (2H, m), 6.47 (4H, m), 8.58 (6H, d, $\text{C}(\text{Me})_2$).

Erythritol (N 508)

meso-1,4-Dibenzyloxybutane-2,3-diol (1.15 g) in ethanol (10 ml) was hydrogenated at atmospheric pressure with 10% palladium on charcoal as a catalyst. After approximately the theoretical uptake had occurred (149 ml), the reaction mixture was filtered and stirred for 8 days with acid ion-exchange resin (IR 120, 3 g), then filtered and concentrated under reduced pressure. The cooled residue was triturated with ether, and the solid recrystallised from ethanol to give pure erythritol (0.28 g; 69%), m.p. 118.5-120° (lit.,¹⁵⁷ 121.5°).

1,2,3,4-Tetraacetylerythritol (N 511)

Erythritol (0.1 g), acetic anhydride (0.37 g) and pyridine (0.7 g)

were stirred together at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the residue crystallised from ethanol. Recrystallisation from ethanol gave the pure title compound (177 mg; 75%) m.p. $85.0-85.5^{\circ}$, m.m.p. with an authentic sample (supplied by Professor Owen) $82.5-84^{\circ}$.

DL-1,4-Dibenzoyloxybutane-2,3-diol (i) (N 447)

The procedure of Clarke and Owen¹⁴⁷ was used. A solution of potassium permanganate (0.518 g) and magnesium sulphate (anhydrous, 0.392 g) in water (10 ml) was added over 110 minutes to a solution of trans-1,4-dibenzoyloxy-2-butene (1.1 g) in ethanol (8 ml) at between -10° and -15° . Sodium metabisulphite solution was added until no more manganese dioxide remained, and the reaction mixture extracted with dichloromethane (3 x 10 ml). The combined extracts were dried, concentrated and t.l.c. (dichloromethane) gave the crude product. A second purification by t.l.c. (methanol) gave crystalline material which after t.l.c. (ether) and recrystallisation from ether/petroleum gave the pure title product (0.317 g; 26%) m.p. $61.5-62.5^{\circ}$ (lit.,¹⁶³ $61.5-62.5^{\circ}$).

cis-2-Butene-1,4-diol dibenzoate (N 347)

cis-2-Butene-1,4-diol (Commercial, 50.0 g) and dry pyridine (180 g) were mixed, benzoyl chloride (314 g) cautiously added and the reaction mixture left at room temperature overnight. Water (300 ml) was added, and the mixture extracted with dichloromethane (total 600 ml). The combined extracts were dried and concentrated under reduced pressure. Residual pyridine was removed at the oil pump and the crude product crystallised from n-butanol. Final traces of pyridine were removed by washing a dichloromethane solution with dilute hydrochloric acid and concentrating to give the title product (130 g; 77%). Recrystallisation,

three times from ethanol and once from petroleum (b.p. 60-80°) gave pure cis-2-butene-1,4-diol dibenzoate m.p. 65.5-66.5° (lit.,¹⁶⁴ 65-66°).

cis-2-Butene-1,4-diol (N 423, 365, 405)

cis-2-Butene-1,4-diol dibenzoate (35.0 g) was covered with dry methanol (150 ml) and traces of sodium metal added until the solution was basic to phenolphthalein. The mixture was stirred overnight, neutralised with dilute hydrochloric acid and concentrated under reduced pressure. Distillation of the residue gave pure cis-2-butene-1,4-diol (8.33 g; 80%) b.p. 84-86° at 0.32 mmHg (lit.,¹⁶⁴ 101-102° at 2 mmHg).

cis-1,4-Dibenzzyloxy-2-butene (N 444)

cis-2-Butene-1,4-diol (8.0 g), dry benzene (100 ml), benzyl bromide (60 g) and powdered potassium hydroxide (17 g) were stirred together at room temperature for 5 days. The reaction mixture was diluted with benzene (100 ml) and then washed with 100 ml quantities of water, hydrochloric acid (0.1 N), aqueous sodium bicarbonate solution and water respectively. The reaction mixture was dried (sodium sulphate), the benzene removed under reduced pressure and the residue distilled to give the crude product (18.95 g; 78%) b.p. 146° at 0.08 mmHg (lit.,¹⁶⁵ 137-139° at 1 mmHg). T.l.c. (dichloromethane) gave pure cis-1,4-dibenzzyloxy-2-butene, n_D^{20} 1.5487.

trans-1,4-Dibenzzyloxy-2,3-epoxybutane (N 359, 273, 289, 308, 339, 434)

The method of Kiss and Sirchman¹⁴⁵ was followed, except that m-chloroperbenzoic acid was used instead of monoperphthalic acid. trans-1,4-Dibenzzyloxy-2-butene (5.0 g), m-chloroperbenzoic acid (5.0 g) and dry ether (100 ml) were stood together at -7° for 2 weeks and then at

room temperature for 10 days. Excess peracid was destroyed by washing the reaction mixture with aqueous sodium sulphite solution, the ether layer shaken vigorously with aqueous sodium bicarbonate solution, washed with water, dried, and concentrated under reduced pressure. The residue was distilled to give the title compound contaminated with a little of the starting material (4.32 g; 81%) b.p. 160-170° at ~0.1 mmHg (lit.¹⁴⁵ b.p. 236-238° at 2 mmHg).

cis-1,4-Dibenzylloxy-2,3-epoxybutane (N 507, 466)

cis-1,4-Dibenzylloxy-2-butene (1.5 g), m-chloroperbenzoic acid (1.6 g) and dry ether (25 ml) were refluxed together for 27 hours. After this time, the reaction was almost complete (t.l.c.), and further refluxing produced no change. Work up as for the trans-compound and t.l.c. (dichloromethane) gave the title compound contaminated with a little starting material (1.39 g; 87%). Repurification by t.l.c. (dichloromethane) gave pure cis-1,4-dibenzylloxy-2,3-epoxybutane, (oil), ν_{max} : 1502, 1315, 758 and 720 cm^{-1} (soln), τ : 2.63 (10H, s, aromatic), 5.42 (4H, s), 6.37 (4H, m), 6.68 (2H, m), (Found: C, —; H, —. $\text{C}_{18}\text{H}_{20}\text{O}_3$ requires C, 76.03; H, 7.09%).

1,4-Di-O-benzyl-2-thioerythritol (N 317, 291, 297)

A solution of potassium hydroxide (1.38 g) in ethanol (17 ml) was saturated with hydrogen sulphide at 0°. trans-1,4-Dibenzylloxy-2,3-epoxybutane (1.98 g) was added dropwise over a period of 130 minutes with hydrogen sulphide bubbling through the solution. Stirring was continued for a further 30 minutes at 0°, the system sealed, and stirring continued overnight at room temperature. The reaction mixture was diluted with water (25 ml), acidified with dilute sulphuric acid and extracted with dichloromethane (3 x 25 ml). The combined extracts were washed with aqueous sodium bicarbonate solution (5%, 15 ml), dried and

concentrated to give crude 1,4-di-O-benzyl-2-thioerythritol (2.47 g; 76% based on active SH). Distillation of a portion of the crude product failed to give a pure sample (64% pure, based on active SH), $\nu_{\max}$: 3440 (OH), 2580 (SH), 755 and 717 cm^{-1} (film), τ : 2.6 (10H, s, aromatic), 5.4 (4H, d), 5.82-6.55 (5H, m), 6.85 (2H, m), 7.15 (1H, m, exch.).

cis-4,5-Bis(benzyloxymethyl)-1,3-oxathiolan-2-thione (N 319)

Crude 1,4-di-O-benzyl-2-thioerythritol ($\approx$ 1.31 g), pyridine (13 ml) and chloroform (25 ml) were stirred together at 0° , and a solution of N,N'-thiocarbonyldiimidazole (1.96 g) in chloroform (25 ml) added dropwise and stirring continued overnight at room temperature. Usual work up and t.l.c. (dichloromethane/petroleum (5:1)) gave the crude product which was recrystallised from ether/petroleum to give pure cis-4,5-bis(benzyloxymethyl)-1,3-oxathiolan-2-thione (0.643 g; 43%), m.p. $53-55^\circ$, $\nu_{\max}$: 1500, 1199, 1110 and 715 cm^{-1} (soln), τ : 2.68 (10H, s, aromatic), 4.83 (1H, q), 5.57 (4H, d), 5.67-6.53 (5H, m), (Found: C, 63.27; H, 5.57; S, 17.23. $\text{C}_{19}\text{H}_{20}\text{O}_3\text{S}_2$ requires C, 63.30; H, 5.59; S, 17.79%).

meso-1,4-Dibenzyloxybutane-2,3-diol (ii) (N 460, 355, 369)

trans-1,4-Dibenzyloxy-2,3-epoxybutane (420 mg), water (5 ml), dioxan (6 ml) and perchloric acid (70%, 1 drop) were refluxed together for 4 days. The reaction mixture was cooled, diluted with water (10 ml) and extracted with dichloromethane. The combined extracts were dried, concentrated under reduced pressure and triturated with petroleum/ether to give the crude product. Recrystallisation from ether/petroleum gave the pure diol (332 mg; 74%), m.p. $55-57^\circ$, identical with the sample prepared previously from trans-1,4-dibenzyloxy-2-butene.

cis-4,5-Bis(benzyloxymethyl)-1,3-dioxolan-2-thione (N 379, 456)

A solution of N,N'-thiocarbonyldiimidazole (0.39 g) in dry dichloromethane (8 ml) was added dropwise to a stirred solution of meso-1,4-dibenzyloxybutane-2,3-diol (322 mg) in dry dichloromethane (8 ml) and the mixture stirred overnight at room temperature. Usual work up gave the title product which was further purified by t.l.c. (ether/petroleum (1:1)) and recrystallisation from ether/dichloromethane gave pure cis-4,5-bis(benzyloxymethyl)-1,3-dioxolan-2-thione (326 mg; 89%), m.p. 107.5-108.5°, $\nu_{\max}$: 1502, 1293, 1110, 926 and 716 cm^{-1} (soln), τ : 2.67 (10 H, s, aromatic), 5.00 (2H, m), 5.48 (4H, s), 6.2 (4H, m) (Found: C, 66.51; H, 5.83; S, 9.31. $\text{C}_{19}\text{H}_{20}\text{O}_4\text{S}$ requires C, 66.30; H, 5.85; S, 9.31%).

cis-4,5-Bis(benzyloxymethyl)-1,3-oxathiolan-2-one (N 333)

cis-4,5-bis(Benzyloxymethyl)-1,3-oxathiolan-2-thione (354 mg) in glacial acetic acid (13 ml) was reacted with mercuric acetate (1.0 g) according to the general procedure. The product (274 mg; 81%) was rectystallised from ether/petroleum to give pure cis-4,5-bis(benzyloxymethyl)-1,3-oxathiolan-2-one, m.p. 51-54.5°, $\nu_{\max}$: 1737, 1100, 715 and 682 cm^{-1} (soln), τ : 2.63 (10H, s, aromatic), 5.15 (1H, q), 5.47 (4H, d), 5.75-6.48 (5H, m) (Found: C, 66.44; H, 5.88; S, 9.32. $\text{C}_{19}\text{H}_{20}\text{O}_4\text{S}$ requires C, 66.26; H, 5.85; S, 9.31%).

cis-4,5-Bis(benzyloxymethyl)-1,3-dioxolan-2-one (N 398)

cis-4,5-bis(Benzyloxymethyl)-1,3-dioxolan-2-thione (500 mg) in glacial acetic acid (5.3 ml) was reacted with mercuric acetate (140 mg) according to the general procedure to give the title product. Recrystallisation from dichloromethane/petroleum gave pure cis-4,5-bis(benzyloxymethyl)-1,3-

dioxolan-2-one (110 mg; 83%), m.p. 70-72.5°, $\nu_{\max}$: 1805, 1513, 1193 and 742 cm^{-1} (soln), τ : 2.68 (10H, s, aromatic), 5.20 (2H, m), 5.52 (4H, s), 6.25 (4H, m) (Found: C, 69.49; H, 6.34. $\text{C}_{19}\text{H}_{20}\text{O}_5$ requires C, 69.50; H, 6.14%).

1,4-Di-O-benzyl-2-thiothreitol (N 468)

A solution of potassium hydroxide (0.7 g) in dry ethanol (7.7 ml) was saturated with hydrogen sulphide at 0°C, and cis-1,4-dibenzyloxy-2,3-epoxybutane (1.0 g) added over 5 minutes. Stirring was continued for 1 hour at 0° and then overnight at room temperature. Work up as for 1,4-di-O-benzyl-2-thioerythritol gave crude 1,4-di-O-benzyl-2-thiothreitol (1.01 g) 32%, based on active SH).

trans-4,5-Bis(benzyloxymethyl)-1,3-oxathiolan-2-thione (N 469)

A solution of N,N'-thiocarbonyldiimidazole (0.79 g) in dry dichloromethane (15 ml) was added dropwise to a stirred solution of crude 1,4-di-O-benzyl-2-thiothreitol (1.0 g $\approx$ 0.352 g pure) in dry dichloromethane (15 ml) and stirring continued overnight. Usual work up, followed by t.l.c. (dichloromethane/petroleum (1:2)), then t.l.c. (petroleum b.p. 80-100°/ether (4:1)) gave pure trans-4,5-bis(Benzyloxymethyl)-1,3-oxathiolan-2-thione (172 mg; 43%), (oil), $\nu_{\max}$: 1327, 1217, 759 and 719 cm^{-1} (film), τ : 2.62 (10H, s, aromatic), 4.83 (1H, m), 5.42 (4H, t), 5.87 (1H, m), 6.1-6.47 (4H, m) (Found: C, 63.32; H, 5.55; S, 17.68. $\text{C}_{19}\text{H}_{20}\text{O}_3\text{S}_2$ requires C, 63.30; H, 5.59; S, 17.79%).

DL-1,4-Dibenzyloxybutane-2,3-diol (ii) (N 471)

cis-1,4-Dibenzyloxy-2,3-epoxybutane (129 mg), water (5 ml) dioxan (7 ml) and perchloric acid (70%, 1 drop) were refluxed together for

4 days. Work up as for the meso-diol gave the title product which was crystallised from ether/petroleum (b.p. 60-80°) to give pure DL-1,4-dibenzyloxybutane-2,3-diol (75 mg; 55%) m.p. 60-62°, m.m.p. with an authentic sample, 60-61.5°.

trans-4,5-Bis(benzyloxymethyl)-1,3-dioxolan-2-thione (N 500, 452, 472)

A solution of N,N'-thiocarbonyldiimidazole (160 mg) in dry dichloromethane (24 ml) was added dropwise to a stirred solution of DL-1,4-dibenzyloxybutane-2,3-diol (41.5 mg) in dry dichloromethane (24 ml) and stirring continued overnight at room temperature. Usual work up, with the omission of the washing of the dichloromethane layer with dilute hydrochloric acid, gave the title product (46.9 mg; 99%). Recrystallisation from dichloromethane/petroleum (b.p. 60-80°) gave pure trans-4,5-bis(benzyloxymethyl)-1,3-dioxolan-2-thione, m.p. 68.5-70°, $\nu_{\max}$: 1286, 1121, 1025 and 910 cm^{-1} (soln), τ : 2.67 (10H, s, aromatic), 5.08 (2H, m), 5.42 (4H, s), 6.32 (4H, m) (Found: C, 66.14; H, 5.58; S, 9.21. $\text{C}_{19}\text{H}_{20}\text{O}_4\text{S}$ requires C, 66.26; H, 5.85; S, 9.31%).

trans-4,5-Bis-(benzyloxymethyl)-1,3-oxathiolan-2-one (N 475)

trans-4,5-bis(Benzyloxymethyl)-1,3-oxathiolan-2-thione (68.6 mg) in glacial acetic acid (2.5 ml) was reacted with mercuric acetate (194 mg) according to the general procedure to give the title product. Repurification (three times) by t.l.c. (dichloromethane) gave pure trans-4,5-bis(benzyloxymethyl)-1,3-oxathiolan-2-one (45.7 mg; 70%), (oil), $\nu_{\max}$: 1742 and 1096 cm^{-1} (soln), τ : 2.62 (10H, s, aromatic), 4.92-5.35 (1H, m), 5.38 (4H, s), 5.92 (1H, m), 6.33 (4H, m) (Found: C, 66.16; H, 5.83; S, 9.03. $\text{C}_{19}\text{H}_{20}\text{O}_4\text{S}$ requires C, 66.26; H, 5.85; S, 9.31%).

trans-4,5-Bis(benzyloxymethyl)-1,3-dioxolan-2-one (N 473, 512)

trans-4,5-bis(Benzyloxymethyl)-1,3-dioxolan-2-thione (38.6 mg) in glacial acetic acid (1.5 ml) was reacted with mercuric acetate (140 mg) according to the general procedure. The crude crystalline product was recrystallised from ether/petroleum (b.p. 60-80°) to give pure trans-4,5-bis(benzyloxymethyl)-1,3-dioxolan-2-one (32.3 mg; 88%), m.p. 88-90°, $\nu_{\max}$: 1797 cm^{-1} (soln), τ : 2.63 (10H, s, aromatic), 5.13-5.5 (2H, m), 5.38 (4H, s), 6.32 (4H, m) (Found: C, 69.51; H, 6.35. $\text{C}_{19}\text{H}_{20}\text{O}_5$ requires C, 69.50; H, 6.14%).

Reactions of trans-1,4-dibenzyloxy-2,3-epoxybutane with methyl xanthate salts

(i) at room temperature (N 353)

Carbon disulphide (0.3 ml) was added to a solution of sodium (0.085 g) in dry methanol (10 ml), the starting material (0.4 g) added, and the reaction mixture stood at room temperature ($\sim 20^\circ$) for 6 days. Usual work up gave slightly impure trithiocarbonate, which, after repurification by t.l.c. (ether/petroleum (1:4)), crystallised out on standing under petroleum at 0° . Recrystallisation from dichloromethane/petroleum gave pure cis-4,5-bis(benzyloxymethyl)-1,3-dithiolan-2-thione (55.8 mg; 11%), m.p. 67.5-68.5, $\nu_{\max}$: 1501, 1079, 889 and 709 cm^{-1} (soln), τ : 2.63 (10H, s, aromatic), 5.07-5.6 (2H, m), 5.43 (4H, s), 5.73-6.57 (4H, m) (Found: C, 60.42; H, 5.56; S, 25.72. $\text{C}_{19}\text{H}_{20}\text{O}_2\text{S}_3$ requires C, 60.60; H, 5.35; S, 25.55%).

(ii) at 31° (N 375)

Carbon disulphide (0.3 ml) was added to a solution of sodium (0.09 g) in dry methanol (10 ml), the starting material (140 mg) added and the mixture stirred at 31° for 4 days. Usual work up gave cis-4,5-bis(benzyl-

oxymethyl)-1,3-dithiolan-2-thione (63.4 mg; 34%).

(iii) at 46° (N 373)

Carbon disulphide (0.3 ml) was added to a solution of sodium (0.09g) in dry methanol (10 ml), the starting material (150 mg) added, and the mixture stirred at 40° for 4 days. Usual work up gave the same cis-trithiocarbonate (102 mg; 51%).

(iv) at 49° (N 383)

Carbon disulphide (0.3 ml) was added to a solution of sodium (0.09g) in dry methanol (10 ml), the starting material (112 mg) added, and the mixture stirred at 49° for 4 days. Usual work up gave the same cis-trithiocarbonate (73.8 mg; 50%).

(v) at 64.5° (N 367)

Carbon disulphide (0.7 ml) was added to a solution of sodium (0.21g) in methanol (25 ml). Starting material (1.0 g) was added, and the reaction mixture refluxed for 4 days and then left for 10 days at room temperature. No trithiocarbonate was isolated on usual work up.

(vi) at 60-63° in a sealed tube (N 487)

Carbon disulphide (0.53 ml) was added to a solution of potassium hydroxide (332 mg) in dry methanol (5.5 ml), and 0.97 ml of this mixture added to the starting material (33.7 mg) in a glass tube, which was sealed and heated at 60-63° for 4 days. Usual work up, and t.l.c. (chloroform) gave the cis-trithiocarbonate (23.3 mg; 52%).

Reaction of cis-4,5-bis(benzyloxymethyl)-1,3-dithiolan-2-thione with sodium methyl xanthate (N 385)

Carbon disulphide (0.3 ml) was added to a solution of sodium (0.09 g) in dry methanol (10 ml), the starting material (30 mg) added, and the

mixture refluxed for 3 days. On usual work up, no trithiocarbonate was recovered.

Reactions of cis-1,4-dibenzyloxy-2,3-epoxybutane with methyl xanthate salts

(i) at 45° (N 470)

Carbon disulphide (0.4 ml) was added to a solution of sodium (0.12 g) in dry methanol (13 ml), the starting material (211 mg) added and the mixture stirred at 45° for 4 days. Usual work up gave the trans-trithiocarbonate. Repurification by t.l.c. (ether/petroleum (1:3)) gave pure trans-4,5-bis(benzyloxymethyl)-1,3-dithiolan-2-thione (213 mg; 76%), (oil), $\nu_{\max}$: 1494, 1076 and 870 cm^{-1} (soln), τ : 2.58 (10H, s, aromatic), 5.27-5.7 (2H, m), 5.40 (4H, s), 5.97-6.48 (4H, m) (Found: C, 60.61; H, 5.24; S, 25.72. $\text{C}_{19}\text{H}_{20}\text{O}_2\text{S}_3$ requires C, 60.50; H, 5.35; S, 25.55%).

(ii) at 64.5° (N 477)

Carbon disulphide (2.0 ml) was added to a solution of sodium (57 mg) in dry methanol (5.6 ml), the starting material (225 mg) added, and the mixture refluxed for 4 days. Usual work up, and several repurifications by t.l.c. (chloroform) gave a small quantity of yellow material, identified as trithiocarbonate by comparative t.l.c., and assumed to be trans on the basis of the previous reaction (9.4 mg; 3%).

(iii) at 60-63° in a sealed tube (N 486, 509)

Carbon disulphide (0.53 ml) was added to a solution of potassium hydroxide (332 mg) in dry methanol (5.5 ml) and 0.76 ml of this mixture added to the starting material (26.4 mg) in a glass tube, which was sealed and heated at 60-63° for 4 days. Usual work up, and t.l.c. (chloroform) gave the trans-trithiocarbonate (27.5 mg; 79%).

cis-4,5-Bis(benzyloxymethyl)-1,3-dithiolan-2-one (N 396)

cis-4,5-bis(Benzyloxymethyl)-1,3-dithiolan-2-thione (131 mg) in glacial acetic acid (5.3 ml) was reacted with mercuric acetate (504 mg) according to the general procedure to give the title product which was crystallised from ether/petroleum to give pure cis-4,5-bis(benzyloxymethyl)-1,3-dithiolan-2-one (107.8 mg; 86%) m.p. 69-70°, $\nu_{\max}$: 1729; 1663, 1645, 1510, 970 and 884 cm^{-1} (soln), τ : 2.65 (10H, s, aromatic), 5.37-5.8 (2H, m), 5.48 (4H, s), 5.97-6.4 (4H, m) (Found: C, 63.40; H, 5.65; S, 17.93. $\text{C}_{19}\text{H}_{20}\text{O}_3\text{S}_2$ requires C, 63.30; H, 5.59; S, 17.79%).

trans-4,5-Bis(benzyloxymethyl)-1,3-dithiolan-2-one (N 510, 474)

trans-4,5-bis(Benzyloxymethyl)-1,3-dithiolan-2-thione (231.6 mg) in glacial acetic acid (9 ml) was reacted with mercuric acetate (912 mg) according to the general procedure to give pure trans-4,5-bis(benzyloxymethyl)-1,3-dithiolan-2-one (97.4 mg; 44%), (oil), $\nu_{\max}$: 1711, 1651, 1111, 884, 763 and 722 cm^{-1} , τ : 2.65 (10H, s, aromatic), 5.43 (4H, s), 5.43-5.97 (2H, m), 6.1-6.53 (4H, m), (Found: C, 62.98; H, 5.56; S, 17.97. $\text{C}_{19}\text{H}_{20}\text{O}_3\text{S}_2$ requires C, 63.30; H, 5.59; S, 17.79%).

erythro-1,4-Dibenzyloxy-2-chlorobutan-3-ol (N 442)

trans-1,4-Dibenzyloxy-2,3-epoxybutane (4.0 g), dioxan (60 ml), hydrochloric acid (2N, 15 ml) and water (5 ml) were stirred together at room temperature for 17 days. The reaction mixture was diluted with water (~10 ml) and extracted with dichloromethane (4 x 10 ml). The combined extracts were dried and concentrated to give the crude product (3.58 g; 79%). Purification by t.l.c. (dichloromethane) gave pure erythro-1,4-Dibenzyloxy-2-chlorobutan-3-ol, (oil), $\nu_{\max}$: 3450 (OH), 1222, 1113, 760 and 720 cm^{-1} (film), τ : 2.6 (10H, s, aromatic), 5.37 (4H, d),

5.68-6.38 (5H, m), 7.18 (1H, m, exch); and meso-1,4-dibenzyloxybutane-2,3-diol (133 mg, 3%) m.p. 56-58°.

For the following reactions with potassium methyl xanthate, the reagent solution used consisted of carbon disulphide (1.06 ml) added to a solution of potassium hydroxide (0.472 g) in dry methanol (11.0 ml). A quantity of this solution was added to the starting material in a glass tube, which was sealed and heated at 64-66° for 4 days. Usual work up gave the product(s).

Reaction of cis-4,5-bis(benzyloxymethyl)-1,3-oxathiolan-2-thione with potassium methyl xanthate (N 499)

The starting material (31.5 mg) was reacted with the reagent solution (0.91 ml) by the general method to give cis-4,5-bis(benzyloxymethyl)-1,3-dithiolan-2-thione (25.3 mg; 77%), m.p. 68-70°, m.m.p. with an authentic sample 66.5-68°, p.m.r. spectrum identical with that of an authentic sample,

Reaction of trans-4,5-bis(benzyloxymethyl)-1,3-oxathiolan-2-thione with potassium methyl xanthate (N 504)

The starting material (39.5 mg) was reacted with the reagent solution (1.14 ml) by the general method to give trans-4,5-bis(benzyloxymethyl)-1,3-dithiolan-2-thione (38.8 mg; 90%), p.m.r. spectrum identical with that of an authentic sample.

Reaction of cis-4,5-bis(benzyloxymethyl)-1,3-oxathiolan-2-one with potassium methyl xanthate (N 496)

Starting material (22,3 mg) was reacted with the reagent solution

(0.64 ml) by the general method to give cis-4,5-bis(benzyloxymethyl)-1,3-dithiolan-2-thione (21.2 mg; 87%), which was recrystallised from dichloromethane/petroleum, m.p. 68-69.5°, m.m.p. with an authentic sample, 66-68°.

Reaction of trans-4,5-bis(benzyloxymethyl)-1,3-oxathiolan-2-one with potassium methyl xanthate (N 503)

Starting material (9.3 mg) was reacted by the general method with the reagent solution (0.27 ml) to give trans-4,5-bis(benzyloxymethyl)-1,3-dithiolan-2-thione (9.6 mg; 94%), p.m.r. spectrum identical with that of an authentic sample.

Reaction of cis-4,5-bis(benzyloxymethyl)-1,3-dioxolan-2-thione with potassium methyl xanthate (N 493)

Starting material (145 mg) was reacted with the reagent solution (0.42 ml) according to the general method to give a trace of trithiocarbonate (assumed to be cis-) and meso-1,4-dibenzyloxybutane-2,3-diol (4.5 mg, 35%), identified by comparative t.l.c. (dichloromethane).

Reaction of trans-4,5-bis(benzyloxymethyl)-1,3-dioxolan-2-thione with potassium methyl xanthate (N 502)

Starting material (32.6 mg) and the reagent solution (0.95 ml) were reacted together by the general method to give a trace of trithiocarbonate (assumed to be trans-) and DL-1,4-dibenzyloxybutane-2,3-diol (2.9mg; 10%) which was recrystallised from ether/petroleum, m.p. 61-62.5°, m.m.p. with an authentic sample 60.5-62.5°.

Reaction of cis-4,5-bis(benzyloxymethyl)-1,3-dioxolan-2-one with potassium methyl xanthate (N 506, 497)

Starting material (8.1 mg) and the reagent solution (0.24 ml) were reacted according to the general method to give meso-1,4-dibenzyloxybutane-2,3-diol (3.2 mg; 43%) m.p. 57-58.5°.

Reaction of trans-4,5-bis(benzyloxymethyl)-1,3-dioxolan-2-one with potassium methyl xanthate (N 501)

Starting material (9.6 mg) was reacted by the general method with the reagent solution (0.28 ml) to give DL-1,4-dibenzyloxybutane-2,3-diol (1.6 mg; 18%) which was crystallised from ether/petroleum, m.p. 55-57°, m.m.p. with an authentic sample 53-56°.

Reaction of cis-4,5-bis(benzyloxymethyl)-1,3-dithiolan-2-one with potassium methyl xanthate (N 498)

Starting material (34.8 mg) and the reagent solution (1.0 ml) were reacted according to the general method to give cis-4,5-bis(benzyloxymethyl)-1,3-dithiolan-2-thione (27.9 mg; 76%), which was crystallised from dichloromethane/petroleum, m.p. 68.5-70.5°, m.m.p. with an authentic sample 66.5-68.0°.

Reaction of trans-4,5-bis(benzyloxymethyl)-1,3-dithiolan-2-one with potassium methyl xanthate (N 505)

Starting material (18.7 mg) was reacted with the reagent solution (0.54 ml) according to the general procedure to give trans-4,5-bis(benzyloxymethyl)-1,3-dithiolan-2-thione (13.9 mg; 71%), p.m.r. spectrum identical with that of an authentic sample.

Reaction of meso-1,4-dibenzyloxybutane-2,3-diol with potassium methyl xanthate (N 495)

Starting material (36.7 mg) and the reagent solution (1.06 ml) were reacted by the general method to give recovered meso-1,4-dibenzyloxybutane-2,3-diol (32.1 mg; 88%).

Reaction of erythro-3-chloro-1,4-dibenzyloxybutan-2-ol with potassium methyl xanthate (N 494)

Starting material (23.5 mg) was reacted with the reagent solution by the general method to give cis-4,5-bis(benzyloxymethyl)-1,3-dithiolan-2-thione (12.7 mg; 46%), p.m.r. spectrum identical with that of an authentic sample.

Reaction of cis-4,5-bis(benzyloxymethyl)-1,3-dioxolan-2-thione with sodium methyl xanthate at 43° (N 394, 459)

Carbon disulphide (0.3 ml) was added to a solution of sodium (0.1 g) in dry methanol (10 ml) and the mixture added to the starting material (54 mg) and the whole stirred at 43° for 13 days. Usual work up gave cis-4,5-bis(benzyloxymethyl)-1,3-dioxolan-2-one (38.6 mg; 75%) which was recrystallised from dichloromethane/petroleum (b.p. 60-80°) and then from dichloromethane/petroleum, m.p. 71-73.5°, m.m.p. with an authentic sample 68.5-71.5°. A further quantity (3.8 mg; 7.5%) was isolated on crystallisation of two faster running t.l.c. bands.

Reaction of trans-4,5-bis(benzyloxymethyl)-1,3-dioxolan-2-thione with sodium methyl xanthate at 43° (N 458).

Carbon disulphide (0.3 ml) was added to a solution of sodium (0.1 g) in dry methanol (10 ml), the starting material (17 mg) added and the mixture stirred at 43° for 16 days. Usual work up gave DL-1,4-dibenzyl-oxybutane-2,3-diol (7.2 mg; 48%) which was crystallised from ether/

petroleum (b.p. 60-80°), m.p. 60.5-62.5°, m.m.p. with an authentic sample 60.5-61.5°. No traces of the trans-carbonate were detected.

Synthesis of some cyclohexane thiocarbonates and related compounds and their reactions with xanthate

Cyclohexenyl acetate (N 71)

The procedure used by Bedoukian¹⁶⁶ was followed. A mixture of cyclohexanone (205 g), acetic anhydride (428 g) and p-toluenesulphonic acid (2 g) was heated for 6 hours at 125°. The reaction mixture was cooled and diluted with water (200 ml). The organic layer was washed with water, aqueous sodium carbonate solution (5%), extracted with ether, and the combined extracts dried and concentrated. The residue was distilled to give cyclohexenyl acetate (52.9 g; 19%) b.p. 78-80° at 19 mmHg (lit.,¹⁶⁶ 74-76° at 17 mmHg).

cis-Diacetyl-2-mercaptopcyclohexanol (N 205, 73, 75, 99, 109, 117, 143, 157, 158, 174)

The method of Behringer and Kley¹⁴⁸ was used. Air was passed through cyclohexenyl acetate (14.5 g) overnight, thiolacetic acid (16 ml) added, the mixture stood at room temperature for 2 hours, and then refluxed for 2 hours. Fractional distillation gave the title product (9.2 g; 41%) b.p. 100-103° at 0.9 mmHg (lit.,¹²⁸ 97-98° at 0.3 mmHg).

cis-2-Mercaptopcyclohexanol (N 206, 176, 162, 75)

The procedure described by Meloy⁶⁰ was followed. A mixture of cis-diacetyl-2-mercaptopcyclohexanol (9.0g), methanol (15 ml) and methanolic hydrogen chloride (10% by weight, 63 ml) were stood together at room

temperature for $5\frac{1}{2}$ days. The methanol and hydrogen chloride were removed under reduced pressure, and fractional distillation gave the title compound (4.2 g; 76%), b.p. $42-43.5^{\circ}$ at 0.13 mmHg (lit.,⁶⁰ b.p. $89-91^{\circ}$ at 8 mmHg).

cis-4,5-Cyclohexano-1,3-oxathiolan-2-thione (N 217, 87, 179, 424)

A solution of N,N'-thiocarbonyldiimidazole (3.0g) in dry dichloromethane (35 ml) was added dropwise to a stirred mixture of cis-2-mercaptocyclohexanol (2.03 g), pyridine (10 ml) and dry dichloromethane (25 ml) and stirring continued overnight at room temperature. Usual work up gave a slightly impure product (2.60 g; 90%) which on repurification by t.l.c. (run 4 times in petroleum then once in petroleum/ether (1:1)) gave pure cis-4,5-cyclohexano-1,3-oxathiolan-2-thione (oil), $\nu_{\max}$: 1280, 1200, 1073, 950 and 756 cm^{-1} (film), τ : 4.93 (1H, m), 6.10 (1H, m), 7.20-9.27 (8H, m) (Found: C, 48.43; H, 5.71; S, 36.51. $\text{C}_7\text{H}_{10}\text{OS}_2$ requires C, 48.24; H, 5.78; S, 36.80%).

trans-4,5-Cyclohexano-1,3-oxathiolan-2-thione (N 255)

trans-2-Mercaptocyclohexanol (supplied by Professor Owen, 109 mg) was stirred with pyridine (0.6 ml) and dry dichloromethane (5 ml). A solution of N,N'-thiocarbonyl diimidazole (0.25 g) in dry dichloromethane (5 ml) was added dropwise and stirring continued overnight at room temp. Usual work up gave the title product (131.2 mg; 91%) m.p. $58.5-60.5^{\circ}$ (lit.,¹⁶⁷ $58-59^{\circ}$).

cis-4,5-Cyclohexano-1,3-oxathiolan-2-one (N 425, 418)

cis-4,5-Cyclohexano-1,3-oxathiolan-2-thione (302 mg) in glacial acetic acid (6 ml) was reacted with mercuric acetate (540 mg) according

to the general procedure and t.l.c. (dichloromethane/petroleum (1:1)) gave the pure title product (52.6 mg; 19%), ν_{max} . 1750, 1715, 1167, 982 and 944 cm^{-1} (lit., ⁶⁰ ν_{max} : 1754, 1715 (sh), 1159, 1071 and 975 cm^{-1} (soln)).

cis-Cyclohexane-1,2-dithiol (N 103, 404, 428)

The method used by Bateman et al.,⁴⁸ on octene was followed. Cyclohexene (102 g) and sulphur (13.9 g) were heated at $120-150^{\circ}$ for 5 hours in an autoclave. Cooling was allowed to take place overnight. The reaction mixture was removed from the autoclave with dry T.H.F. (100 ml), filtered and the filtrate added dropwise to lithium aluminium hydride (10 g) in dry T.H.F. (250 ml) over 4 hours. Stirring was continued overnight, followed by refluxing for $3\frac{1}{2}$ hours. The reaction mixture was cooled, ethyl acetate, followed by water was cautiously added, filtered, the filtrate dried and concentrated under reduced pressure. Fractional distillation of the residue gave cis-cyclohexane-1,2-dithiol (5.6 g; 18%) b.p. $46-51^{\circ}$ at 0.16 mmHg (lit.,⁴⁹ $99-100^{\circ}$ at 0.9 mmHg), $n_D^{17.5}$ 1.5540 (lit.,⁴⁹ n_D^{20} 1.5550).

cis-4,5-Cyclohexano-1,3-dithiolan-2-thione (N 119, 213)

A solution of N,N'-thiocarbonyldiimidazole (0.8 g) in dry dichloromethane (12 ml) was added dropwise to a stirred mixture of cis-cyclohexane-1,2-dithiol (0.26 g), pyridine (4 ml) and dry dichloromethane (8 ml) and stirring was continued overnight at room temperature. Usual work up gave the crude title compound (0.27 g; 82%) which was recrystallised three times from ether/petroleum to give pure cis-4,5-cyclohexano-1,3-dithiolan-2-thione m.p. $100.5-101.5^{\circ}$ (lit.,⁴⁹ $98-99^{\circ}$).

cis-4,5-Cyclohexano-1,3-dithiolan-2-one (N 231, 215)

cis-4,5-Cyclohexano-1,3-dithiolan-2-thione (0.375 g) in glacial acetic acid (29 ml) was reacted with mercuric acetate (2.9 g) according to the general procedure to give pure cis-4,5-cyclohexano-1,3-dithiolan-2-one (0.28 g; 82%) (oil), ν_{max} : 1716, 1641, 1283, 1003, 874 and 755 cm^{-1} (film) τ : 5.75 (2 H, m), 7.40-8.90 (8H, m) (Found: C, 48.47; H, 5.95; S, 36.56. $\text{C}_7\text{H}_{10}\text{OS}_2$ requires C, 48.24; H, 5.78; S, 36.80%).

Reaction of cis-4,5-cyclohexano-1,3-oxathiolan-2-one with potassium methyl xanthate (N 427)

Carbon disulphide (0.13 ml) was added to a solution of potassium hydroxide (0.1 g) in dry methanol (3.2 ml), starting material (50 mg) added, and the mixture refluxed for 4 days. Usual work up, followed by repurification by t.l.c. (dichloromethane/petroleum (1:1)) gave a small quantity of yellow material, identified as cyclohexane trithiocarbonate by t.l.c. comparison with an authentic sample and assumed to be the trans-isomer.

trans-4,5-Cyclohexano-1,3-dithiolan-2-thione from cis-4,5-cyclohexano-1,3-oxathiolan-2-thione(i) (N 221, 91, 196, 237, 243)

Carbon disulphide (0.63 ml) was added to a solution of potassium hydroxide (0.53 g) in methanol (4 ml), the starting material (0.4 g) added, the mixture left overnight at room temperature and then refluxed. Usual work up gave trans-4,5-cyclohexano-1,3-dithiolan-2-thione (39.8 mg; 9%) which was recrystallised from dichloromethane, m.p. $169.5\text{--}170.5^\circ$ (lit.,⁵⁹ $169\text{--}170^\circ$).

(ii) (N 488)

Carbon disulphide (0.53 ml) was added to a solution of potassium hydroxide (0.33 g) in dry methanol (5.5 ml) and 0.46 ml of this mixture added to the starting material (9.8 mg) in a glass tube, which was sealed and heated at 60-63° for 4 days. Usual work up gave the trans-trithiocarbonate (1.2 mg; 11%), which was recrystallised from chloroform/petroleum m.p. 168.5-170°, and recovered starting material (3.4 mg), an overall yield of trithiocarbonate of 17%, based on consumed starting material.

cis-4,5-Cyclohexano-1,3-dithiolan-2-thione from cis-4,5-cyclohexano-1,3-dithiolan-2-one (N 235)

Carbon disulphide (0.63 ml) was added to a solution of potassium hydroxide (0.53 g) in dry methanol. This solution was added to the starting material (0.28 g), and the mixture refluxed for 4 days. Usual work up and crystallisation from dichloromethane/petroleum gave the pure cis-trithiocarbonate (0.12 g; 40%) m.p. 102-103°; m.m.p. with an authentic sample 98-100.5°. T.l.c. (dichloromethane/petroleum (1:1)) of the residue gave a further quantity (24.1 mg, 8%).

Reaction of trans-4,5-cyclohexano-1,3-dithiolan-2-thione with potassium methyl xanthate (N 386)

Carbon disulphide (1.0 ml) was added to a solution of potassium hydroxide (0.6 g) in dry methanol (10 ml). Starting material (255 mg) was added and the mixture refluxed for 4 days. Usual work up gave recovered starting material (193 mg, 76%) and after standing for 1 day, the aqueous residues were re-extracted to give a further quantity of the starting material (42 mg; 16.5%) m.p. 168.5-170°.

cis-4,5-Cyclohexano-1,3-dithiolan-2-thione from cis-cyclohexane-1,2-dithiol (N 349)

Carbon disulphide (1.0 ml) was added to a solution of potassium hydroxide (0.6 g) in dry methanol (10 ml) and this solution added to the starting material (239 mg) and the mixture refluxed for 90 hours. Usual work up gave the crude cis-trithiocarbonate, which was roughly purified by passage down a small column (dichloromethane/silica) and recrystallised from dichloromethane/petroleum to give the pure title product (232 mg; 81%) m.p. 100-101° (lit.,⁴⁹ 98-99°).

trans-4,5-Cyclohexano-1,3-dithiolan-2-thione from cis-2-mercaptocyclohexanol (N 345)

Carbon disulphide (1.0 ml) was added to a solution of potassium hydroxide (0.6 g) in dry methanol (10 ml). Starting material (150 mg) was added and the mixture refluxed for $1\frac{3}{4}$ days. Usual work up gave the crude product which was purified by passage down a small column (dichloromethane/silica) and then by t.l.c. (ether/petroleum (1:1)) to give the pure trans-trithiocarbonate (27.5 mg; 14%) identified as trans- by comparative t.l.c. (ether/petroleum (1:1)) with authentic samples of cis- and trans-trithiocarbonates.

trans-4,5-Cyclohexano-1,3-dithiolan-2-thione from trans-2-mercaptocyclohexanol (N 373)

Carbon disulphide (2.0 ml) was added to a solution of potassium hydroxide (1.2 g) in dry methanol (22 ml), starting material (342 mg) added and the whole refluxed for 4 days. Usual work up gave the trans-trithiocarbonate (314 mg; 64%), m.p. 168-170°. After standing for 1 week the aqueous residues were re-extracted to give a further quantity of

the title product (1 mg, 0.2%).

Attempted isomerisation of trans-4,5-cyclohexano-1,3-oxathiolan-2-thione
(N 257)

(i) Heating a sample in carbon tetrachloride in a sealed n.m.r. tube at 60° for 2 days produced no change in the p.m.r. spectrum.

(ii) Refluxing the starting material (23.3 mg) in ethanol (5 ml) for 9 hours produced no change in the p.m.r. spectrum.

(iii) Refluxing the starting material (54 mg) with a solution of sodium hydroxide (3.4 g) in dry ethanol (5 ml) for 30 hours, work up as for xanthate reactions, and t.l.c. (dichloromethane/petroleum) gave none of the isomerisation product, trans-4,5-cyclohexano-1,3-dithiolan-2-one.

Reaction of cyclohexanol with potassium methyl xanthate (N 417)

Carbon disulphide (6.0 ml) was added to a solution of potassium hydroxide (3.5 g) in dry methanol (64 ml), cyclohexanol (1.0 g) added, and the mixture refluxed for 4 days. Usual work up gave only a small quantity of extractable material, which was shown by t.l.c. (dichloromethane) to consist of several bands, none of which was present in sufficient quantity for identification.

Cyclohexene sulphide from trans-4,5-cyclohexano-1,3-oxathiolan-2-one
(N 491, 440, 443)

Starting material (0.47 g) and potassium carbonate (100 mg) were heated up to 200° and the volatile products collected in a cold trap (liquid nitrogen). On warming, cyclohexene sulphide was identified as the product by its smell. Insufficient product was formed for further

characterisation.

Studies on the Synthesis of Decalin Thiocarbonates

Attempted preparation of 2 β ,3 α -(thiocarbonyloxythio)-trans-decalin (N 207, 192, 245, 431)

A solution of N,N'-thiocarbonyldiimidazole (0.64 g) in dry dichloromethane (15 ml) was added dropwise to a stirred mixture of 2 β -hydroxy-3 α -mercapto-trans-decalin (0.5 g), pyridine (19.0 g) and dry dichloromethane (10 ml). Stirring was continued overnight at room temperature and usual work up, followed by t.l.c. (dichloromethane/ether (1:1)) gave a yellow product, which on repurification by t.l.c. (dichloromethane/ether (1:4)) gave four separate yellow bands, one of which was recrystallised from dichloromethane and identified as 2 β -hydroxy-3 α -(imidazolyl-1-thiocarbonylthio)-trans-decalin (69.5 mg; 9%), m.p. 150-151.5 $^{\circ}$, $\nu_{\max}$: 3250 (OH), 1281, 1230, 1079 and 857 cm^{-1} (mull), τ : 1.43 (1H, s), 2.13 (1H, s), 2.83 (1H, s), 5.77 (1H, m), 7.35 (1H, s, OH, exch), 7.20-9.77 (14H, m) (Found: C, 56.61; H, 6.68; N, 9.37; S, 21.42. $\text{C}_{14}\text{H}_{20}\text{N}_2\text{OS}_2$ requires C, 56.72; H, 6.80; N, 9.45; S, 21.16%).

trans- and cis- Δ^2 -Octalin (N 432)

The procedure of Johnson et al.,¹⁵¹ was followed. Impure trans- Δ^2 -octalin dibromide (supplied by Professor Owen, 9.9 g) was added over 3 minutes to a slurry of zinc dust (17.6 g) in dry ethanol (78 ml) and stirring continued for 1 hour at room temperature and then for a further 2 hours at 70-75 $^{\circ}$. The reaction mixture was left overnight, diluted with ether (35 ml) and filtered. The ether layer was washed with water, then with saturated aqueous sodium chloride solution, dried (CaCl_2), concentrated and distilled to give the title products (2.75 g; 60%)

b.p. 112-114° at 250 mmHg (lit.,¹⁵¹ for trans-isomer b.p. 59° at 8 mmHg).

2β,3β-Dimercapto-trans-decalin, 2β,3β-dimercapto-cis-decalin, and 2α,3α-dimercapto-cis-decalin (N 446, 441)

The procedure used by Shields and Kurtz⁵¹ on norbornene was followed. Amorphous sulphur (0.5 g), stirred in dry D.M.F. was treated by bubbling ammonia through the solution at ~30° until it turned blue. trans- and cis-Δ²-Octalin (1.2 g) was added and the mixture stirred at 110° for 1 day. The reaction mixture was left for 2 days, diluted with water (20 ml) and extracted with dichloromethane (2 x 20, 2 x 10 ml). The combined extracts were dried and concentrated to give the crude trithio compounds (0.77 g; 37%). The crude product (0.77 g) in dry ether (150 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (2.7 g) in dry ether (50 ml) and the mixture refluxed overnight. Ethyl acetate (~1 ml) was added, followed by water (~2 ml) and the reaction mixture acidified with dilute hydrochloric acid. The reaction mixture was extracted with ether (total 200 ml) and the combined extracts washed with aqueous sodium bicarbonate solution, dried and concentrated to give the crude thiols, a golden yellow oil (0.18 g; 27%).

2β,3β-(Thiocarbonyldithio)-trans-decalin, 2β,3β-(thiocarbonyldithio)cis-decalin and 2α,3α-(thiocarbonyldithio)-cis-decalin (N 449)

A solution of N,N'-thiocarbonyldiimidazole (0.4 g) in dry dichloromethane (15 ml) was added to a stirred solution of the crude decalin dithiols (0.18 g) in dry dichloromethane (5 ml). Stirring was continued overnight at room temperature, and usual work up gave a small quantity of the mixed trithiocarbonates. Repurification by t.l.c. (ether/petroleum (1:3)) gave trace amounts of 2β,3β-(thiocarbonyldithio)-trans-decalin

m.p. $174.5-177^{\circ}$, $2\beta,3\beta$ -(thiocarbonyldithio)-cis-decalin and $2\alpha,3\alpha$ -(thiocarbonyldithio)-cis-decalin, m.p.s $115-122^{\circ}$ and $164-166^{\circ}$. The mass spectra of the trans compound and one of the cis-isomers were recorded, and have been reported on p 84.

PART 2 STUDIES ON A POTENTIAL ROUTE TO CIS-DITHIOLS

trans-2-(Phenylthiocarbamoylthio)cyclohexyl acetate and trans-2-[(acetylthio)(phenylimino)-methylthio]cyclohexyl acetate (N 177, 202, 275)

The method of Ali *et al.*⁵⁴ was followed. A mixture of trans-2-(phenylthiocarbamoylthio)cyclohexanol (supplied by Professor Owen, 2.3 g) acetic anhydride (4.5 g) and pyridine (2.6 g) was heated on a steam bath for 35 minutes. The mixture was left at room temperature for a further $4\frac{1}{2}$ hours, concentrated at the oil pump and fractionally crystallised from carbon tetrachloride/petroleum to give trans-2-(phenylthiocarbamoylthio)cyclohexyl acetate (0.248 g; 9.3%) m.p. $132-133.5^{\circ}$ (lit.,⁵⁴ 136°). Further concentration and crystallisation from methanol gave pure trans-2-[(acetylthio)(phenylimino)-methylthio]cyclohexyl acetate (0.657 g; 21.7%) m.p. $89-90.5^{\circ}$ (lit.,⁵⁴ 92°) and a further amount slightly contaminated with the monoacetate (0.26 g, 8.6%).

trans-2-phenylimino-4,5-cyclohexano-1,3-dithiolan

(i) from trans-2-(phenylthiocarbamoylthio)cyclohexyl acetate (N 281, 181, 203, 233)

The procedure of Owen¹⁵² was followed. Potassium hydroxide solution (N, ethanolic, 2.2 ml) was added to a heated solution of the starting material (0.626 g) in ethanol (9 ml). After standing overnight, water (7 ml) was added, the white sticky solid filtered off and recrystallised from aqueous methanol to give trans-2-phenylimino-4,5-cyclohexano-1,3-dithiolan (0.273 g; 54%) m.p. $110-110.5^{\circ}$ (lit.,¹⁵² 108°) $\nu_{\max}$: 1578, 964, 950, 788 and 719 cm^{-1} (mull), τ : 2.38-3.15 (5H, m), 6.4 (2H, m), 7.45-8.78 (8H, m) (Found: C, 62.72; H, 6.13; N, 5.35; S, 25.35. $\text{C}_{13}\text{H}_{15}\text{NS}_2$ requires C, 62.61; H, 6.06; N, 5.62; S, 25.71%).

T.l.c. (dichloromethane) of the residue gave a further quantity of the title product (57 mg, 11%) and phenylthiourethane (40 mg, 11%) m.p. 63.5-65.5° (lit.,¹⁵⁷ 71-72°). The mass spectrum of the title product was recorded and has been reported on p 94.

(ii) from trans-2-[(acetylthio)(phenylimino)-methylthio]cyclohexyl acetate (N 180, 197)

Ethanollic potassium hydroxide solution (N, 1.5 ml) was added to a heated solution of the starting material (0.358 g) in ethanol (6 ml). The reaction mixture turned colourless immediately and was left overnight at room temperature. Work up as for the previous preparation gave the crude title product (0.165 g; 68%) which was recrystallised from aqueous methanol to give the pure product m.p. 105-107° and a little phenylthiourethane.

Attempted oxidation of trans-2-phenylimino-4,5-cyclohexano-1,3-dithiolan (N 186, 185, 198, 204, 209, 219)

trans-2-Phenylimino-4,5-cyclohexano-1,3-dithiolan (77.6 mg) in glacial acetic acid (2.5 ml) was reacted with mercuric acetate (0.255 g) at 40-45° for 45 minutes. The reaction mixture was cooled, diluted with dichloromethane, filtered, and the filtrate concentrated to dryness. The residue was diluted with water and the solution extracted with dichloromethane. The combined extracts were washed with aqueous sodium bicarbonate solution, dried, and concentrated to give the crude product. Recrystallisation from methanol gave a pure product, identified as an adduct between mercuric acetate and 3,4-6,7-dicyclohexano-1,2;5-trithiepan (5 mg), m.p. 153-4°, $\nu_{\max}$: 1741, 1256, and 1058 cm^{-1} (mull). The main peaks in the mass spectrum appeared at m/e 488 (20), 193 (49), 144 (20), 133 (77), 112 (74), 81 (100), 79 (48).

Hydrolysis of trans-2-phenylimino-4,5-cyclohexano-1,3-dithiolan (N 285, 247)

The starting material (100 mg), glacial acetic acid (12.6 ml) water (12.6 ml) and concentrated hydrochloric acid (2.7 ml) were heated together at 100° for 70 hours. The reaction mixture was cooled, diluted with water (20 ml) and extracted with dichloromethane (1 x 40, 2 x 20 ml). The combined extracts were dried and concentrated. T.l.c. (dichloromethane) of the residue gave trans-4,5-cyclohexano-1,3-dithiolan-2-one (58.2 mg; 83%) m.p. 109-110.5°, m.m.p. with an authentic sample 108-110.5° (Found: C, 48.12; H, 5.76. Calculated for $C_7H_{10}OS_2$ C, 48.24; H, 5.78%).

Attempted cyclisations of trans-2-(phenylthiocarbamoylthio)cyclohexyl acetate

(i) (N 137)

The starting material (174.1 mg) in dry D.M.S.O. (0.5 ml) was heated at 100-102° for 2 hours. Water (4 ml) was added and the solid material filtered off; concentration of the filtrate gave a further quantity. Infra-red spectra showed both these solids to consist of starting material and traces of trans-2-[(acetylthio)(phenylimino)-methylthio]cyclohexyl acetate.

(ii) (N 138)

The starting material (68 mg) was heated in dry D.M.S.O. at ~95° for 3½ days. Concentration of the reaction mixture and t.l.c. (dichloromethane/petroleum (1:1)) gave starting material and trans-2-phenylimino-4,5-cyclohexano-1,3-dithiolan (18.7 mg; 34%) which was sublimed to give a very pure sample m.p. 109.5-110°.

(iii) (N 208)

Potassium acetate (0.1 g) was added to a heated solution of the starting material (291.4 mg) in ethanol (8 ml). The mixture was shaken and left overnight at room temperature. The crystals formed were filtered off and were identified as starting material. Concentration of the filtrate gave more starting material.

(iv) (N 211)

Potassium acetate (0.06 g) and starting material (170.7 mg) were stirred in ethanol (8 ml) at 40-50° for 3 days and then left overnight at room temperature. Water (20 ml) was added, and starting material filtered off. Concentration of the filtrate gave more starting material, contaminated with traces of other products.

(v) (N 222)

Starting material (392 mg) and potassium acetate (0.14 g) were refluxed in ethanol (7 ml) for 3 days and then left at room temperature for a further 24 hours. The reaction mixture was extracted with dichloromethane (2 x 15 ml) after diluting with water (5 ml) and the combined extracts dried and concentrated. T.l.c. (dichloromethane) showed the presence of four products, the major one being phenylthiourethane (46.2 mg, 19%), identified from its p.m.r. spectrum.

(vi) (N 241)

Carbon disulphide (0.63 ml) was added to a solution of potassium hydroxide (0.53 g) in methanol (15 ml), starting material (79 mg) added, and the mixture stirred at room temperature for 3 days. The reaction mixture was diluted with water (20 ml), extracted with dichloro-

methane (3 x 10 ml) and the combined extracts dried and concentrated. T.l.c. (dichloromethane) of the residue gave mostly starting material, and an unidentified product.

(vii) (N 299)

Carbon disulphide (0.8 g) was added to a solution of sodium (0.15 g) in methanol (8 ml), starting material (100 g) added and the mixture refluxed for $3\frac{1}{2}$ days. Work up as for (vi) gave two main products which were repurified by t.l.c. (dichloromethane/petroleum (4:1)) to give small quantities of O-methyl N-phenylthiocarbamate m.p. $93.5-94^{\circ}$ (lit.,¹⁵⁷ 97°), $\nu_{\max}$: 3390 (NH), 1600, 1520, 1205, 1153 and 1065 cm^{-1} (soln), (Found: C, 63.80; H, 6.00; N, 9.05. Calculated for $\text{C}_8\text{H}_9\text{NO}_2$ C, 63.56; H, 6.00; N, 9.27%); and methyl carbanilide m.p. $46.5-47^{\circ}$ (lit.,¹⁵⁷ 47°), $\nu_{\max}$: 3430, 3320, 1725, 1605, 1528, 1326, 1230 and 1083 cm^{-1} (soln) (Found: C, 57.97; H, 5.46; N, 8.32. Calculated for $\text{C}_8\text{H}_9\text{NO}_3$ C, 57.48; H, 5.43; N, 8.38%).

Attempted thermal cyclisation of trans-2-[(acetylthio)(phenylimino)-methylthio]cyclohexyl acetate (N 189)

Starting material (0.269 g) was stirred in D.M.S.O. (1 ml) at $80-90^{\circ}$ for 1 day. Water (4 ml) was added and the reaction mixture extracted with dichloromethane (total 10 ml). The combined extracts were dried and concentrated; t.l.c. (dichloromethane) of the residue showed the presence of many products.

cis-2-(Phenylthiocarbamoylthio)cyclohexanol (N 321)

The procedure used by Ali et al.⁵⁴ for the trans- compound was followed. A solution of phenylisothiocyanate (1.05 g) in dry benzene

(3 ml) was added dropwise over 10 minutes to a stirred mixture of cis-2-mercaptocyclohexanol (1.0 g), triethylamine (0.1 g) and dry benzene (6 ml). Stirring was continued overnight at room temperature. The reaction mixture was concentrated to an oil and stored overnight under benzene/petroleum at 0°. Trituration gave a precipitate which was filtered off, washed with petroleum and recrystallised from carbon tetrachloride to give pure cis-2-(phenylthiocarbamoylthio)cyclohexanol (1.21 g; 60%) m.p. 135-137.5°, $\nu_{\max}$: 3370 (OH), 3200 (NH), 1599, 1332, 1046 and 706 cm^{-1} (mull), τ : 0.42 (1H, m, NH, exch), 2.43 (5H, m, aromatic), 5.63 (2H, m), 7.57 (1H, m, OH, exch), 7.67-8.83 (8H, m) (Found: C, 58.56; H, 6.66; N, 5.23; S, 24.22. $\text{C}_{13}\text{H}_{17}\text{NOS}_2$ requires C, 58.39; H, 6.41; N, 5.24; S, 23.98%).

cis-2-[Acetylthio](phenylimino)-methylthio]cyclohexyl acetate (N 325)

The method described by Ali *et al.*⁵⁴ for the trans-compound was used. A mixture of cis-2-(phenylthiocarbamoylthio)cyclohexanol (1.0 g), pyridine (1.1 g) and acetic anhydride (2.0 g) was heated on a steam bath for 12 minutes and then left overnight at room temperature. Addition of petroleum gave the title product as an oil (0.75 g; 58%). A portion was further purified by t.l.c. (dichloromethane) and recrystallised from ether/petroleum to give pure cis-2-[acetylthio](phenylimino)-methylthio]cyclohexyl acetate m.p. 115-117°, $\nu_{\max}$: 1726, 1702, 1599, 1495, 1233, 1163, 1081 and 713 cm^{-1} (soln), τ : 2.32-2.88 (5H, m, aromatic), 4.63 (1H, m), 5.82 (1H, m), 7.88 (3H, s, SAc), 7.93 (3H, s, OAc), 7.75-8.58 (8H, m,) (Found: C, 57.78; H, 5.86; N, 4.01; S, 18.60. $\text{C}_{17}\text{H}_{21}\text{NO}_3\text{S}_2$ requires C, 58.09; H, 6.02; N, 3.99; S, 18.25%).

cis-2-(Phenylthiocarbamoylthio)cyclohexyl acetate

(i) from cis-2-(phenylthiocarbamoylthio)cyclohexanol (N 343)

Starting material (233 mg) and pyridine (0.8 ml) were stirred together at room temperature and 1 ml of a mixture of acetic anhydride (0.445 g) and pyridine (10 ml) added dropwise over four hours and stirring continued overnight. The reaction mixture was diluted with water (20 ml), extracted with dichloromethane (total 70 ml) and the combined extracts dried and concentrated. T.l.c. (dichloromethane) gave starting material (39.5 mg) and the title product (60.9 mg; 37% based on consumed starting material), which was recrystallised from ether/petroleum to give pure cis-2-(phenylthiocarbamoylthio)cyclohexyl acetate m.p. 86-99°, $\nu_{\max}$: 3355 (NH), 1731, 1601, 1503, 1246, 1038, and 711 cm^{-1} (soln), τ : 1.05 (1H, m, NH), 2.55 (5H, m, aromatic), 4.70 (1H, m), 5.67 (1H, m), 7.95 (3H, s, OAc), 7.70-8.70 (8H, m) (Found: C, 58.28; H, 6.14; N, 4.43; S, 20.50. $\text{C}_{15}\text{H}_{19}\text{NO}_2\text{S}_2$ requires C, 58.22; H, 6.19; N, 4.53; S, 20.73%).

(ii) from cis-2-[(acetylthio)(phenylimino)-methylthio]cyclohexyl acetate (N 351, 388)

A solution of the starting material (0.51 g) in chloroform (5 ml) was shaken with hydrochloric acid (3N, 8 ml) until the deep yellow colour had faded to a pale yellow (30 minutes). The chloroform layer was washed with aqueous sodium bicarbonate solution, dried and concentrated to an oil. T.l.c. (dichloromethane) and recrystallisation from ether/petroleum/carbon tetrachloride gave cis-2-(phenylthiocarbamoylthio)cyclohexyl acetate (0.304 g; 67%) m.p. 85-93.5°, p.m.r. and infra-red spectra identical with those of an authentic sample.

Reaction of cis-2-(phenylthiocarbamoylthio)cyclohexyl acetate with base (N 414)

Starting material (115 mg) was dissolved in warm ethanol (2.0 ml), ethanolic potassium hydroxide solution (N, 0.5 ml) added and the mixture left overnight at room temperature. Water (25 ml) was added and the reaction mixture extracted with dichloromethane (total 25 ml). The combined extracts were dried, concentrated and t.l.c. (dichloromethane) gave phenylthiourethane (25 mg, 37%) and cis-2-(phenylthiocarbamoylthio)cyclohexanol (46 mg; 46%) m.p. 130-2°; both compounds were identified by their infra-red and p.m.r. spectra.

Reaction of cis-2-[(acetylthio)(phenylimino)-methylthio]cyclohexyl acetate with base (N 335)

Starting material (214 mg) was dissolved in hot ethanol (4 ml) and ethanolic potassium hydroxide solution (N, 1.5 ml) added. The reaction mixture was left overnight at room temperature, water (10 ml) added, and after 4 hours at 0°, phenylthiourethane (31 mg) was filtered off. The filtrate was extracted with dichloromethane (3 x 5 ml) and the combined extracts dried, and concentrated. T.l.c. (dichloromethane) of the residue gave more phenylthiourethane (35 mg; total 76 mg, 72%) m.p. 68-69° and a small quantity of cis-2-(phenylthiocarbamoylthio)cyclohexanol (15.5 mg, 8%) identified by t.l.c. comparison with an authentic sample.

trans-4,5-Cyclohexano-1,3-dithiolan-2-thione methyl iodide (N 476, 311, 329, 341, 381)

trans-4,5-Cyclohexano-1,3-dithiolan-2-thione (0.5 g) was dissolved in dry dichloromethane (6 ml); methyl iodide (0.75 g) was added and the mixture left for 1 week. The dark red crystals were filtered off, washed with a little benzene to remove traces of unreacted trithiocarbonate and dried to give trans-4,5-cyclohexano-1,3-dithiolan-2-thione methyl iodide (0.304 g; 34%), m.p. 123-125°, (Found: C, 16.32;

H, 2.24; S, 19.75; I, 66.58. $C_8H_{13}S_3I \cdot 4CH_3I$ requires C, 16.01; H, 2.80; S, 10.69; I, 70.50%). Attempts at recrystallisation resulted in disproportionation.

trans-2-Phenylimino-4,5-cyclohexano-1,3-dithiolan (N 361)

trans-4,5-Cyclohexano-1,3-dithiolan-2-thione methyl iodide (62.2 mg) was covered with methanol (1.5 ml), aniline (~40 mg) added and the reaction mixture left over the week-end. Ether (3 ml) and a trace of petroleum, were added and the solution was washed with sodium hydroxide solution (~2N, 8 ml); the ether layer was separated and the aqueous layer extracted with ether (5 ml). The combined ether solutions were dried, concentrated and t.l.c. (dichloromethane) gave the title product (8.5 mg; 50%) m.p. 110-111°, m.m.p. 108-111°, infra-red and p.m.r. spectra identical with those of the sample prepared from trans-2-(phenylthiocarbamoylthio)cyclohexyl acetate; and trans-4,5-cyclohexano-1,3-dithiolan-2-one (6.2 mg; 52%), identified from its infrared spectrum. The mass spectrum of trans-2-phenylimino-4,5-cyclohexano-1,3-dithiolan was recorded and has been reported on p 94.

cis-4,5-Cyclohexano-1,3-dithiolan-2-thione methyl iodide (N 363)

cis-4,5-Cyclohexano-1,3-dithiolan-2-thione (236 mg) was dissolved in dry dichloromethane (3 ml), methyl iodide (0.36 g) added and the mixture left for several days. The dark red crystals were filtered off and further crops obtained by cautious addition of petroleum and leaving overnight, but this process was not carried out to completion. The crystals were dried to give cis-4,5-cyclohexano-1,3-dithiolan-2-thione methyl iodide (103 mg; 16%) m.p. 86-88° (Found: C, 21.33; H, 2.87; S, 21.87. $C_8H_{13}S_3I$ requires C, 28.91; H, 3.94; S, 28.95. $C_8H_{13}S_3I \cdot 1.5CH_3I$ requires C, 20.93; H, 3.23; S, 17.6%).

cis-2-Phenylimino-4,5-cyclohexano-1,3-dithiolan

(i) (N 371)

cis-4,5-Cyclohexano-1,3-dithiolan-2-thione methyl iodide (43 mg) was covered with dry methanol (1.0 ml), aniline (50 mg) added and the mixture left overnight at room temperature. The mixture was diluted with ether (3 ml), shaken with dilute aqueous sodium hydroxide solution ($\sim 2N$, 8 ml) and the aqueous layer extracted with ether (12 ml). The combined ether solutions were dried and concentrated and t.l.c. (dichloromethane) gave the crude product (19.2 mg; 37%). Repurification by t.l.c. (ether/petroleum (1:1)) and recrystallisation from ether/petroleum gave pure cis-2-phenylimino-4,5-cyclohexano-1,3-dithiolan m.p. 101.5-103°, m.m.p. with trans-isomer 70-71°, $\nu_{\max}$: 1584, 1496, 959 and 711 cm^{-1} (soln), τ : 2.43-3.27 (5H, m, aromatic), 5.97 (2H, m), 7.7-8.67 (8H, m), (Found: C, 52.86; H, 6.03; N, 5.59; S, 25.24. $\text{C}_{13}\text{H}_{15}\text{NS}_2$ requires C, 62.61; H, 6.03; N, 5.62; S, 25.71%). The mass spectrum was recorded and has been reported on p 94.

(ii) (N 416, 403)

cis-Cyclohexane-1,2-dithiol (240 mg) and phenylisothiocyanate (~ 0.4 g) were heated at 150-155° for 30 minutes and then allowed to cool for 1 hour. Trituration with petroleum, cooling to 0° and filtering, gave a little diphenylthiourea. The filtrate was concentrated and t.l.c. (dichloromethane) gave three main products which were repurified by t.l.c. (ether/petroleum (various proportions)) to give cis-4,5-cyclohexano-1,3-dithiolan-2-thione, recrystallised from ether/petroleum (15.9 mg; 5%) m.p. 99-100°, m.m.p. with an authentic sample 98.5-100°; cis-2-phenylimino-4,5-cyclohexano-1,3-dithiolan, recrystallised from aqueous methanol, (30.4 mg; 8%) m.p. 100-102°, m.m.p. with an

authentic sample $98.5-102^{\circ}$, and diphenylthiourea, recrystallised from aqueous methanol (170 mg) m.p. $153-154^{\circ}$ (lit.,¹⁵⁷ $154-155^{\circ}$). A small quantity of diphenylthiourea (42 mg) m.p. $167.5-168.5^{\circ}$ was also isolated m/e 228 (M^{+}) (14), 194 (16), 135 (71), 93 (100), 77 (64).

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