A Thesis entitled

" i) THE SYNTHESIS OF OPTICALLY ACTIVE THIOLS AND RELATED COMPOUNDS

and

ii) THE OXIDATION OF SOME THIOCARBONATES"

presented by

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ABSTRACT

Part I

(R)- and (S)-2,3-dimercaptopropanols, (R)-3-mercaptopropane-1,2-diol, (S)-2-mercaptopropanol and related compounds have been synthesised by stereospecific routes from D-mannitol via (S)-1,2-O-isopropylideneglycerol. These thiols, of known absolute configurations, thus provide reference compounds of potential use for other stereochemical correlations.

A racemic product was obtained when attempts were made to synthesise (R)-2,3-dimercaptopropanol from 1,2,5,6-tetradeoxy-3,4-O-isopropylidene-1,2:5,6-di(thiocarbonyldithio)-L-iditol by a process involving the reduction of (R)-2,3-(carbonyldithio)glyceraldehyde. This fact suggested that a carbanion stabilised by resonance involving a 3d orbital of sulphur and the carbonyl group might be an intermediate during the reduction of the aldehyde.

Part II

The oxidation of a number of cyclic thiocarbonates was studied. It was observed that the nature of the product depends on the structure of the thiocarbonate, the nature of the oxidant, and the experimental conditions. Thus trans-1,2-(thiocarbonyldithio)cyclohexane on oxidation with lead tetra-acetate (or peracetic acid) gave trans-1,2-(oxythiocarbonyldithio)cyclohexane. With an excess of peracetic acid, the same trithiocarbonate yielded trans-cyclohexane-1,2-disulphonic acid and trans-1,2-(methylenedisulphonyl)cyclohexane. Similar results were also obtained with trans-2,3-(thiocarbonyldithio)tetralin.

With an excess of peracetic acid, trans-1,2-(carbonyldithio)cyclohexane yielded only trans-cyclohexane-1,2-disulphonic acid. trans-1,2-(Thiocarbonyldioxy)cyclohexane gave trans-1,2-(carbonyldioxy)cyclohexane on oxidation with either lead tetra-acetate or perphthalic acid. Similarly, the thiocarbonyl group of trans-(thiocarbonyloxythio)cyclohexane was converted to the carbonyl group by lead tetra-acetate.

A disulphide of unusual structure was obtained from 1,2-(thiocarbonyldioxy)benzene by oxidation with lead tetra-acetate.

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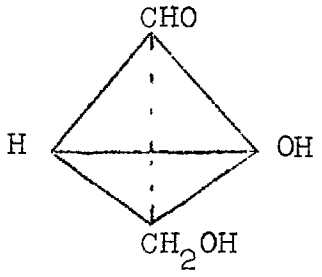
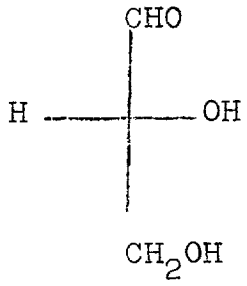
P A R T I

INTRODUCTORY SURVEY

Ever since van't Hoff and Le Bel established the relationship between the tetrahedral arrangement of the valencies of carbon and optical activity, chemists were beset with the problem of assigning an absolute configuration to an optical isomer. Until 1951, there was no method available by which this intriguing problem could be solved. At best, it was possible to assign configuration relative to a standard compound which itself had been given an arbitrary configuration. Dextrorotatory glyceraldehyde



(1)



(2)

was chosen as the reference compound and was given the arbitrary configuration (1). Formula (1) indicates that the asymmetric carbon is on the paper and in the centre of a tetrahedron, while the aldehyde and hydroxymethyl groups are below and hydrogen and the hydroxyl group above the plane. The projection of this perspective formula (1) on

the plane of the paper gives the formula (2) for (+)-glyceraldehyde. The configurations of other compounds which had been correlated with (+)-glyceraldehyde were considered to be relative ones. However, in 1951, Bijvoet et al[1]. determined by a special X-ray technique the absolute configuration of (+)-tartaric acid as its sodium rubidium salt and, fortunately, the absolute configuration was found to be the same as that deduced from the arbitrary configuration of (+)-glyceraldehyde. Consequently, it was established that all 'relative' configurations and also the arbitrary configuration of (+)-glyceraldehyde actually represent the absolute ones.

The direct determination of absolute configuration by X-ray technique is not always practicable since it is a time consuming method which requires expert interpretation; moreover, the method requires a crystalline solid containing appropriate atoms placed conveniently. However, methods[2,3,4] are available by which the absolute configuration of a compound can be established by correlating it with one (or more than one) compound of known configuration. Since the work to be described in this part of the thesis was concerned with the synthesis of optically active thiols and related compounds whose absolute configurations were determined by sterochemical correlations, it is appropriate

to discuss some of the methods which are available for this purpose.

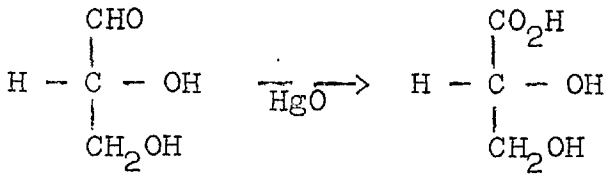
Methods for Correlating Configurations

A. By chemical interconversion not affecting bonds leading to asymmetric centres.

Of all the methods used for stereochemical correlation, this is probably the most reliable and satisfactory. The principle of the method is that if none of the bonds of an asymmetric centre is disturbed during a chemical transformation [as in the change from (3) to (4)], the configuration of the transformed compound will correspond to

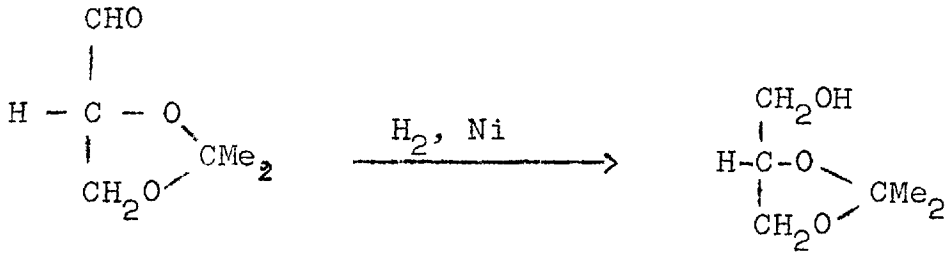
(3) (4)

that of the original. A classical example is the correlation of the configuration of (-)-glyceric acid (5) with (+)-glyceraldehyde (2)[5]. Since the acid (5) is produced by converting the aldehyde group of (2), by



(2) (5)

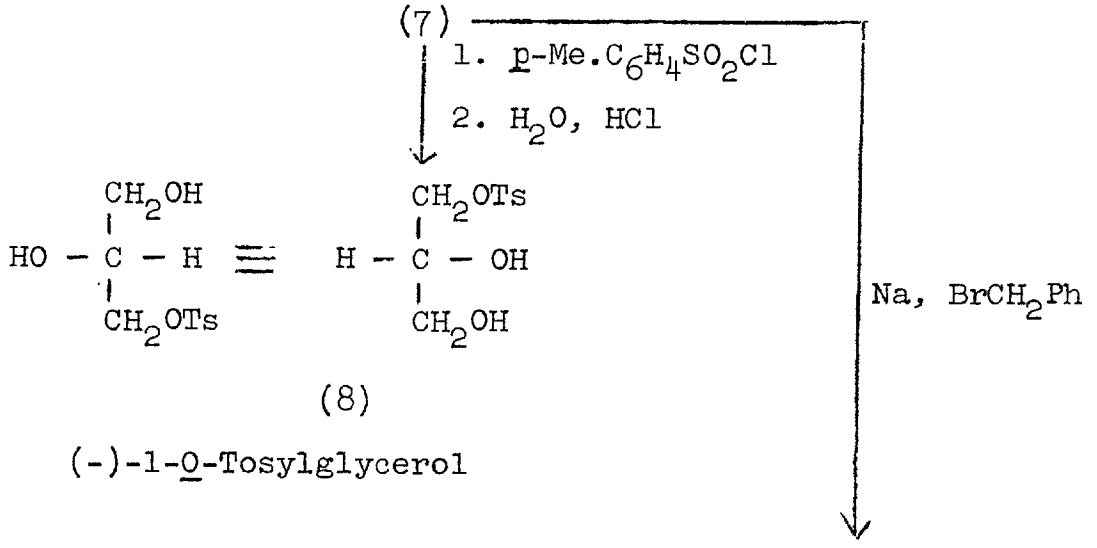
a process which is not expected to affect the bonds of the asymmetric carbon, both the compounds should have similar configurations. By analogous methods, the configurations of a number of asymmetric derivatives of glycerol[6-10] have been correlated. Those shown by the formulae (6) to (11) provide examples which are particularly relevant to the work subsequently to be described.



(6) (7)

(+)-2,3-O-Isopropylidene-glyceraldehyde

(+)-1,2-O-Isopropylidene-glycerol



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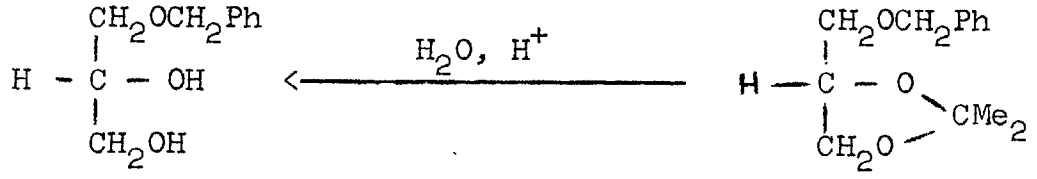
(-)-1-O-Tosylglycerol

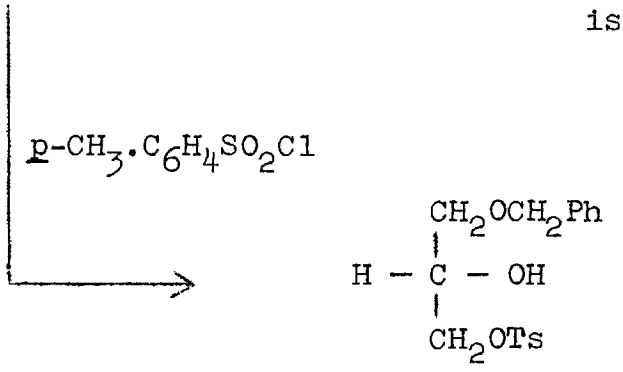


(10)

(+)-1-O-Benzylglycerol

(9)

(+)-1-O-Benzyl-2,3-isopropylideneglycerol

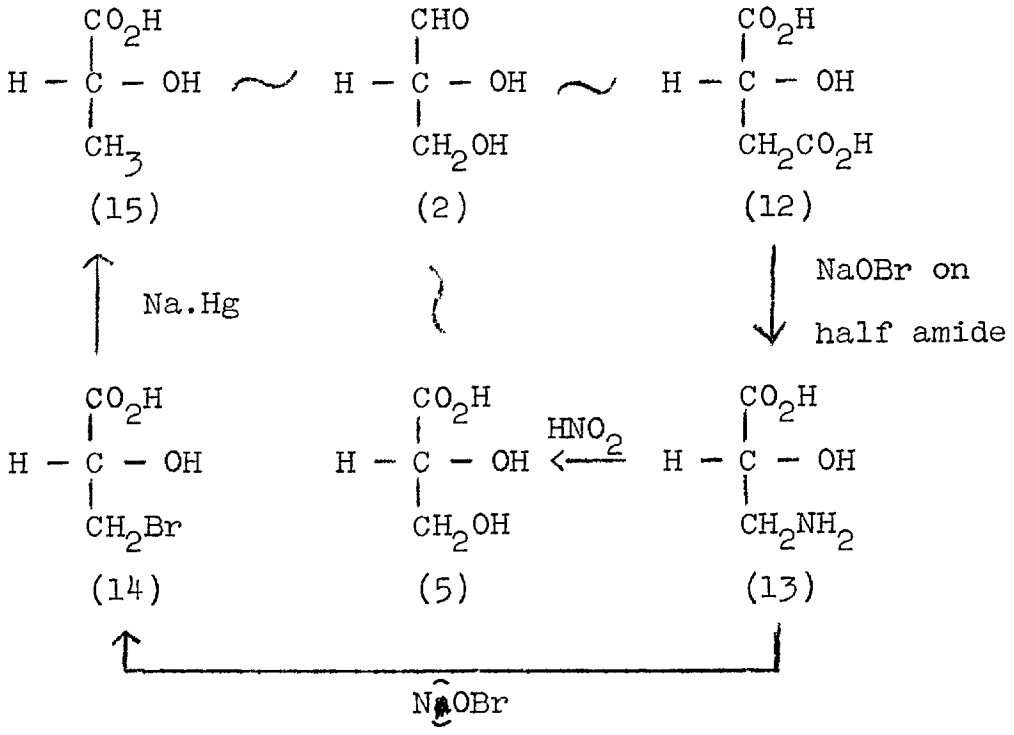


(11)

(+)-1-O-Benzyl-3-O-Tosylglycerol

Frequently, correlation between two or more compounds is achieved by relay (or indirect method) as illustrated by establishing relationships between (+)-malic acid (12) and (-)-lactic acid (15)[11] by correlating each with (+)-glyceraldehyde (2). The key compound is (+)-isoserine (13) which is obtained from (+)-malic acid. On the one hand, (+)-isoserine was correlated with (-)-glyceric acid (5) and hence to (+)-glyceraldehyde (2); while on the other hand it gave (-)-bromolactic acid (14) and thence (-)-lactic acid (15). Consequently, the relationship between these compounds was established.

(In the formulae below, the sign ~ means 'corresponds in configuration to'.)



B. By chemical reactions involving a bond (or bonds) leading to the asymmetric centre, with knowledge of the mechanism of transformation.

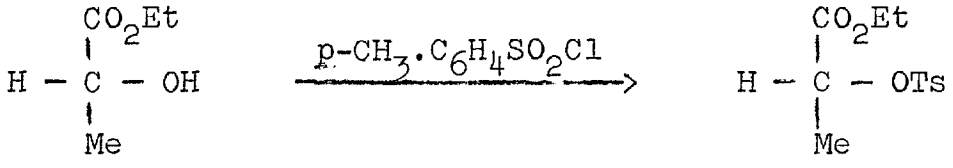
The problem of assigning absolute configuration becomes more complex when a transformation involves a bond of the asymmetric centre as in the case of many nucleophilic displacement and rearrangement reactions. Stereochemical implications in these two cases will be dealt with separately.

(a) Nucleophilic displacement reactions

When a nucleophilic displacement occurs at an asymmetric centre, there are three possibilities, namely (i) the incoming group may occupy an identical position in space as that of the group being displaced (retention of configuration), (ii) the incoming group may occupy the opposite position (inversion) or (iii), both (i) and (ii) may take place simultaneously (racemisation). Kenyon, Phillips and coworkers[12,13] developed a method which is helpful in determining whether a change of configuration has taken place at a particular stage. Thus by carrying out a series of reactions they established that when the toluene-p-sulphonyloxy group of (+)-ethyl 2-O-tosyl-lactate

(18) was replaced by the benzoate anion, inversion of configuration took place. It was argued that since in the process of esterification of an alcohol, the oxygen atom of the hydroxyl group is expected to be retained in the ester, no change of configuration took place when (+)-ethyl

(The sign ⟶ indicates inversion of configuration.)



(16) (18)

(+)-Ethyl lactate (+)-Ethyl 2-O-tosyl-lactate

(17) (19)

(-)-Ethyl 2-O-Benzoyl-lactate (+)-Ethyl 2-O-Benzoyl-lactate

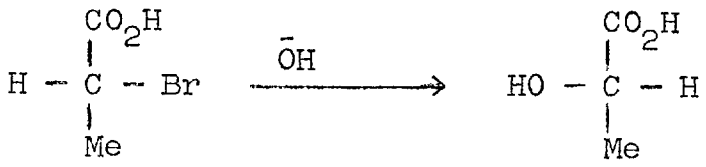
lactate (16) was converted into (-)-ethyl 2-O-benzoyl-lactate (17) or (+)-ethyl 2-O-tosyl-lactate (18) by reaction with benzoyl chloride or toluene-p-sulphonyl chloride respectively. Since the reaction of (18) with the benzoate anion resulted in the formation of the enantiomorph of (17), inversion must have taken place at this stage and hence (+)-ethyl 2-O-benzoyl-lactate was assigned the configuration (19). By analogy, it was assumed[12,13] that when a chloride ion replaces the toluene-p-sulphonyloxy group, inversion of configuration takes place.

Probably a more rational approach to the problem of stereochemical correlation would be to ascertain the mechanism of the displacement reaction involved in a transformation since some of these reactions (such as S_N2) follow predictable steric courses. The stereochemistry of different types of nucleophilic displacement reactions will be considered.

(i) Stereochemistry of the S_N2 reaction.

The extensive study by Ingold, Huges and co-workers[14] has established that the bimolecular substitution (S_N2) reaction proceeds with inversion of configuration. One example of such a transformation is the hydrolysis of

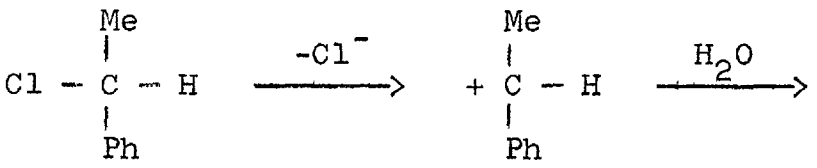
(+)-α-bromopropionic acid (20) to (+)-lactic acid (21) under conditions suitable for an S_N2 reaction[15].



(20) (21)

(ii) Stereochemistry of the S_N1 reaction.

Unimolecular nucleophilic substitution (S_N1) reactions proceed by way of ionisation to a carbonium ion. Since the carbonium ion is flat, racemisation is expected to take place. However, racemisation is generally accompanied by a certain amount of inversion, the extent being dependent on various factors, the chief being the shielding effect of the departing group. The hydrolysis of (+)-1-phenylethyl chloride (22) is one of the many examples giving almost complete racemisation[16].



(22)

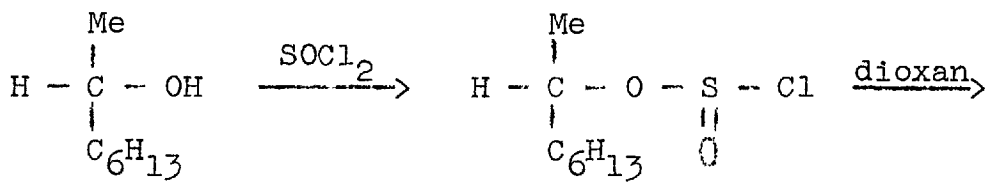
(+)-1-Phenylethyl chloride — Planar carbonium ion

2
5½%

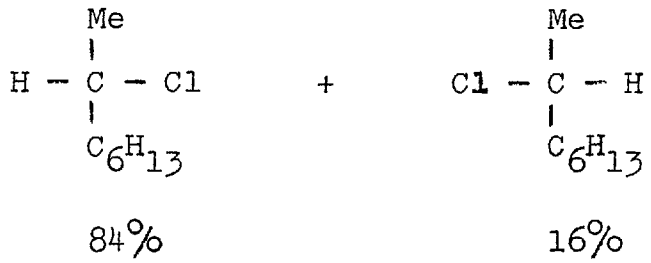
48%

(iii) Stereochemistry of the S_Ni reaction

Frequently it is found that complete or almost complete retention of configuration takes place when an asymmetric alcohol reacts with such a reagent as thionyl chloride. In such a case, a chlorosulphite ester is first formed which undergoes an intramolecular rearrangement (S_Ni). An example is provided by conversion of optically active octan-2-ol (23), through its chlorosulphite (24) to the chloride (25) with predominant retention of configuration[17].

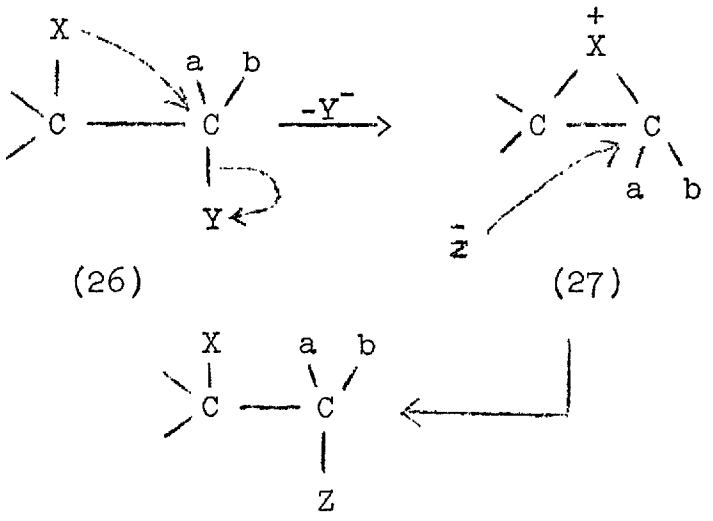


(23)



(iv) Stereochemistry of nucleophilic displacement reactions involving neighbouring group participation

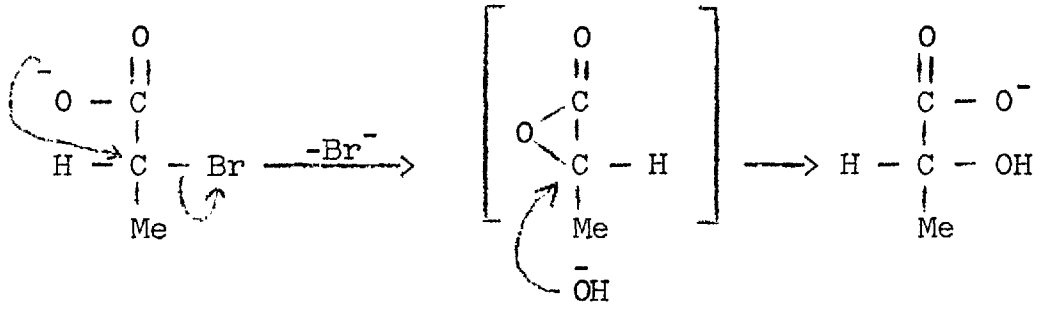
Influence of a neighbouring group (known as neighbouring group participation) is evident in many instances of displacement reactions. Commonly an adjacent group [such as X in (26)] attacks the seat of substitution in the first stage producing a cyclic intermediate such as (27). In the second stage, it may revert back to the original position being attacked by the external nucleophile (such as Z^-) to give (28). Since in both the steps inversion takes place at the same site, overall retention of configuration results ultimately. An example of such a situation



(26) (27)

(28)

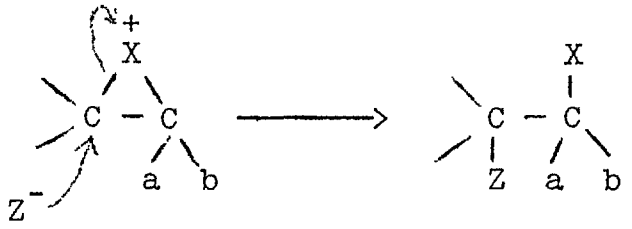
is the hydrolysis of the optically active α-bromopropionate anion (29) where complete retention of configuration is observed under conditions kinetically controlled for a first order reaction[14,15]. However, there may be



(29) (30)

complications due to the possibility of rearrangement, since in the second stage the attack by the external

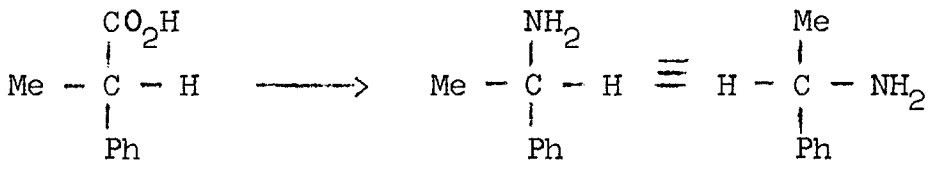
nucleophile may take place on that carbon atom to which the neighbouring group was originally attached:



Yet another possibility is that both of the above two processes (complete retention and rearrangement) may take place simultaneously.

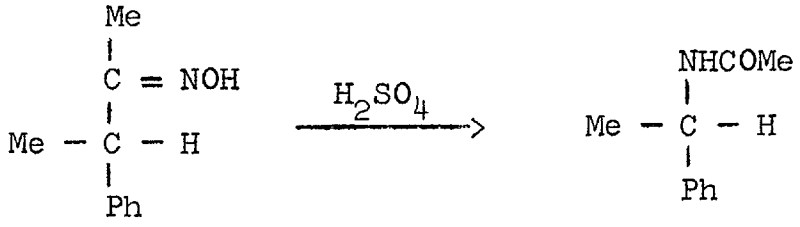
(b) Rearrangement Reactions.

The steric course followed by many rearrangement reactions is well known and such reactions offer potential means for correlation of configurations. Kenyon and coworkers[18,19,20] studied the stereochemistry of Hofmann, Curtius, Lossen, Schmidt and Beckmann reactions and established that configuration is retained if any of these reactions involve an asymmetric carbon atom. This was demonstrated by converting (+)-hydratropic acid (33) to (-)-α-phenylethylamine (34) under conditions secured for either a Hofmann[18], Curtius[19], Lossen[20] or Schmidt[20] reaction.



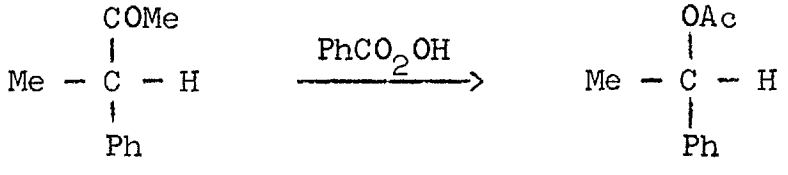
(33) (34)

That the configuration is also retained in a Beckmann rearrangement is shown by converting the Ketoxime (35) to the amide (36)[20].



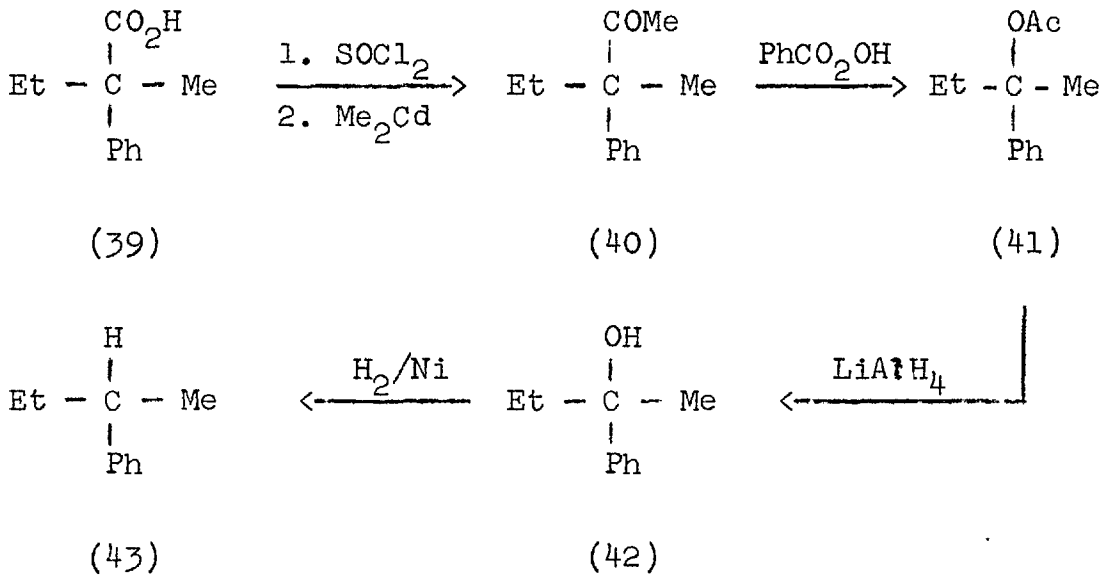
(35) (36)

By converting (+)-3-phenyl butan-2-one (37) to the laevorotatory acetate (38), Mislow and Brenner established that the oxidative cleavage of alkyl ketones by peracids (Baer-Villiger rearrangement) proceeds without configurational modification[21]. This fact helped to correlate



(37) (38)

the configurations of (+)2-methyl-2-phenylbutanoic acid (39) and (-)-2-phenylbutan-2-ol (42) and by correlating (42) with (-)-2-phenylbutane (43) (configuration of which was already known), the absolute configurations of the former two compounds were determined[22].



C. By the study of quasi-racemic compounds.

The principle of this method is based upon the fact that two similarly constituted asymmetric molecules having opposite configurations such as (A) and (B) often undergo compound (quasi-racemic compound) formation and hence if the configuration of one is known that of the other can be

deduced. Compound formation can easily be detected from the nature of the melting point-composition curve for the

(A) (B)

pair. If there is compound formation the idealised curve will be similar to (a) of Fig. 1 (p. 18) while (b) indicates a mixture and curve (c) a solid solution. This method was successfully used to determine the configuration of (-)-methylsuccinic acid (48)[23] by correlating it with (-)-malic acid (44), the configuration of which was already known. The method of correlation is exemplified by the formulae (44) to (48). (-)-Malic acid was converted into the xanthate (45) which was found to form a quasi-racemic compound with the xanthate derivative (46) of (+)-2-mercaptosuccinic acid (47), thus indicating that the two xanthates and therefore (-)-malic acid and (+)-2-mercaptosuccinic acid are of opposite configuration. Since (+)-2-mercaptosuccinic acid and (-)-methylsuccinic also formed a compound, the configuration of the latter should be as shown in (48).

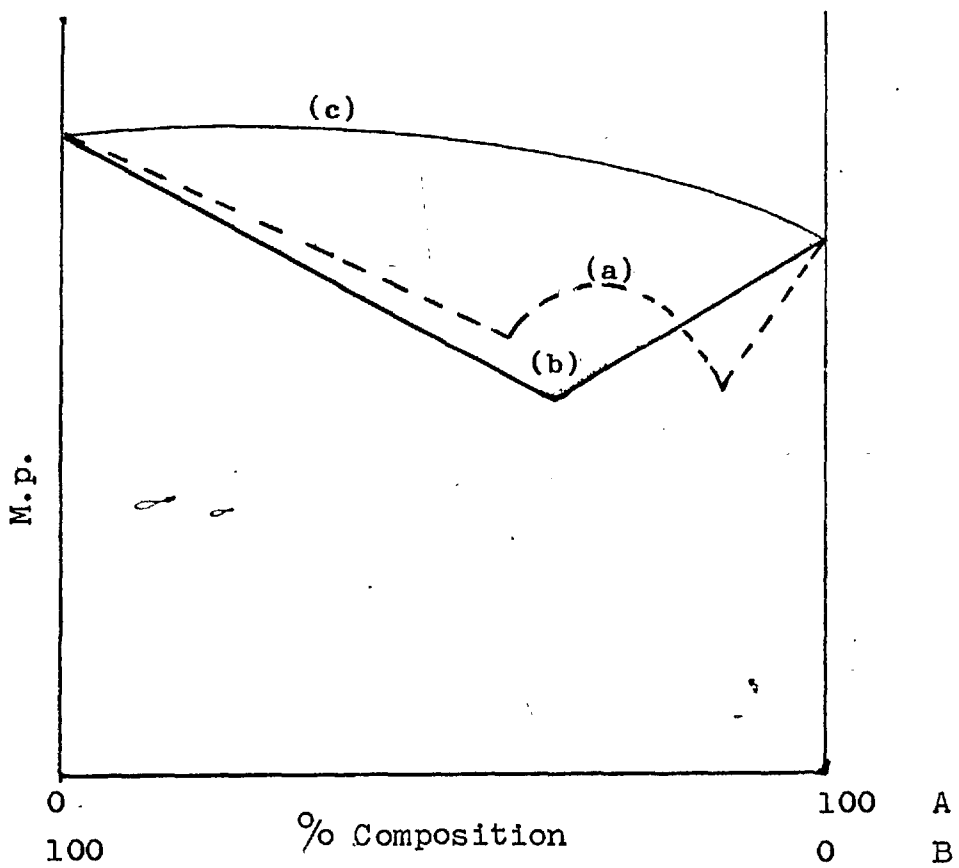
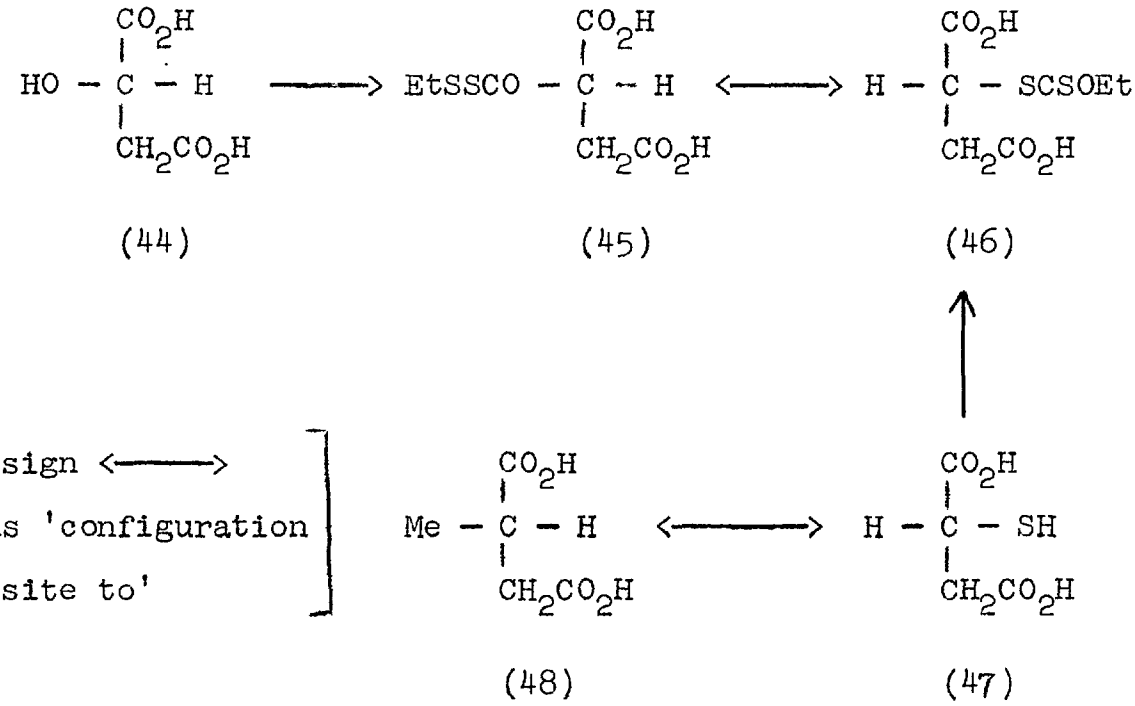
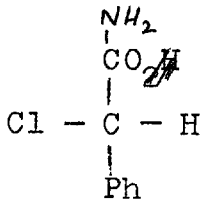


Fig. 1. Melting point-composition curves for two similar compounds having opposite configurations (A and B)



The above method for stereochemical correlation has many limitations. It requires a solid sample and the results are not reliable if the compounds compared are not chemically very similar. Moreover, no information is available, if no compound formation takes place between A and B or the enantiomorph of A and the enantiomorph of B. A variation of the method is due to Mislow and Heffler[24] who postulated that if two similar substances (say A' and B') form a solid solution, and A' and the enantiomorph of B' [or B' and the enantiomorph of A'] form a mixture, then A' and B' are of the same configuration. It was observed that (+)-2-chloro-2-phenylacetamide and (+)-hydratropmide form a solid solution,

whereas (-)-2-chloro-2-phenylacetamide and (+)-hydratropamide form a mixture. Thus it was established that (+)-2-chloro-2-phenylacetamide and (+)-hydratropamide possess the same configuration, as indicated by (49) and (50) respectively. The above result provided an extra support for the configuration (33) assigned to (+)-hydratropic acid.



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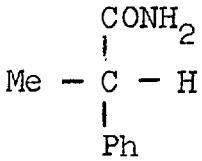

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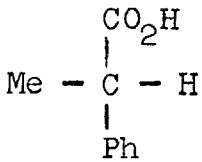
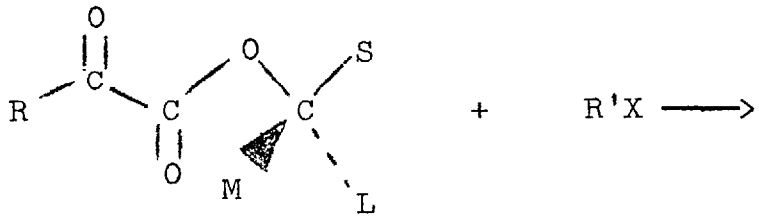


(33)

D. By asymmetric synthesis.

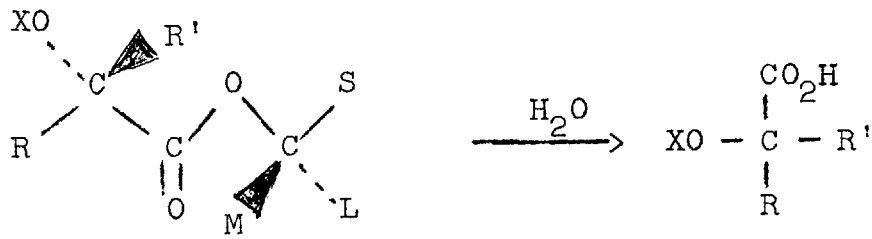
It is a common experience that when a new asymmetric centre is created in a compound which is already asymmetric, one of the two possible diastereoisomers predominates, the reason being the steric influence of an asymmetric centre (already present) on the site of reaction. This phenomenon has recently found use for the determination of configurations[25,26]. An empirical rule which is due to Prelog[25] is useful for the purpose of correlation. The rule predicts that if a glyoxalate is so oriented as shown in (51), the

reaction with a reagent, R'X (such as Grignard reagent) will give predominantly (52) which in turn will give the acid (53) on hydrolysis.



(51)

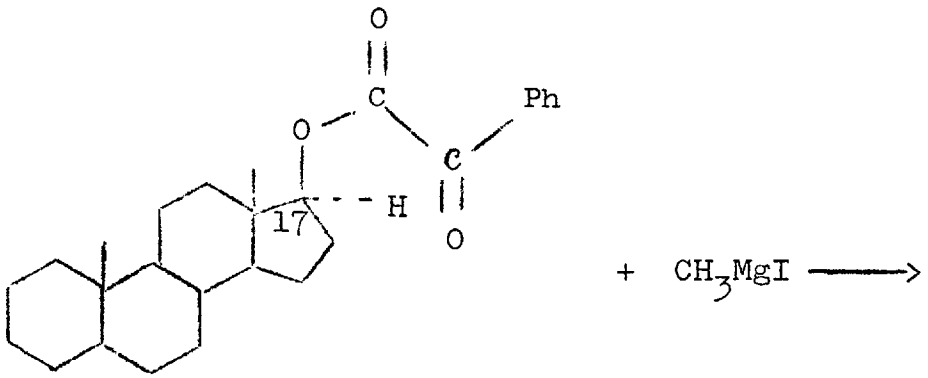
(S, M and L represent small, medium and large substituents respectively)



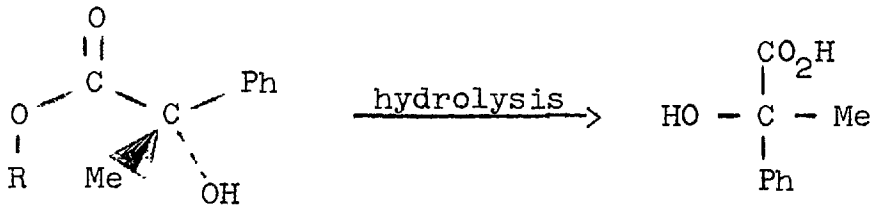
(52) (53)

If the configuration of the acid, $RR'C(OX)CO_2H$ is known or can be determined, the configuration of the asymmetric centre in the alcoholic part of the glyoxalate can be easily deduced. Conversely, knowing the configuration of the glyoxalate (51), that of the acid, $RR'(OX)CO_2H$ can be ascertained. An illustration of the usefulness of this rule is the determination of the configuration at C_{17} of

androstan-17β-ol by correlating its phenylglyoxalate (54) with (+)-atrolactic acid (55)[27].



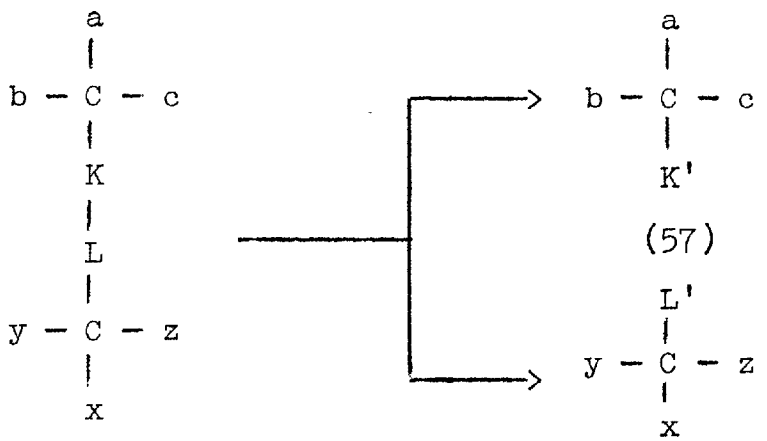
(54)



(55)

E. By chemical reactions involving diastereoisomers

This involves an asymmetric compound having at least two asymmetric centres such as (56) where it is possible to separate each asymmetric atom without a bond leading to it

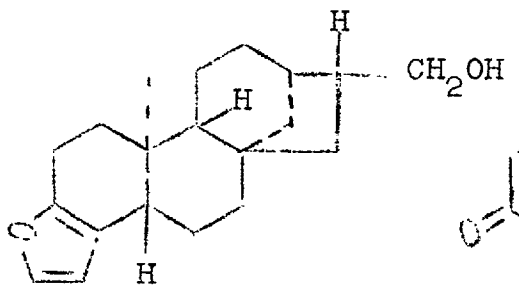


being broken to give optically active fragments such as (57) and (58). If the absolute configuration of (57) can be established and if the relative configuration of the two asymmetric centres in (56) is known, the absolute configuration of the xyzC-centre and hence the configuration of (58) can be deduced.

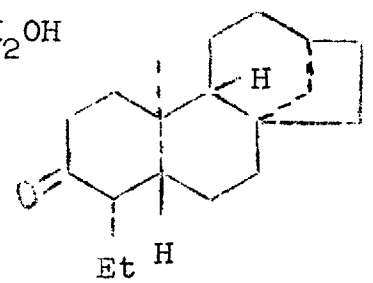
F. By optical rotatory dispersion

In a number of cases[28], the nature of Cotton effect curves has been used to correlate configurations. The principle of this method is based upon the fact that if two compounds contain the same chromophore and if the environments in the vicinity of the chromophore in both compounds

are structurally and configurationally the same, the Cotton effect curves for these compounds will be similar; if the environment in one is the mirror image of that in the other, the Cotton effect curves will also show a mirror image relationship. A successful application of the method is the determination of the absolute configuration of cafestol (59)[29,30]. This was effected by converting the compound to its carbonyl derivative (60) and comparing the Cotton effect curve of the latter with that of 4α-ethyl-cholestan-3-one (61), the configuration of which was already established. Since the two Cotton effect curves were mirror images (Fig. 2, p. 25)[30], it was concluded that the environments in the vicinity of the carbonyl chromophore are of opposite configuration. Consequently, cafestol was represented as in (59).



(59)



(60)

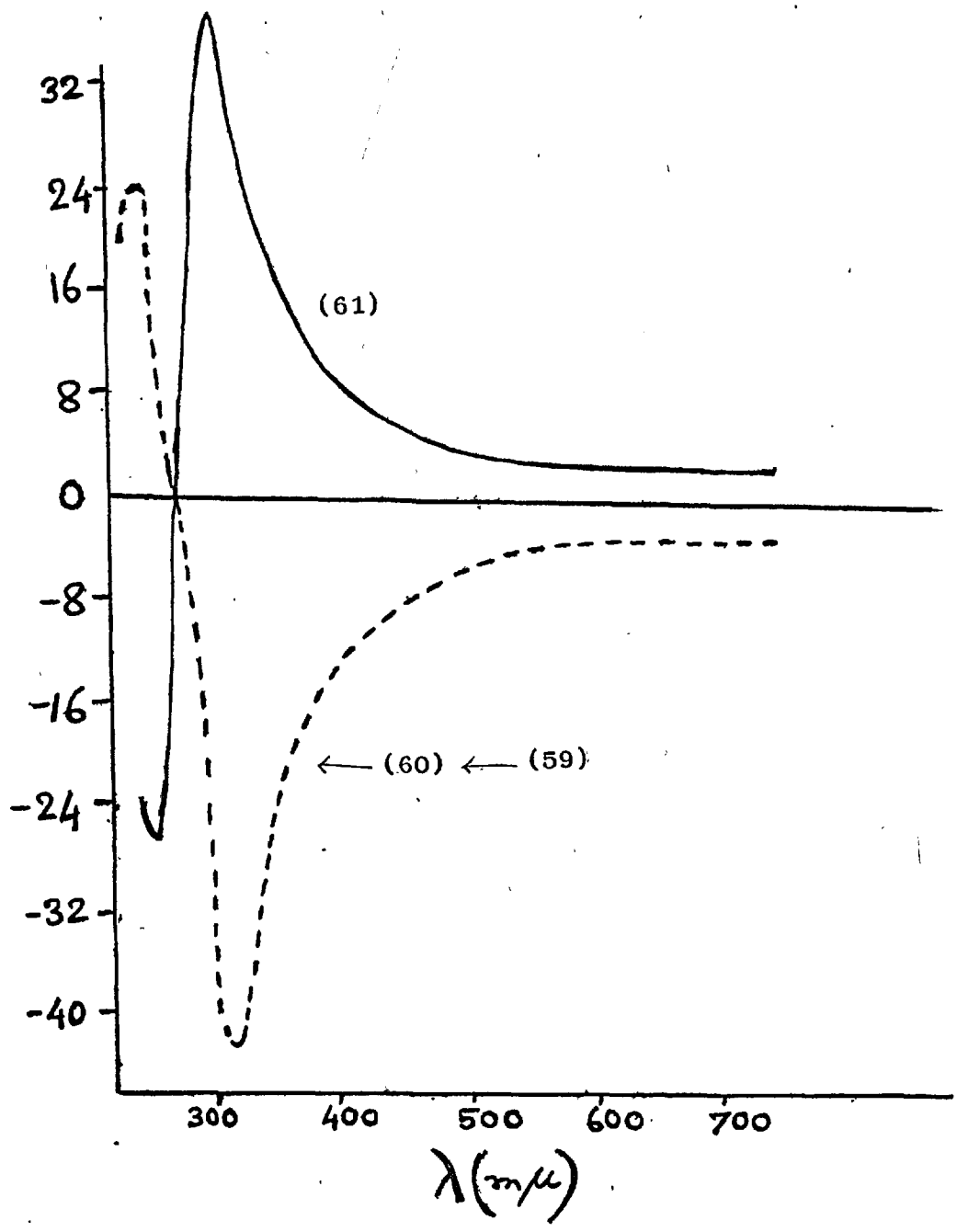
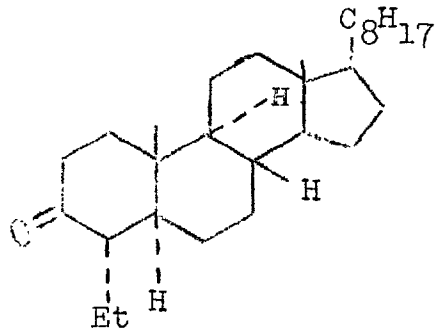


Fig. 2. Optical rotatory curves (methanol) of 4α-ethylcholestan-3(one) (61) and of the degradation product (60) of cafestol (59)



(61)

G. By 'partial resolution'

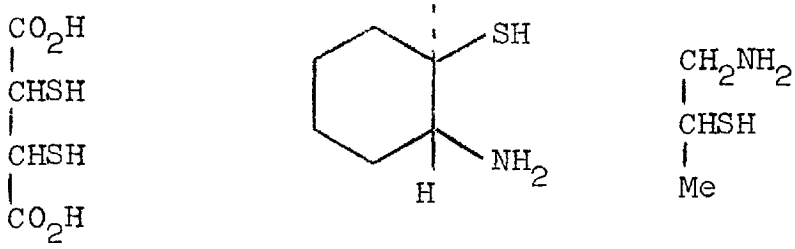
In the kinetic method of resolution of a racemic modification, a racemate is allowed to react with an insufficient amount of an optically active reagent. Due to differing rates of reaction of the two antipodes, there is always an excess of one of them over the other at the end of the reaction, thus affecting partial resolution. This fact forms the basis of a method of stereochemical correlation[31], where an optically active secondary alcohol is allowed to react with (±)-α-phenylbutyric acid, $PhCH(Et)CO_2H$ (as the anhydride or acid chloride). Since one enantiomorph of the acid will react with the alcohol

faster than the other (due to steric effect of the alcohol), the other enantiomorph will predominate as the unreacted acid. From the sign of rotation of the acid the configuration of the active alcohol may be established.

P A R T I

DISCUSSION

Thiols find wide applications in a variety of fields, including chemotheraphy[32] and analysis[33], but their stereochemistry has been less extensively exploited than that of their oxygen analogues. In the literature, there are a few scattered examples of optically active thiols, but in many cases either the optical purity of a sample is doubtful or the absolute configuration is not established. Levene[34] reported the synthesis of laevorotatory octane-2-thiol but the different fractions of a distilled sample were reported to have different specific rotations. Gerecke et al.[35] have isolated antipodes of DL-2,3-dimercaptosuccinic acid (1). Optical isomers of trans-2-aminocyclohexanethiol (2)[36] and 1-aminopropane-2-thiol (3)[37] are also known. But in none of these examples has the absolute

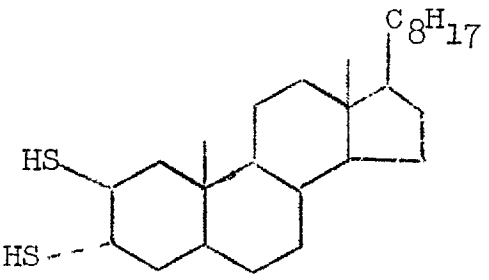


(1) (2) (3)

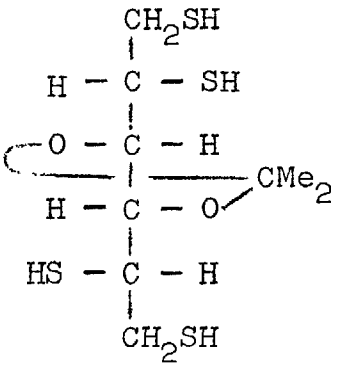
configuration of an optical isomer been ascertained.

In the domains of carbohydrates[38,39] and steriods[40]

the absolute configurations of a few complex thiols such as (4) and (5) have been established on the basis of stereo-specific reactions by which the thiol groups were introduced.

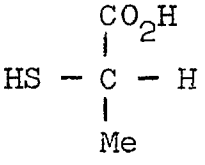


(4)

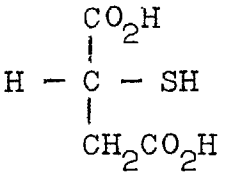


(5)

Fredga[23,41,42] used the method of quasi-racemic compound formation to determine the configurations of the carboxylic thiols (6)-(8). By determining the configuration of



(6)



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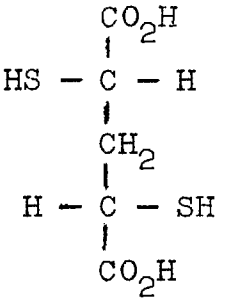
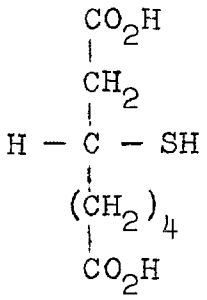


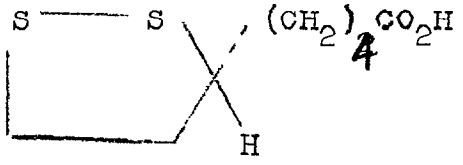
(8)

(-)-3-mercapto-octanoic acid (9) and correlating it with

biologically important (+)-α-lipoic acid (10), the configuration of the latter was established[43].

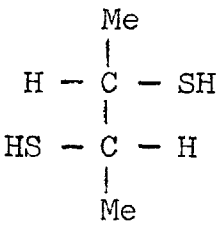


(9)

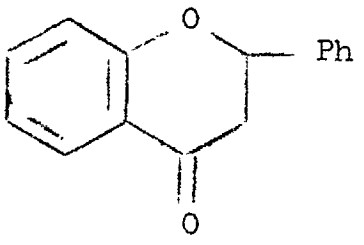


(10)

L-(+)-Butane-2,3-dithiol (11) was synthesised by Corey and Mitra[44] to resolve racemic flav-4-one (12).



(11)



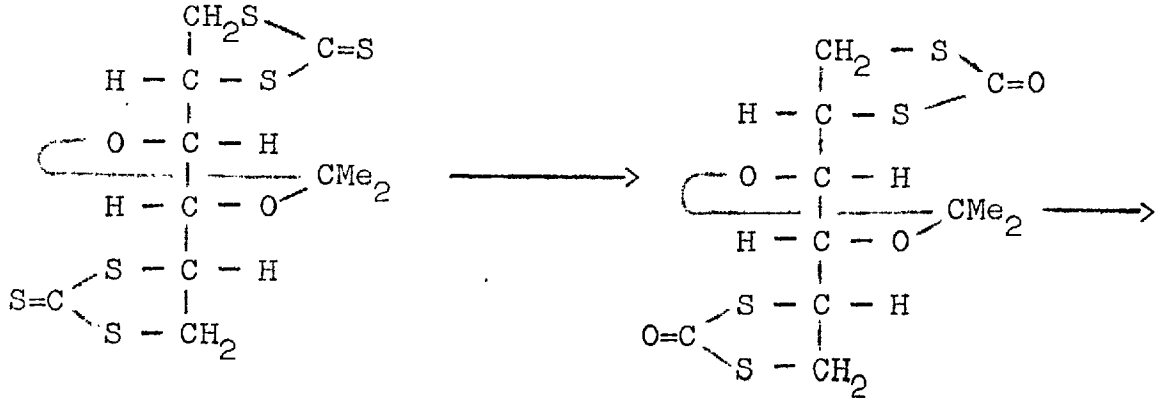
(12)

The synthesis of simple hydroxy-thiols and related compounds forms the basis of the work to be described below. The mechanisms and consequent stereochemistry of the different steps involved in these syntheses are well established, and thus it was possible to assign absolute configurations to

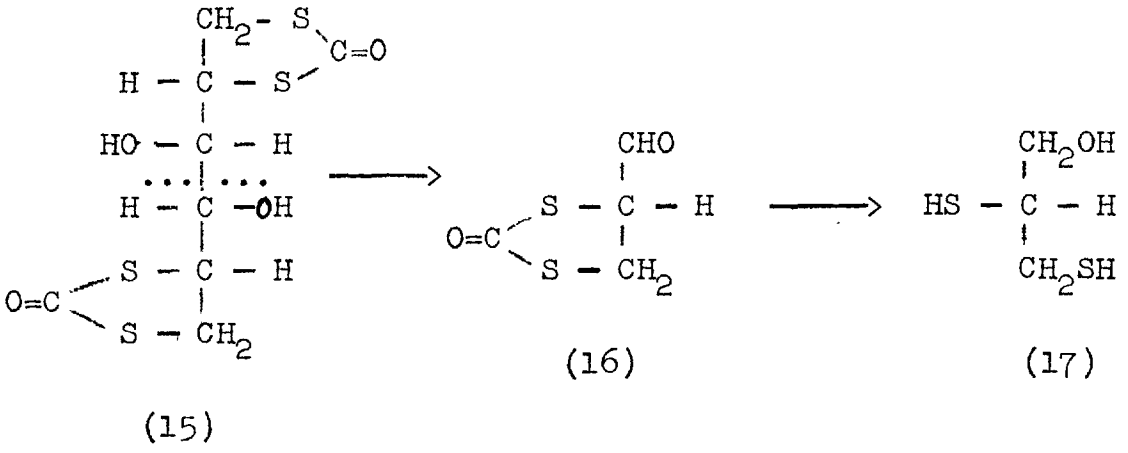
these compounds. Because of their known configurations, such compounds may find interesting applications in stereochemical studies.

Racemisation During the Attempted Preparation of (R)-2,3-Dimercaptopropanol from D-Mannitol

With the object of synthesising (R)-2,3-dimercaptopropanol (17), D-mannitol was selected as the starting compound. Iqbal and Owen[39] prepared 1,2,5,6-tetradeoxy-3,4-O-isopropylidene-1,2:5,6-di(thiocarbonyldithio)-L-iditol (13) from 1,2:5,6-dianhydro-3,4-O-isopropylidene-D-mannitol. It was hoped that the bistrithiocarbonate (13) would yield (R)-2,3-dimercaptopropanol (17) in accordance with the following scheme:

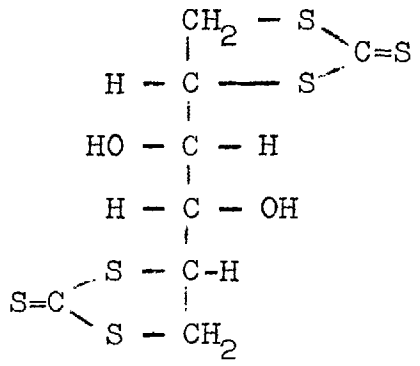


(13) (14)

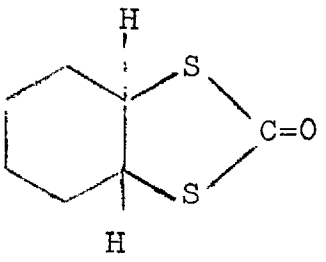


(15) (16) (17)

The reason for attempting to prepare 1,2,5,6-tetradeoxy-1,2:5,6-di(carbonyldithio)-L-iditol (15) rather than the corresponding bistrithiocarbonate (18) was the fact that a vicinal dithiol group is better protected as a cyclic dithiocarbonate than as a trithiocarbonate. This



(18)

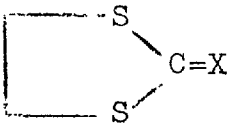


(19)

conclusion was drawn from the work of Adley[45] and Moppett[46] who found that cyclic trithiocarbonates are susceptible to

oxidation by lead tetra-acetate whereas the oxidant does not affect a dithiocarbonate such as (19).

Challenger et al.[47] prepared the dithiocarbonate (21) from the trithiocarbonate (20) by treatment with mercuric acetate, and with this reagent the bistrithiocarbonate (13) was converted into the bisdithiocarbonate (14).

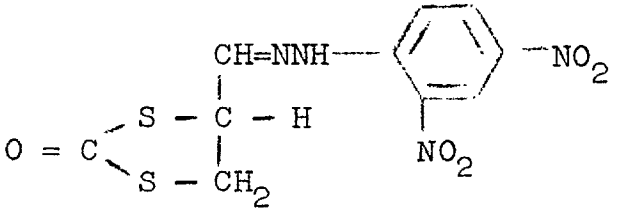


(20), X = S

(21), X = O

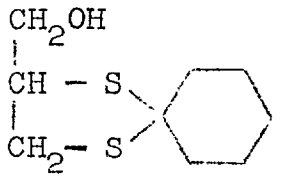
Due to the presence of the two hydrolysable terminal dithiocarbonate group in (14), the selective removal of the isopropylidene group from this compound posed a problem. However, this was effectively solved by using 40% aqueous acetic acid to hydrolyse (14) to give 1,2,5,6-tetradeoxy-1,2:5,6-di(carbonyldithio)-L-iditol (15).

Oxidation of the diol (15) with lead tetra-acetate gave a crude aldehyde, characterised as the pure 2,4-dinitrophenylhydrazone (22).



(22)

The crude aldehyde on reduction with lithium aluminium hydride yielded a sample of 2,3-dimercaptopropanol which was optically inactive; even when examined by the O.R.D. method (by Professor W. Klyne) negligible activity could be detected (see fig. 3, p. 35). The cyclohexylidene derivative (23) of the sample was also optically inactive.



(23)

The optically active forms of 2,3-dimercaptopropanol were eventually obtained by another route to be described later, and it therefore follows that during the above preparation of 2,3-dimercaptopropanol, racemisation took place.

In a control experiment, no racemisation was observed when a sample of crude D-2,3-O-isopropylideneglyceraldehyde (25), obtained by oxidising 1,2:5,6-di-O-isopropylidene-D-mannitol (24) with lead tetra-acetate, was reduced with lithium aluminium hydride to give D-1,2-O-isopropylideneglycerol (26) (this reduction has previously been carried out[6] only by hydrogenation of the aldehyde over

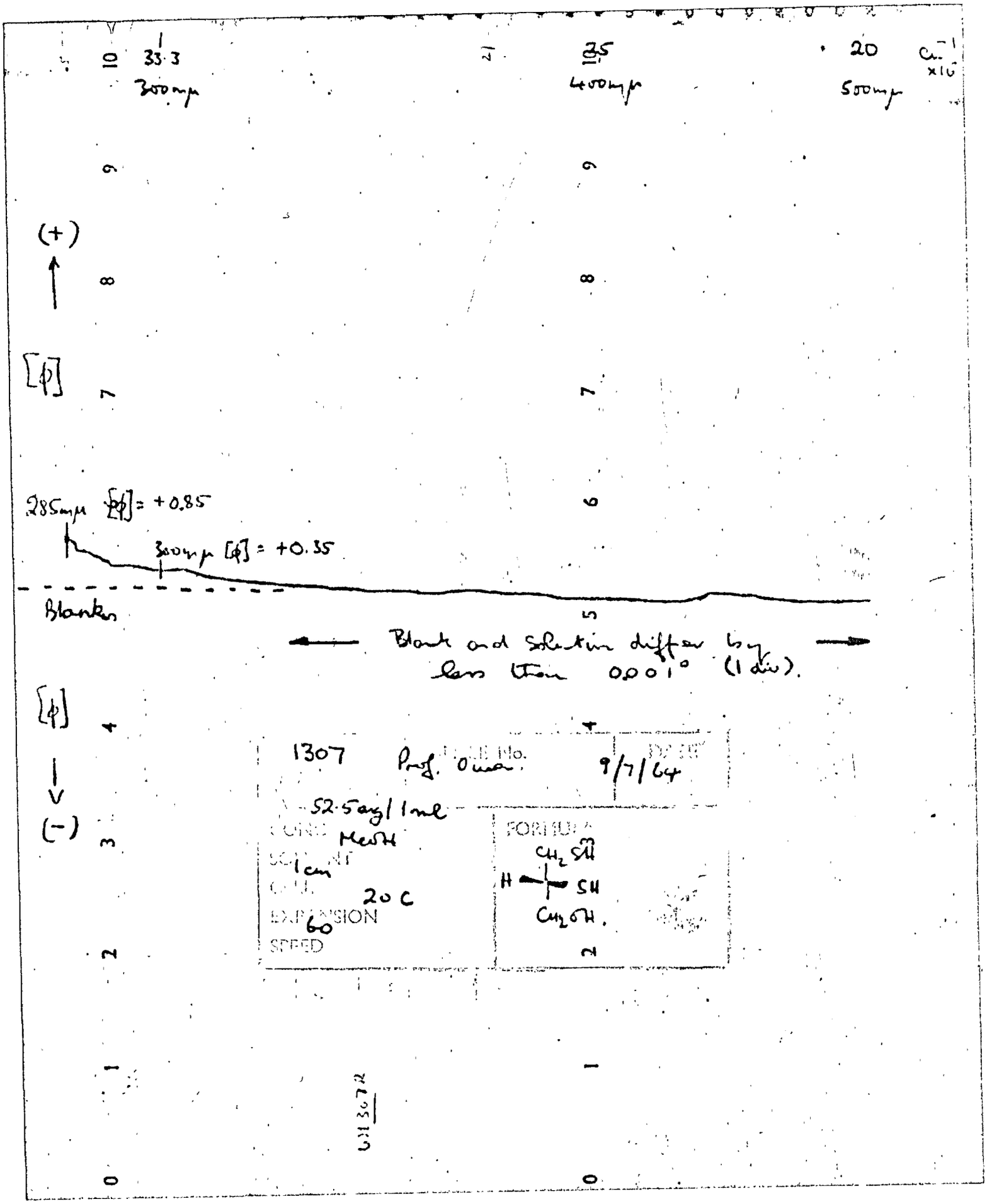
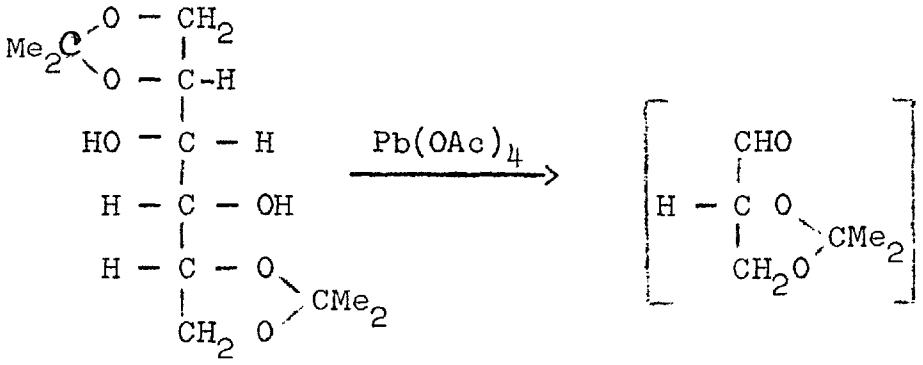
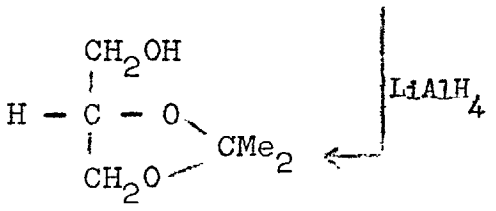

10
33·3
300mμ
9
8
7
6
5
4
3
2
1
0
(+)
[φ]
(−)
285mμ [φ] = +0.85
300mμ [φ] = +0.35
Blanks
Blank and Solution differ by less than 0.001° (1 div).
35
400mμ
20
cm⁻¹ x10⁻³
500mμ
1307
Prof. Djerassi
9/7/64
52·5 mg/1 ml
MeOH
1 cm
20 C
60
CH₂OH
H
OH
CH₂OH.

Fig. 3

Raney nickel); it therefore appeared the presence of sulphur in the molecule must be responsible for the racemisation observed in the reduction of the aldehyde (16).

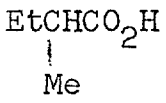


(24) (25)



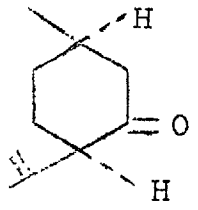
(26)

A large number of examples are available including the optically active acid (27)[48] where reduction of a carbonyl group by lithium aluminium hydride does not affect an adjacent asymmetric centre. However, in a few cases such a reduction proceeds with racemisation[49,50]. Ohloff et al.[49] observed partial epimerization of the neighbouring centre during the reduction of the cyclic ketone (28). Partial



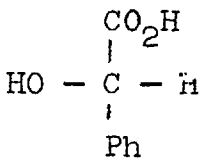
(27)

(+)-2-Methylbutanoic acid



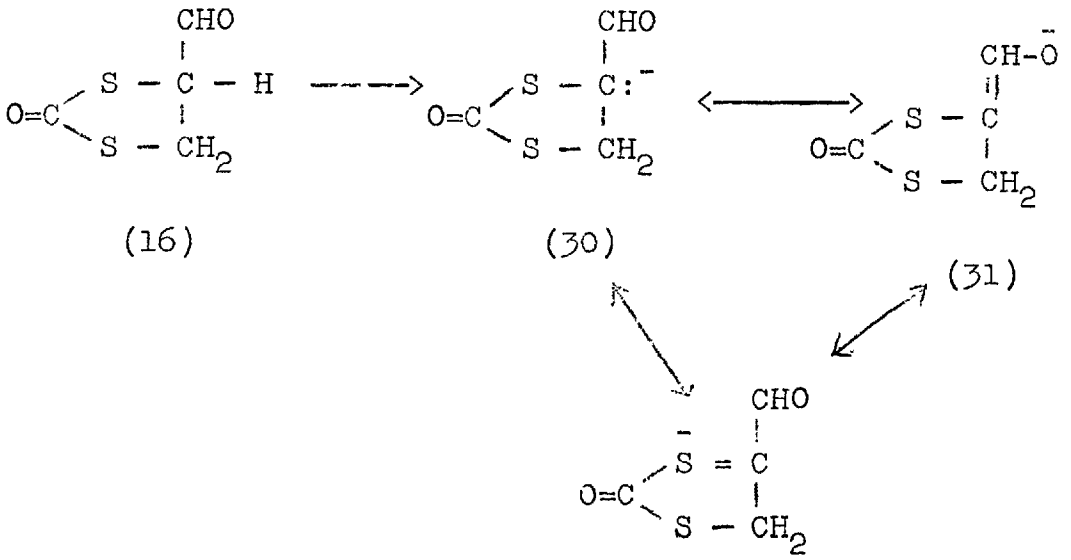
(28)

racemisation (at least 31%) was reported when (+)-mandelic acid (29) was reduced with lithium aluminium hydride[50].



(29)

In the present example, the racemisation may be due to the initial formation of the carbanion (30) by the action of lithium aluminium hydride on the aldehyde (16). The carbanion once formed may resonate with such mesomeric forms as (31) and (32) whereby the asymmetry is lost and hence racemisation takes place.



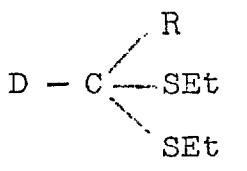
(16) (30) (31) (32)

An enhanced tendency to form a carbanion is expected if it is assumed that the anion is stabilised by resonance involving the vacant 3d orbital of the sulphur atom and the adjacent carbonyl group as already indicated by the hypothetical resonance forms (30)-(32).

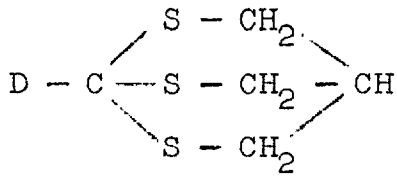
In many compounds containing the $S-CH_2-S$ group, a tendency to form a carbanion is observed. Thus Corey and Seebach[51] reported the formation of the anion (34) by reacting the 1,3 dithian (33) with n-butyl-lithium.

(33) (34)

Oae et al.[52] studied the base catalysed hydrogen-isotope exchange of a number of sulphur-containing compounds including (35a) to (36) and found that whereas isotope exchange readily takes place with these compounds, no exchange is observed with their oxygen analogues. This result was explained on the basis of a carbanion stabilisation due to resonance involving 3d orbitals of sulphur.



(35a), R = Et
(35b), R = SEt
(35c), R = Ph

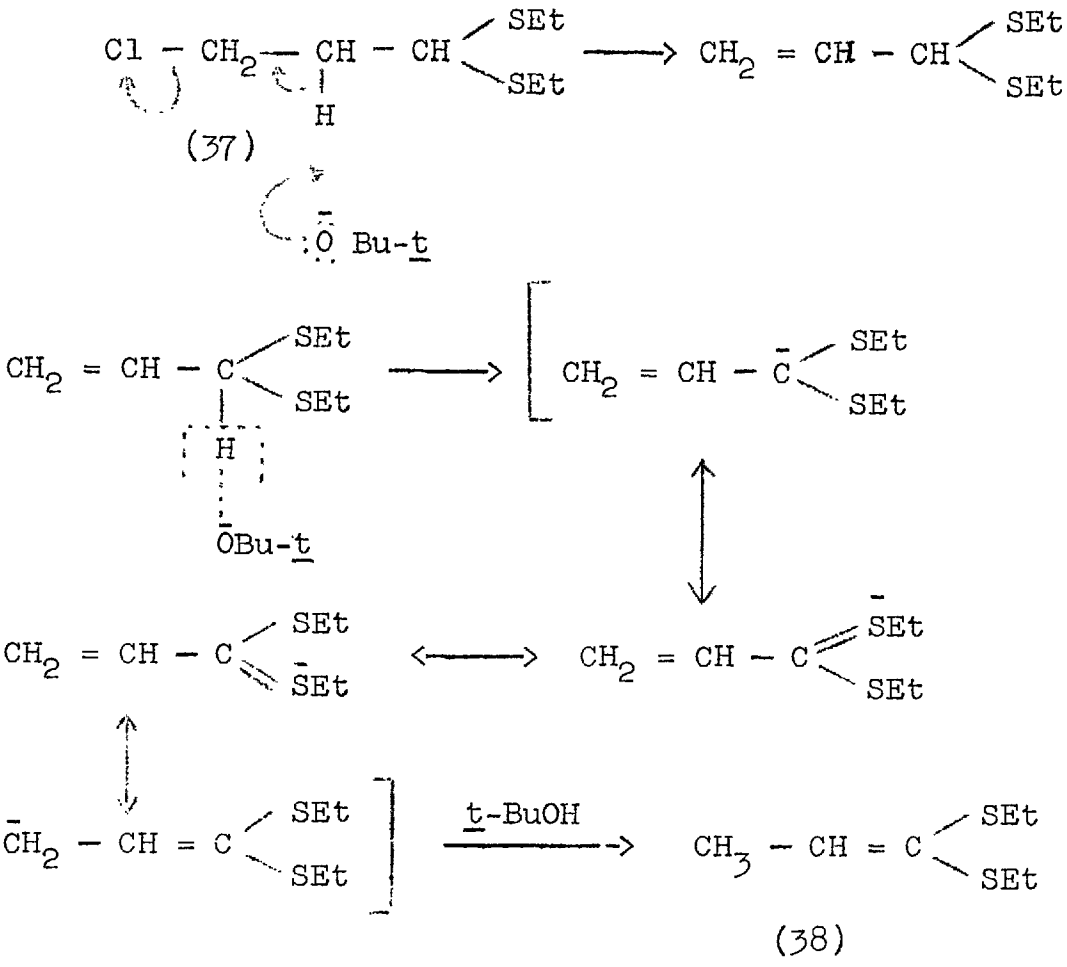


(36)

As is expected for such an argument, the rate of exchange was found to increase with the number of sulphur atoms attached to the deuterium-bearing carbon atom. A phenyl group (due to its ability to participate in resonance) in the α-position also increases the rate considerably and the relative rates for the compounds (35a) to (35c) fall in the order: (35c) > (35b) > (35a). It was also observed that the participation of 3d orbital of sulphur in resonance becomes more effective when the sulphur atoms are

in ring structures. Thus the experimental rate of isotope exchange of (36) is three powers of ten larger than (35b).

The base catalysed reaction of 3-chloro-1,1-bis(ethylmercapto)propane (37) with t-butanol to give (38) is also thought to proceed through a carbanion intermediate stabilised by resonance involving 3d orbital of sulphur (aided by allylic resonance) as shown by the following mechanism[52]:

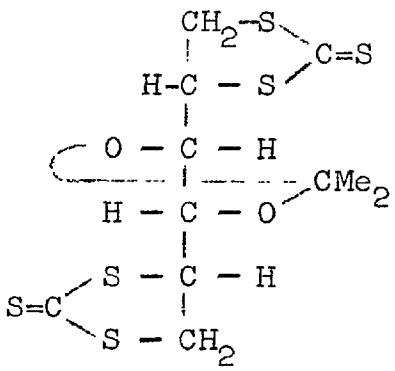


(38)

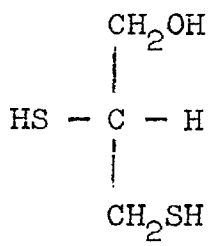
A similar explanation for the racemisation observed by the present author therefore seems reasonable. It appears to be the first case, however, where stabilisation under normal conditions is brought about by only <u>one</u> neighbouring sulphur atom, but of course the effect is no doubt facilitated by the additional presence of the carbonyl group in the aldehyde.

<u>(R)-2,3-Dimercaptopropanol</u>

Since the attempts to prepare (R)-2,3-dimercapto-propanol (17) from the bistrithiocarbonate (13) were not successful, the synthesis of the compound by another route was tried. Exploratory experiments, to establish

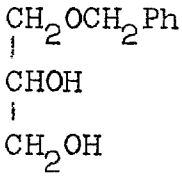


(13)

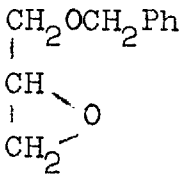


(17)

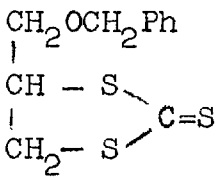
the experimental route, were carried out by using DL-1-O-benzylglycerol[53] (39). The diol (39) on treatment with toluene-p-sulphonyl chloride and pyridine followed by reaction with sodium methoxide gave DL-1-O-benzyl-2,3-epoxypropanol (40)[54]. Reaction of the epoxide (40) with



(39)



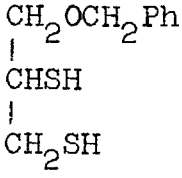
(40)



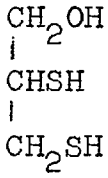
(41)

potassium methyl xanthate yielded DL-1-O-benzyl-2,3-(thiocarbonyldithio)propanol (41). This method of preparation of a trithiocarbonate from an epoxide was developed by Culvenor and co-workers[55]; other methods[56,57], in which an epoxide is heated under high pressure in the presence of a catalyst with carbon disulphide, give poorer yields.

Following the method developed by Iqbal and Owen[39] for the preparation of a number of vicinal dithiols, the trithiocarbonate (41) was reduced by lithium aluminium hydride to DL-1-O-benzyl-2,3-dimercaptopropanol (42).

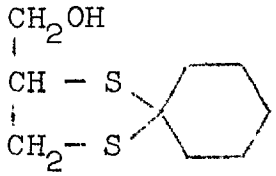


(42)

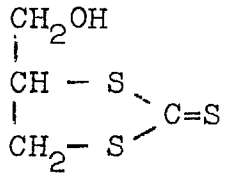


(43)

The benzyl group in the crude dithiol (42) was then removed by reaction with sodium and liquid ammonia to give DL-2,3-dimercaptopropanol (43). The dithiol (43) was characterised as its cyclohexylidene derivative (23)[58] and by reaction with potassium methyl xanthate to give DL-2,3-(thiocarbonyldithio)propanol (44).

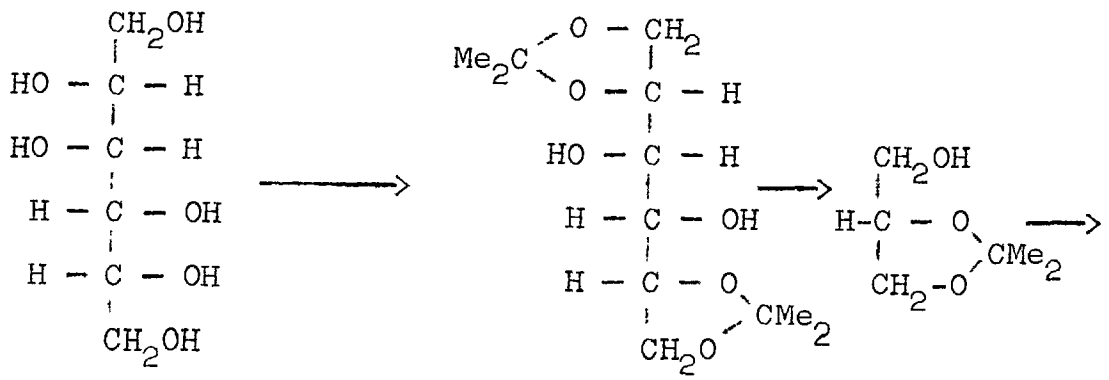


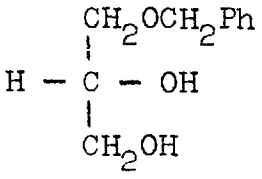
(23)



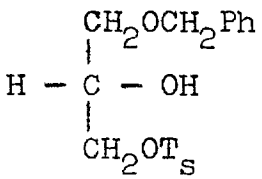
(44)

Having thus established the new synthetical route to DL-2,3-dimercaptopropanol, the synthesis of (R)-2,3-dimercaptopropanol was next attempted. (R)-1-O-Benzyl-glycerol (45) was prepared by published methods[6,8,59] from D-mannitol via (S)-1,2-O-isopropylideneglycerol.(45)



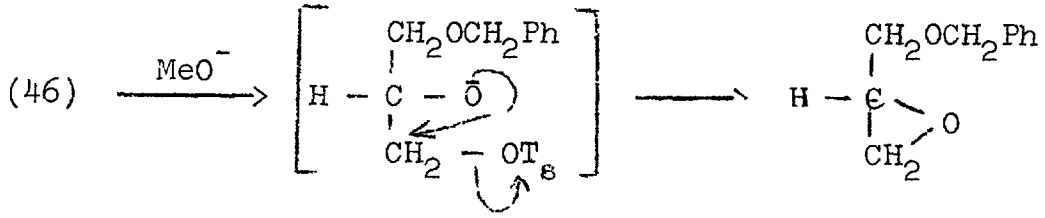


(45)

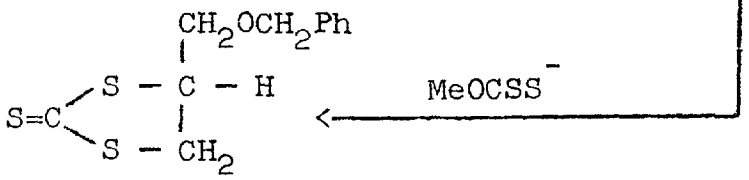


(46)

was converted into (S)-1-O-benzyl-3-O-tosylglycerol (46) by a method which was essentially the same as that described by Belleau and Puranen[9]. Reaction of the monotosyl compound (46) with sodium methoxide gave (S)-1-O-benzyl-2,3-epoxypropanol (47). Further reaction of the epoxide (47)



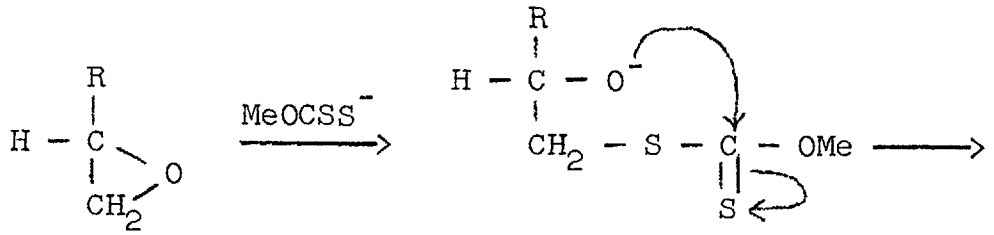
(47)

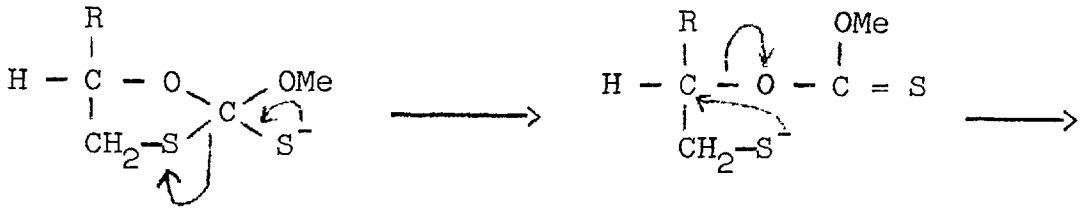


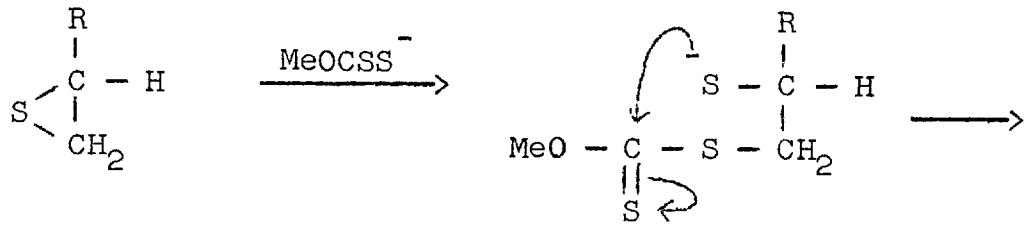
(48)

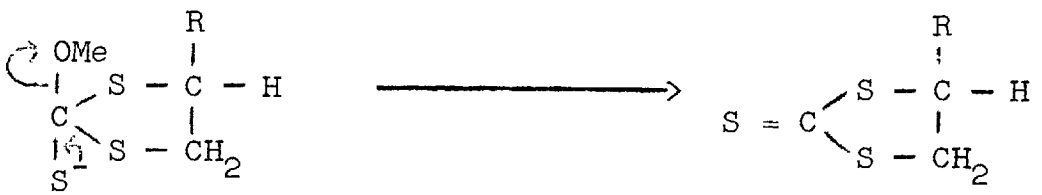
with potassium methyl xanthate gave dextrorotatory (R)-1-O-benzyl-2,3-(thiocarbonyldithio)propanol (48). The

formation of a trithiocarbonate from an epoxide proceeds by way of an episulphide intermediate[56] and the mechanism[38] of its formation is outlined below:



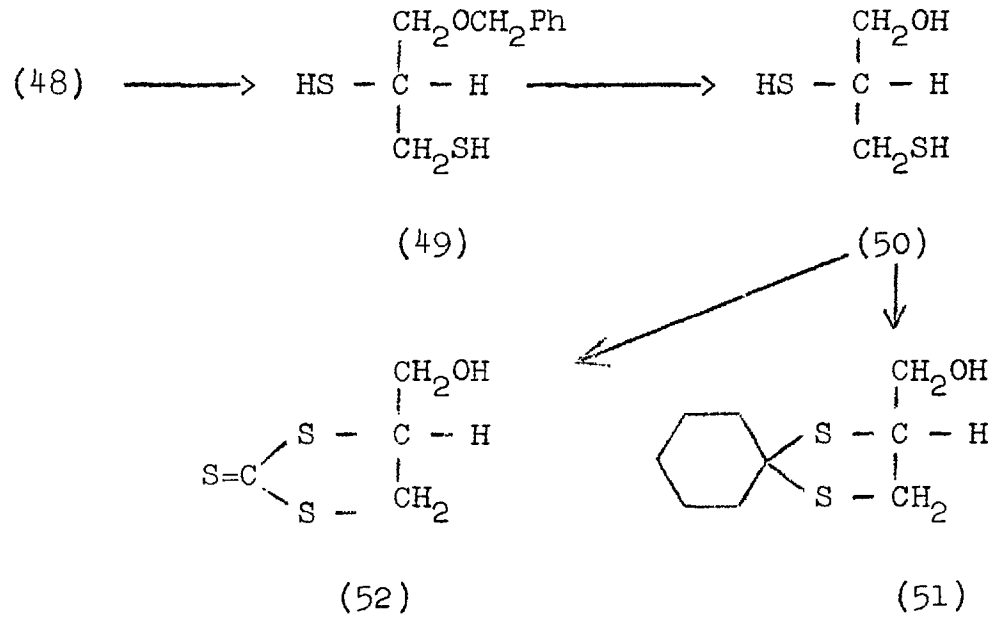






From the above mechanism it is apparent that inversion of configuration takes place when a terminal epoxide is converted into a trithiocarbonate whereas the formation of the same derivative from a terminal episulphide does not involve any modification of configuration. Consequently, the dextrorotatory 1-O-benzyl-2,3-(thiocarbonyldithio)-propanol should be assigned the (R)-configuration as shown in (48).

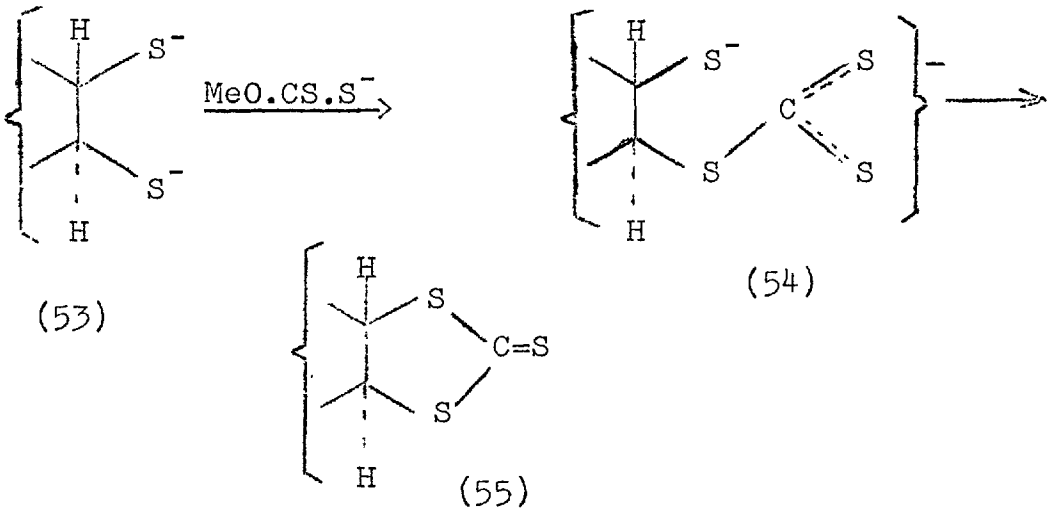
Reduction of the trithiocarbonate (48) with lithium aluminium hydride gave laevorotatory (R)-1-O-benzyl-2,3-dimercaptopropanol (49). The reductive fission of an



asymmetric trithiocarbonate does not affect the asymmetric

centre[39,40] and hence both dextrorotatory 1-O-benzyl-2,3-(thiocarbonyldithio)propanol (48) and laevorotatory 1-O-benzyl-2,3-dimercaptopropanol (49) have the same configuration. Removal of the benzyl group from the dithiol (49) by reacting it with sodium and liquid ammonia produced (R)-2,3-dimercaptopropanol (50). The cyclohexylidene derivative (51) of the latter was found to have a lower melting point than a similar derivative (23) from racemic 2,3-dimercaptopropanol (43). One interesting property of the dithiol (50) is that it is dextrorotatory in chloroform but laevorotatory in methanol. On reaction with potassium methyl xanthate, the dithiol (50) yielded dextrorotatory (R)-2,3-(thiocarbonyldithio)propanol (52).

Kyaw and Owen[6c] who studied the reaction between vicinal cyclic dithiols and potassium methyl xanthate gave the following mechanism of the formation of a trithiocarbonate from a vicinal dithiol:



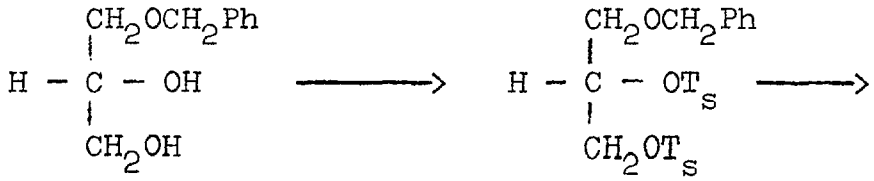
(53) (54) (55)

The first step involves the attack by a thiol anion on the xanthate with the elimination of the methoxide ion to give the mesomeric intermediate (54) which by the introamolecular displacement of sulphide ion produce a trithiocarbonate. Such a mechanism requires that the configuration of dithiol is not modified in its transformation to a trithiocarbonate. Hence it follows that the trithiocarbonate (52) has the same configuration as (R)-2,3-dimercaptopropanol.

Confirmation of the identical configuration of both the dextrorotatory trithiocarbonates (48) and (52) came from the nature of their Cotton effect curves as shown in fig. 4 (p. 49) and fig. 5 (p. 50) respectively (determined by Professor C. Djerassi). Both the compounds possess positive Cotton effect curves and the two curves are almost identical with each other.

(S)-2,3-Dimercaptopropanol

The diol (45) reacted with a requisite amount of



(45) (56)

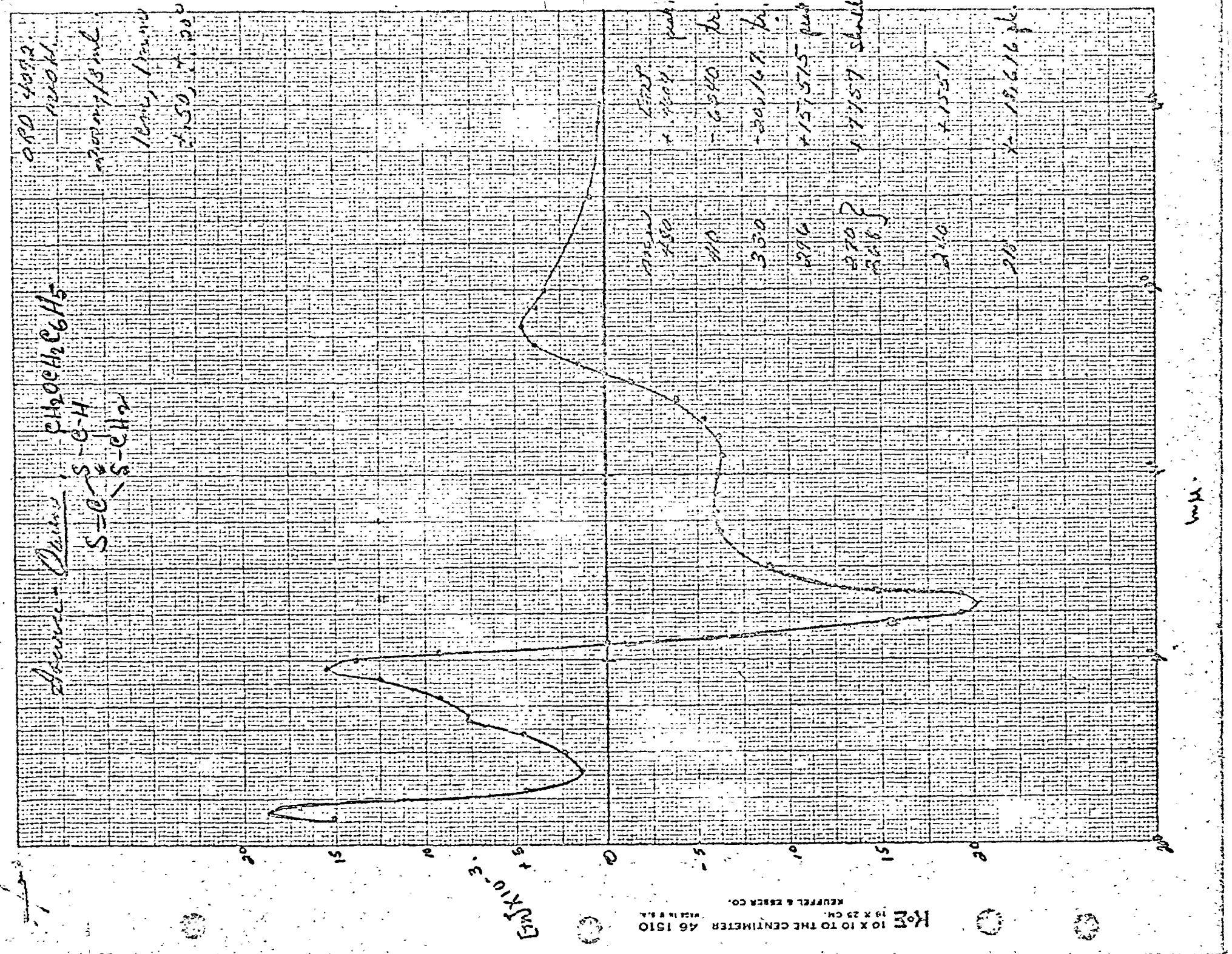


Fig. 4
KODAK
KEUFFEL & ESSER CO.
46 1510
10 X 10 TO THE CENTIMETER
18 X 25 CM.
MADE IN U.S.A.
49

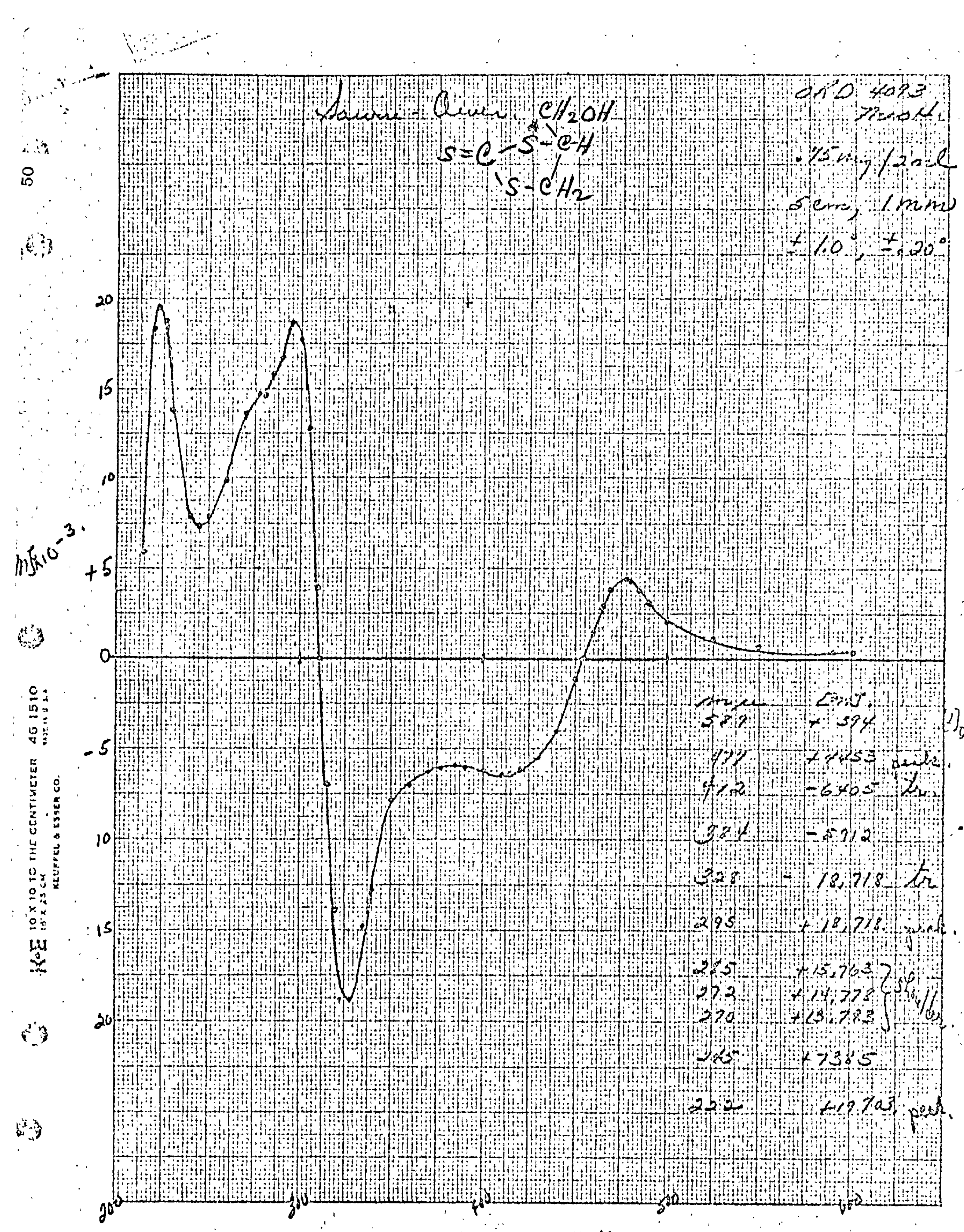
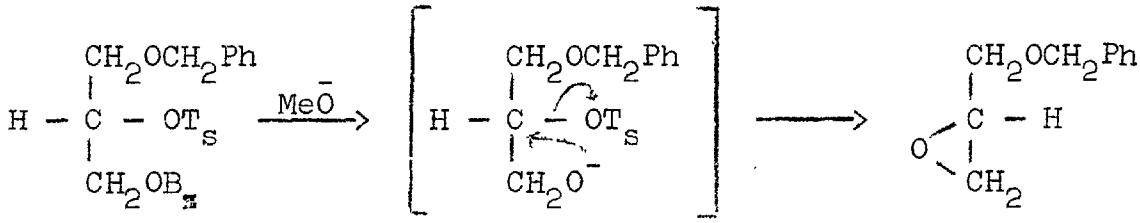
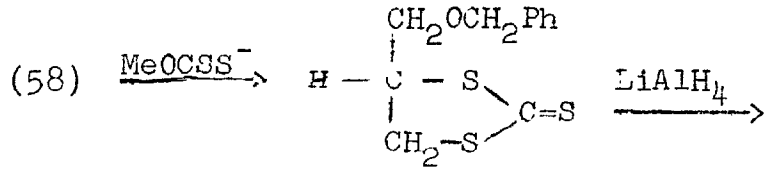

ORD 4093
CH2OH
S=C-S-CH
S-CH2
.75 mg/2 ml
5 cm, 1 mm
±1.0°, ±.20°
MΦx10^-3.
20
15
10
+5
0
-5
10
15
20
200
300
400
500
600
mμ
mμ
Φ
587
+394
412
-6405
384
-5712
328
-18,718
295
+18,718
285
+15,763
272
+14,778
270
+13,783
245
+7355
232
+19,703
K&E 10 X 10 TO THE CENTIMETER 46 1510
KEUFFEL & ESSER CO.

Fig. 5

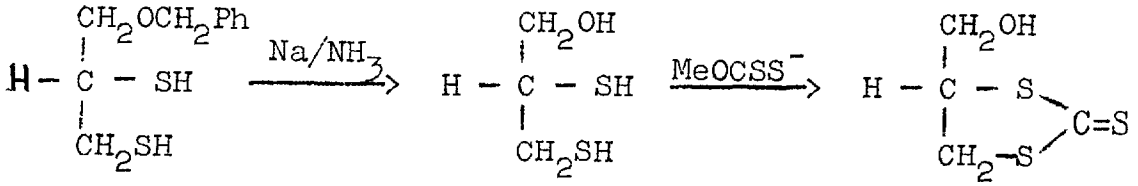


(57) (58)

toluene-p-sulphonyl chloride in the presence of pyridine to give (S)-1-O-benzyl-2,3-di-O-tosylglycerol (56). Selective replacement of the primary toluene-p-sulphonyloxy group of the ditosyl compound (56) by a benzoyloxy group was effected by treating (56) with one mole of sodium benzoate in dimethylformamide; the (S)-3-O-benzoyl-1-O-benzyl-2-O-tosylglycerol (57) which was obtained reacted further with sodium methoxide to yield (R)-1-O-benzyl-2,3-epoxypropanol (58). Treatment of the epoxide (58) with potassium methyl xanthate produced (S)-1-O-benzyl-2,3-(thiocarbonyldithio)propanol (59). Reduction of the



(59)

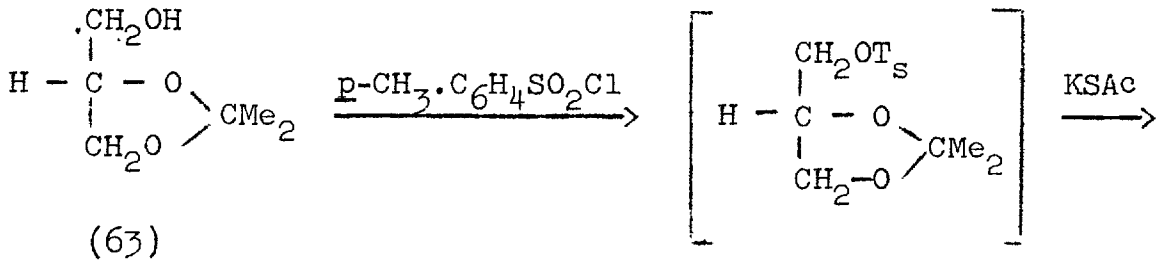


(60) (61) (62)

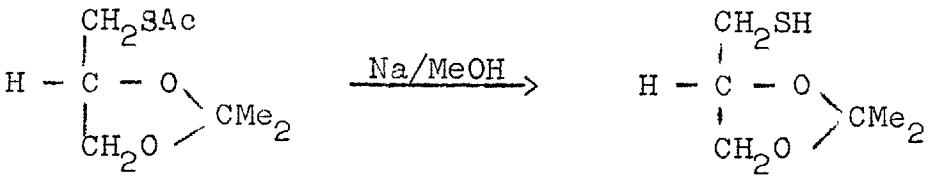
trithiocarbonate (59) with lithium aluminium hydride yielded (S)-1-O-benzyl-2,3-dimercaptopropanol (60). Debenzylation of (60) with sodium and liquid ammonia produced (S)-2,3-dimercaptopropanol (61), which when treated with potassium methyl xanthate gave (S)-2,3-(thiocarbonyldithio)propanol (62). The optical rotations of (61) and (62) were essentially the same as those recorded for the (R)-forms, but opposite in sign.

(R)-3-Mercaptopropane-1,2-diol

(S)-1,2-O-Isopropylideneglycerol (63)[6] on reaction with toluene-p-sulphonyl chloride gave a crude toluene-p-sulphonate which on further reaction with potassium thiolacetate in acetone yielded (R)-1,2-O-isopropylidene-3-acetylthiopropane-1,2-diol (64). The infrared spectrum (liquid film) of the compound showed ν max. 1690 $cm.^{-1}$

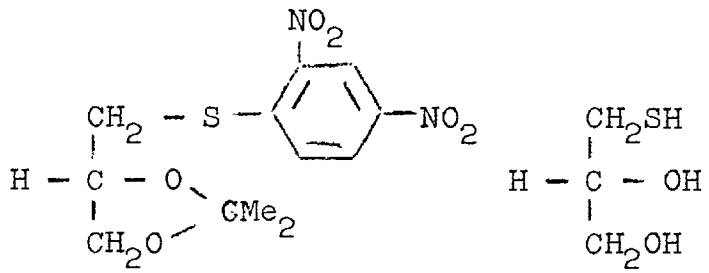


(63)



(64) (65)

(-SAc) and its ultraviolet spectrum had a band at 231 mμ (ε 4300) which is characteristic for the -SAc group. On hydrolysis with sodium methoxide in methanol, the thiolacetate (64) yielded (R)-1,2-O-isopropylidene-3-mercaptopropane-1,2-diol (65) which gave the solid derivative (66) after reaction with 2,4-dinitrochlorobenzene. Acid hydrolysis of (64) yielded laevorotatory (R)-3-mercaptopropane-1,2-diol (67).

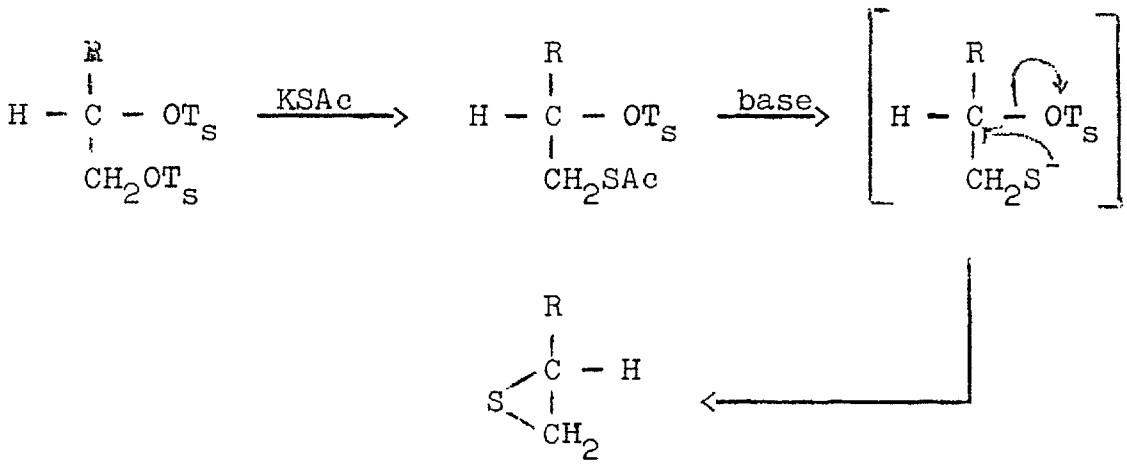


(66) (67)

(S)-2-Mercaptopropanol

Chapman and Owen[61] extensively studied the reaction

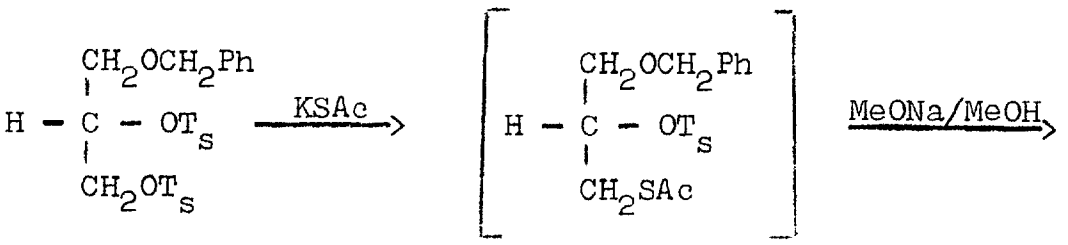
between potassium thiolacetate and a number of toluene-p-sulphonates and found that while a primary toluene-p-sulphonyloxy group is readily replaced by the acetylthio group, a secondary tosyl group either does not react or requires more drastic conditions. This difference in reactivity between a primary and a secondary tosyl group was conveniently used by Creighton and Owen[38] to prepare carbohydrate episulphides from vicinal ditosyl compounds by the following reaction sequence:



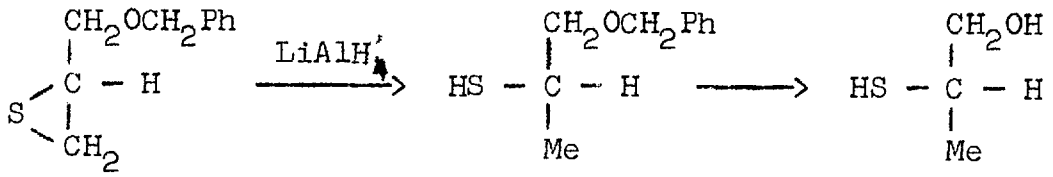
The final stage involves the attack by the thiol anion on the asymmetric carbon bearing the secondary tosyl group, thereby inverting the configuration of the starting ditosyl compound.

A similar procedure has now been employed to prepare (R)-1-O-benzyl-2,3-epithiopropanol (68). Reaction of the

ditosyl compound (56) with 1 mole of potassium thiolacetate gave a product the infrared spectrum (liquid film) of which showed the expected bands at 1695 (-SAc) and



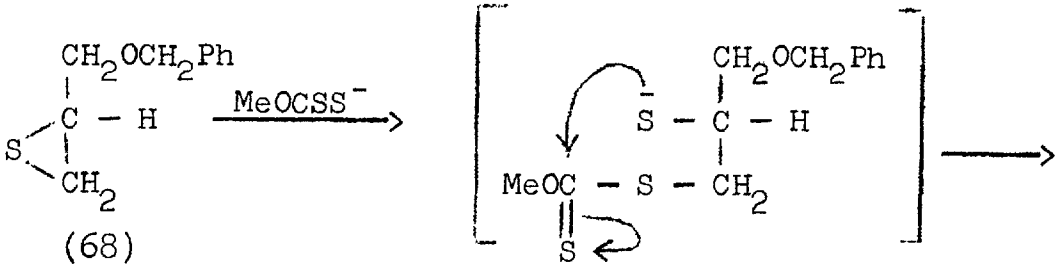
(56)



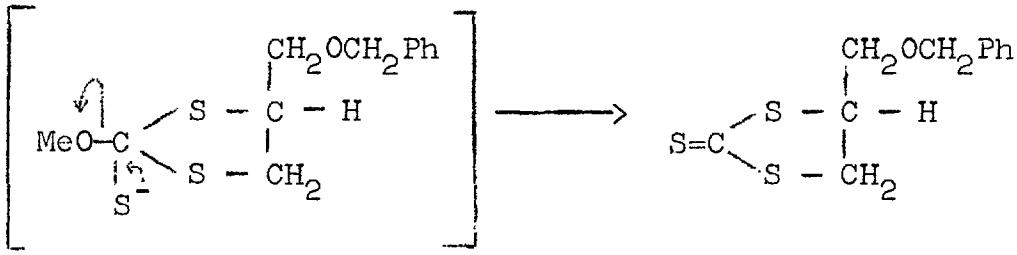
(68) (69) (70)

1375 $cm.^{-1}$ ($-OSO_2-$). The crude product on treatment with sodium methoxide in methanol gave (R)-1-O-benzyl-2,3-epithiopropanol (68).

Although the configuration of the episulphide is obvious from its method of preparation, this was confirmed by preparing the trithiocarbonate (48) from (68):



(68)



(48)

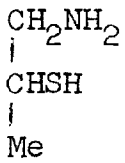
This trithiocarbonate was identical in specific rotation and physical properties to that obtained earlier (p. 44).

The episulphide (68) on reduction with lithium aluminium hydride gave (S)-1-O-benzyl-2-mercaptopropanol (69). Bordwell[62] et al. have shown that terminal episulphides are converted to secondary thiols by this reagent. Other workers[38] used the same reducing agent to prepare optically active secondary thiols in the carbohydrate field:

Removal of the benzyl group in the thiol (69) with sodium and liquid ammonia then gave (S)-2-mercaptopropanol (70).

This stereospecific synthesis of the hydroxythiol is of potential importance for establishing the absolute configurations of the enantimorphs of 1-amino-2-mercaptopropane

(3). If it is possible to replace the amino group in either of the antipodes of (3) by a hydroxy group, then by comparing the optical property of the hydroxy compound produced with that of (70), the configurations of the enantiomorphs of (3) could be established.

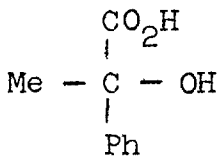


(3)

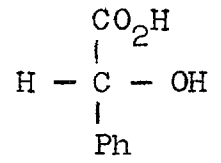
Application of the Rule of Shift to Some of the Compounds Synthesised

An empirical rule known as Freudenberg's "rule of shift", is sometimes useful for stereochemical correlations. The rule states that if two related compounds X and Y having molecular rotations M_1 and M_2 respectively are chemically transformed in the same direction to produce X' and Y' having respective molecular rotations M_1' and M_2', then the molecular rotation differences $(M_1 - M_1')$ and $(M_2 - M_2')$ will have the same sign. The rule was applied by Freudenberg to assign the configuration of

(-)-atrolactic acid (71) by correlating it with D-(-)-mandelic acid (72)[63]. A series of similar derivatives



(71)



(72)

were prepared from these two acids and their molecular rotations were recorded, as given in table I[63]. As is evident from the data in the table, similar transformations of the two acids produced similar changes in the molecular rotations (with two exceptions). Hence it was concluded that the two acids have the same configuration as shown in (71) and (72).

Table I

Molecular Rotation of (-)-Mandelic and (-)-Atrolactic Acids and Some of Their Derivatives at 578 mμ.

(in Angular Degrees)

Compound	Rotation of derivatives of			
	Atrolactic Acid		Mandelic Acid	
		M-M'		M-M'
Free acid	- 86		- 240	
Ethyl ester	- 59	- 27	- 210	- 30
Amide	+ 9	- 95	- 137	- 103
Benzoyl ethyl ester	- 67	- 19	- 404	. 164
Acetyl ethyl ester	- 40	- 46	-280	+ 40
Amide acetone derivative	+ 103	- 189	- 181	- 59
Methyl ether methyl ester	+ 110	- 196	- 197	- 43
Methyl ether dimethyl amide	+ 395	- 481	+ 290	- 530

An illustration of the usefulness of the rule of shift is provided by some of the compounds which were synthesised in the present work. The molecular rotations of these compounds are listed in table II. It is noted that as one moves from left to right along a horizontal column, the sign of molecular rotation difference ($[M]_{compound} - [M]_{derivative}$) is positive for the three series (A) to (C). In moving down along a vertical column, the sign of molecular rotation differences are as follows:

(i) Change from (A) to (B)

(a) positive for the compound column

(b) positive for the derivative column

(ii) Change from (A) to (C)

(a) positive for the compound column

(b) positive for the derivative column.

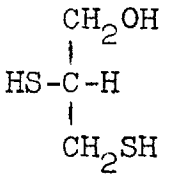
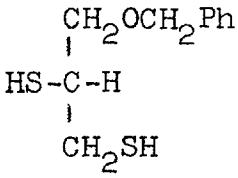
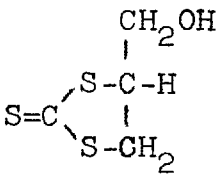
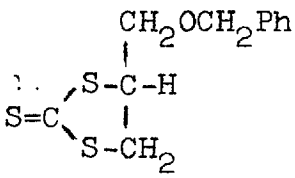
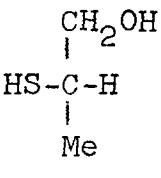
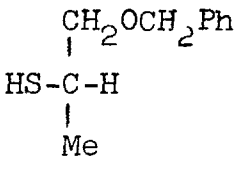
(iii) Change from (B) to (C)

(a) nnegative for the compound column

(b) negative for the derivative column.

Table II

Molecular Rotation of Some of the Compounds Synthesised (in Angular Degrees)

Series	Compound	$[M]_D$	Derivative	$[M']_D$	M-M'
A		+ 3.7		- 16	+ 19.7
B		+ 484		+ 448	+ 36
C		+ 22.6		+ 9	+ 13.6

$$[M]_D = [\alpha]_D \times \frac{\text{M.W}}{100} \text{ in } CHCl_3$$

EXPERIMENTAL

PART I

Numerals in brackets following sub-headings refer to page numbers in the original laboratory note book.

Melting points were determined on a Kofler block and are uncorrected.

Infra-red spectra were run in chloroform (unless otherwise stated) on a Unicam S.P. 200 spectrometer and ultra-violet spectra in ethanol on a Unicam S.P. 800 instrument.

Professors W. Klyne and C. Djerassi kindly recorded the R.D. data.

Authentic samples of DL-2,3-dimercaptopropanol and DL-1,2-O-isopropylideneglycerol were kindly supplied by Professor L. N. Owen.

Racemization During the Attempted Preparation of (R)-2,3-Dimercaptopropanol from D-Mannitol

1,2:3,4:5,6-Tri-O-isopropylidene-D-mannitol.(79)

Condensation of mannitol with acetone in the presence of concentrated sulphuric acid yielded the mannitol-derivative m.p. 69-70°. Lit.[64] m.p. 69-70°.

3,4-O-Isopropylidene-D-mannitol.(79)

Partial hydrolysis of the triisopropylidene-compound with 70% acetic acid gave the monoisopropylidene-derivative m.p. 86-87°. Lit.[64] m.p. 86-87°.

1,2:5,6-Dianhydro-3,4-O-isopropylidene-D-mannitol. (87)

Reaction of the isopropylidene-compound successively with toluene-p-sulphonyl chloride and sodium methoxide gave the dianhydro-compound, b.p. 76-78°/0.02 mm., n_D^{22}1.4540. Lit.[39], b.p. 75°/0.02 mm., n_D^{18}1.4552.

1,2,5,6-Tetradeoxy-3,4-O-isopylidene-1,2:5,6-di(thiocarbonyldithio)-L-iditol. (87)

The dianhydro-compound reacted with potassium methyl xanthate to yield the bistrithiocarbonate m.p. 146°. Lit.[39] m.p. 144-146°.

1,2,5,6-Tetradeoxy-3,4-O-isopropylidene-1,2:5,6-di(carbonyldithio)-L-iditol. (91)

The bistrithiocarbonate (10.5 g.) was stirred with mercuric acetate (65 g.) in acetic acid (250 c.c.) and when the yellow colour of the compound disappeared, the insoluble material was filtered off and washed thoroughly with chloroform. The combined filtrate and washings were concentrated, water (100 c.c.) was added and the mixture was extracted with chloroform (3 x 100 c.c.). The extract was washed with sodium bicarbonate solution and water, and the dried extract was evaporated to a crystalline residue (9.5 g.). After crystallisation from ethanol, the bisdithiocarbonate (5 g., 52%) had m.p. 130-131°, $[\alpha]_D^{25}$ + 157° (c, 4.5 in chloroform). (Found: C, 39.4; H, 4.2; S, 37.9. $C_{11}H_{14}O_4S_4$ requires C. 39.0; H, 4.2; S, 37.9%) $\nu_{max.}$ 1660 and 1720 cm^{-1}.

1,2:5,6-Di(carbonyldithio)-1,2,5,6-tetradeoxy-L-iditol. (95)

A mixture of the isopropylidene-compound (3.5 g.) and 40% aqueous acetic acid (100 c.c.) was heated under reflux for 20 hours. On cooling, white crystals deposited which were recrystallised from ethanol and finally from chloroform. The bisdithiocarbonate (2.5 g., 81%) had m.p. 203°. (Found: C, 32.3; H, 3.15; S, 43.4. $C_8H_{10}O_4S_4$ requires C, 32.2; H, 3.4; S, 43.0%) ν max. (Nujl mull) 1638, 1645 and 3475 $cm.^{-1}$, $[\alpha]_D^{23.5}$ + 175.4° (c, 1 in acetone).

Oxidation of 1,2:5,6-di(carbonyldithio)-1,2,5,6-tetradeoxy--L-iditol with lead tetra-acetate. (141)

The iditol derivative (9.7 g.) was stirred with a solution of lead tetra-acetate (20.0 g.) and water (25 c.c.) in glacial acetic acid (200 c.c.) for 2 hours. Most of the solvent was removed by distillation under reduced pressure at 40°. The residue was extracted with chloroform. The dried extract on evaporation gave crude L-2,3-(carbonyldithio)propionaldehyde (6 g.) which was characterised as the 2,4-dinitrophenylhydrazone (see below). Without further purification the crude aldehyde was reduced by lithium aluminium hydride.

Preparation of 2,4-dinitrophenylhydrazone of the crude aldehyde. (874)

The crude aldehyde (75 mg.) in acetic acid (10 c.c.) was treated with a solution of 2,4-dinitrophenylhydrazine (110 mg.) in acetic acid (100 c.c.). After keeping for 15 minutes, the reaction mixture was diluted with water (100 c.c.) and extracted with dichloromethane (3 x 100 c.c.). The extract was washed with water, dried and evaporated to a yellow solid which was purified by chromatography on bentonite-kieselguhr mixture (4:1 $^{w}/_{w}$) using chloroform as the eluent. The 2,4-dinitrophenylhydrazone (70 mg.) had m.p. 166-167° (decomposition) after crystallisation from methanol, $[\alpha]_D^{22}$ + 54.8° (c, 0.8 in ethyl acetate). (Found: C, 37.0; H, 2.5; N, 16.9. $C_{10}H_8N_4O_5S_2$ requires C, 36.6; H, 2.5; N, 17.1%).

Reduction of crude L-2,3-(carbonyldithio)propionaldehyde with lithium aluminium hydride. (103, 143)

A solution of the crude aldehyde (3.5 g.) in dry ether (100 c.c.) was added slowly to a slurry of lithium aluminium hydride (4 g.) and ether (100 c.c.), and the mixture was refluxed under nitrogen for 2 hours. On cooling to 0°,

the excess of hydride was destroyed by the cautious addition of ice-cold water. The mixture was acidified with 6N-hydrochloric acid (at 0°), saturated with sodium chloride, and the ether layer was separated. The aqueous portion was extracted twice more with ether. The combined extracts were dried and evaporated to a liquid residue which on distillation yielded 2,3-dimercaptopropanol (1.5 g.) b.p. 65-67°/10^{-4} mm. n_D^{23} 1.5660-1.5674, $[\alpha]_D^{26}$ 0° (c, 15 in methanol), RD (c, 5.2 in methanol), 20° $[\emptyset]_{300}$ + 0.35°, $[\emptyset]$ + 0.85°. (Found: thiol-S, 50.5. $C_3H_8OS_2$ requires S, 51.6%) Lit.[285] b.p. 71-75°/1 mm., n_D^{15} 1.5723-1.5730 (for racemic 2,3-dimercaptopropanol). The dithiol was characterised as its derivative with cyclohexanone (see below).

Cyclohexylidene derivative of 2,3-dimercaptopropanol. (105)

A solution of the above dithiol (125 mg.) in benzene (2 c.c.) was treated with cyclohexanone (100 mg.) and a trace of concentrated hydrochloric acid. After keeping overnight, the solution was evaporated to a solid (0.2 g.). The cyclohexylidene derivative had m.p. 62-63° after crystallisation from benzene-petroleum (b.p. 40-60°); undepressed on admixture with the cyclohexylidene derivative of an authentic specimen of racemic 2,3-dimercaptopropanol.

(Found: C, 52.9; H, 7.9; S, 31.5. $C_9H_{16}OS_2$ requires C, 52.9; H, 7.9; S, 31.4%) $[\alpha]_D^{25}0^\circ$ (c, 12 in methanol). Stocken[58] reports m.p. 70° for 2,2-pentamethylene-4-hydroxymethyl-1,3-dithiolan.

DL-2,3-Dimercaptopropanol from Racemic 1,2-O-isopropylideneglycerol

DL-1-O-Benzyl-2,3-O-isopropylideneglycerol. (165)

Reaction of racemic-1,2-O-isopropylideneglycerol with benzyl chloride in the presence of sodium hydroxide gave the benzyl derivative, b.p. 104-106°/0.4 mm., n_D^{22} 1.4930. Lit.[66], b.p. 93-96°/0.1 mm.

DL-1-O-Benzylglycerol. (167)

Hydrolysis of the isopropylidene-derivative with 10% acetic acid solution gave the benzyl-compound, b.p. 117-118°/10^{-4} mm., n_D^{20} 1.5330. Lit.[53] b.p. 140-145/1 mm.

DL-1-O-Benzyl-2,3-epoxypropanol. (226)

A solution of toluene-p-sulphonyl chloride (38.7 g.) and pyridine (26 g.) in chloroform (300 c.c.) was added dropwise to the glycerol derivative (34.5 g.) in chloroform (300 c.c.) at 0°. After keeping at room temperature for 24 hours, the reaction mixture was washed with N-hydrochloric

acid, sodium bicarbonate and water. The dried solution was then treated at -5° with sodium methoxide solution [prepared by dissolving sodium (4.8 g.) in methanol (160 c.c.)] also at -5°. The mixture was stirred for 2 hours and the temperature was allowed to rise but not above 7°. The excess of sodium was neutralised by adding solid carbon dioxide and water was added to dissolve potassium toluene-p-sulphonate. The chloroform layer was separated and the aqueous layer was extracted once more with chloroform. The combined extracts were dried, and evaporated to a residue, which on distillation gave the crude product (20 g.) b.p. 60-74°/10^{-3} mm., n_D^{19} 1.5175-1.5190. Redistillation furnished the epoxide, b.p. 62-63° /10^{-3} mm., $n_D^{19.5}$ 1.5175. Baizer et al.[54] report b.p. 76-81°/0.3-0.7 mm., 1.5148-1.5150.

DL-1-O-Benzyl-2,3-(thiocarbonyldithio)propanol.

(a) From DL-1-O-Benzyl-2,3-epoxypropanol. (238)

The epoxide (2.4 g.) was heated under reflux with a solution of potassium hydroxide (5.0 g.) and carbon disulphide (8.0 g.) in methanol for 2 hours. On cooling, water (100 c.c.) was added and the mixture was extracted

with chloroform (3 x 30 c.c.). The extract was washed with water, dried and evaporated to an oil which on chromatography on alumina using benzene as the eluent furnished the trithiocarbonate (2.3 g., 61.5%) m.p. 42-43° after crystallisation from ether-petroleum (b.p. 40-60°) (Found: C, 51.3; H, 4.7; S, 37.7. $C_{11}H_{12}OS_3$ requires C, 51.5; H, 4.7; S, 37.5%).

(b) By mixing equal amounts of D and L-isomers of the trithiocarbonate. (770)

Equal portions of dextrorotatory and laevorotatory 1-O-benzyl-2,3-(thiocarbonyldithio)propanols (syntheses to be described later) were mixed together and crystallised from ether-petroleum (b.p. 40-60°). The racemic trithiocarbonate had m.p. 42-43°; undepressed on admixture with the sample of trithiocarbonate obtained by method (a).

Reduction of the racemic trithiocarbonate with lithium aluminium hydride. (256)

The trithiocarbonate (11 g.) in ether (100 c.c.) was slowly added to a mixture of lithium aluminium hydride (4 g.) and ether (100 c.c.). After stirring for 2 hours, excess of hydride was destroyed by adding ethyl acetate to the

cooled mixture, which was then acidified with 6N-hydrochloric acid (at 0°), and the ether layer was separated. The aqueous portion was extracted with more ether and the combined extracts were washed with sodium bicarbonate solution and dried. Evaporation and distillation gave crude DL-1-O-benzyl-2,3-dimercaptopropanol (8.3 g.), b.p. 99-120° /10^{-4} mm., n_D^{21} 1.5740-1.5760 (Found: S, 28.6. $C_{10}H_{14}OS_2$ requires S, 29.9%). The crude dithiol was treated with sodium and liquid ammonia without purification (see below).

DL-2,3-Dimercaptopropanol. (274)

Small pieces of sodium were added to a solution of the crude dithiol (5 g.) in liquid ammonia (50 c.c.) till a persistent blue colour was obtained. The excess of sodium was removed by adding ammonium chloride and most of the ammonia was evaporated. The residue was extracted with chloroform and the extract on evaporation gave a liquid which on distillation yielded 2,3-dimercaptopropanol (1.6 g.), b.p. 68-69°/3 x 10^{-4} mm., n_D^{24} 1.5712 (Found: thiol-S, 50.6. $C_3H_8OS_2$ requires S, 51.6%) ν max. (liquid film) 2550 and 3450 $cm.^{-1}$ (and the entire infrared spectrum was identical with that of an authentic sample). The cyclohexylidene-derivative of the thiol had m.p. 63°;

undepressed on admixture with the cyclohexylidene derivative of the authentic thiol.

DL-2,3-(Thiocarbonyldithio)propanol. (404)

The dithiol (620 mg.) was mixed with a solution of potassium hydroxide (1.40 g.) and carbon disulphide (2.5 c.c.) in methanol (20 c.c.); the mixture was then set aside. After 7 days, the reaction mixture was diluted with water and extracted with chloroform. The extract was washed with water, dried and evaporated to an oil which was purified by distillation and chromatography on silica gel using chloroform as the eluent. The trithiocarbonate (350 mg., 43.5%) had b.p. 150-160° (bath)/10^{-4} mm.. (Found: C, 28.9; H, 3.7; S, 57.5. $C_4H_6OS_3$ requires C, 28.9; H, 3.6; S, 57.85%) λ max. 317 mμ (ε 14700).

(R)-2,3-Dimercaptopropanol

1,2:5,6-Di-O-isopropylidene-D-mannitol. (282, 690)

Condensation of D-mannitol with acetone in the presence of zinc chloride gave the diisopropylidene-derivative m.p. 116-119°. Baer[59] reports m.p. 117-119°.

(S)-1,2-O-Isopropylideneglycerol. (306, 694, 700)

Oxidation of the mannitol derivative with lead tetra-acetate gave (S)-2,3-O-isopropylideneglyceraldehyde[6] which was reduced to (S)-1,2-O-isopropylideneglycerol by the following methods.

(a) Reduction by hydrogen and nickel.

On reduction by hydrogen (100 atmosphere) in the presence of Raney nickel catalyst, the aldehyde gave the glycerol derivative, b.p. 85°/13-15 mm., n_D^{18} 1.4350, $[\alpha]_D^{25}$ + 11.3° (c, 9.9 in methanol). Lit.[6] b.p. 80-80.5/ 11-12 mm., n_D^{20} 1.4347, $[\alpha]_D^{20}$ + 10.7 (c, 13.2 in methanol).

(b) Reduction by lithium aluminium hydride.

A solution of the crude aldehyde (2.4 g.) in dry ether (50 c.c.) was heated under reflux for half an hour with a slurry of lithium aluminium hydride (1 g.) and dry ether (30 c.c.). The excess of hydride was destroyed by adding ethyl acetate, the mixture was cooled to 0° and made slightly acidic by careful addition of N-hydrochloric acid (at 0°). The ether layer was separated and the aqueous portion was extracted twice more with ethyl acetate. The combined extracts were dried and evaporated to a liquid which on distillation gave the glycerol derivative b.p. 56°/1 mm., $n_D^{20.5}$ 1.4345, $[\alpha]_D^{23.5}$ + 10.7° (c, 5.1 in methanol).

(S)-1-O-Benzyl-2,3-isopropylidene glycerol. (316, 702).

Reaction of the isopropylidene derivative with sodium hydroxide and benzyl chloride gave the benzyl derivative, b.p. 122-126°/ 1 mm., n_D^{19} 1.4950, $[\alpha]_D^{22}$ + 21.3° (c, 4.5 in chloroform). Lit.[7] b.p., 95-97°/0.3 mm., n_D^{16} 1.4970, $[\alpha]_D$ + 16.8° (neat).

(R)-1-O-Benzylglycerol (705)

Hydrolysis of (S)-1-O-benzyl-2,3-isopropylideneglycerol with 10% aqueous acetic acid solution yielded the benzylglycerol, b.p. 142-146°/0.6 mm., $n_D^{18.5}$ 1.5325, α_D^{20} + 6.5 (1 dm., neat). Lit.[7] b.p. 138-139°/0.3 mm., n_D^{16} 1.534, $[\alpha]_D$ + 5.3° (neat).

(S)-1-O-Benzyl-3-O-tosylglycerol (710)

Reaction of the diol at 0° with one mole of toluene-p-sulphonyl chloride and chromatography of the crude reaction product on silica gel using ether-petroleum (b.p. 60-80°) as the eluent gave the monotosyl compound, m.p. 53-54°, $[\alpha]_D^{21}$ + 8.5° (c, 5.8 in methanol). Lit.[9] m.p. 48°, $[\alpha]_D^{23}$ + 4.6° (c, 5 in methanol).

(S)-1-O-Benzyl-2,3-epoxypropanol (716)

The monotosyl-derivative (5 g.) in chloroform (25 c.c.) was treated at -5° with a solution of sodium (0.35 g.) in methanol (25 c.c.) also at -5°, and after a further 15 minutes at 0° the excess of sodium methoxide was neutralised with solid carbon dioxide. Water (20 c.c.) was added to

dissolve potassium toluene-p-sulphonate and the chloroform layer was separated. The aqueous layer was extracted once more with chloroform and the combined extracts were dried and evaporated to a liquid which on distillation yielded the epoxy-compound (2.01 g., 82%) b.p. $68^{\circ}/10^{-4}$ mm., n_D^{15} 1.5187, d^{20} 1.06 $[\alpha]_D^{20}$ - 15.3° (neat) (Found: C, 73.2; H, 7.2. $C_{10}H_{12}O$ requires C, 73.1; H, 7.4%).

(R)-1-O-Benzyl-2,3-(thiocarbonyldithio)propanol

(a) From (S)-1-O-Benzyl-2,3-epoxypropanol. (726)

The epoxide (401 mg.) was mixed with a solution of potassium hydroxide (800 mg.) and carbon disulphide (1.6 c.c.) in methanol (5 c.c.) and kept at room temperature for 2 days. The solution was then heated under reflux for one hour, cooled and diluted with water (10 c.c.). The mixture was extracted with chloroform (2 x 15 c.c.) and the extract was washed with water, dried and evaporated to a solid. Crystallisation from ether-petroleum (b.b. 40-60°) yielded the trithiocarbonate (306 mg., 49%) m.p. 64°, $[\alpha]_D^{23}$ + 174.5° (c, 2 in chloroform), ORD (c, 0.066 in methanol), $[\phi]_{480}$ + 4604° (peak), $[\phi]_{410}$ - 6540° (trough), $[\phi]_{330}$ - 20167° (trough), $[\phi]_{294}$ + 15515° (peak), $[\phi]_{270,268}$ 7757° (shoulder), $[\phi]_{240}$ + 1551°, $[\phi]_{218}$ + 18616°

(peak) (Found: C, 51.8; H, 4.6; S, 37.35. $C_{11}H_{12}OS_3$ requires C, 51.5; H, 4.7; S, 37.5%).

(b) From (R)-1-O-Benzyl-2,3-epithiopropanol. (568)

The episulphide (40 mg.) (synthesis to be described later) was heated under reflux for 1.75 hours with a solution of potassium hydroxide (100 mg.) and carbon disulphide (200 mg.) in methanol (5 c.c.). On working up as described above, the reaction mixture gave the trithiocarbonate (52 mg., 91%) m.p. 64°; undepressed on admixture with the sample obtained by method (a), $[\alpha]_D^{23}$ + 172.5° (c, 3.2 in chloroform).

(R)-1-O-Benzyl-2,3-dimercaptopropanol. (382)

A solution of the trithiocarbonate (7.0 g.) in ether (150 c.c.) was added to a stirred slurry of lithium aluminium hydride (2.6 g.) and ether (50 c.c.), under nitrogen. When the yellow colour of the trithiocarbonate disappeared, the excess of the hydride was destroyed by the addition of ethyl acetate (at 0°) and the reaction mixture was acidified with 6N-hydrochloric acid (at 0°). The ether layer was separated and the aqueous portion, saturated with sodium chloride, was extracted twice more with

ether. The combined extracts were washed with water and sodium bicarbonate solution and dried. On evaporation, a liquid residue was obtained which on distillation gave the dithiol (5 g., 85.5%) b.p. 93-95°/5 x 10^{-4} mm., n_D^{19} 1.5732, $[\alpha]_D^{24.5}$ - 7.6° (c, 14.5 in chloroform) (Found: C, 56.2; H, 6.45; S, 30.1; thiol-S, 29.3. $C_{10}H_{14}OS_2$ requires C, 56.0; H, 6.6; S, 29.9%).

(R)-2,3-Dimercaptopropanol. (388)

To a solution of the benzyl derivative (4 g.) in liquid ammonia (50 c.c.), small pieces of sodium were added till a blue colour persistent for 20 minutes was obtained. Ammonium chloride was added to destroy the excess of sodium and most of ammonia was removed with a current of nitrogen. The residue was extracted with chloroform and the extract was dried and evaporated to a liquid. The hydroxy-dithiol (1.7 g., 77%) had b.p. 65°/10^{-4} mm., n_D^{18} 1.5740, $[\alpha]_D^{25}$ + 3° (c, 9 in chloroform), $[\alpha]_D^{22}$ - 9.6° (c, 7 in methanol) (Found: C, 29.4; H, 6.4; S, 52.0; thiol-S, 51.4. $C_3H_8OS_2$ requires C, 29.0; H, 6.5; S, 51.6%).

(R)-2,3-(Thiocarbonyldithio)propanol. (436)

The dithiol (500 mg.) was mixed with a solution of potassium hydroxide (1 g.) and carbon disulphide (2.2 c.c.) in methanol (16 c.c.) and left at room temperature for 7 days. Working up gave a product which was purified by distillation and chromatography on silica gel using chloroform as the eluent. The trithiocarbonate (350 mg., 56%), b.p. 150-160° (bath)/10^{-4} mm., $[\alpha]_D^{25.5}$ + 290.8° (c, 2.9 in chloroform), ORD (c, 0.0375 in methanol), $[\phi]_{589}$ + 394°, $[\phi]_{477}$ + 4453° (peak), $[\phi]_{412}$ - 6405° (trough), $[\phi]_{384}$ - 5912°, $[\phi]_{328}$ - 18718° (trough), $[\phi]_{295}$ + 18718° (peak), $[\phi]_{285}$ + 15763° (shoulder), $[\phi]_{272}$ + 14778° (shoulder), $[\phi]_{270}$ + 13723° (shoulder), $[\phi]_{245}$ + 7385°, $[\phi]_{222}$ + 19703° (peak) (Found: C, 29.2; H, 3.2; S, 57.65. $C_4H_6OS_3$ requires C, 28.9; H, 3.6; S, 57.85%) $\nu_{max.}$ 1085 and 3425 cm^{-1}.

Cyclohexylidene derivative of (R)-2,3-dimercaptopropanol. (540)

The dithiol (50 mg.) was treated with cyclohexanone and a trace of concentrated hydrochloric acid in benzene solution as described for the racemic compound (p. 67).

Working up gave the crude reaction product (60 mg.). On crystallisation from benzene-petroleum (b.p. 40-60°), the cyclohexylidene derivative had m.p. 50-51° (Found: C, 52.5; H, 7.9. $C_9H_{16}OS_2$ requires C, 52.9; H, 7.9%).

(S)-2,3-Dimercaptopropanol

(S)-1-O-Benzyl-2,3-di-O-tosylglycerol (724)

(R)-1-O-Benzylglycerol (48.2) in pyridine was treated at 0° with a solution of toluene-p-sulphonyl chloride (101 g.) in pyridine (175 c.c.). After keeping at room temperature for 3 days, the reaction mixture was diluted with chloroform (500 c.c.) and washed with N-sulphuric acid, water, sodium bicarbonate solution and again with water. The dried extract was evaporated to a residue which after crystallisation from methanol yielded the ditosyl-compound (116 g., 89%) m.p. 60-61°, $[\alpha]_D^{23}$ - 2.7° (c, 15 in pyridine) (Found: C, 58.8; H, 5.3; S, 13.4. $C_{24}H_{26}O_7S_2$ requires C, 58.8; H, 5.35; S, 13.1%).

(S)-3-Benzoyl-1-O-benzyl-2-O-tosylglycerol (780)

A mixture of the dityosyl compound (20 g.), sodium benzoate (6 g.) and dimethyl formamide (600 c.c.) was heated with stirring in an oil bath at 92-95° for 5 hours. The solvent was removed by distillation under reduced pressure and the residue was extracted with chloroform

(100 c.c.). The extract was washed with water, dried and evaporated to a solid. Crystallisation from ether gave the monobenzoate (9.7 g., 54%), m.p. 106°, $[\alpha]_D^{22}$ + 26.4° (c, 7.8 in chloroform) (Found: C, 65.7; H, 5.2; S, 7.4. $C_{24}H_{24}O_6S$ requires C, 65.5; H, 5.5; S, 7.3%) $\nu_{max.}$ in chloroform 1715 cm^{-1}.

(R)-1-O-Benzyl-2,3-epoxypropanol. (782)

A solution of the benzoate (19.5 g.) in chloroform (125 c.c.) was cooled to -5° and treated with sodium (1.1 g.) in methanol (50 c.c.), also cooled to -5°. The resulting mixture was stirred for 1 hour at 0-2° and solid carbon dioxide was added to neutralise the excess of sodium. After adding water (60 c.c.) to dissolve potassium toluene-p-sulphonate, the chloroform layer was separated. The aqueous layer was extracted twice more with chloroform and the combined extracts were dried. On evaporation, a liquid was obtained which on distillation gave the epoxy-compound (5.0 g., 69%) b.p. 63°/10^{-4} mm., n_D^{14} 1.5190, d^{14} 1.07, $[\alpha]_D^{21}$ + 15° (neat) (Found: C, 73.2; H, 7.3. $C_{10}H_{12}O_2$ requires C, 73.1; H, 7.4%).

(S)-1-O-Benzyl-2,3-(thiocarbonyldithio)propanol. (786)

The epoxy-compound (4.6 g.) was refluxed with a solution of potassium hydroxide (14 g.) and carbon disulphide (23 c.c.) in methanol (60 c.c.) for 3 hours. On cooling, the reaction mixture was diluted with water (60 c.c.) and extracted with chloroform (3 x 60 c.c.). The extract was washed with water, dried and evaporated to a solid. The trithiocarbonate (4.2 g., 58.5%) had m.p. 64° after crystallisation from ether-petroleum (b.p. 40-60°), $[\alpha]_D^{24}$ - 175.7° (c, 2.4 in chloroform), $\lambda_{max.}$ 317 mμ (ε 15500) (Found: C, 51.6; H, 4.6; S, 37.8. $C_{11}H_{12}OS_3$ requires C, 51.5; H, 4.7; S, 37.5%).

(S)-1-O-Benzyl-2,3-dimercaptopropanol. (820)

A solution of the trithiocarbonate (4 g.) in dry ether (100 c.c.) was added slowly to a stirred slurry of lithium aluminium hydride (1.5 g.) and ether (50 c.c.). When all the yellow colour of the trithiocarbonate disappeared, the excess of the hydride was destroyed by adding ethyl acetate to the cooled mixture. The ether layer was separated after acidification with 6N-hydrochloric acid (at 0°) and the aqueous portion was saturated with sodium

chloride and extracted twice more with ether. The combined extracts were washed with water, dried, and evaporated to a liquid. Distillation yielded the dithiol (2.7 g., 81%), b.p. 93-96°/10^{-4} mm., n_D^{26} 1.5725; $[\alpha]_D^{26}$ + 7.2° (c, 9.7 in chloroform) (Found: C, 55.8; H, 6.6; thiol-S, 29.2. $C_{10}H_{14}OS_2$ requires C, 56.0; H, 6.6; S, 29.9%).

(S)-2,3-Dimercaptopropanol (834)

To a stirred solution of the above benzyl ether (2.0 g.) in liquid ammonia (40 c.c.), small pieces of sodium were added till a persistent blue colour was obtained. The excess of sodium was destroyed by adding ammonium chloride, ammonia was removed in a current of nitrogen and the residue was extracted with 2N-sodium hydroxide solution (20 c.c.). The extract was washed with chloroform, acidified at 0° with concentrated hydrochloric acid (at 0°) and reextracted with chloroform. The dried extract was evaporated to a liquid which on distillation gave the dithiol (0.76 g., 66%), b.p. 65°/10^{-4} mm., n_D^{23} 1.57 15, $[\alpha]_D^{25}$ + 9.55° (c, 6.2 in methanol) (Found: C, 29.0; H, 6.2; S, 51.4. $C_3H_8OS_2$ requires C, 29.0; H, 6.5; S, 51.6%).

(S)-2,3-(Thiocarbonyldithio)propanol. (844)

The dithiol (300 mg.) was treated with potassium methyl xanthate [prepared by dissolving potassium hydroxide (600 mg.) and carbon disulphide (1.2 c.c.) in methanol (5 c.c.)] and the mixture was kept at room temperature for 7 days. Working up the reaction in the usual way gave a crude product which on chromatography on silica gel using chloroform as the eluent gave the trithio carbonate (210 mg., 52%), b.p. 150-160° (bath)/10^{-4} mm., $[\alpha]_D^{24.5}$ - 298.7° (c, 1.35 in chloroform) (Found: S, 58.1. $C_4H_6OS_3$ requires S, 57.85%) $\nu_{max.}$ 1085 and 3425 cm^{-1}.

(R)-3-Mercaptopropane-1,2-diol

(R)-1,2-O-Isopropylidene-3-acetylthiopropane-1,2-diol. (515, 526)

A solution of (S)-1,2-O-isopropylideneglycerol (7.2 g.) in pyridine (20 c.c.) was cooled to -5° and treated with toluene-p-sulphonyl chloride (11.5 g.) in pyridine (20 c.c.). The reaction mixture was kept at -5° for 3 hours and at room temperature for 15 hours. After treating with ice-water (300 g.), the mixture was extracted with chloroform (2 x 100 c.c.), and the extract was washed with water and dried. On evaporation a syrup (15.0 g.) was obtained which was dissolved in acetone (300 c.c.) and refluxed with stirring for 19 hours with potassium thiolacetate (7.5 g.). The insoluble material was filtered off, the filtrate was concentrated, treated with water (50 c.c.) and extracted with ether (4 x 50 c.c.). The extract was washed with water, dried and evaporated to a liquid. The thiolacetate (8.64 g., 83%) had b.p. 118°/20-22 mm., $n_D^{17.5}$ 1.4750, $[\alpha]_D^{19}$ - 7.4° (c, 14 in chloroform)(Found: C, 50.6; H, 7.9; S, 16.6. $C_8H_{14}O_3S$ requires C, 50.5; H, 7.4; S, 16.85%) $\nu_{max.}$ (liquid film) 1690 cm^{-1} (-SAc),

λ max. 231 mμ (ε 4300). Fitt and Owen[66] report b.p. 114°/15 mm., n_D^{22} 1.4740 for the DL-isomer.

(R)-1,2-O-Isopropylidene-3-mercaptopropane-1,2-diol (536)

A solution of the thiolacetate (1.3 g.) and sodium (15 mg.) in methanol (25 c.c.) was kept at room temperature for 6 days under nitrogen. The excess of sodium was neutralised by adding solid carbon dioxide, methanol was removed and the residue was extracted with ether. The extract on evaporation gave a liquid residue (0.6 g.) which on distillation furnished the thiol (0.36 g., 35.5%), b.p. 82°/26-28 mm., $n_D^{20.5}$ 1.4632, $[\alpha]_D^{23}$ + 31.4° (c, 5.5 in chloroform) (Found: C, 48.4; H, 8.7; thiol-S, 21.55. $C_6H_{12}O_2S$ requires C, 48.6; H, 8.2; S, 21.7%). Sjöberg[67] reports b.p. 46-47°/3 mm., n_D^{20} 1.4651 for the DL-isomer.

(R)-1,2-O-Isopropylidene-3-(2,4-dinitrophenylthio)propane-1,2-diol. (546)

The thiol (66 mg.) was mixed with ethanol (3 c.c.) and 5% sodium hydroxide (1 c.c.). The solution was then refluxed with 2,4-dinitrochlorobenzene (90 mg.) in ethanol (2 c.c.) for 10 minutes. The precipitate (120 mg.) was

collected by filtration, washed with water and crystallised from ethanol. The dinitrophenyl-thioether had m.p. 115-116° (Found: C, 45.4; H, 4.6; N, 9.15. $C_{12}H_{14}O_6N_2S$ requires C, 45.85; H, 4.5; N, 8.9%).

(R)-3-Mercaptopropane-1,2-diol (555, 585)

(R)-1,2-O-Isopropylidene-3-acetylthiopropane-1,2-diol (4.7 g.) was refluxed with concentrated hydrochloric acid (6.5 c.c.) and methanol (30 c.c.) for 24 hours under nitrogen. The excess of acid was neutralised by adding powdered sodium carbonate, insoluble particles were filtered off and the filtrate was concentrated to a residue which was extracted with ethyl acetate. The extract was evaporated to a liquid which on distillation gave the crude dihydroxy-thiol (1.9 g.), b.p. 90-105°/0.9 mm., n_D^{21} 1.4950-1.5220 (Found: S, 28.3. $C_3H_8O_2S$ requires S, 29.65%). A portion (0.9 g.) of the crude product was heated under reflux with concentrated hydrochloric acid (2 c.c.) and methanol (25 c.c.) for a further 15 hours. Working up as described above and distillation furnished (R)-3-mercaptopropane-1,2-diol (0.7 g.), b.p. 102°/0.9 mm., $n_D^{21.5}$ 1.5230, $[\alpha]_D^{25}$ - 8° (c, 11.2 in ethanol) (Found: C, 33.6; H, 7.8; S, 29.4; thiol-S, 29.55. $C_3H_8O_2S$

requires C, 33.3; H, 7.5; S, 29.65%). Sjöberg[67] reports b.p. 97°/0.9 mm; n_D^{20} 1.5268 for the DL-isomer.

(S)-2-Mercaptopropanol

(R)-1-O-Benzyl-2,3-epithiopropanol. (728, 732)

A mixture of (S)-1-O-benzyl-2,3-di-O-tosylglycerol (20 g.) acetone (300 c.c.) and potassium thiolacetate (5.2 g.) was heated under reflux with stirring for 22.5 hours. On cooling, the insoluble material was filtered off, the filtrate was concentrated and the residue was extracted with ether. The extract was washed with water, dried and evaporated to a residue (15.5 g.) $\nu_{max.}$ (liquid film) 1695 (- SAc) and 1375 $cm.^{-1}$ ($-OSO_2-$). The residue was dissolved in chloroform (150 c.c.) and treated at -5° with a solution of sodium (0.97 g.) in methanol (60 c.c.). After 15 minutes at 0°, the excess of sodium methoxide was neutralised with solid carbon dioxide and water (40 c.c.) was added to the mixture. The chloroform layer was separated and the aqueous portion was extracted with more chloroform. The combined extracts were dried and evaporated to a liquid which on distillation furnished the episulphide (5.5.g., 75%), b.p. $79-82^{\circ}/10^{-4}$ mm., n_D^{15} 1.5610, $[\alpha]_D^{23}$ + 11.8° (c, 8.5 in chloroform) (Found: C, 66.7; H, 6.2; S, 18.2. $C_{10}H_{12}OS$ requires C, 66.6; 6.7; S, 17.8%). On treatment with potassium methylxanthate the episulphide gave (R)-1-O-benzyl-2,3-(thiocarbonyldithio)-propanol m.p. 64°, as described on p. 78 .

(S)-1-O-Benzyl-2-mercaptopropanol. (744)

The episulphide (5.5 g.) in ether (100 c.c.) was refluxed under nitrogen for 5 hours with a mixture of lithium aluminium hydride (3 g.) and ether (50 c.c.). The excess of the hydride was destroyed by adding ethyl acetate and the mixture was acidified at 0° with 6N-hydrochloric acid. After saturating with sodium chloride, the ether layer was separated and the aqueous portion was extracted once more with ether. The combined extracts were washed with water, sodium bicarbonate solution and again with water. Evaporation of ether from the dried extract gave a liquid residue which on distillation yielded the thiol (4.3 g., 77%), b.p. 57°/10^{-4} mm., n_D^{15} 1.5330, $[\alpha]_D^{24}$ + 5° (c, 9.6 in chloroform) (Found: C, 65.9; H, 7.8; S, 17.9; thio-S, 17.9. $C_{10}H_{14}OS$ requires C, 65.9; H, 7.7; S, 17.6%).

(S)-2-Mercaptopropanol. (776)

Freshly cut pieces of sodium were added to a solution of the benzyl-thiol (1.8 g.) in liquid ammonia (50 c.c.) till a blue colour persistent for 20 minutes was obtained. The excess of sodium was destroyed by adding ammonium chloride and most of the ammonia was removed with a current

of nitrogen. The residue was taken up in chloroform (25 c.c.) and extracted with 2N-sodium hydroxide solution (2 x 10 c.c.). The extract was washed with chloroform and acidified at 0° with concentrated hydrochloric acid and finally reextracted with chloroform. The dried extract on evaporation gave a liquid residue (0.7 g.) which on distillation yielded the thiol (0.5 g., 55%) b.p. $50\text{-}51^{\circ}/20\text{-}25$ mm., n_D^{12} 1.4870, $[\alpha]_D^{22}$ + 24.5° (c, 13.6 in chloroform) (Found: C, 38.95; H, 8.8; S, 35.3; thiol-S, 35.2. C_3H_8OS requires C, 39.1; H, 8.7; S, 34.9%).

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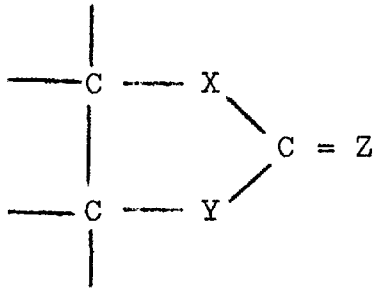
P A R T II

INTRODUCTORY SURVEY

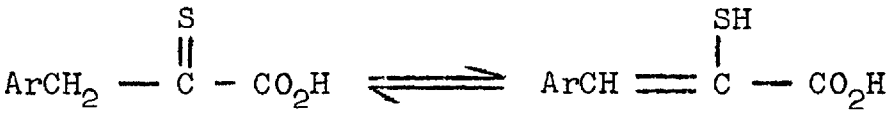
Although much is known about the oxidation of simple organic sulphur compounds such as thiols and sulphides only little is known, to date, about the oxidation of complex sulphur-containing functional groups such as trithiocarbonates. The work to be described in this part of the thesis is concerned with the oxidation of cyclic thiocarbonates of the type (A) (where X, Y and Z represent either sulphur or oxygen).



(A)

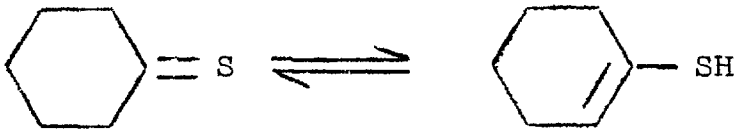
In such a structure, there are two possible environments for sulphur. When it is present in the ring, the sulphur atom is bound to two carbon atoms by two σ-bonds (like the sulphur atom in organic sulphides). On the other hand, in the thiocarbonyl group it is joined to only one carbon atom by one σ- and one π-bonds.

Quite often, the thiocarbonyl group is in equilibrium with the thiol form. For example, arylthiopyruvic acids (1) exist almost exclusively as enethiols[1].



(1)

Sen[2] has also reported a similar equilibrium in thiocyclohexanone (2)



(2)

It is therefore relevant to review briefly the oxidation of thiols, thioethers and thiocarbonyl compounds.

Oxidation of Thiols.

Thiols are very susceptible to oxidation and a variety of oxidants are available for this purpose[3]. The nature of the oxidation product will depend, to a great extent, on the type of oxidant used. Mild oxidation with such

reagents as oxygen, halogens, and sodium hypochlorite generally produces a disulphide, and thiols can be quantitatively titrated with iodine[4].

Disulphides are produced in good yields when sodium[5] or lead[6] salts of thiols are oxidised with iodine:

$$2RSNa + I_2 \longrightarrow RSSR + 2NaI$$
$$(RS)_2Pb + I_2 \longrightarrow RSSR + PbI_2.$$

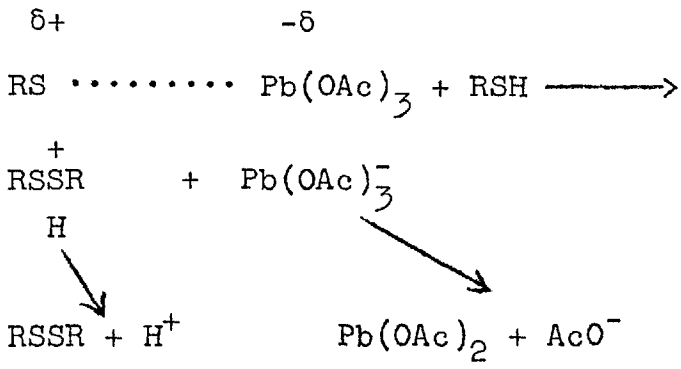
More recently, Field and Lawson[7] reported high yields of disulphides from both alkyl and aryl thiols using lead tetra-acetate as the oxidant. It was found that two moles of a thiol required one mole of lead tetra-acetate, thus conforming to the equation:

$$2RSH + Pb(OAc)_4 \longrightarrow RSSR + Pb(OAc)_2 + 2AcOH.$$

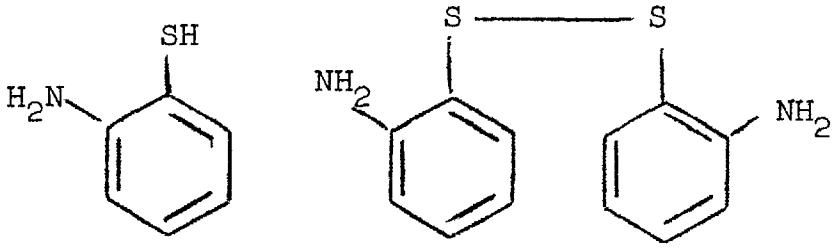
They envisaged an ionic mechanism for the transformation:

$$RSH + \overset{\delta+\ \delta-}{Pb(OAc)_4} \longrightarrow \overset{+}{RSPb(OAc)_3}\ \overset{H}{} + \overset{-}{AcO}$$

$$\overset{+}{RSPb(OAc)_3}\ \overset{H}{} \searrow\ RSPb(OAc)_3 + H^+$$



A novel and mild method of oxidation of thiols is the use of dimethyl sulphoxide[8,9]. One possible advantage of this reagent is that it is not expected to oxidise other sensitive sites such as an aldehyde or an amino group. Thus by using this reagent, the disulphide (8) was prepared in 80% yield from (7), dimethyl sulphide being obtained as the by-product.



(7) (8)

Wallace[9] has found that the rate of oxidation with dimethyl sulphoxide is greatly influenced by the acidity of the thiols. This is illustrated by the results summarised in the following table[9]:

Table I

Effects of thiol acidity on reaction rate with dimethyl sulphoxide at 100° ± 1

Thiol	pk_a	Time for 50% conversion
Benzene	6-7	1 min.
Toluene-α-	10.5	290 min.
Dodecane-1	14	100 hr.

The rate dependence on thiol acidity suggests the following mechanism for the oxidation of thiols with sulphoxides[9].

$$R_2SO + HSR_1 \rightleftharpoons [R_2SOH]^+ \bar{S}R_1$$

$$[R_2SOH]^+ \bar{S}R_1 + HSR_1 \underset{+H_2O}{\overset{-H_2O}{\rightleftharpoons}}$$

$$[R_2SSR_1]^+ \bar{S}R_1 \rightleftharpoons R_2S + R_1SSR_1$$

Tetramethylene sulphoxide has also been found to be effective in oxidising thiols to disulphides[9].

The use of metal oxides such as manganese dioxide, ferric oxide, cobaltic oxide and cupric oxide, for oxidation of thiols in hydrocarbon solutions, to disulphide has been

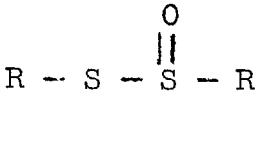
reported[9a]. It is found that thiol acidity and structure do not influence the rate, and the mechanism of oxidation by manganese dioxide is envisaged as[9a]:

$$RSH + Mn^{IV}O_2 \longrightarrow RS\cdot + HOMn^{III}O$$

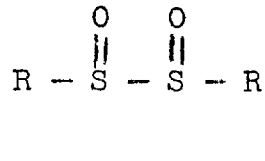
$$RSH + HOMn^{III}O \longrightarrow RS\cdot + Mn^{II}O + H_2O$$

$$2RS\cdot \longrightarrow RSSR.$$

With vigorous oxidising agents such as nitric acid, potassium permanganate or hydrogen peroxide, the disulphide formed initially may undergo further oxidation producing a variety of intermediates of the type (9)-(13), the final product of oxidation being a sulphonic acid (14).



(9)



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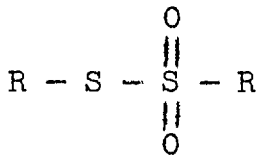

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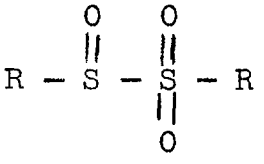

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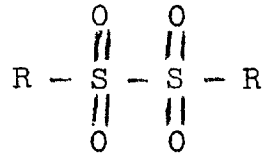

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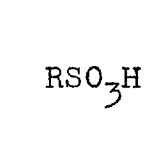


(14)

Nitric acid has been used to prepare butane-1[10] and hexane-2[11] sulphonic acids (15) and (16) respectively.

$CH_3CH_2CH_2CH_2SO_3H$ (15)

$CH_3CH_2CH_2CH_2CH(SO_3H)CH_3$ (16)

Noller and Gordon[12] have shown that better yields of sulphonic acids are obtained by using a lead salt instead of a free thiol.

Oxidation of Organic Sulphides (Thioethers).

As in the case with thiols, a large number of oxidising agents including nitrogen tetroxide[13], nitric acid[14], potassium permanganate[15], hypohalites[16] and selenium dioxide[17] have been used. A few reviews[18,19,20,21] on this subject are available.

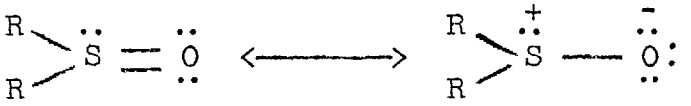
In the oxidation of sulphides two types of change are generally observed. As a first step, a sulphide (17) is converted to a sulphoxide (18) which may undergo further oxidation to a sulphone (19):

$$RSR \xrightarrow{[O]} R-S(=O)-R \xrightarrow{[O]} R-S(=O)_2-R$$

(17) (18) (19)

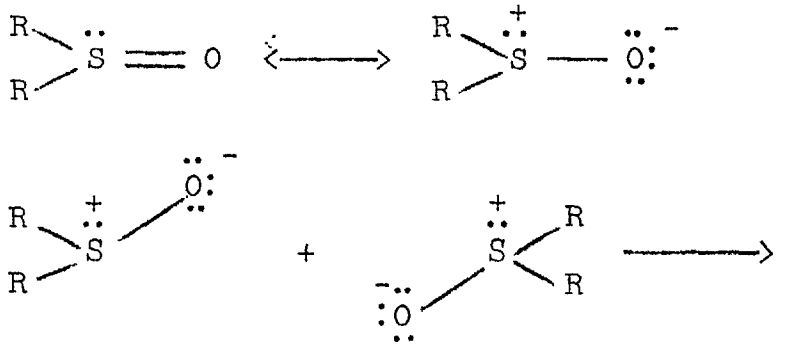
A point of interest about the structures of the sulphoxides and sulphones is the nature of the bonding between sulphur and oxygen. In these compounds, sulphur is probably joined to oxygen by a σ-bond and by a p_π-d_π-bond produced by the overlapping of a filled p_π-orbital of oxygen with a vacant d-orbital of sulphur[22].

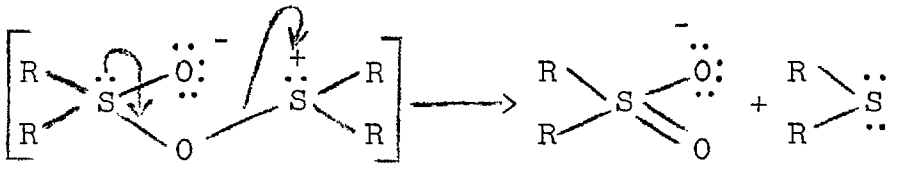
For normal valency-bond representations, sulphoxides and sulphones can be satisfactorily represented by the resonance hybrid structures (B) and (C) respectively.

(B) 

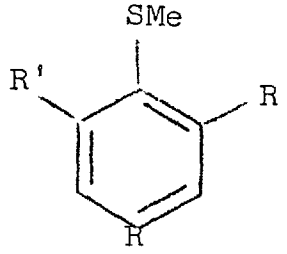
(C) 

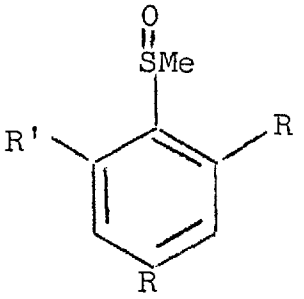
Although sulphones are produced from sulphoxides by oxidation, it is not the only process for such a transformation. Disproportionation of sulphoxides may also produce sulphones. A possible mechanism[19] for disproportionation is as follows:





Böeseken and Arrias[23] studied the kinetics of the oxidation of sulphides to sulphoxides and of sulphoxides to sulphones and found that the rate in the first stage is much faster than that in the second stage. Steric factors however, have very important effects on the rate. The comparative study on the oxidations of the sulphides[24] (20), (21) and (22) reveals that introduction of one orthosubstitu-





(20), R = H, R' = H

(21), R = H, R' = Me

(22), R = Me, R' = Me

(23), R = H, R' = H

(24), R = H, R' = Me

(25), R = Me, R' = Me

ent retards the oxidation rate slightly while with two ortho substituents a large retardation of rate takes place. Analogous oxidation[18] of (23), (24) and (25) to the corresponding sulphones show that a large steric effect is observed when one ortho group is present, while introduction

of another methyl group in second ortho position slows down the reaction only slightly.

Although most of the reagents used for the oxidation of sulphides generally produce mixtures of sulphoxides and sulphones, the state of oxidation achieved can be controlled by a careful combination of three factors, namely, the nature of the sulphide, the type of oxidant and the reaction conditions. The selectivity, limitations and the mechanism of oxidation (if studied) for some of these oxidising agents will now be considered.

(a) Hydroperoxides.

These reagents are satisfactory for the preparation of sulphoxides. The oxidation of sulphides may be performed either in alcohols or in hydrocarbon solvents. Bateman and Hargrave[25] studied the kinetics of oxidation of cyclohexyl methyl sulphide using cyclohexenyl and t-butyl hydroperoxides. Certain characteristic observations were made:

(i) The stoichiometry of oxidations could be represented by the equation

$$ROOH + R'R''S \longrightarrow ROH + R'R''S{=}O.$$

(ii) In alcoholic solutions, the reactions were first order with respect to each reactant. When hydrocarbons were used as solvents, the reactions were second order with respect to hydroperoxide.

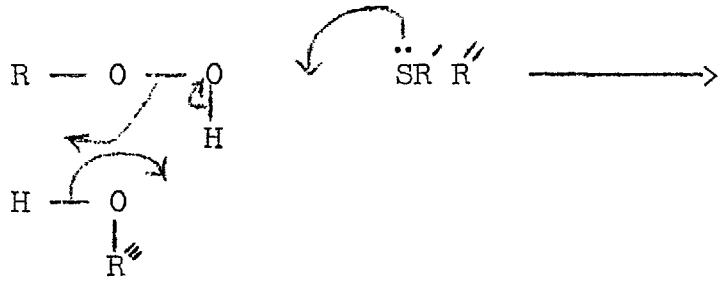
(iii) No effect on rate of reactions was observed by the addition of a free radical inhibitor or a catalyst.

(iv) The reactions were catalysed by acids.

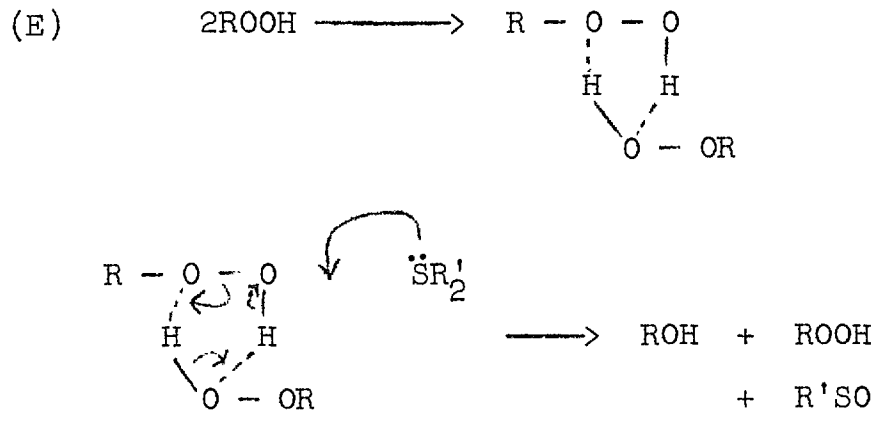
(v) In the case of oxidations in alcohols, the initial addition of cyclohexyl methyl sulphoxide was without any effect on the rate, while in hydrocarbon solvents, considerable retardation took place.

From considerations of kinetic results, the mechanisms (D) and (E) respectively for the oxidations in hydrolytic and in non-hydrolytic solvents were envisaged[25,26].

(D)



$$ROH + R'R''S^{+} - O^{-} + R'''OH$$

(E) 

A requirement for mechanism (D) is that for a given combination of hydroperoxide and sulphide, the rate of reaction should increase as the hydrogen lability of the solvent ($R''OH$) increases. This was found to be the case when the oxidation was carried in a series of alcohols of different acidity[27].

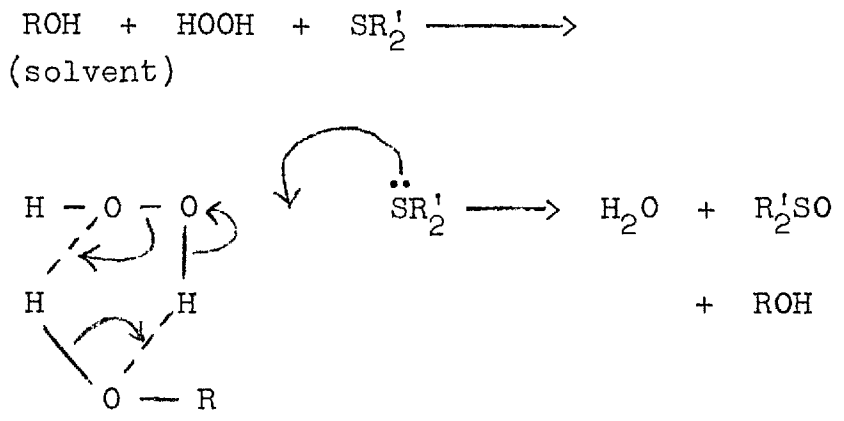
Retardation of rate of reaction observed by the initial addition of a sulphoxide in hydrocarbon solvents is consistent with the mechanism (E). This may be explained by assuming that the added sulphoxide associates (due to its weakly basic character) with hydroperoxide molecules, thereby decreasing the concentration of the hydroperoxide dimer which is the active oxidant.

Hargrave[28] has reported that in the case of oxidation of an unsaturated sulphide with a hydroperoxide in benzene

solution, the yield of sulphoxide is comparatively poor. This is due to a side reaction of the sulphoxide, with the oxidant and the sulphide producing a complex mixture.

(b) Hydrogen peroxide.

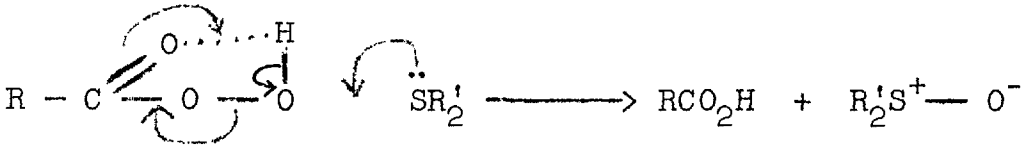
The oxidative behaviour of this reagent is similar to that of hydroperoxides. An analogous mechanism is proposed for the oxidation[29].



It is evident from the above mechanism, that the oxidisibility of sulphides will decrease with the decrease of electron availability on the sulphur atom. This has been proved experimentally[30]. The relative reactivities are in the following order: Et_2S > $EtSCH_2CH_2Cl$ > $S(CH_2CH_2Cl)_2$.

(c) Peracids.

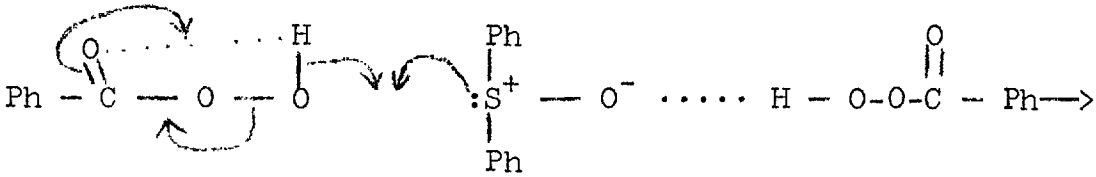
Organic peracids such as perbenzoic acid and peracetic acid rapidly oxidise the sulphoxide initially formed from a sulphide, to produce a sulphone. The mechanism in the first stage involves the nucleophilic attack by sulphur on the hydrogen bonded peracid[31].

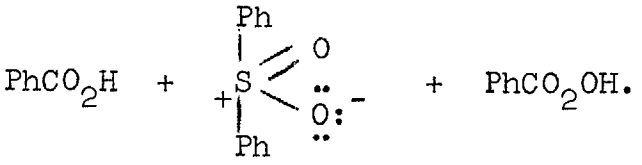


The support for such a mechanism came from the fact that for a series of para-substituted perbenzoic acids, the rate of oxidation of p,p'-dichlorobenzyl sulphide increases with electron withdrawing capacity of the para-substituent. The experimental values are in the order:

p - Me < p - O Me < p - H < p - Cl < p - NO_2.

The second stage of oxidation (sulphoxide to sulphone), probably proceeds by way of nucleophilic attack on sulphur by the peracid[32]:





(d) Chromic acid.

Chromium trioxide in glacial acetic acid is a selective reagent for preparing sulphoxides from sulphides[33]. Chromic acid in pyridine has also been used[34].

(e) Iodobenzene.

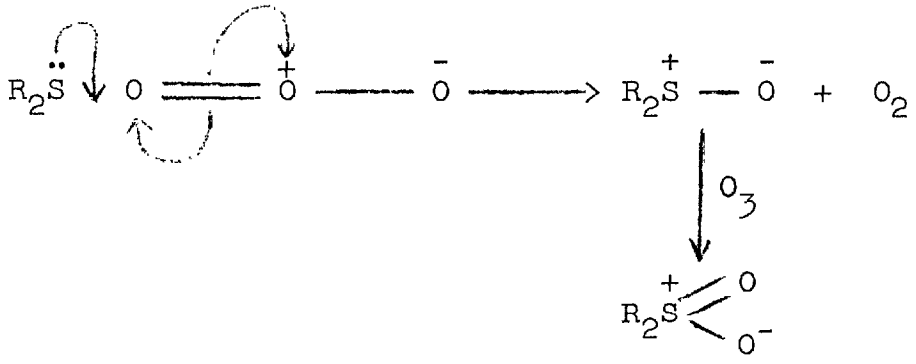
Iodobenzene is a mild reagent and it can be used for the preparation of sulphoxides from unsaturated sulphides[35].

(f) Manganese dioxide.

Edward and Stenlake[34] have used manganese dioxide in light petroleum for the preparation of sulphoxides. The yield is good in the case of saturated sulphide but poor with a compound such as diallyl sulphide.

(g) Ozone.

Ozone oxidises sulphides to sulphoxides and then to sulphones. By using a requisite amount of ozone and controlling the reaction conditions, both the products could be obtained satisfactorily. It is interesting that oxidation of sulphides by ozone has commercial significance in the rubber industry[37]. The mechanism of oxidation might be envisaged as[26]:



(h) Lead tetra-acetate.

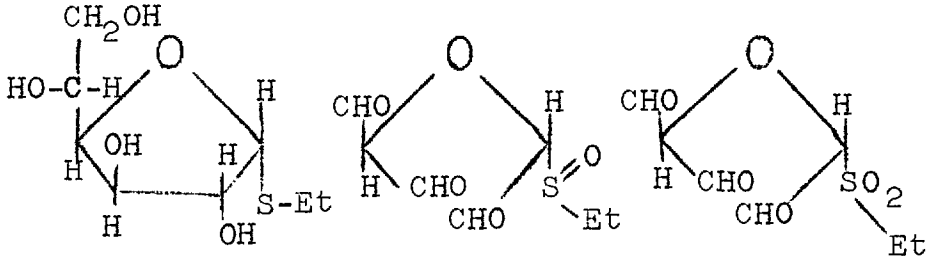
This reagent may also be used for the preparation of sulphoxides. Thus (27) was obtained from (26), the yield being dependent on the dielectric constant of the solvent used[38].

$(CH_3CH_2CH_2CH_2)_2S$ $(CH_3CH_2CH_2CH_2)_2SO$

(26) (27)

(i) Periodic acid and sodium metaperiodate.

Periodic acid, which is a common reagent for cleaving a glycol group, may also oxidise a sulphide group. Okui[39] thus obtained (29) by oxidising (28) with periodic acid.



(28) (29) (30)

On further oxidation the sulphone (30) was produced.

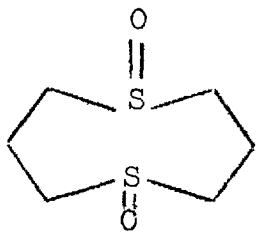
Adley[40] and Moppett[41] found that (31) consumed rapidly 1 mole of periodic acid while (32) took up 2 moles. Their observations might be interpreted by assuming that (33) and (34) respectively were produced by oxidation.

$MeSCH_2CH_2OH$ (31)

$MeSCH_2CH(OH)CH_2OH$ (32)

$MeS(O)CH_2CH_2OH$ (33)

$MeS(O)CH_2CHO$ (34)



(35)

Sulphoxides free from contamination with sulphones may be prepared by using sodium metaperiodate as the oxidant[42]. Alkyl, aryl and also cyclic sulphoxides such as (35) have been prepared in good yield from the corresponding sulphides. The reaction can be performed at comparatively low temperature in water or methanol-water mixture.

(j) Dimethyl sulphoxide.

This reagent exchanges oxygen with sulphides to produce higher sulphoxides[43]. Thus (38) and (39) have been produced from (36) and (37) respectively.

$(CH_3CH_2CH_2)_2S$ (36)

$(CH_3CH_2CH_2CH_2)_2S$ (37)

$(CH_3CH_2CH_2)_2SO$ (38)

$(CH_3CH_2CH_2CH_2)_2SO$ (39)

(k) Selenoxides.

Dibenzyl selenoxide and diphenyl selenoxide have been found to be satisfactory oxidants for the preparation of sulphoxides. Acetic acid is a suitable solvent for the oxidation. The oxidisibility of a sulphide is greatly influenced by its structure. The results summarised in table II[44] will illustrate this point.

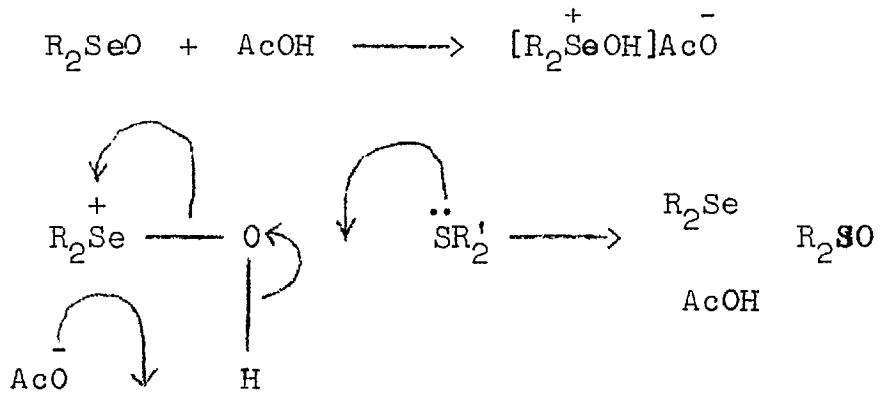
Table II

The oxidation of sulphides by dibenzyl selenoxide (0.038 M) in acetic acid at 20°C.

Sulphide (0.53 M)	Reaction after 2 hrs (%)
di n-butyl	98
thiacyclopentane	96
di-isopropyl	77
di-t-butyl	68
t-butyl ethyl	64
cyclohexyl methyl	56
benzyl methyl	39
cyclohex-2-enyl methyl	26
t-butyl isopropyl	17
dibenzyl	4

The structure of the selenoxide also exerts an influence on the rate. Thus diphenyl selenoxide is 85% as reactive as the dibenzyl compound.

Since oxidation with these reagents does not take place in such solvents as methanol and benzene, it has been proposed that a salt-like selenoxide-acid complex is the active oxidant[44]:



Oxidation of Thiocarbonyl Compounds

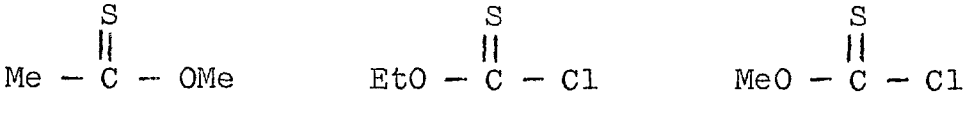
The oxidation of a thiocarbonyl group can occur in several ways:

A. Oxidation to a carbonyl group.

(a) By air.

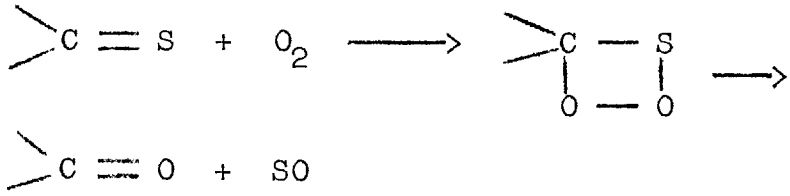
Delépine[45] reported that the thiocarbonyl compounds

(40), (41) and (42) were oxidised spontaneously by air.

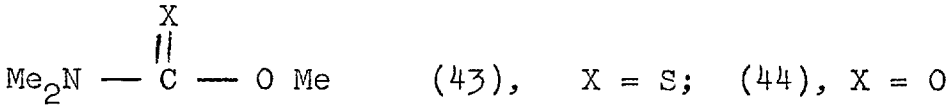


(40) (41) (42)

He envisaged the following mechanism for the oxidation of thiocarbonyl compounds by oxygen[46].

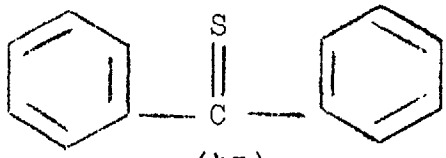


Billeter[47] also obtained (44) by oxidising (43) by oxygen in the presence of sodium carbonate.



(43), X = S; (44), X = O

The oxidation of thiobenzophenone (45) by air or oxygen was more extensively studied[48,49]. Benzophenone and a compound, $C_{26}H_{20}S_3$ were isolated.



(45)

The stoichiometry of oxidation by oxygen conforms to the equation[49]:

$$6(C_6H_5)_2C = S + O_2 \longrightarrow 2(C_6H_5)_2C = O + 2\ C_{26}H_{20}S_3.$$

Staudinger and Freudenberg[49] envisaged the intermediate (46) in the oxidation of thiobenzophenone by oxygen.

$$2(C_6H_5)_2C{=}S + O_2 \longrightarrow \left[\begin{array}{c} Ph \\ Ph \end{array}\!\!>C\!<\!\begin{array}{c} S-S \\ O-O \end{array}\!\!>C\!<\!\begin{array}{c} Ph \\ Ph \end{array}\right] \longrightarrow$$

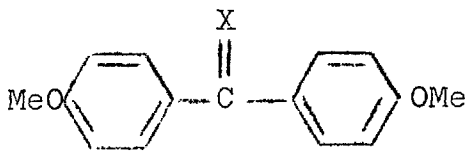
(46)

$$2(C_6H_5)_2C{=}O + 2S$$

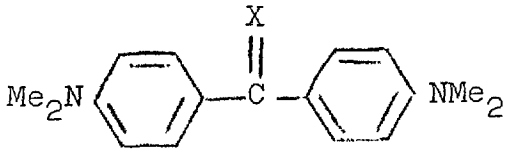
$$2(C_6H_5)_2C{=}S + S \longrightarrow C_{26}H_{20}S_3.$$

The "nascent" sulphur produced in the first step was believed to react with more thiobenzophenone to give $C_{26}H_{20}S_3$.

Sulphur dioxide, sulphur and benzophenone or substituted benzophenone (48) or (50) were obtained when the solution of (45), (47) or (49) in benzene was oxidised by air[50].



(47), X = S
(48), X = O



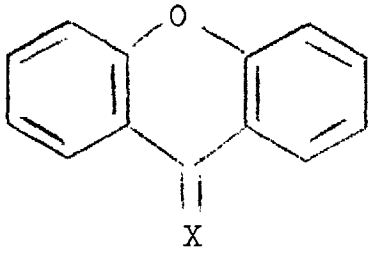
(49), X = S
(50), X = O

The course of oxidation by oxygen in benzene is possibly as follows[51]:

$$2\ Ar_2C{=}S \;+\; 2\ O_2 \longrightarrow 2\left[Ar_2C\begin{array}{l}-S{=}O\\ \diagdown\ \diagup\\ \ \ O\end{array}\right]$$

$$\longrightarrow\ 2\ Ar_2C{=}O \;+\; SO_2 \;+\; S.$$

More recently, Ried and Klug [52] have shown that xanthen-9-thione (51) is oxidised by oxygen in the presence of sodium cyanide to the carbonyl compound (52).

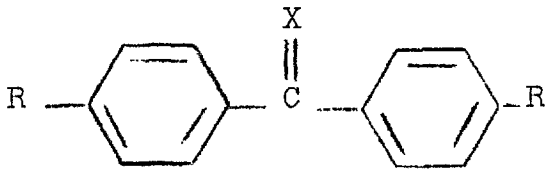


(51), X = S

(52), X = O

(b) By hydrogen peroxide.

Kitamura[53] studied the oxidation of a number of thiocarbonyl compounds including (53) and (54) using alkaline hydrogen peroxide. In each case the corresponding carbonyl compound such as (55) or (56) was obtained.



(53), R = OMe, X = S

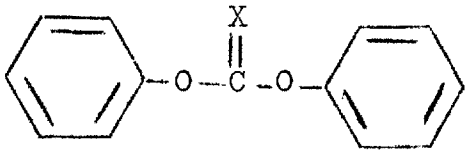
(54), R = OEt, X = S

(55), R = OMe, X = O

(56), R = OEt, X = O

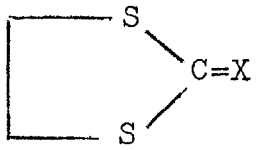
(c) By mercuric compounds.

Mercuric oxide[54,55] and mercuric acetate[56] is also known to oxidise a thiocarbonyl group. Schönberg et al.[55] prepared (58) by oxidising (57) with mercuric oxide in benzene.



(57), X = S

(58), X = O



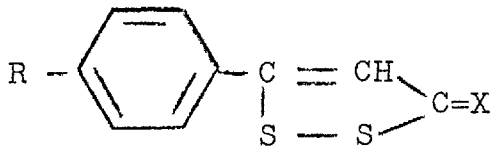
(59), X = S

(60), X = O

Oxidation of ethylene trithiocarbonate (59) with mercuric acetate[56] gave the dithiocarbonate (60).

(d) By potassium permanganate.

Potassium permanganate in acetone was used to prepare (63) and (64) from (61) and (62) respectively.



(61), R = H, X = S

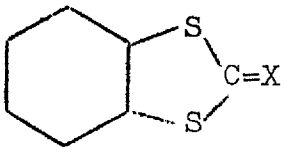
(62), R = OMe, X = S

(63), R = H, X = O

(64), R = OMe, X = O

(e) By nitric acid.

Husemann[58] and later Razuvaev et al.[59] reported the oxidation of the trithiocarbonate (65) to the dithiocarbonate (66) by using nitric acid.



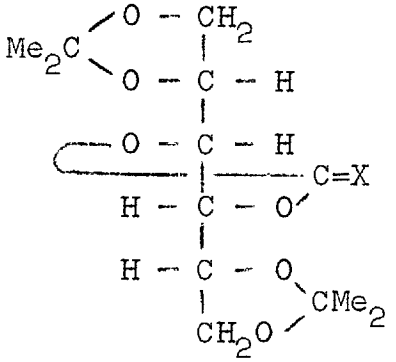
(65), X = S

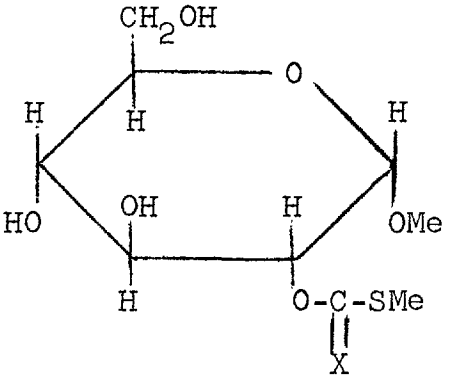
(66), X = O

(f) By silver compounds.

The use of silver carbonate is illustrated by the preparation of (68) from (67)[60].

Silver nitrate has been used to convert (69) to (70)[61]:





(67), X = S

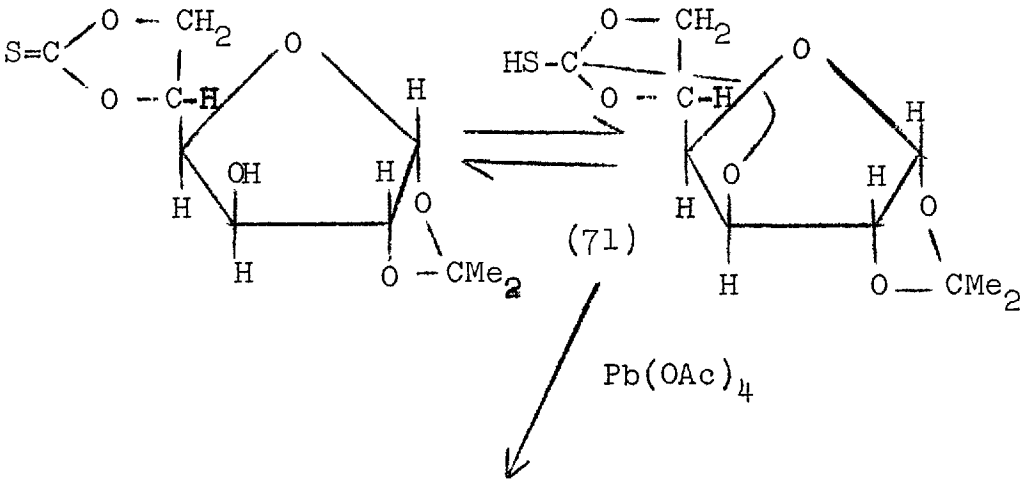
(68), X = O

(69), X = S

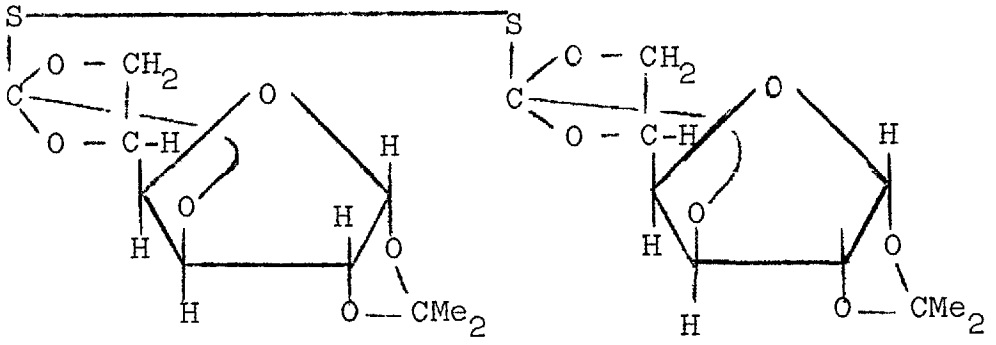
(70), X = O

B. Oxidation to a disulphide.

As has been mentioned previously, a thiocarbonyl compound may equilibrate with a thiol. When there is the possibility of such a phenomenon, the oxidation of a thiocarbonyl compound might proceed via the thiol form. Thus the oxidation of (71) with lead tetra-acetate gives the disulphide (72)[62].

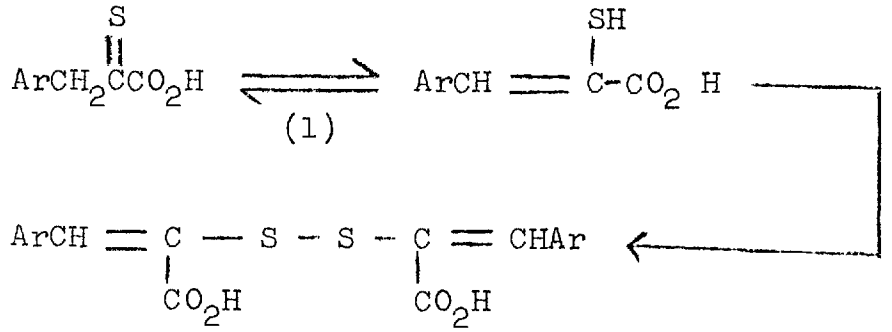


(71)



(72)

On oxidation with iodine arylpyruvic acids (1) produce the disulphides (73)[1]

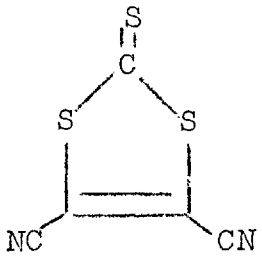


(73)

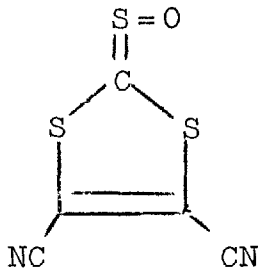
C. Oxidation to an oxythiocarbonyl group.

(a) By peracetic acid.

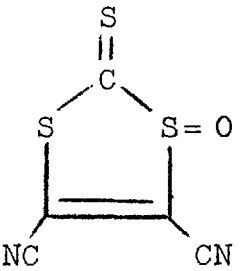
Kleingsberg[63] has reported that the oxidation of the biscyano-trithiocarbonate (74) with peracetic acid in acetone gives the oxythiocarbonyl compound (75). This structure is preferred to (76) because of the absence of a thiocarbonyl peak in the infrared spectrum.



(74)



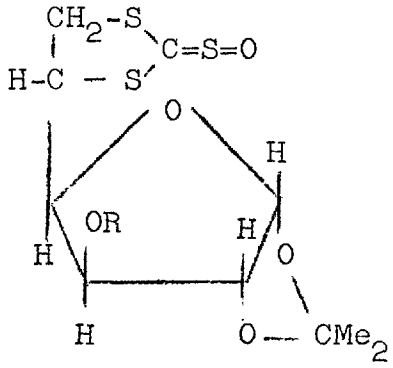
(75)



(76)

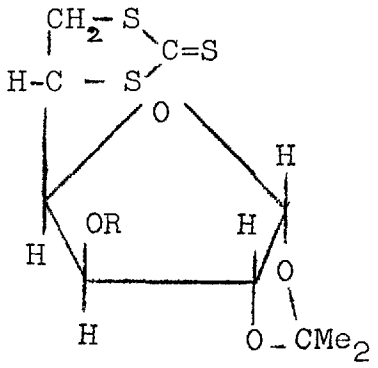
(b) By lead tetra-acetate.

The use of lead tetra-acetate is illustrated by the preparations of the oxythiocarbonyl compounds (77), (78) and (79) from the trithiocarbonates (80), (81) and (59) respectively[62].



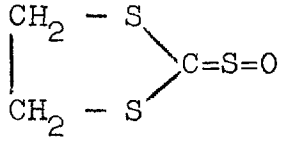
(77), R = H

(78), R = Ts

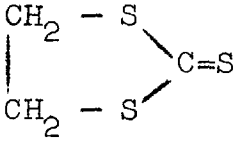


(80), R = H

(81), R = Ts



(79)

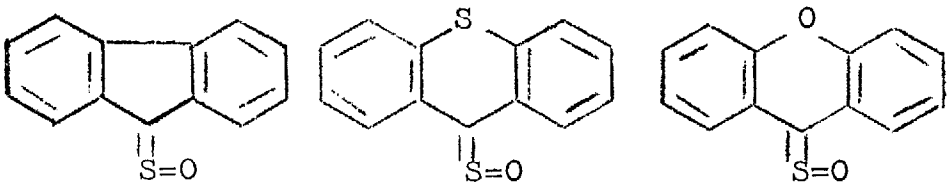


(59)

(c) By perphthalic acid.

Perphthalic acid is advocated as a specific reagent for converting a thiocarbonyl group into an oxythiocarbonyl group[64]. By using this oxidant the oxythiocarbonyl

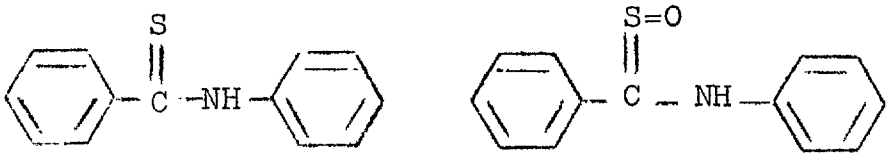
compounds (80), (81) and (82) were prepared from the corresponding thiocarbonyl compounds[64].



(80) (81) (82)

(d) By neutral hydrogen peroxide.

Several secondary and tertiary thioamides have been converted into the corresponding S-oxides by oxidation with neutral hydrogen peroxide[64a]. Thus (84) was obtained from (83).

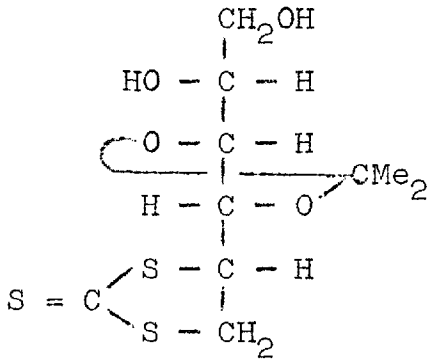


(83) (84)

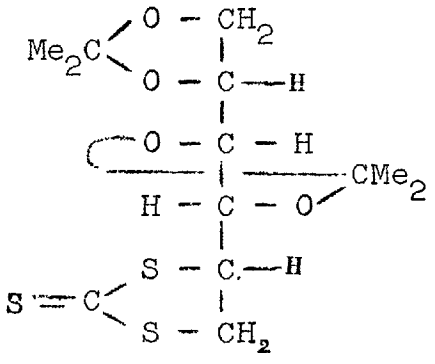
P A R T II

DISCUSSION

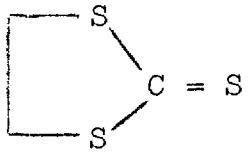
During investigations on the synthesis of thio-carbohydrates, Adley[40] found that when the mono-isopropylidene-trithiocarbonate (1) was treated with an excess of lead tetra-acetate, two moles of the oxidant were rapidly consumed. The corresponding di-isopropylidene-derivative (2) when oxidised under identical conditions took up only one mole of the reagent. It was apparent therefore, that as well as oxidising a vicinal diol system, lead tetra-acetate was capable of attacking a trithiocarbonate group.



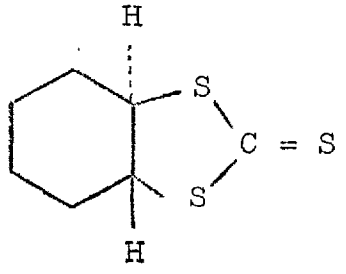
(1)



(2)



(3)



(4)

Adley[40] and later Moppett[41] made further investigations on the action of lead tetra-acetate on such model compounds as ethylene trithiocarbonate (3) or cyclohexene trithiocarbonate (4). It was found that in each case one mole of the oxidant was consumed per mole of the substance under investigation. An oxy-compound $C_7H_{10}OS_3$ was isolated from the oxidation of the trithiocarbonate (4).

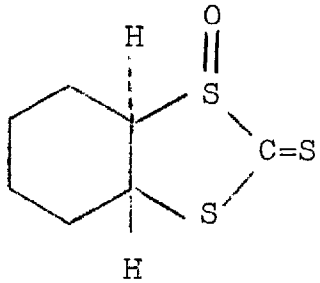
The present study was undertaken to investigate more thoroughly the oxidation of a number of cyclic thiocarbonates (mono, di and trithio) by lead tetra-acetate. The action of other oxidising agents such as peracetic acid and perphthalic acid was also studied.

Oxidation of trans-1,2-(Thiocarbonyldithio)cyclohexane.

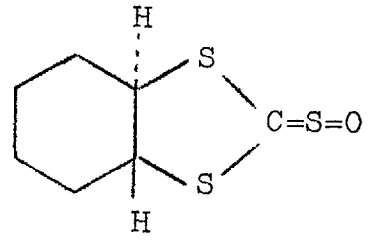
When the trithiocarbonate (4) was oxidised with an excess of peracetic acid, approximately five moles of the oxidant were consumed during two hours. A slower oxidation took place subsequently and nine moles of peracetic acid were taken up during 184 hours. To isolate the products, a controlled oxidation with one mole of the reagent and also a reaction with a large excess of peracetic acid were performed.

(a) Oxidation with one mole of peracetic acid (or lead tetra-acetate).

The trithiocarbonate on oxidation with one mole of peracetic acid gave an oxy-compound, $C_7H_{10}OS_3$. The same compound was produced when (4) reacted with lead tetra-acetate[40,41] and Adley assigned the structure (5) for the oxy-compound. But by examining the ultraviolet, infrared and n.m.r. spectra, it was apparent that the compound had the alternative structure (6). The ultraviolet spectrum



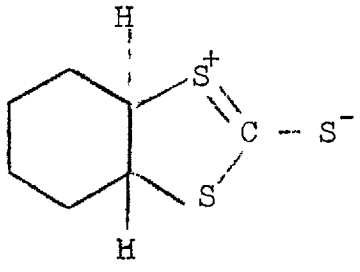
(5)



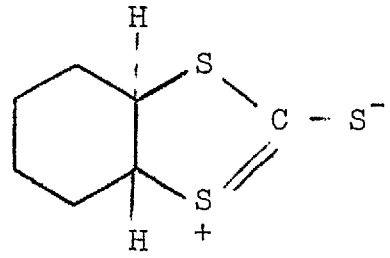
(6)

showed peaks at 284 and 349 mμ (ε 5350 and 10740 respectively in ethanol) which are characteristic for a $(S)_2C=S=O$ group[62] and the strong absorption at 1005 cm^{-1} in the infrared spectrum could be due to an oxythiocarbonyl group[63,65]. The proton magnetic resonance spectrum showed multiplets at τ 6.5 (2H) and 7.5-8.8 (8H) which support the structure (6).

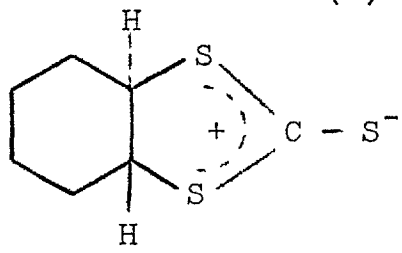
From the point of view of mechanism, the formation of (6) is more probable than (5). The resonance forms such as (7), (8) and (9) might contribute to the actual structure of cyclohexene trithiocarbonate. As a consequence, the



(7)



(8)

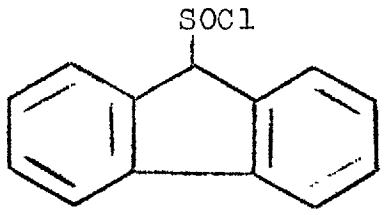


(9)

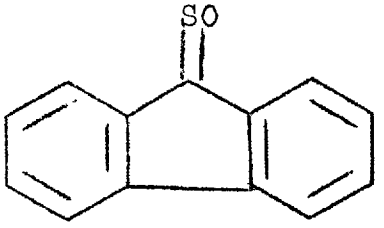
electron availability on the thiocarbonyl sulphur will be greater than that on the ring sulphur. Since there is a direct relationship between electron availability on sulphur and its oxidisibility (at least in the oxidation of organic sulphides with peracids and peroxides), oxidation of (4) is expected to produce (6) rather than (5).

Several sulphur compounds containing the oxythiocarbonyl group have been reported recently[62-67]. A few

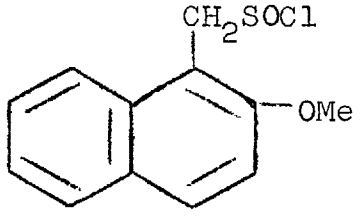
of these have been prepared by the elimination of a mole of hydrogen chloride from sulphinyl chlorides. Thus (11)[65] and (13)[67] are prepared from (10) and (12).



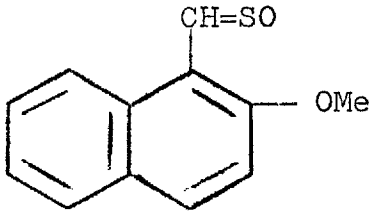
(10)



(11)

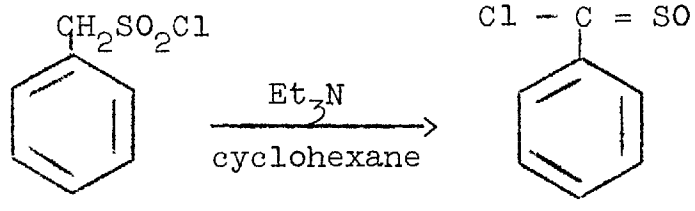


(12)



(13)

By treating a suitable sulphonyl chloride with a base such as triethylamine, chloro-oxythiones may be prepared. King and Durst[66] obtained (15) from (14).

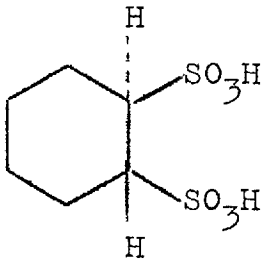


(14) (15)

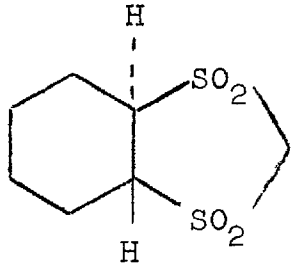
The preparation of oxythiones by the oxidation of thiocarbonyl compounds has been discussed already (page 125).

(b) Oxidation with an excess of peracetic acid.

On oxidation with an excess of peracetic acid, the trithiocarbonate gave trans-cyclohexane-1,2-disulphonic acid (16) and a compound $C_7H_{12}O_4S_2$. The disulphonic acid was characterised as its phenylhydrazine salt and the dihydrate of its barium salt. Sperling[68] probably prepared the same disulphonic acid (also characterised as the phenyl hydrazine salt and dihydrate of the barium salt) by reacting cyclohexene with thiocyanogen and oxidising the resulting 1,2-cyclohexene dithiocyanate with nitric acid,



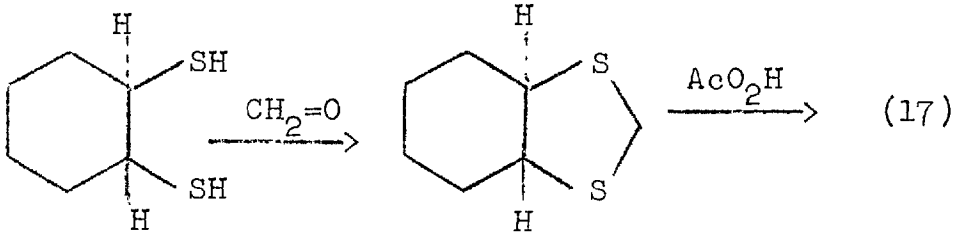
(16)



(17)

but a cis-configuration was given to the product. Etlis[69] also got a cyclohexane-1,2-disulphonic acid by oxidising a

cyclohexene trithiocarbonate with hydrogen peroxide, but no configuration was assigned either to the disulphonic acid or the trithiocarbonate. The infrared spectrum of the compound $C_7H_{10}O_4S_2$ in carbon tetrachloride showed strong absorptions at 1360, 1340 and 1180 $cm.^{-1}$ ($-SO_2-$). The nuclear magnetic resonance spectrum had signals at τ 5.7 (2H, sharp singlet), 6.6 (2H) and 7.3-9.0 (8H). The sharp singlet at τ 5.7 indicated the presence of a $-SO_2-CH_2-SO_2-$ group and the compound was assigned the structure (17). This structure was confirmed by synthesis. Condensation of <u>trans</u>-cyclohexane-1,2-dithiol (18) with formaldehyde gave <u>trans</u>-1,2-(methylenedithio)cyclohexane (19) which on oxidation with peracetic acid gave the disulphone (17).

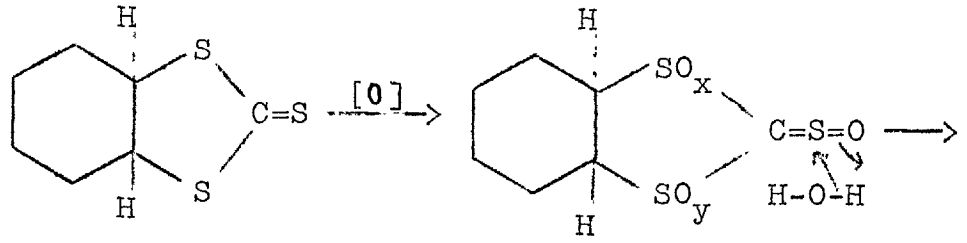


(17)

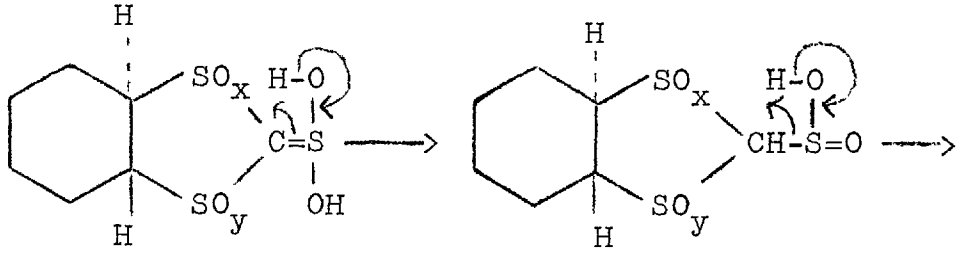
(18) (19)

Although the mechanism of formation of (17) from cyclohexene trithiocarbonate was not established, one possibility is that the transformation may proceed by way of the

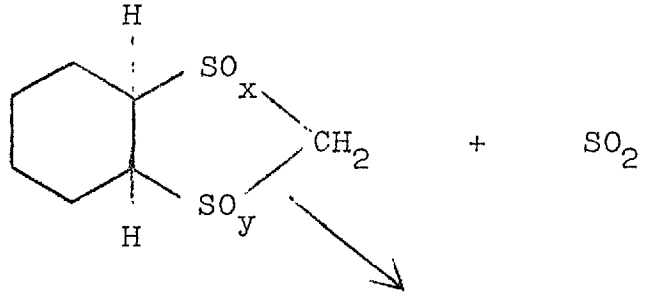
intermediate (A) which undergoes intramolecular hydrogen transfer with subsequent cleavage of the C-S-linkage:



[x,y = 0, 1 or 2]

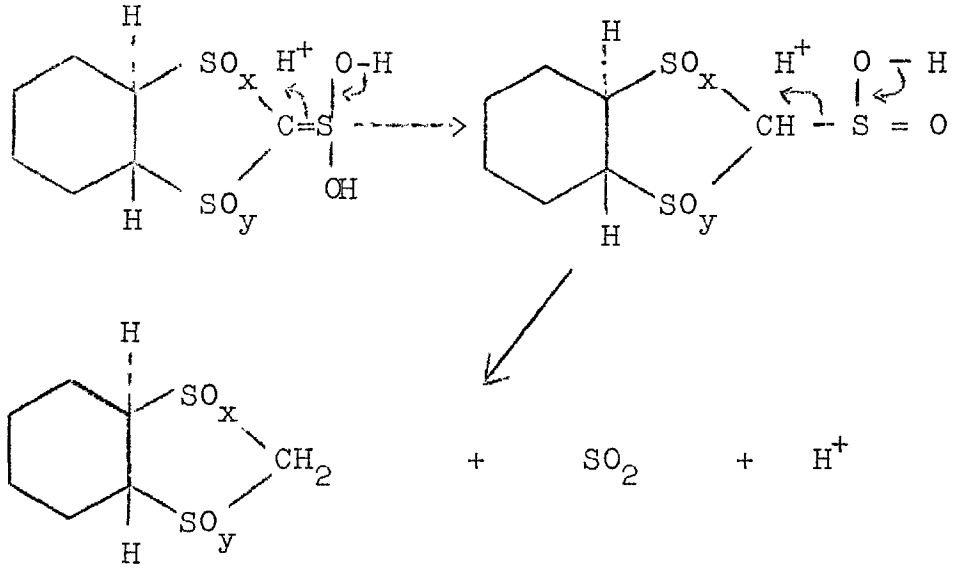


(A)



(17)

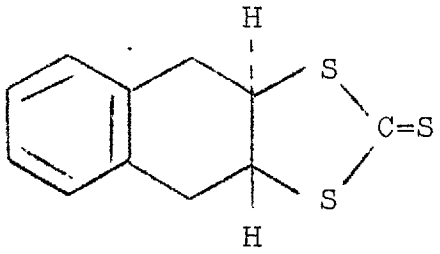
There is however the possibility that the hydrogen transfer may be assisted by the acidic solvent:



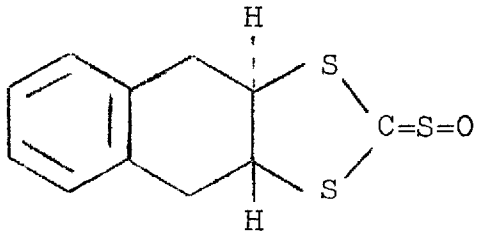
Oxidation of trans-2,3-(Thiocarbonyldithio) tetralin

(a) By lead tetra-acetate (or one mole of peracetic acid).

When the trithiocarbonate (20) reacted with an excess of lead tetra-acetat, only one mole of the reagent was used up; this behaviour is similar to that of the cyclohexene trithiocarbonate. In a preparative experiment, treatment of the compound with one mole of lead tetra-acetate or of peracetic acid gave a compound $C_{11}H_{10}OS_3$ which showed characteristic ultraviolet absorptions for the $\{S\}_2C=S=O$



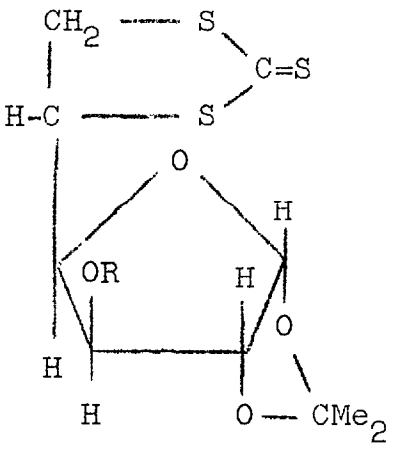
(20)



(21)

group at 283 and 357 mμ (ε 4600 and 11200 respectively in ethanol). Its infrared spectrum showed strong absorption at 1000 cm^{-1}. The nuclear magnetic resonance spectrum had peaks at τ 2.7 (4H), 6.1 (2H) and 6.7 (4H). From analogy with the oxidation product from cyclohexene trithiocarbonate, this oxy-compound can be assigned the structure (21).

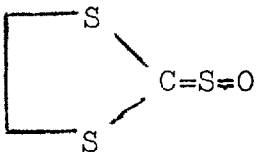
Thus it became apparent that lead tetra-acetate might be used as a specific and convenient reagent for converting a $\{S\}_2C=S$ group to a $\{S\}_2C=SO$ group. The independent observations by Doane et al.[62] that ethylene trithiocarbonate (3) and the carbohydrate-trithiocarbonates (22), (23) and (24) are oxidised to the corresponding oxythiones (25), (26), (27) and (28) by lead tetra-acetate, support this view. As has been mentioned already, such a transformation can also be brought about by the use of a limited amount of peracetic acid.



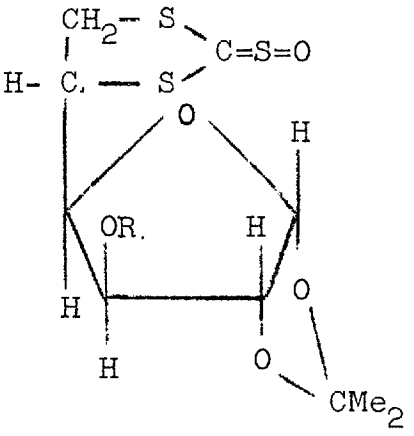
(22), R = H

(23), R = Ac

(24), R = Ts



(25)



(26), R = H

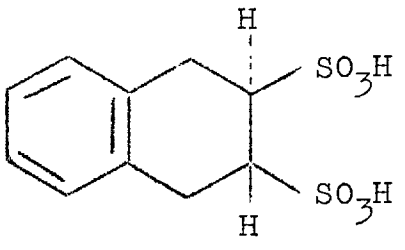
(27), R = Ac

(28), R = Ts

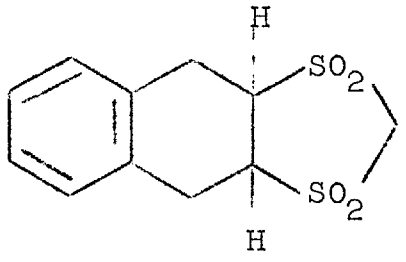
(b) By an excess of peracetic acid.

With an excess of peracetic acid, trans-2,3-(thiocarbonyldithio)tetralin (20) gave trans-tetralin-2,3-disulphonic acid (29), sulphuric acid and

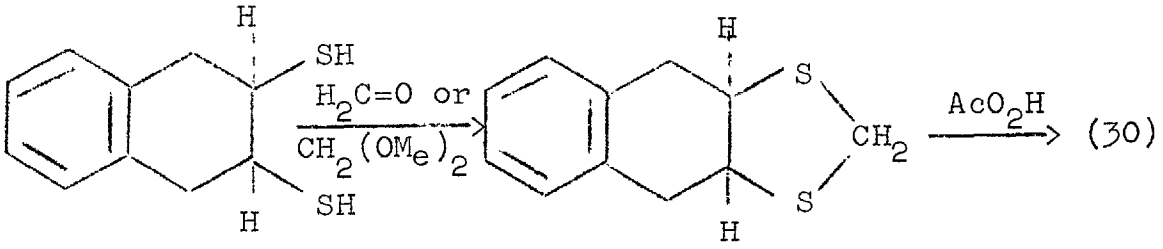
trans-2,3-(methylenedisulphonyl)tetralin (30). The same products were obtained when trans-2,3-(oxythiocarbonyldithio)-tetralin (21) was oxidised under identical conditions. The disulphonic acid was characterised as its salt with phenylhydrazine. The formation of sulphuric acid was also established by isolating its phenylhydrazine salt. The infrared spectrum of the disulphone (30) showed peaks at 1360 and 1340 cm^{-1}. The nuclear magnetic resonance spectrum of this compound showed τ values of 5.4 (2H, sharp singlet) and 6.0 (2H). The signals at higher field were obscured by the solvent (acetonitrile). The sharp singlet at τ 5.4 is due to the protons of the $-SO_2-CH_2SO_2-$ group. The structure (30) was confirmed by the synthesis of the disulphone. By reacting trans-tetralin-2,3-dithiol (31) with formaldehyde or dimethoxy-methane, trans-2,3-(methylenedithio)tetralin (32) was prepared, which on oxidation with peracetic acid gave (30). The formation of



(29)



(30)

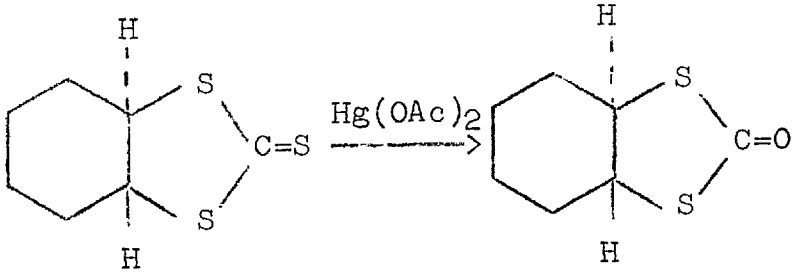


(31) (32)

(30) from (20) thus provided another example of a novel Wolff-Kishner type of transformation involving a C=S group.

Oxidation of trans-1,2-(Carbonyldithio)cyclohexane.

The dithiocarbonate (33) was prepared by oxidising cyclohexene trithiocarbonate (4) with mercuric acetate, and the further oxidation of (33) was then studied.



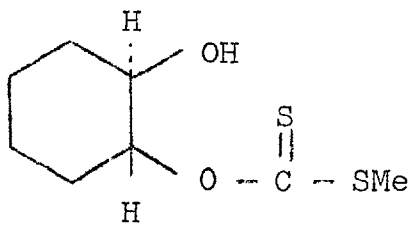
(4) (33)

Although (33) was found to be resistant towards oxidation by lead tetra-acetate[40,41], it consumed six moles of peracetic acid over a period of 78.5 hours. trans-Cyclohexane-1,2-disulphonic acid was obtained by oxidising it with an excess of peracetic acid. The disulphonic acid was characterised as its salt with phenylhydrazine.

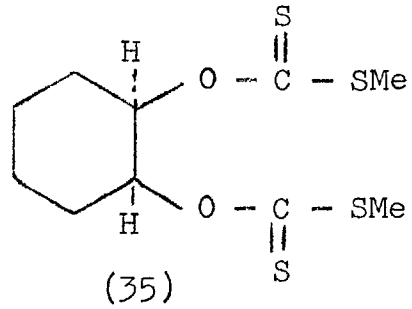
Synthesis and Oxidation of trans-1,2-(Thiocarbonyldioxy)cyclohexane.

(a) Synthesis.

To synthesise the monothiocarbonate (37), trans-cyclohexane-1,2-diol (36) was treated successively with sodium hydride, carbon disulphide and methyl iodide. A very poor yield of the compound (37) was obtained. The major products were 1-O-[(methylthio)thiocarbonyl]cyclohexane-trans-1,2-diol (34) and 1,2-di-O-[(methylthio)thiocarbonyl]cyclohexane-trans-1,2-diol (35).

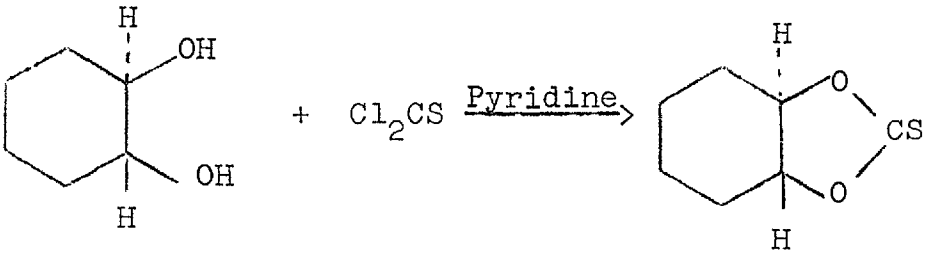


(34)



(35)

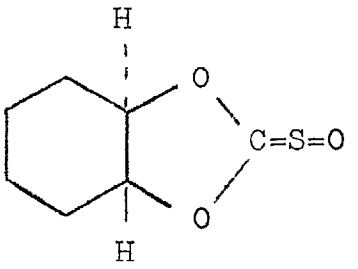
However, by condensing (36) with thiophysgene in the presence of pyridine, (37) was obtained in good yield



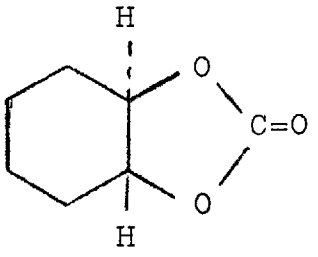
(36) (37)

(b) Oxidation.

Since the oxidation of cyclohexane-trithiocarbonate (4) and tetralin-trithiocarbonate (20) with lead tetra-acetate gave the corresponding oxythiocarbonyl-compounds (6) and (21) respectively, it was believed that (37) on oxidation with the same reagent would also give the oxythione (38). Accordingly, (37) was treated with an excess of lead tetra-acetate, and it was found to take up one mole of the oxidant within 20 minutes. A slower reaction took place subsequently and after 142 hours 2.4 moles of the reagent were used up. To isolate a product, (37) was allowed to react with lead tetra-acetate for half an hour and by working up the reaction mixture, a compound which contained no sulphur was isolated. The analysis data was consistent with the



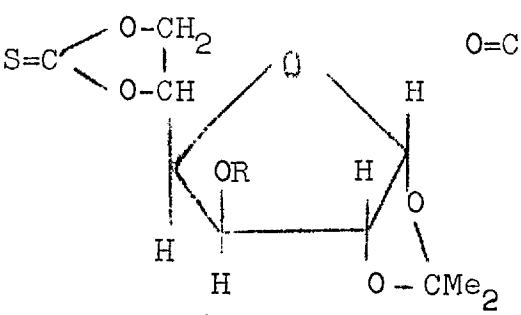
(38)



(39)

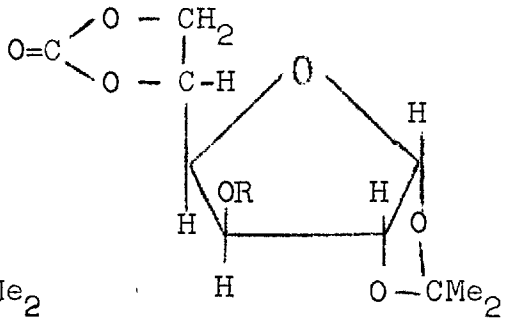
formula $C_7H_{10}O_3$. The infrared spectrum of the compound showed absorptions at 1795 and 1810 $cm.^{-1}$ which indicated the presence of a cyclic carbonate group[70,71] and the compound was assigned the structure (39). The product was found to be identical with a sample of (39) obtained by reacting the monothiocarbonate (37) with silver nitrate.

Doane et al.[62], have also independently observed that thionocarbonates are converted into carbonates on oxidation with lead tetra-acetate. Thus (42) and (43) were obtained from (40) and (41) respectively.



(40), R = Ac

(41), R = Ts



(42), R = Ac

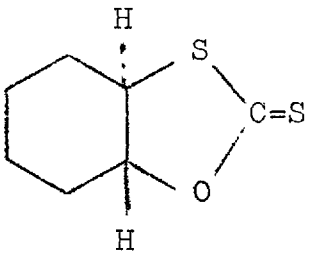
(43), R = Ts

Perphthalic acid has been claimed to be specific for converting a thiocarbonyl group to the corresponding oxythiocarbonyl group[64] and the oxidation of the monothiocarbonate (37) with this reagent was therefore examined. However, the only product which could be isolated was the carbonate (39).

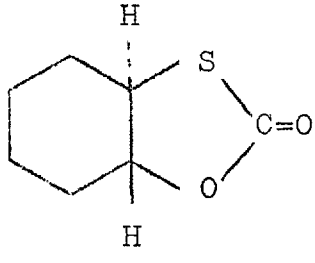
The failure to isolate (38) may be due to the possibility that compounds containing the $\{O\}_2C=S=O$ group may be too unstable.

Oxidation of trans-1,2-(Thiocarbonyloxythio)-cyclohexane.

By heating a mixture of cyclohexene oxide, carbon disulphide and tetraethylammonium bromide, the dithiocarbonate (44) was prepared[59]. When (44) was allowed to



(44)



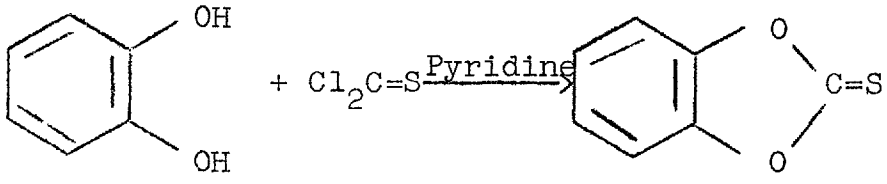
(45)

react with an excess of lead tetra-acetate, it consumed during 2 hours one mole of the oxidant. Practically, no increase of uptake of the reagent was observed even after 19 hours. A distillable product was obtained by oxidising the dithiocarbonate with lead tetra-acetate for 2 hours. The compound had a strong absorption at 1730 $cm.^{-1}$, and the whole infrared spectrum was identical in all respects with that of an authentic specimen[72] of the monothiocarbonate (45).

Synthesis and Oxidation of 1,2-(Thiocarbonyldioxy)benzene.

(a) Synthesis.

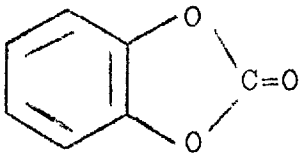
By modifying the literature method[73], the monothiocarbonate (47) was prepared in very good yield by condensing catechol (46) with thiophosgene in the presence of pyridine.



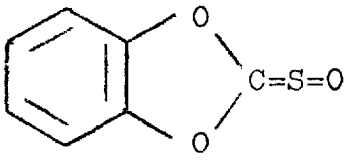
(46) (47)

(b) Oxidation.

When the monothiocarbonate (47) reacted with an excess of lead tetra-acetate in acetic acid, 0.5 mole of the reagent was consumed during 40 minutes after which the rate of oxidation slowed down drastically. In a preparative experiment, the reaction was stopped after 1 hour and a solid product was isolated. In view of the results of oxidation of tetralin trithiocarbonate and also of the thiocarbonates (4), (37) and (44), the product might be expected to have either the structure (48) or (49), although, if this were so, more than 0.5 mole of oxidant would be expected to be consumed. However, these structures were not acceptable since analysis data gave the molecular formula, $C_{18}H_{14}O_8S_2$. The nuclear magnetic resonance spectrum showed that in

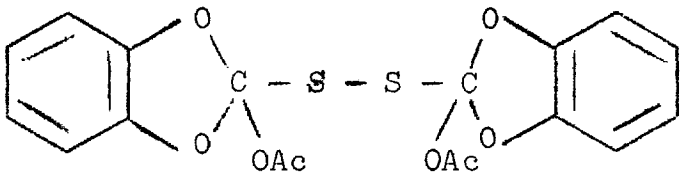


(48)



(49)

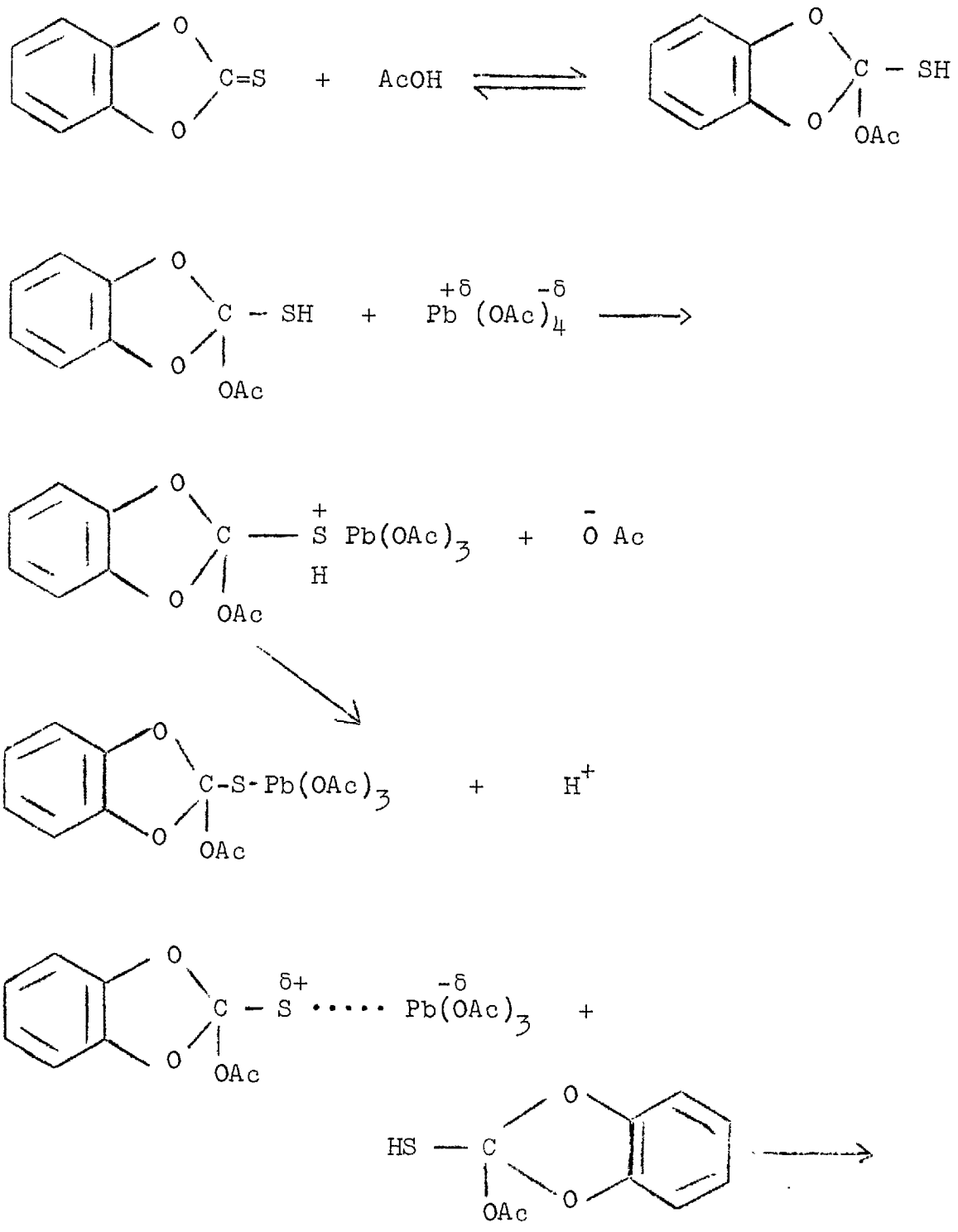
addition to the signal at τ 3.10 (4H) due to the aromatic protons, a sharp singlet (3H) was present at τ 7.93. The extra peak could be due to the presence of the acetate group in the molecule. The infrared spectrum revealed a strong absorption at 1780 cm^{-1}. Although acetates generally absorb in the 1735-1750 cm^{-1} region, a compound such as 1,1-diacetoxypropane shows the characteristic absorption at a higher wave number[74] (1761 cm^{-1}). On the basis of the above results, the oxidation product could be assigned the structure (50).

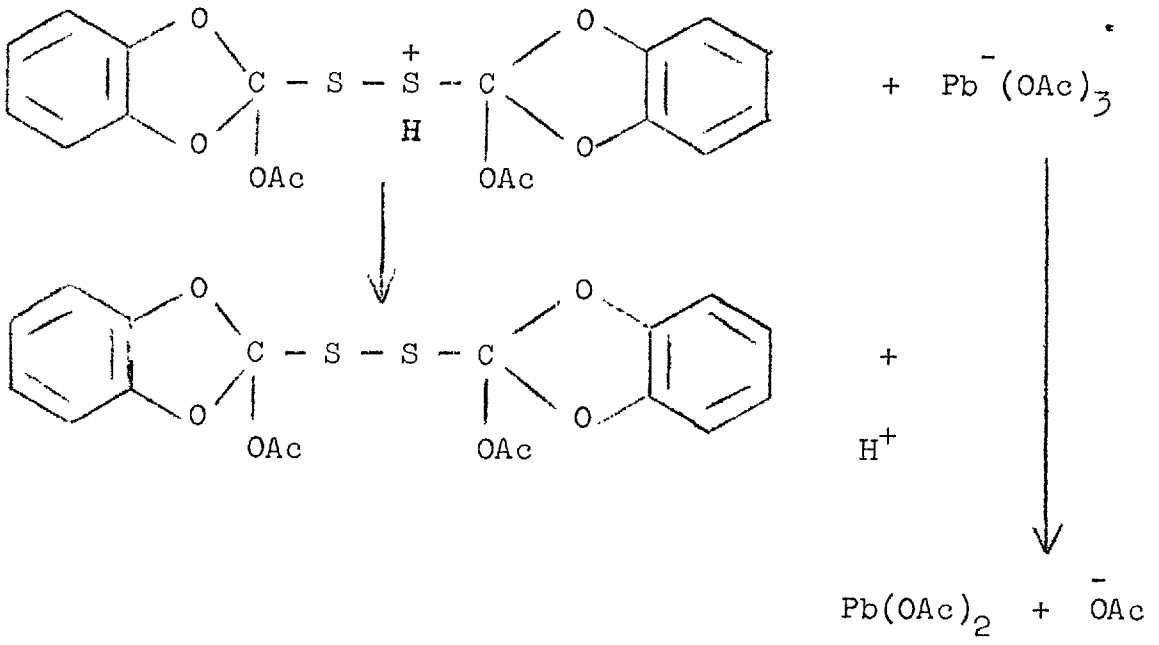


(50)

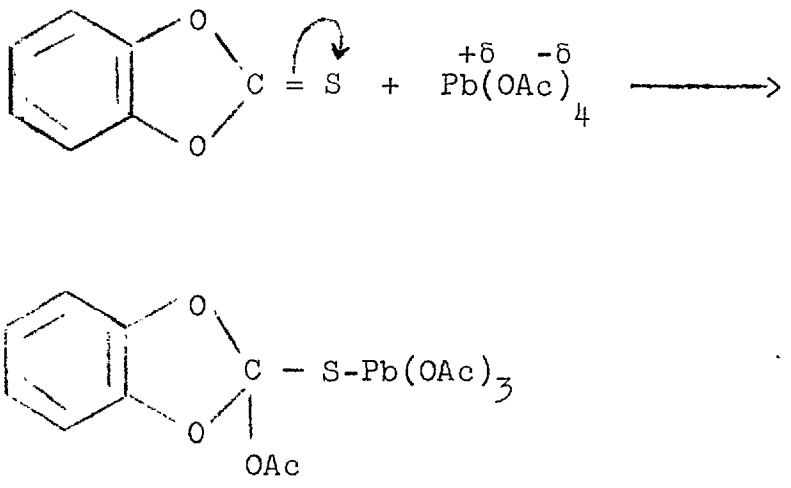
Two mechanisms might be envisaged for the formation of (50) from (47) by oxidation with lead tetra-acetate:

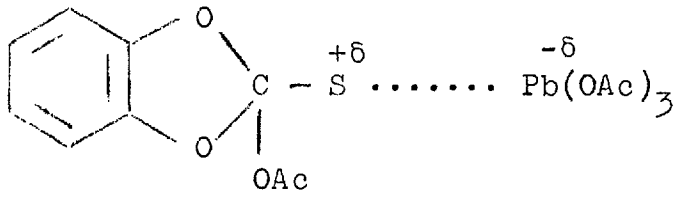
(B)

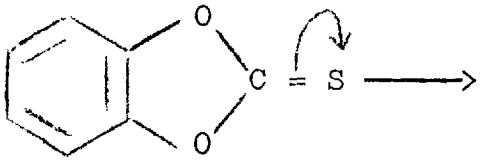


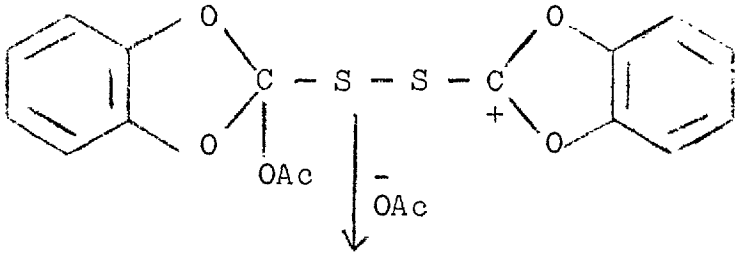


(C)

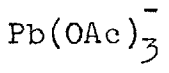


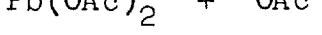






(50)





In one mechanism (B), it is postulated that a thiol intermediate is formed by the interaction of the thiocarbonate (47) with acetic acid. The thiol then undergoes oxidation to the disulphide. However, such a mechanism seems unlikely since a solution of (47) in acetic acid fails to consume iodine.

From the foregoing results, it is thus apparent that the nature of the oxidation product from a thiocarbonate depends to a great extent on the structure of the compound being oxidised. For example, using lead tetra-acetate as the oxidant, trans-1,2-(thiocarbonyldithio)cyclohexane (4) was converted into the corresponding oxy-thiocarbonyl compound (6), trans-1,2-(thiocarbonyloxythio)cyclohexane (44) and trans-1,2-(thiocarbonyldioxy)cyclohexane (37) gave the carbonyl compounds (45) and (39) respectively, and the thiocarbonate (47) yielded the disulphide (50). Further illustration of the effect of the structure of a thiocarbonate on the nature of the product (or products) is provided by the fact that with an excess of peracetic acid, trans-1,2-(carbonyldithio)cyclohexane (33) gave only the disulphonic acid (16) while a mixture of (16) and the disulphone (17) was obtained from the trithiocarbonate (4).

The nature of the oxidising agent also has an influence on the state of oxidation achieved. Thus with lead

tetra-acetate, the oxidation of the trithiocarbonate (20) stopped at the oxythiocarbonyl stage while further oxidation was observed when peracetic acid was used.

EXPERIMENTAL

PART II

Numerals in brackets following sub-headings refer to page numbers in the original note book.

Melting points were determined on a Kofler block and are uncorrected.

Unless otherwise stated, infra-red spectra were run in chloroform on a Unicam S.P. 200 spectrometer and proton magnetic resonance (by Mrs. A. I. Boston) in deutero-chloroform on a Varian A. 60 instrument. Ultraviolet spectra were recorded in ethanol on Unicam S.P. 800 instrument.

The stock peracetic acid reagent for preparative experiments was made (if not stated otherwise) by diluting a 30% hydrogen peroxide solution ten times with glacial acetic acid.

Professor L. N. Owen kindly supplied an authentic sample of trans-1,2-(thiocarbonyldithio)cyclohexane.

Oxidation of trans-1,2-(Thiocarbonyldithio)cyclohexane and of trans-1,2-(Carbonyldithio)cyclohexane

Mercuric acetate oxidation of 1,2-(thiocarbonyldithio)-cyclohexane.(812)

A mixture of the trithiocarbonate (2.0 g.), mercuric acetate (8.0 g.) and glacial acetic acid (100 c.c.) was stirred vigorously for 40 minutes at 40°. The milky mixture was diluted with chloroform (100 c.c.) and the white insoluble material was filtered off. On evaporation, the filtrate gave a solid to which water (30 c.c.) was added. The mixture was extracted with chloroform (2 x 30 c.c.). The extract was washed with aqueous sodium bicarbonate solution and dried. Evaporation gave a solid which was crystallised from methanol. trans-1,2-(Carbonyldithio)-cyclohexane (1.5 g., 82%) had m.p. 109-110°.
Lit.[40] m.p. 106-107°.

Reactions with Peracetic Acid: Quantitative Measurements:

A stock solution was prepared by mixing 30% hydrogen peroxide solution (10 c.c.), glacial acetic acid (1000 c.c.) and concentrated sulphuric acid (5 c.c.). The stock

solution was kept overnight. A known volume of this solution (250 c.c.) was pipetted into a flask containing a weighed amount (ca. 1 millimole) of the compound under investigation. Simultaneously a blank run was carried out. Aliquots were removed at intervals and added to an excess of aqueous potassium iodide solution. The liberated iodine was titrated with standard thiosulphate solution using starch as the indicator. The number of moles of peracetic acid taken up per mole of the sample was calculated:

$$A = \frac{t \times N \times M}{2000 \times w}$$

where

A = number of moles of peracetic acid taken up per mole of the sample,

t = titration difference,

N = normality of thiosulphate,

M = molecular weight of the compound,

w = wt. of the compound in each aliquot.

Time (hours)	Moles of peracetic acid consumed per mole of the sample	
	trans-1,2-(Thiocarbonyldithio)-cyclohexane (816)	trans-1,2-(Carbonyldithio)-cyclohexane (818)
0.33	3.25	0.75
0.75	4.00	0.87
2	4.94	1.62
24	6.64	4.43
51.5	7.50	----
78.5	7.75	6.16
101.5	----	6.13
125	8.05	----
184	9.06	----

trans-1,2-(Oxythiocarbonyldithio)cyclohexane

(a) By lead tetra-acetate oxidation of trans-1,2-(thiocarbonyldithio)cyclohexane.(202)

A solution of lead tetra-acetate (2.2 g.) in glacial acetic acid (100 c.c.) was added dropwise to a stirred solution of the trithiocarbonate (1.0 g.) in glacial acetic

acid (150 c.c.). The resulting solution was left at room temperature for 15 minutes. Most of the acetic acid was removed under reduced pressure. To the residue, water (30 c.c.) was added and the mixture was extracted with chloroform (2 x 20 c.c.). The extract was washed with sodium bicarbonate solution and dried. Removal of chloroform gave a pale yellow solid which was crystallised from methanol. The oxythicarbonyldithio-compound (0.66 g., 61%) after recrystallisation from ethanol had m.p. 95-96°. Adley[40] reported m.p. 94-96°. (Found: O, 7.6. $C_7H_{10}OS_3$ requires O, 7.8%) $\nu_{max.}$ 1005 cm^{-1}; $\lambda_{max.}$ 284 and 349 mμ (ε 5350 and 10740 respectively); n.m.r., multiplets at τ 6.5 (2H) and 7.5-8.8 (8H).

(b) By peracetic acid oxidation of the trithiocarbonate. (356)

To a stirred solution of the trithiocarbonate (384 mg., ca. 2 millimole) in glacial acetic acid (70 c.c.), the stock peracetic acid solution (2.5 c.c., ca. 2 millimole) was added dropwise. The reaction mixture was shaken for $20\frac{1}{2}$ hours at room temperature. Acetic acid was removed under reduced pressure and the residue was dissolved in chloroform (20 c.c.). The solution was washed with water and dried. Removal of solvent gave a solid which

was purified by crystallisation from ethanol. The oxythiocarbonyldithio-compound had m.p. 95-96°; undepressed on admixture with the sample obtained by methol (a).

Oxidation of trans-1,2-(thiocarbonyldithio)cyclohexane with excess of peracetic acid.(59, 262)

To the trithiocarbonate (4.5 g.), peracetic acid solution (225 c.c.) was added. The resulting solution was kept at room temperature for 27 hours (or 67 hours). Most of the solvent was carefully removed by evaporation under reduced pressure at 35°. To the residue, water (50 c.c.) was added and the mixture was extracted with chloroform (3 x 30 c.c.). The extract was washed with water, dried and evaporated to a solid. trans-1,2-(Methylendisulphonyl)cyclohexane (0.5 g.) had m.p. 178° (sublimation) after crystallisation from ethanol; undepressed on admixture with an authentic sample (synthesis described later). (Found: C, 37.7; H, 5.5; S, 28.8; M, 222.9. $C_7H_{12}O_4S_2$ requires C, 37.7; H, 5.4; S, 28.6%; M, 224.3) $\nu_{max.}$ in carbon tetrachloride 1360, 1340 and 1180 $cm.^{-1}$ ($-SO_2-$); n.m.r. τ 5.7 (2H, sharp singlet), 6.6 (2H) and 7.3-9.0 (8H). The aqueous layer on evaporation and drying gave crude trans-cyclohexane-1,2-disulphonic

acid (5.0 g). It was characterised as its bisphenylhydrazine and barium salts (see below).

Bisphenyl hydrazine salt of the disulphonic acid.(38)

A solution of the crude disulphonic acid (0.7 g.) in ethanol (10 c.c.) was added to a solution of freshly distilled phenylhydrazine (0.75 g.) in alcohol (5 c.c.). The solid (1.2 g.) that separated out was purified by crystallisation from aqueous alcohol. The bisphenylhydrazine salt had m.p. 264-265°. (Found: N, 11.9. $C_{18}H_{28}N_4O_6S_2$ requires N, 12.2%). Sperling[68] gives m.p. 264-265° for a compound claimed to have the cis-configuration.

Barium salt of the disulphonic acid.(39)

A solution of the crude disulphonic acid (0.5 g.) in water (40 c.c.) was heated to boiling, and an aqueous solution of barium hydroxide was added dropwise till the solution became alkaline. Excess of barium hydroxide was neutralised with carbon dioxide. The insoluble material was removed by filtering the hot solution. The filtrate on concentration and cooling gave the barium salt of the disulphonic acid as its dihydrate (0.4 g.). (Found S, 15.1.

$C_6H_{10}BaO_6\{^{S_2}\ 2H_2O$ requires S, 15.4%). Sperling[68] reported a similar dihydrate assumed to the cis-compound.

trans-1,2-(Methylenedithio)cyclohexane.(270)

A mixture of trans-cyclohexane-1,2-dithiol[75] (2.0 g.) and formalin (5.1 c.c.) was shaken for 6 days. Concentrated hydrochloric acid (0.5 c.c.) was then added and the mixture was shaken for 2 more days. It was extracted with chloroform (2 x 20 c.c.) and the extract was washed and dried. Removal of solvent gave an oil which was distilled to give the methylenedithio-compound (1.35 g., 66%), b.p. 64-66/10^{-4} mm., n_D^{23} 1.5720. (Found S, 39.8. $C_7H_{12}S_2$ requires S, 40.0%).

trans-1,2-(Methylenedisulphonyl)cyclohexane.(302)

To the above mentioned methylenedithio-compound (82.4 mg.), glacial acetic acid (1 c.c.) and 30% hydrogen peroxide solution (1 c.c.) were added. The mixture was then heated on a steam bath for 35 minutes. Most of the solvent was removed by evaporation under reduced pressure and the residue was washed with water and dried. Crystallisation from ethanol gave the authentic disulphone (61 mg., 53%), m.p. 178° (sublimation).

Oxidation of trans-1,2-(carbonyldithio)cyclohexane with peracetic acid.(29)

The dithiocarbonate (1.3 g.) was dissolved in the stock peracetic acid solution (80 c.c.) and was kept at room temperature for 6 days. Excess of peracetic acid was removed by hydrogenation at atmospheric pressure in the presence of Adams' catalyst (42 mg.). Acetic acid was removed and the residue was extracted with water (50 c.c.). Removal of solvent gave crude trans-cyclohexane-1,2-disulphonic acid (1.3 g.). Its bisphenylhydrazine salt had m.p. 265°; undepressed on admixture with the salt of the sample of disulphonic acid obtained from cyclohexane trithiocarbonate (p. 158).

Oxidation of trans-2.3-(Thiocarbonyldithio)tetralin

Reaction with lead tetra-acetate: Quantitative Measurement: (428)

Essentially the same procedure was adopted as that employed for the peracetic acid oxidation of 1,2-(thiocarbonyldithio)cyclohexane. The stock solution was prepared by dissolving lead tetra-acetate (2.5 g.) in glacial acetic acid (100 c.c.). A portion (50 c.c.) of this solution was added to the trithiocarbonate (0.23 g.).

Time (minutes)	Moles of lead tetra-acetate consumed per mole of the trithiocarbonate
15	1.0
30	1.0
60	1.0

trans-2,3-(Oxythiocarbonyldithio)tetralin

(a) By lead tetra-acetate oxidation of trans-2,3-(thiocarbonyldithio)tetralin.(432)

A solution of lead tetra-acetate (0.5 g.) in glacial acetic acid (20 c.c.) was added to the trithiocarbonate (232 mg.). After 30 minutes, acetic acid was removed at 30° and water (25 c.c.) was added to the residue. The mixture was then extracted with chloroform (2 x 20 c.c.). The extract was washed with sodium bicarbonate solution, dried and evaporated to a solid. Crystallisation from ethanol gave the oxythiocarbonyldithio-compound (230 mg., 92%), m.p. 176°. (Found: C, 52.15; H, 4.2; O, 6.4. $C_{11}H_{10}OS_3$ requires C, 51.9; H, 4.0; O, 6.3%), ν max. 1000 $cm.^{-1}$; λmax. 283 and 347 mμ (ε 4600 and 11200 respectively); n.m.r. τ 2.71 (4H), 6.1 (2H) and 6.7 (4H).

(b) By peracetic acid oxidation of the tetralin trithiocarbonate.(408)

Stock peracetic acid solution (2.6 c.c., ca. 2 millimole) was added to the trithiocarbonate (0.5 g., ca. 2 millimole) in glacial acetic acid (90 c.c.) and the mixture was shaken for 21 hours. Acetic acid was removed at

40° and the residue was dissolved in chloroform (50 c.c.). The solution was washed with water, dried and evaporated to a solid. The oxythiocarbonyldithio-compound (0.5 g., 94%) had m.p. 176° after crystallisation from ethanol; undepressed on admixture with the sample obtained by methol (a).

Oxidation of trans-2,3-(thiocarbonyldithio)tetralin with excess of peracetic acid.(630)

A mixture of the trithiocarbonate (0.95 g.), glacial acetic acid (12 c.c.) and 30% hydrogen peroxide (8 c.c.) was heated on a steam bath for 15 minutes. After cooling, water (20 c.c.) was added and the mixture was extracted with chloroform (3 x 15 c.c.). The extract was washed with water, and sodium bicarbonate solution. The residue from the dried extract gave trans-2,3-(methylenedisulphonyl)-tetralin (70 mg.), m.p. 265-266° after crystallisation from ethanol; undepressed on admixture with the authentic sample (synthesis described later). From the aqueous layer crude trans-tetralin-2,3-disulphonic acid (1.0 g.) was obtained. It was characterised by preparing its bisphenylhydrazine salt (see below).

Bisphenylhydrazine salt of the disulphonic acid.(597)

A solution of phenylhydrazine (0.15 g.) in ethanol (1 c.c.) was added to a solution of the crude disulphonic acid (0.1 g.) in ethanol (1 c.c.). The precipitate was collected by filtration. Dilution of the filtrate with ether gave the bisphenylhydrazine salt m.p. 243-244° (decomposition). (Found: N, 11.0. $C_{22}H_{28}N_4O_6S_2$ requires N, 11.0%). The precipitate on crystallisation from aqueous alcohol gave the phenylhydrazine salt of sulphuric acid m.p. 89-92° (decomposition); undepressed on admixture with the authentic phenylhydrazine salt of sulphuric acid.

Peracetic acid oxidation of trans-2,3-(oxythiocarbonyldithio)tetralin.(598)

Acetic acid (12 c.c.) and 30% hydrogen peroxide solution (8 c.c.) were added to the oxythiocarbonyldithio-compound (0.9 g.) and the mixture was heated on a steam bath for 15 minutes. Most of the acetic acid was removed by evaporation under reduced pressure. Water (25 c.c.) was added and the mixture was extracted with ether (2 x 25 c.c.). The extract was dried and evaporated to

a solid. Crystallisation from ethanol gave trans-2,3-(methylenedisulphonyl)tetralin (50 mg.), m.p. 265-266°; undepressed on admixture with an authentic sample. (Found: C, 48.6; H, 4.5; S, 23.2. $C_{11}H_{12}O_4S_2$ requires C, 48.5; H, 4.4; S, 23.5%) $\nu_{max.}$ 1103, 1345, 1360 and 1300 cm^{-1}.

On evaporating the aqueous layer, crude trans-tetralin-2,3-disulphonic acid (1.3 g.) was obtained. The bisphenylhydrazine salt had m.p. 243-244°; undepressed on admixture with the salt of the sample of disulphonic acid obtained by oxidising tetralin trithiocarbonate with peracetic acid.

trans-2,3-(Methylenedithio)tetralin

(a) By the reaction of trans-tetralin-2,3-dithiol and formaldehyde. (842)

A mixture of the dithiol[76] (1.0 g.), formalin (5 c.c.) and concentrated hydrochloric acid (0.2 c.c.) was shaken for 3 days. The mixture was extracted with chloroform (2 x 10 c.c.). The extract was washed with water, dried and evaporated to an oil. Chromatography through silica gel with benzene gave the methylenedithio-compound (70 mg.), m.p. 98-100° after crystallisation from petroleum (b.p.40-60°).

(Found: C, 63.1; H, 5.8; S, 30.9; M, 204.1. $C_{11}H_{12}S_2$ requires C, 63.4; H, 5.8; S, 30.8%; M, 208.3).

(b) By the reaction of the dithiol and dimethoxymethane. (842)

A solution of the dithiol (0.5 g.) and p-toluenesulphonic acid (0.3 g.) in dimethoxymethane (50 c.c.) was heated under reflux for 3 hours and the mixture was then kept at room temperature for 48 hours. Solvent was removed and the residue was extracted with ether (20 c.c.). The extract was washed with water, normal sodium hydroxide solution and dried. Removal of ether gave a sticky residue (0.6 g.) which was purified by chromatography through silica gel using benzene as the eluent. The methylenedithio-compound had m.p. 98-100° after crystallisation from methanol; undepressed on admixture with the sample obtained by method (a).

trans-2,3-(Methylenedisulphonyl)tetralin.(628)

The mixture of trans-2,3-(methylenedithio)tetralin (20 mg.), glacial acetic acid (0.2 c.c.) and 30% hydrogen peroxide solution (0.2 c.c.) was heated on a steam bath, for 30 minutes. After cooling, the mixture was diluted

with water (5 c.c.) and extracted with chloroform (3 x 5 c.c.). The extract was washed with water and sodium bicarbonate solution. Evaporation of the dried solution gave a solid which was crystallised from ethanol. The methylenedisulphonyl-compound (21 mg., 80%) had m.p. 265-266°, and was identical with the product described on p.164.

Oxidation of trans-1,2-(Thiocarbonyldioxy)cyclohexane

Synthesis of trans-1,2-(thiocarbonyldioxy)cyclohexane

(a) By the reaction of trans-cyclohexane-1,2-diol, sodium hydride, carbon disulphide and methyl iodide. (544)

The mixture of the diol (5 g.), dry tetrahydrofuran (60 c.c.) and a 50% dispersion of sodium hydride in a mineral oil (2.35 g.) was heated under reflux for 1 hour. On cooling to room temperature, a solution of carbon disulphide (3.5 g.) in dry tetrahydrofuran (50 c.c.) was added dropwise and the mixture was kept at reflux for 10 minutes. Methyl iodide (7.0 g.) in tetrahydrofuran (50 c.c.) was slowly added and the mixture was again refluxed for 1 hour. The solvent was removed and the residue was extracted with chloroform. On evaporating the dried extract an oil (10 g.) was obtained. Chromatography through silica gel using benzene as the eluent gave three products: (A), trans-1,2-(thiocarbonyldioxy)cyclohexane (0.3 g.), m.p. 109° after crystallisation from benzene-light petroleum (b.p. 40-60°). (Found: C, 53.2; H, 6.7; S, 20.3; M, 159.7. $C_7H_{10}O_2S$ requires C, 53.1; H, 6.4; S, 20.3%;

M, 158.2) $\nu_{max.}$ in carbon tetrachloride 1288 and 1314 $cm.^{-1}$; λ max. 238 mμ (ε 16000). Corey[77] reported no physical constants for this compound. (B), 1-O-[(methylthio)thiocarbonyl]cyclohexane-trans-1,2-diol (4.5 g.), m.p. 53° after crystallisation from benzene-light petroleum (b.p. 40-60°). (Found: S, 31.3. $C_8H_{14}O_2S_2$ requires S, 31.1%) $\nu_{max.}$ in carbon tetrachloride 1065, 1230, 2925 and 3625 $cm.^{-1}$; λ max. 227 and 279 mμ (ε 11000 and 7450 respectively) and (C), essentially 1,2-di-O-[(methylthio)thiocarbonyl]cyclohexane-trans-1,2-diol (4 g.), b.p. 150-160° (bath)/10^{-4} mm. (Found: S, 43.8. $C_{10}H_{16}O_2S_4$ requires S, 43.3%). $\nu_{max.}$ in carbon tetrachloride 1070, 1210, 2850, and 2925 $cm.^{-1}$; λ max. 227 and 280 mμ (ε 20200 and 13000 respectively); n.m.r. τ 4.3 (2H), 7.5 (6H) and 7.7-8.6 (8H).

(b) By the reaction of the diol and thiophosgene.(654)

A solution of thiophosgene[78] (0.8 g.) in dry benzene (15 c.c.) was added dropwise to a stirred solution of the diol (0.4 g.) and pyridine (2.0 g.) in benzene (15 c.c.). The mixture was stirred for 15 hours and the insoluble material was filtered off. The filtrate was washed with water, 2N-hydrochloric acid and again with water. The dried extract was evaporated to a crystalline solid. Chromatography through silica gel, using benzene as the

eluent, gave the thiocarbonyldioxy-compound (0.3 g., 55%), m.p. 109° after crystallisation from benzene-petroleum (b.p. 40-60°); undepressed on admixture with the sample obtained by method (a).

Reaction of trans-1,2-(thiocarbonyldioxy)cyclohexane with lead tetra-acetate: Quantitative Measurement: (658)

The stock solution was prepared by dissolving lead tetra-acetate (2.65 g.) in glacial acetic acid (100 c.c.). A portion (50 c.c.) of this solution was added to the monothiocarbonate (115.7 mg.).

Time (hours)	Moles of lead tetra-acetate consumed per mole of the compound
0.33	1.0
1	1.1
17	1.5
142	2.4

trans-1,2-(Carbonyldioxy)cyclohexane

(a) By the lead tetra-acetate oxidation of trans-1,2-(thiocarbonyldioxy)cyclohexane. (672)

The mono-thiocarbonate (0.3 g.) was dissolved in a solution of lead tetra-acetate (1.8 g.) in glacial acetic acid (60 c.c.). After 30 minutes acetic acid was removed under reduced pressure and water (30 c.c.) was added to the residue. The mixture was extracted with chloroform (2 x 30 c.c.). The extract was washed with sodium bicarbonate solution, dried and evaporated. The residue on crystallisation from ether-petroleum ether (b.p. 40-60°) gave the carbonate (0.15 g., 56%), m.p. 54-55°. (Found: C, 59.0; H, 7.0. $C_7H_{10}O_3$ requires C, 59.15; H, 7.1%) ν max. 1795 and 1810 cm^{-1}.

(b) By the reaction of the monothiocarbonate and silver nitrate. (686)

Silver nitrate (0.3 g.) was added to a solution of the monothiocarbonate (63 mg.) in acetone (5 c.c.) containing a few drops of water. After 5 minutes barium carbonate (0.1 g.) was added and the mixture was stirred for 30 minutes. Insoluble material was filtered off and the filtrate was evaporated. The residue was extracted with chloroform

(15 c.c.). The extract was washed with water, dried and evaporated to a solid. Crystallisation from ether-light petroleum (b.p. 40-60°) gave the carbonate (40 mg., 71%), m.p. 54-55°; undepressed on admixture with the sample obtained by method (a).

(c) By the perphthalic acid oxidation of the monothiocarbonate. (806)

An ethereal solution of perphthalic acid[79] (9.5 c.c., ca. 1.25 millimole) was added to the monothiocarbonate (79 mg., ca. 0.5 millimole). After dilution with ether the mixture was kept at room temperature for 15 minutes. Ether was removed by evaporation under reduced pressure and the residue was extracted with chloroform (10 c.c.). The extract was washed with sodium bicarbonate solution, dried and evaporated to a residue. Crystallisation from ether-light petroleum (b.p. 40-60°) gave the carbonate (10 mg.), m.p. 54-55°; undepressed on admixture with the sample obtained by method (b). The residue (55 mg.) from the mother liquor showed ν max. 1795 and 1810 cm^{-1}.

Oxidation of trans-1,2-(Thiocarbonyloxythio)cyclohexane

Synthesis of trans-1,2-(thiocarbonyloxythio)cyclohexane. (848)

Reaction of cyclohexylene oxide with carbon disulphide in the presence of tetraethyl ammonium bromide yielded the dithiocarbonate m.p. 58-59°; νmax. 1010, 1060, 1085, 1145 and 1185 $cm.^{-1}$; λmax. 229 and 283 mμ (ε 15300 and 4770 respectively). Razuvaev et al.[59] report m.p. 58-59°.

Reaction of the dithiocarbonate with lead tetra-acetate: Quantitative Measurement: (856)

The stock solution was prepared by dissolving lead tetra-acetate (1.3 g.) in glacial acetic acid (50 c.c.). A portion (25 c.c.) of this solution was added to the dithiocarbonate (87 mg.).

Time (minutes)	Moles of lead tetra-acetate consumed per mole of the dithiocarbonate
10	0.84
30	0.94
60	0.97
120	1.00
1140	1.14

Oxidation of 1,2-(thiocarbonyloxythio)cyclohexane by lead tetra-acetate. (864)

The solution of the dithiocarbonate (87 mg.) and lead tetra-acetate (267 mg.) in glacial acetic acid (10 c.c.) was kept at room temperature for 2 hours. Acetic acid was removed under reduced pressure and the residue was extracted with chloroform (15 c.c.). The extract was washed with water and aqueous sodium bicarbonate solution. Removal of the solvent from the dried extract gave a liquid b.p. 150° (bath)/10^{-4} mm.; $\nu_{max.}$ 1090, 1150 and 1730 cm^{-1}. [infrared spectrum was found to be identical with that of an authentic sample of trans-1,2-(carbonyloxythio)cyclohexane[72]].

Oxidation of 1,2-(Thiocarbonyldioxy)benzene

Synthesis of 1,2-(Thiocarbonyldioxy)benzene. (670)

To a stirred solution of catechol (1.0 g.) and pyridine (8 c.c.) in dry benzene (40 c.c.), a solution of thiophosgene (3.0 g.) in benzene (20 c.c.) was added. After stirring the mixture for 15 hours, the insoluble material was filtered off. The filtrate was washed with water and 2N-hydrochloric acid. The dried extract was evaporated to a solid which was purified by chromatography through silica gel. By eluting with benzene the thiocarbonate (1.5 g., 75%) was obtained. It had m.p. 157-158° after crystallisation from methanol. (Found: M, 150.0. $C_7H_4O_2$ requires M, 152.2) νmax. 1300, 1340 and 1360 $cm.^{-1}$; λmax. 246, 255, 256 and 284 mμ (ε 10400, 12200, 11300 and 22000). Lit[80] m.p. 154°.

Reaction of 1,2-(thiocarbonyldioxy)benzene with lead tetra-acetate: Quantitative Measurement: (736)

The stock solution was prepared by dissolving lead tetra-acetate (5.4 g.) in glacial acetic acid (200 c.c.).

A portion (100 c.c.) of this solution was added to the monothiocarbonate (0.21 g.).

Time (hours)	Moles of lead tetra-acetate consumed per mole of the monothiocarbonate
0.16	0.44
0.33	0.46
0.66	0.50
1.0	0.51
2	0.56
5	0.58
70	1.20

Oxidation of 1,2-(thiocarbonyldioxy)benzene with lead tetra-acetate. (870)

A solution of lead tetra-acetate (2.0 g.) in glacial acetic acid (60 c.c.) was added to the thiocarbonate (175 mg.). After keeping the resulting solution at room temperature for 1 hour, the excess of lead tetra-acetate was destroyed by the addition of ethylene glycol. Acetic acid was removed under reduced pressure and water (40 c.c.) was added to the residue. The mixture was then extracted with chloroform (40 c.c.). The extract was washed with water and aqueous

sodium bicarbonate solution. Removal of the solvent from the dried extract gave a crystalline residue. After crystallisation from methanol di[acetoxy-(o-phenylene-dioxy)methy]disulphide (200 mg., 82%) had m.p. 152-156°. (Found: C, 50.8; H, 3.2; S, 15.4; M, 412. $C_{18}H_{14}O_8S_2$ requires C, 51.2; H, 3.3; S, 15.2%; M, 422), $\nu_{max.}$ 995, 1100, 1490 and 1780 $cm.^{-1}$; n.m.r. τ 3.1 (8H) and 7.93 (6H). The disulphide seemed to decompose on keeping at room temperature (gradual lowering of melting point).

Treatment of a solution of 1,2-(thiocarbonyldioxy)benzene in acetic acid with iodine. (746)

The solution of the thiocarbonate (0.10 g.) and iodine (0.09 g.) in glacial acetic acid (100 c.c.) was kept at room temperature for 1 hour. The excess of iodine (0.09 g.) was estimated by titration with a standard sodium thio-sulphate solution. Thus it was apparent that the solution did not consume any iodine.

1,2-(Carbonyldioxy)benzene. (682)

Condensation of catechol with phosgene in toluene solution in the presence of pyridine gave the carbonate

m.p. 120-121°, $\nu_{max.}$ 1013, 1115, 1335, 1493, 1795 (shoulder), 1830 and 1845 cm^{-1}. Lit.[8i] m.p. 120°.

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