

THE PREPARATION OF OPTICALLY ACTIVE THIOLS VIA ISO-THIURONIUM  
SALTS. ADDITION AND OTHER REACTIONS OF ASYMMETRIC THIOLS.

Being a thesis submitted to the University of  
London for the degree of Doctor of Philosophy

by

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July 1956



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The work described in this thesis has been carried out in the Organic Chemistry Research Laboratory at Battersea Polytechnic under the direction of Dr.F.R.Goss. The author wishes to express his thanks to Dr.C.L.Arcus who supervised the work, for his continued interest and invaluable advice.

ABSTRACT of THESIS

(-)-Octane-2-thiol has been prepared by alkaline decomposition of the thiuronium salt derived from thiourea and (+)-2-bromo-octane. Fractional crystallisation of (+)-2-octyl (+)-camphor-10-sulphonate failed to effect resolution into the diastereoisomeric salts.

(+)- and (-)-1-Methyl-2-phenylethyl toluene-p-sulphonate have been converted into the thiuronium toluene-p-sulphonates, which on decomposition gave (-)- and (+)-1-phenylpropane-2-thiol.

A mechanism is proposed for the reaction of thiourea with 2-bromo-octane and with 1-methyl-2-phenylethyl toluene-p-sulphonate.

Addition (peroxide- and base-catalysed) of (+)-, (+)-, and (-)-1-phenylpropane-2-thiol to w-nitrostyrene has been investigated, two diastereoisomeric sulphides (or sulphones) being obtained in each case; configurational relationships are proposed for these products. With neither catalyst is the reaction sterically unilateral. It is tentatively concluded that free radical addition proceeds in a symmetrical manner, whereas the base-catalysed addition proceeds disymmetrically.

(-)-1-Methyl-2-phenylethyl 2:4-dinitrophenyl sulphone has been shown to be optically stable under acidic conditions employed for oxidation.

Addition of (+)-1-phenylpropane-2-thiol to trans-1:2-dibenzoyl ethylene gave a solid and an oily sulphide. Oxidation of these sulphides, in glacial acetic acid with hydrogen peroxide gave a common sulphone; enolisation of the keto-sulphide, or sulphone, is thought to occur. Oxidation with the hot reagent causes elimination; a tentative mechanism is proposed. Oxidation of the benzyl thiol addition product also proceeds with (partial) elimination in hot solution.

From the addition of (+)-1-phenylpropane-2-thiol to 4'-nitrochalcone a single isomer of (+)-2-(p-nitrobenzoyl)-1-phenyl-1'-benzyl diethyl sulphide has been isolated; the benzyl thiol addition product of 4'-nitrochalcone has also been prepared.

Alkylation reactions of (+)-1-phenylpropane-2-thiol have been carried out with two symmetrical carbinols (yielding solid sulphides) and with four disymmetric carbinols, of which two yielded solid sulphides; a single isomer of (+)-1-methyl-2-phenylethyl p-diphenylphenylmethyl sulphide and two isomers of (+)-1-methyl-2-phenylethyl p-dimethylamino-diphenylmethyl sulphide have been isolated.

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Introduction.Object of the present work.

For the further investigation of partial asymmetric synthesis by addition of asymmetric compounds to olefins, thiols recommended themselves by virtue of their ease of addition to certain classes of olefin. The thiol to be used in the investigation was chosen so as to have its asymmetric centre adjacent to the thiol group in order to give the maximum possibility of asymmetric synthesis, since the configuration in which the new asymmetric centre is formed from the olefin would be expected to be more strongly influenced by the original centre of asymmetry the greater the proximity of this centre.

It was found necessary to develop a method whereby such a thiol could be prepared in a state of optical purity and in reasonable quantity.

The olefins chosen for the investigation were of structure,  $RCH=CHX$ , where X is an electron-attracting group facilitating the addition of thiol,  $R^*SH$ ; a new asymmetric centre is thus created:

$$R^*CH \cdot CH_2X$$

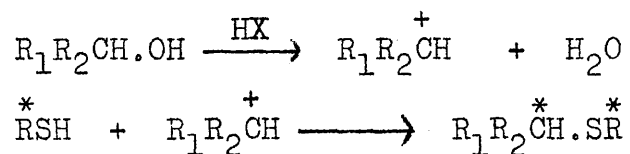
$$\quad \quad \quad |$$

$$\quad \quad \quad SR^*$$

The operation of asymmetric synthesis leads to the formation of the diastereoisomerides of this sulphide in unequal quantity, whence asymmetric

synthesis can (in principle) be detected and evaluated by fractional separation of the reaction product. The procedure is applicable to both free-radical and anionic (Michael) addition of thiols.

A second type of reaction, to which this method of investigation is applicable, is the alkylation of an asymmetric thiol with a carbon cation, derived from a ( $\pm$ )-carbinol, of such a structure that on combination it gives rise to a new asymmetric centre. The alkylation would be expected to proceed dissymmetrically, giving rise to a partial asymmetric synthesis, the degree of which is determinable from the weight-ratio of the diastereoisomeric products:



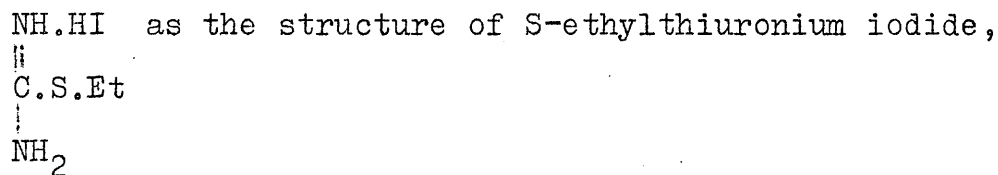
SECTION I

The Preparation of Optically Active Thiols.

Thiuronium Salts

The formation of S-alkylthiuronium salts was first reported by Claus (1) who prepared S-ethylthiuronium bromide by heating ethylbromide and thiourea. The compound analysed as a 1:1 mixture of the reactants; heating, however, caused decomposition to ethyl thiol, Claus' account of his work is, however, imprecise. In the same year Nencki (2) prepared S-ethylthiuronium oxalate by interaction of thiourea and ethyl oxalate.

Structural formulae for these compounds were proposed by Claus (3) and Bernthsen and Klinger (4), but it was not until 1884 that Rathke (5) proposed



which is acceptable as correct. The same worker, by careful addition of alkali, isolated the free thiourea base, as had been reported by Bernthsen and Klinger (4). These workers (6), in 1879, prepared S-benzylthiuronium chloride, and its free base, which was found to be unstable in dilute solution, decomposing to benzyl thiol and dicyandiamide. The first pure specimen of S-benzylthiuronium chloride was obtained by Werner (7) who showed that the compound is dimorphic and exists in two interconvertible forms of differing melting point,

their formation depending on the method of crystallisation; the compound does not, however, occur in two structurally-differing forms as suggested later by Taylor (8).

Since their initial preparation thiuronium salts have been used extensively as intermediates in the preparation of thiols (page 4) and as analytical reagents for the qualitative identification of organic acids.

In 1924 Chambers and Sherer (9) introduced S-benzylthiuronium chloride as a reagent for the identification and separation of several naphthalene sulphonic acids.

The general method was broadly extended later by Donleavy (10), Anderson (11), and Viebel et al. (12) to the preparation of derivatives of carboxylic and sulphonic acids. S-p-halogenobenzylthiuronium chlorides were also found to be suitable reagents, but they suffer from the same disadvantage as the unsubstituted reagent, namely, that the melting points of derivatives of homologous aliphatic acids are close to one another. S-1-Naphthylmethylthiuronium chloride (Bonner, 13) was found to be a more satisfactory reagent.

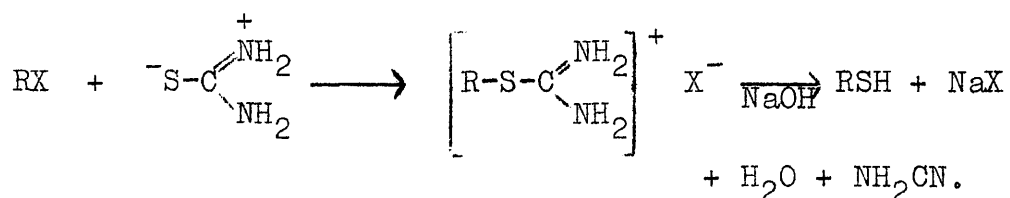
A further logical extension of this work is its modification for the identification of alkyl and aralkyl halides. Brown and Campbell (14) and Levy and

Campbell (15) record sharp melting points of S-alkyl and S-aralkylthiuronium picrates; these compounds can be rapidly prepared in a pure state and show sufficient variation of melting point between members of a homologous series, and between structural isomers, to be useful in the identification of the halides. The use of styphnic and other organic acids has been introduced by Juracek and Vecera (16) and Schotte et al. (17).



The Preparation of Thiols by the Decomposition of  
S-Alkylthiuronium Salts

Alkyl and aralkyl halides (18) and reactive esters (19) react readily with thiourea to give the corresponding thiuronium salts. Decomposition of these salts with alkali, in an inert atmosphere, gives good yields of the thiols, together with dicyandiamide.



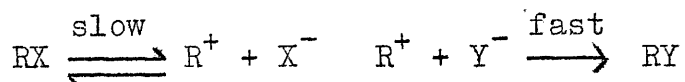
Many types of groups, R, have been introduced including primary (20), secondary (21) and tertiary alkyl (22), allyl (23), active aromatic (24), and heterocyclic (25) groups. It has been generally shown that the rate of reaction is slow with chlorides, but relatively fast with bromides and iodides.

A modification of this method, commencing with an alcohol has been described by Frank and Smith (20). The alcohol, thiourea and concentrated halogen acid are heated together for several hours, the thiol being liberated from the thiuronium salt, which is not isolated, with alkali under nitrogen.

The Stereochemistry of Nucleophilic Substitution  
Reactions

The discussion on the formation of thiuronium salts necessarily involves reference to modes of aliphatic substitution; these are set out, in a summary form, in the present section.

a) The Unimolecular Reaction, S<sub>N</sub>1

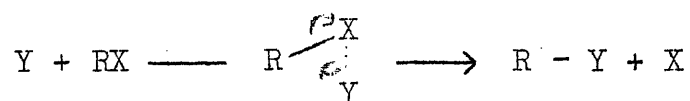


Rate of reaction  $\propto$  [RX].

If the life of the carbonium ion, R<sup>+</sup>, formed in the S<sub>N</sub>1 reaction is long enough for the ion to assume a planar structure, and for the replaced electro-negative group X to recede far enough from the centre of reaction so as not to affect the direction of approach of the reagent Y, then the reaction product will be completely racemic, provided that the configuration of R is not held internally. However, the stereochemical results of the S<sub>N</sub>1 reaction are, frequently, racemisation accompanied by inversion, caused by asymmetric shielding due to the receding group X, or in some cases racemisation accompanied by retention of configuration, the S<sub>N</sub>i reaction.

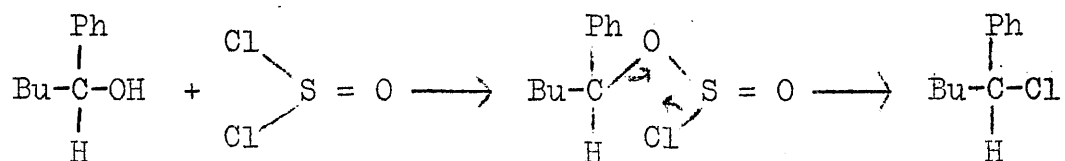
b) The S<sub>N</sub>i Reaction

In this mechanism, RX and Y form a complex involving internal bonding, reaction proceeding via a cyclic transition state



presumably with the rate of reaction proportional to the product of the concentrations of the reactants. Few examples of this type of reaction have been reported and no kinetic investigation has been described.

Most of the reactions investigated apply to alcohols, and may be exemplified by the reaction between 1-phenylamyl alcohol and thionyl chloride (26).



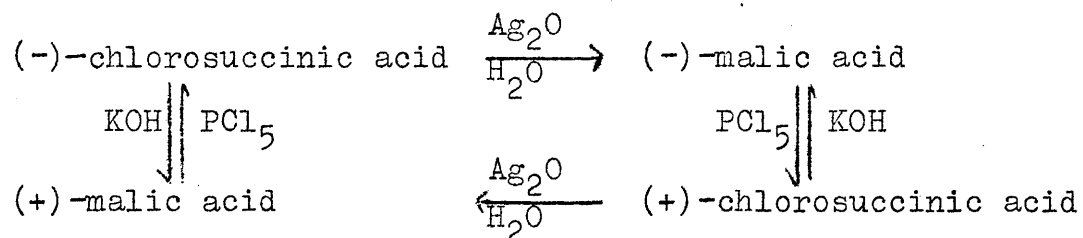
where the entering group assumes the steric position of the displaced group. Reaction of this alcohol with phosphorous pentachloride (27) and hydrogen chloride (28) gives simultaneous S<sub>N</sub>1 and S<sub>N</sub>i reactions.

The reactions of 90% hydrogen peroxide with alcohols also proceed by the S<sub>N</sub>i mechanism, retention of configuration being observed (Feld, 29).

c) The Bimolecular Reaction, S<sub>N</sub>2

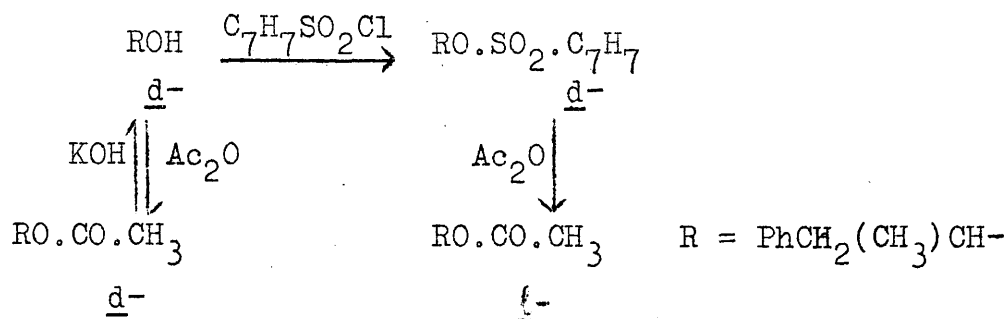
Rate of reaction  $\propto [Y^-].[RX]$ .

In 1896 Walden (30) showed that by two substitutions at the optically active centre, (-)-chlorosuccinic acid could be converted into its enantiomer.



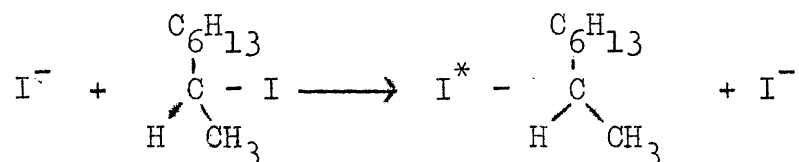
To determine the exact reaction scheme it was necessary to correlate sign of rotation with configuration and thus to ascertain the mechanism whereby inversion occurs. Kenyon, Phillips and their co-workers, from 1923 onwards, established with certainty the relationship between sign of rotation and configuration for a large number of compounds.

An example of their reaction schemes is given by the reactions of (+)-1-phenylpropan-2-ol.



The esterifications of the alcohol with toluene-*p*-sulphonyl chloride and with acetic anhydride do not involve disturbance of the asymmetric centre, whence both give retention of configuration; the action of acetate ions on the sulphonate must therefore proceed with essentially complete inversion.

Inversion of configuration has also been demonstrated by Hughes and his co-workers (31) by means of a halide-exchange experiment. It was shown that for the bimolecular reaction between optically-active 2-octyl iodide and sodium iodide containing radioactive iodine, in dry acetone, the rate of substitution by radioactive iodine was equal to half the rate of racemisation of the iodide.



Since each molecule inverted "neutralises" another of the original configuration, the relationship

$$\frac{\Delta \text{racemisation}}{\Delta t} = 2 \times \frac{\Delta \text{substitution}}{\Delta t} \quad \text{should apply,}$$

and this was in fact found to be so.

Optically Active Thiols

Optically active thiols have been prepared by Levene and Mikeska (32) by reaction of an optically active halide with potassium hydrogen sulphide, the investigations of these authors forming part of a study of the Walden Inversion. The optical rotatory powers of (+)-butane- and (+)-octane-2-thiols recorded by these workers were lower than those obtained by Kenyon, Philips and their co-workers (33). These authors prepared (-)-octane-2-thiol by reaction of (+)-2-octyl toluene-p-sulphonate with potassium hydrogen sulphide, and (-)-butane-2-thiol and (-)-1-phenylpropane-2-thiol were prepared by the following method: reaction of the optically active 2-alkyl toluene-p-sulphonate with potassium thiocyanate gave the alkyl thiocyanate, alkaline hydrolysis of the latter, which was accompanied by oxidation, gave the disulphide, which on reduction yielded the thiol.

For the present work, comparatively large quantities of one, or more, optically pure thiols were required and the decomposition of thiuronium salts, of which there are many examples for the preparation of optically inactive thiols, recommended itself as the most satisfactory general method. The only instances of the

use of optically active reagents in the preparation of thiuronium salts relate to the preparation of sugar and terpene derivatives. S-tetra-O-acetyl- $\beta$ -D-glucosyl-thiuronium bromide has been prepared (34, 35) and yielded the silver salt of l-thio-D-glucose on reaction with methanolic ammonia in the presence of ammoniacal silver nitrate (34). Subluvskey and King (36), by heating camphene and related terpenes with thiourea and toluene-p-sulphonic acid, obtained S-isobornyl thiuronium toluene-p-sulphonate. They also prepared this salt by heating bornyl toluene-p-sulphonate with thiourea; the salt obtained from bornyl ester of 8% optical purity possessed a small rotation but became optically inactive on recrystallisation. Salt of higher rotation was isolated as a crop from the camphene reaction. Optically inactive iso-bornyl thiol (a solid) was obtained by decomposition of active and inactive thiuronium salts. The authors imply that the loss of activity is due to racemisation but it is not less probable that the loss is due to the separation of ( $\pm$ )-material from mixtures of low optical purity. Fractional crystallisation of S-iso-bornyl-thiuronium (+)-camphor-10-sulphonate, prepared from camphene of about 9% optical purity, led to the separation of the diastereoisomeric salts, one of which was obtained optically pure: however these salts were not

converted into thiol.

The literature above points to two methods whereby optically active thiols may be prepared via thiuronium salts:

- 1) The preparation of the ( $\pm$ )-S-alkylthiuronium salt of an optically active acid, followed by its resolution into diastereoisomeric salts by fractional crystallisation; these are then converted into enantiomorphous thiols.
- 2) Conversion of an optically active halide, or reactive ester, into the corresponding thiuronium salt and thence into active thiol.



The Preparation of Optically Active Thiols

Octan-2-ol

 $\alpha_{5893}^{21} -8.10^\circ(\underline{1}, 1)$ 

2-bromo-octane

 $\alpha_{5893}^{20} +20.55^\circ(\underline{1}, 0.5)$ 

Octane-2-thiol

 $\alpha_{5893}^{22} -9.29^\circ(\underline{1}, 0.5)$ 

1-Methyl-2-phenyl-ethyl toluene-p-sulphonate

1-Phenylpropane-2-thiol

1-Phenylpropan-2-ol

 $\alpha_{5893}^{18} +13.6^\circ(\underline{1}, 0.5) [\alpha]_{5893}^{20} + 25.2^\circ$  $\alpha_{5893}^{23} -13.46^\circ(\underline{1}, 1)$  $\alpha_{5893}^{23} -26.24^\circ(\underline{1}, 1) [\alpha]_{5893}^{24} - 22.9^\circ$  $\alpha_{5893}^{17} +6.08^\circ(\underline{1}, 0.5)$

## The Preparation of Optically Active Thiols

### Discussion of Results

(±)-Octane-2-thiol was prepared by alkaline decomposition, in a nitrogen atmosphere, of (±)-S-2-octylthiuronium bromide derived from reaction between thiourea and (±)-2-bromo-octane in ethanol. The intermediate thiuronium bromide could not be induced to solidify; the thiuronium benzoate and (+)-camphor-10-sulphonate, however, are crystalline solids.

(±)-1-Phenylpropane-2-thiol was prepared by alkaline decomposition of (±)-S-1-methyl-2-phenylethylthiuronium toluene-p-sulphonate, obtained by reaction of thiourea with (±)-1-methyl-2-phenylethyl toluene-p-sulphonate in ethanol.

The preparation of thiols by Frank and Smith's method (page 6) failed to yield pure compounds: decomposition of the material obtained by heating (±)-octane-2-ol, thiourea and hydrobromic acid for 9 hours, yielded impure thiol in 72% yield, refractive index measurements indicated a 10% impurity of unreacted (±)-octane-2-ol. Decomposition of the material similarly obtained from (±)-1-phenylpropan-2-ol failed to yield any thiol, the (±)-carbinol being regenerated in 66% yield.

It was thought possible that optically active

thiols could be prepared by decomposition of the diastereoisomers obtained by fractionation of the salt of an optically active acid with a ( $\pm$ )-thiuronium cation. However, repeated fractional crystallisation of ( $\pm$ )-S-2-octylthiuronium (+)-camphor-10-sulphonate from ethyl acetate and from heptan-4-one did not effect any separation. The purified salt, a well defined crystalline compound, yielded ( $\pm$ )-octane-2-thiol on decomposition, and on decomposition of the thiuronium benzoate obtained from it by interaction with sodium benzoate. Decomposition of the (+)-camphor-10-sulphonate in the presence of chloro-2:4-dinitrobenzene yielded optically inactive ( $\pm$ )-2-octyl 2:4-dinitrophenyl sulphide.

It was thus concluded that the solubilities of the diastereoisomeric (+)-camphor-10-sulphonates are not sufficiently at variance to permit separation by the method attempted.

Optically active 2-octane- and 1-phenylpropane-2-thiols were therefore prepared by first resolving octan-2-ol, and 1-phenylpropan-2-ol, and carrying through the successive stages with optically active compounds.

#### (+)- and (-)-octane-2-thiols

( $\pm$ )-octan-2-ol was resolved by fractional crystallisation of the brucine salt of its hydrogen

phthalate according to Kenyon (37).

(+)- and (-)-Octan-2-ol were converted into (-)- and (+)-2-bromo-octane by reaction with phosphorus tribromide at  $-10^{\circ}$ . Of the methods for the conversion of octanol into bromo-octane developed by Gerrard, the procedure was used which appeared to give the most useful combination of optical and chemical yields (38).

#### (+)-octane-2-thiol

Decomposition of (+)-S-2-octylthiuronium bromide, an oil obtained by reaction of thiourea with (-)-2-bromo-octane,  $\alpha_{5893}^{21} -20.65^{\circ}(\underline{1}, 0.5)$ , gave a specimen of (+)-octane-2-thiol,  $\alpha_{5893}^{24} + 5.36^{\circ}(\underline{1}, 0.5)$ ,  $n_D^{20} 1.4475$ . From the refractive index, and the rotatory power, this material is concluded to contain some (+)-octan-2-ol, due to the fact that the thiuronium salt was not separated from unreacted (-)-2-bromo-octane. This octanol, the product of two inversions would no doubt be extensively racemised. Accordingly a solid thiuronium salt was prepared.

#### (-)-octane-2-thiol

Reaction of thiourea with (+)-2-bromo-octane,  $\alpha_{5893}^{20} + 20.55^{\circ}(\underline{1}, 0.5)$ , gave (-)-S-2-octylthiuronium bromide treatment of which with sodium benzoate precipitated the thiuronium benzoate. Alkaline decomposition

of the latter, under nitrogen, yielded (-)-octane-2-thiol,  $\alpha_{5893}^{22} - 9.29^{\circ}(\underline{1}, 0.5)$ ,  $n_D^{20} 1.4520$ , which contained the theoretical quantity of sulphur.

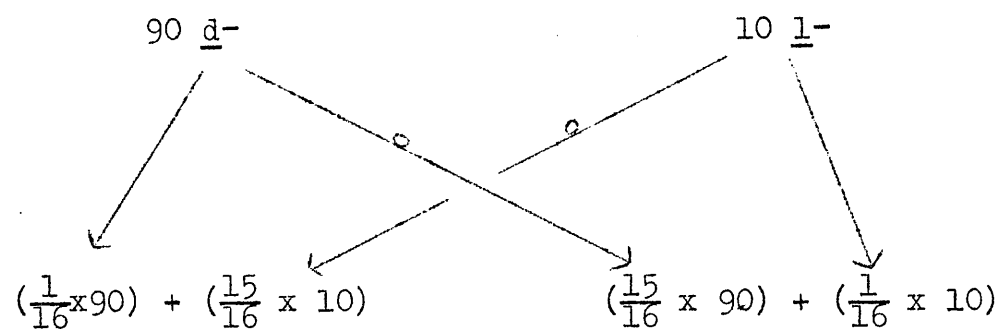
#### Extent of Inversion

The percentage optical purity of the (-)-octane-2-thiol is based on the taking as a standard of a figure interpolated from the rotatory power at seven different wave-lengths published by Kenyon and his co-workers (33). If the maximum specific rotatory power of 2-bromo-octane is assumed to be approximately  $\pm 45^{\circ}$ , this being the maximum value which has been obtained by Gerrard (39), then the reaction of (+)-2-bromo-octane,  $\alpha_{5893}^{20} + 20.55^{\circ}(\underline{1}, 0.5)$ , 84% optically pure, with thiourea to give, on decomposition, (-)-octane-2-thiol,  $\alpha_{5893}^{22} - 9.29^{\circ}(\underline{1}, 0.5)$ , 72% optically pure, is accompanied by 86% "net" inversion of configuration.

This percentage is expressed as a "net" inversion, and not a "true" inversion, which also considers the inversion of configuration of the minor fraction of the material of opposite sign of rotation to the major fraction. For example, reaction of compound of 80% optical purity, to give a compound of opposite configuration of 70% optical purity, occurs with a "net" inversion of 7/8. "True" inversion considers the starting material as being

90%(d)- and 10%(l)- giving 85%(l)- and 15%(d)- compounds, the calculation of the inversion including consideration of the inversion of the 10%(l)- material. The value for "true" inversion is  $\frac{15}{16}$ , as may be shown as follows:

Compound I



Compound II

<u>d</u> -	<u>l</u> -
15%	85%

From the following data it is concluded that 2-bromo-octane reacts with thiourea with inversion of configuration and that substitution may be completely bimolecular:

- 1) Data published by Kenyon et al. (33) on rotatory powers and configurations indicates that the (-)-thiol and (+)-bromide have opposite configurations.
- 2) Hughes, Ingold and Masterman (40) show that 2-bromo-octane reacts with ethoxide ion in ethanol with 100%

inversion and 100% bimolecular reaction, and in aqueous-ethanol (40:60) it reacts with hydroxyl ion with 95% inversion and 95% bimolecular reaction.

(+)- and (-)-1-Phenylpropane-2-thiol

Benzyl methyl ketone was reduced to ( $\pm$ )-1-phenylpropan-2-ol by reaction with aluminium iso-propoxide in iso-propanol. This method, which proved to be satisfactory, has been used in place of the reduction by sodium in ethanol, used by earlier workers (41).

( $\pm$ )-1-Phenylpropan-2-ol was resolved by the method briefly described by Kenyon and Pickard (41), Phillips (42) and Kenyon, Phillips and Cochinaras (33).

( $\pm$ )-1-Methyl-2-phenylethyl hydrogen phthalate, prepared by interaction of ( $\pm$ )-1-phenylpropan-2-ol with phthalic anhydride in pyridine was warmed with a molecular proportion of anhydrous brucine in acetone. After four crystallisations from acetone there was obtained the brucine salt (m.p. 151-3°) of optically pure (+)-1-methyl-2-phenylethyl hydrogen phthalate. Decomposition of this salt, with dilute hydrochloric acid in the presence of ether, yielded (+)-1-methyl-2-phenylethyl hydrogen phthalate as a colourless oil,  $[\alpha]_{5893}^{20} + 48.0^\circ$ ,  $[\alpha]_{5461}^{18} + 57.8^\circ$  (1, 2; c, 4225 in chloroform), after thorough drying in vacuo over phosphoric oxide.

Hydrolysis of this (+)-hydrogen phthalate with 5N sodium hydroxide yielded (+)-1-phenylpropan-2-ol,  $\alpha_{5893}^{19} + 13.60^\circ$ ,  $\alpha_{5461}^{18} + 16.48^\circ$  (1, 0.5).

From the more soluble fractions of brucine salt, there was obtained nearly fully active (-)-1-methyl-2-phenylethyl hydrogen phthalate as a colourless oil,  $[\alpha]_{5893}^{20} - 47.3^\circ$ ,  $[\alpha]_{5461}^{20} - 57.3^\circ$  (1, 2; c, 4.262 in chloroform), hydrolysis of which with 5N sodium hydroxide yielded (-)-1-phenylpropan-2-ol,  $\alpha_{5893}^{23} - 26.24^\circ$ ,  $\alpha_{5461}^{23} - 31.6^\circ$  (1, 1). (+)-1-Methyl-2-phenylethyl toluene-p-sulphonate,  $[\alpha]_{5893}^{20} + 25.2^\circ$ , 100% optically pure, on reaction with thiourea, gave (+)-S-1-methyl-2-phenylethylthiuronium toluene-p-sulphonate, which on treatment with alkali, under nitrogen, gave (-)-1-phenylpropane-2-thiol,  $\alpha_{5893}^{23} - 13.46^\circ$  (1, 1). The (-)-ester,  $[\alpha]_{5893}^{24} - 22.9^\circ$ , 92% optically pure, similarly gave (+)-1-phenylpropane-2-thiol,  $\alpha_{5893}^{17} + 6.08^\circ$  (1, 0.5), 90% of the value obtained for the (-)-thiol.

The optical purity of the toluene-p-sulphonic esters is based on values recorded by Phillips (43). The figure,  $\alpha_{5893} - 15.3^\circ$  (1, 1), for the rotatory power of (-)-thiol reported by Kenyon et al. is that of a single preparation of the thiol by a complicated procedure (page II), the reported refractive index not being in agreement with that found in the present work, nor with the value



calculated from the theoretical molar refractivity.

The (+)- and (-)-sulphonic esters were prepared from (+)- and (-)-1-phenylpropan-2-ol by reaction with toluene-p-sulphonyl chloride and pyridine (Phillips, 43) a process in which the bonds of the asymmetric carbon atom are not disturbed. The reaction of the sulphonic esters with thiourea is therefore considered, from the following data, to proceed with inversion, and probably by the bimolecular mechanism.

(a) The kinetics of the reaction between tetraacetyl- $\beta$ -D-glucosyl bromide and thiourea have been studied polarimetrically by Bonner and Kahn (35), who found the reaction to be of the second order; the thiuronium salt so formed showed no mutarotation, whence it was concluded that the reaction is not reversible. These authors put forward a mechanism similar to that given below.

(b) Conductometric studies of the kinetics of the reaction between alkyl halides and thiourea by Vecera and Juracec (44) show that the rate of formation of S-alkylthiuronium halides increases, F, Cl, Br, I

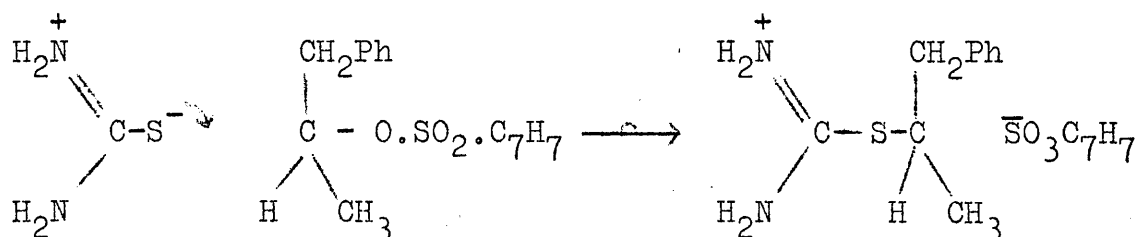


iso-butyl, n-butyl

results consistent with the bimolecular reaction

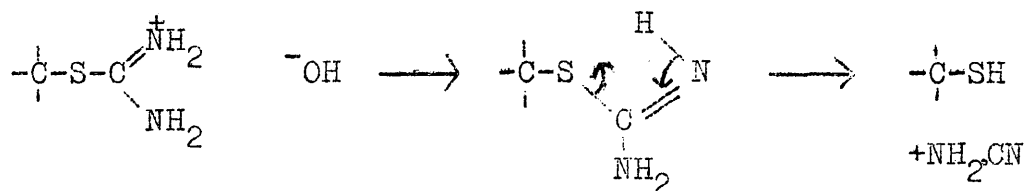
- (c) Kenyon et al. (33) from a comparison of rotatory powers, conclude 1-phenylpropan-2-ol and 1-phenylpropane-2-thiol of opposite signs of rotation to be of opposite configurations.
- (d) 1-Methyl-2-phenylethyl toluene-p-sulphonate reacts with inversion with numerous reagents (33), and with ethanolic potassium acetate and valerate (the two instances in which the alcohol was regenerated by hydrolysis of the product) the inversion is respectively 97 and 96% (43).

The following mechanism is proposed for the reaction of the sulphonic ester with thiourea

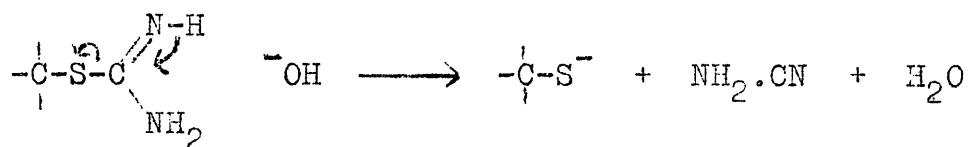


The nitrogenous product of the decomposition of thiuronium salts is dicyandiamide (6). The monomeric cyanamide can be formed from the thiuronium cation by either of two slightly different mechanisms.

- 1) Removal of a proton by hydroxyl ion (or, in the decomposition of S-alkylthiuronium hydrogen carbonates studied by Horak (45), by the  $\text{HCO}_3^-$  ion) followed by rearrangement as shown:



- 2) Formation of the free base followed by its reaction with a second hydroxyl ion, yielding the thiol anion.



In neither mechanism are the bonds of the asymmetric carbon atom disturbed whence it retains the configuration which it had in the thiuronium salt.

Experimental(±)-S-2-Octylthiuronium bromide

Method of Johnson and Sprague (46)

(±)-2-bromo-octane (25.5 g.) and thiourea (10.1 g.) were heated under reflux in ethanol (100 ml.) for 5 hours. The ethanol was removed at reduced pressure, oily (±)-S-2-octylthiuronium bromide being obtained. The oil could not be induced to solidify by freezing nor by attempted crystallization from numerous solvents.

(±)-S-2-Octylthiuronium (+)-camphor-10-sulphonate

To a suspension of (±)-S-2-octylthiuronium bromide (35 g.) in water (100 m.) was added a solution of sodium (+)-camphor-10-sulphonate (33 g.) in water (100 ml.). The product (an oil), was solidified by freezing at  $-80^{\circ}$ , (±)-S-2-octylthiuronium (+)-camphor-10-sulphonate (29 g.) m.p.  $106-112^{\circ}$ ,  $[\alpha]_{589}^{20} + 24.5^{\circ}$  ( $\underline{1}$ ,  $\underline{1}$ ;  $\underline{c}$ , 4.988 in ethanol) being obtained.

Fractionation to constant specific rotation, from ethylacetate and hept-4-one gave pure (±)-S-2-octylthiuronium (+)-camphor-10-sulphonate, m.p.  $119^{\circ}$   $[\alpha]_{589}^{20} + 26.3^{\circ}$  ( $\underline{1}$ ,  $\underline{1}$ ;  $\underline{c}$ , 4.991 in ethanol), no separation of diastereoisomerides being obtained. [Found: N, 6.75; S, 15.50.

$C_{19}H_{36}O_4N_2S_2$  requires N, 6.65; S, 15.30%].

(±)-octane-2-thiol

(±)-S-2-octylthiuronium (+)-camphor-10-sulphonate (12.6 g.,  $[\alpha]_{5893}^{20} + 25.6^{\circ}$ ) was placed in a flask fitted with stirrer reflux condenser and nitrogen inlet. The flask was filled with nitrogen, and 1.5 N sodium carbonate (40 ml.) was introduced with stirring. After 2 hours at  $50^{\circ}$ , the chilled solution was acidified to Congo Red with 3N hydrochloric acid. The solution was thrice extracted with ether. The combined extracts were washed with water and dried ( $\text{Na}_2\text{SO}_4$ ) under nitrogen. The ether was removed in a slow stream of nitrogen, and distillation in nitrogen at reduced pressure gave (±)-octane-2-thiol (25 g.) b.p.  $83-4^{\circ}/26$  mm.  $\alpha_{5893}$  zero (1, 1),  $n_D^{20}$  1.4500.

The attempted preparation of (±)-octane-2-thiol

Method of Frank and Smith (page 6)

(±)-Octan-2-ol (9.1 g.), thiourea (5.3 g.) and 60% hydrobromic acid (16.8 g.) were heated on a steam bath for 9 hours with vigorous stirring. The flask was filled with nitrogen, 10% sodium hydroxide (42 ml.) was added, and the whole was maintained, with stirring, at  $100^{\circ}$  for 2 hours. After cooling, the separation of the organic layer, the aqueous layer was acidified to Congo Red with 3N hydrochloric acid and thrice ether-extracted.

The combined extracts and organic layer were washed with water, and dried ( $\text{Na}_2\text{SO}_4$ ) in nitrogen. The ether was removed in a slow stream of nitrogen; distillation at reduced pressure in nitrogen gave impure ( $\pm$ ) octane-2-thiol (7.4 g.), b.p.  $77-80^\circ/19$  mm.,  $n_D^{20}$  1.4482.

( $\pm$ )-S-2-Octylthiuronium benzoate

i) Addition of a solution of sodium benzoate (0.76 g.) in water (10 ml.) to a suspension of ( $\pm$ )-S-2-octylthiuronium bromide (1.0 g.) in water (10 ml.) gave an immediate precipitate of ( $\pm$ )-S-2-octylthiuronium benzoate (0.9 g.), m.p.  $140-141^\circ$  on ethanolic crystallisation.

ii) Addition of a solution of sodium benzoate (0.76 g.) in water (10 ml.) to a solution of ( $\pm$ )-S-2-octylthiuronium (+)-camphor-10-sulphonate (2.1 g.,  $[\alpha]_{5893}^{20} + 26.3^\circ$ ) in aqueous methanol (10 ml., 9:1) gave an immediate precipitate of ( $\pm$ )-S-2-octylthiuronium benzoate (1.0 g.),  $\alpha_{5893}$  zero ( $\underline{1}$ , 2;  $\underline{c}$ , 5.00 in ethanol), m.p. and mixed m.p. with specimen (i),  $140-141^\circ$  after ethanol crystallisation.

Decomposition of the thiuronium benzoate (6.1 g.), similarly prepared from ( $\pm$ )-S-2-octylthiuronium (+)-camphor-10-sulphonate (8.0 g.,  $[\alpha]_{5893}^{20} + 26.0^\circ$ ) and sodium benzoate (3.0 g.) gave ( $\pm$ )-octane-2-thiol (1.7 g.)

b.p. 78-81°/20 mm.  $\alpha_{5893}^{21}$  zero (1, 0.5).

(±)-2-Octyl 2:4-dinitrophenyl sulphide

i) Solutions of (±)-octane-2-thiol (1.2 g.) in ethanol (16 ml.), chloro-2:4-dinitrobenzene (1.6 g.) in ethanol (10 ml.) and sodium hydroxide (0.36 g.) in 50% aqueous ethanol (3 ml.) were heated under reflux for 10 minutes. The hot solution was rapidly filtered at the pump, crude product (1.2 g.) crystallising from the cold filtrate. Two crystallisations from ethanol gave (±)-2-octyl 2:4-dinitrophenyl sulphide, m.p. 50°.

[Found: N, 8.75, S, 10.05.  $C_{14}H_{20}O_4N_2S$  requires N, 9.00; S, 10.35%].

ii) Solutions of (±)-2-octylthiuronium (+)-camphor-10-sulphonate (2.0 g.,  $[\alpha]_{5893}^{20} + 26.0^\circ$ ) in ethanol (5 ml.), chloro-2:4-dinitrobenzene (1.0 g.) in ethanol (10 ml.) and sodium hydroxide (0.4 g.) in 50% aqueous ethanol (4 ml.) were heated under reflux for 10 minutes. The hot solution was rapidly filtered at the pump, crude product (0.8 g.) crystallising from the filtrate. Crystallisation from ethanol gave (±)-2-octyl 2:4-dinitrophenyl sulphide, m.p. and mixed m.p. with specimen (i), 50°,  $[\alpha]_{5893}$  zero (1, 2; c, 1.00 in methanol).

The resolution of (±)-octan-2-ol

Method of Kenyon (37)

(±)-Octan-2-ol (140 g.) was added to a solution of phthalic anhydride (148 g.) in dry pyridine (100 ml.) and the whole was heated on a steam bath for 4.5 hours; methyl hexyl ketone was then removed by steam distillation, and the cooled reaction mixture was poured with stirring into concentrated hydrochloric acid (130 ml.) and crushed ice (275 g.). The solid ester was crushed, water-washed several times, air-dried and finally desiccated in vacuo over phosphoric oxide. There was obtained (±)-2-octyl hydrogen phthalate (248 g.) m.p. 55°.

(±)-2-Octyl hydrogen phthalate (140 g.) was dissolved in dry acetone (300 ml.), anhydrous brucine (197 g.) was cautiously added and the whole was heated under reflux for 25 minutes.

(+)-2-Octyl hydrogen phthalate

The less-soluble brucine (+)-2-octyl phthalate (189 g.) was covered with acetone, 50% cold hydrochloric acid being added until a clear solution was obtained. Addition of ice and water, with stirring, precipitated (+)-2-octyl hydrogen phthalate (76 g.). Three crystallisations from 90% acetic acid gave optically pure (+)-2-octyl hydrogen phthalate (26 g.), m.p. 73.5 -



74.5°,  $[\alpha]_{5893}^{19} + 48.1^\circ$  ( $\underline{1}$ , 1;  $\underline{c}$ , 5.027 in ethanol).

(-)-2-Octyl hydrogen phthalate

To the acetone solution of brucine (-)-2-octyl phthalate was added cold 50% hydrochloric acid until the solution became clear. Addition of ice and water precipitated (-)-2-octyl hydrogen phthalate (60 g.). Two crystallisations from 90% acetic acid gave the pure ester (38.7 g.), m.p. 74.5°,  $[\alpha]_{5893}^{19} - 48.2^\circ$  ( $\underline{1}$ , 1;  $\underline{c}$ , 4.998 in ethanol).

(+)-Octan-2-ol

Passage of steam through a warm solution of (+)-2-octyl hydrogen phthalate (23 g.,  $[\alpha]_{5893}^{18} - 48.1^\circ$ ) in 6N sodium hydroxide (45 ml.) gave a distillate, which, on ether extraction, drying ( $K_2CO_3$ ), and distillation at reduced pressure gave (+)-octan-2-ol (7.3 g.), b.p. 84°/17 mm.,  $\alpha_{5893}^{18} + 4.09^\circ$  ( $\underline{1}$ , 0.5),  $n_D^{20}$  1.4260.

(-)-Octan-2-ol

Similar decomposition of (-)-2-octyl hydrogen phthalate (34 g.,  $[\alpha]_{5893}^{19} - 48.2^\circ$ ) gave (-)-octan-2-ol (13.7 g.), b.p. 82°/17 mm.,  $\alpha_{5893}^{21} - 8.10^\circ$  ( $\underline{1}$ , 1),  $n_D^{19}$  1.4265.

(+)-2-bromo-octane

Preparation according to Gerrard (38).

Phosphorus tribromide (17.1 g.) was added dropwise to (-)-octan-2-ol (12.4 g.,  $\alpha_{5893}^{21} - 8.10^\circ$ ,  $\underline{1}$ , 1) at  $-10^\circ$ . After 1 hour at room temperature, the reaction mixture was poured into ice-water (35 ml.). The solution was immediately ether-extracted, the combined extracts were washed with sodium carbonate, and with water, and dried ( $\text{Na}_2\text{SO}_4$ ). The ether was evaporated at reduced pressure, distillation yielding (+)-2-bromo-octane (6.3 g.), b.p.  $81-82^\circ/20$  mm.,  $\alpha_{5893}^{20} + 20.55^\circ$  ( $\underline{1}$ , 0.5),  $n_D^{20}$  1.4500.

(-)-2-Bromo-octane

Similarly, (-)-2-bromo-octane (4.9 g.), b.p.  $76^\circ/20$  mm.,  $\alpha_{5893}^{21} - 20.65^\circ$  ( $\underline{1}$ , 0.5),  $n_D^{20}$  1.4500 was obtained from (+)-octan-2-ol (7.1 g.,  $\alpha_{5893}^{18} + 4.09^\circ$ ,  $\underline{1}$ , 0.5).

S-2-Octylthiuronium benzoate

(+)-2-Bromo-octane (6.3 g.,  $\alpha_{5893}^{20} + 20.55^\circ$ ,  $\underline{1}$ , 0.5) and thiourea (3.1 g.) were heated in water (4 ml.) for 3 hours with stirring. To the cooled solution was added a solution of sodium benzoate (3.7 g.) in water (10 ml.), S-2-octyl thiuronium benzoate (0.9 g.)

being precipitated.

From the filtrate there was recovered (+)-2-bromo-octane (2.0 g), b.p.  $88^{\circ}/30$  mm.  $\alpha_{5893}^{18} + 20.20^{\circ}$  (1, 1). This (+)-2-bromo-octane (2.0 g.) was heated under reflux for 5 hours with thiourea (0.78 g.) in ethanol (8 ml.). The ethanol was removed at reduced pressure, and a solution of sodium benzoate (1.5 g.) in water (15 ml.) added to the oily S-2-octylthiuronium bromide. The precipitated S-2-octylthiuronium benzoate (2.2 g.) was ether-washed and dried.

(-)-Octane-2-thiol

S-2-Octylthiuronium benzoate (3.1 g.) was heated at  $100^{\circ}$  with N sodium hydroxide (20 ml.) for 2 hours in a nitrogen atmosphere. After cooling, the organic layer was separated, the aqueous layer was acidified to Congo Red with 3N hydrochloric acid and filtered free of benzoic acid, which had m.p. and mixed m.p.  $121^{\circ}$ . The aqueous layer was thrice ether-extracted, the extracts were combined with the organic layer, the whole was water-washed and dried ( $\text{Na}_2\text{SO}_4$ ) in nitrogen. The ether was evaporated in a slow stream of nitrogen, distillation at reduced pressure in nitrogen gave (-)-octane-2-thiol (1.1 g.), b.p.  $80-2^{\circ}/25$  mm.,  $\alpha_{5893}^{22} - 9.29^{\circ}$  (1, 0.5),  $n_D^{20} 1.4520$ . [Found: S, 21.95. calc. for  $\text{C}_8\text{H}_{18}\text{S}$  S, 21.90%].

The compound on redistillation had identical physical properties.

(Kenyon et al. (33) record b.p. 78-80°/22 mm.

$[\alpha]_{5780}^{25} - 32.0^\circ$ ,  $[\alpha]_{5641}^{25} - 36.4^\circ$   $d_4^{25}$  0.830.)

(+)-Octane-2-thiol

(-)-2-Bromo-octane (4.67 g.,  $\alpha_{5893}^{21} - 20.65^\circ$

1, 0.5) and thiourea (1.25 g.) were heated under reflux for five hours in ethanol (25 ml.). This solution, when cool, had  $\alpha_{5893}^{17} + 0.17^\circ$  (1, 0.5; c, 20 in ethanol).

Evaporation of the ethanol at reduced pressure gave oily (+)-S-2-octylthiuronium bromide. This oil was heated at 50° in nitrogen for 1 hour with 1.5N sodium carbonate (35 ml.). The chilled solution was acidified to Congo Red with 3N hydrochloric acid and thrice ether-extracted: the combined extracts were washed with water and dried (Na<sub>2</sub>SO<sub>4</sub>) in nitrogen. The ether was evaporated in a slow stream of nitrogen; distillation at reduced pressure in nitrogen gave (+)-octane-2-thiol (1.0 g.), b.p. 77°/21 mm.,  $\alpha_{5893}^{24} + 5.36^\circ$  (1, 0.5),  $n_D^{21}$  1.4475. Owing to the fact that a solid thiuronium salt was not found, and bromo-octane thus removed in this preparation, it is considered that the thiol is not pure and contains some (+)-octan-2-ol, the latter no doubt largely racemised.

(+)-2-Octyl 2:4-dinitrophenyl sulphide

(-)-Octane-2-thiol (0.5 g.,  $\alpha_{5893}^{22} - 9.29^\circ$ ,  $\underline{1}$ , 0.5) and solutions of chloro-2:4-dinitrobenzene (0.71 g.) in ethanol (4 ml.) and sodium hydroxide (0.13 g.) in 50% aqueous ethanol (7 ml.) were heated under reflux for 10 minutes. The hot solution was rapidly filtered at the pump, (+)-2-octyl 2:4-dinitrophenyl sulphide (0.61 g.), m.p. 40-45°,  $[\alpha]_{5893}^{22} + 54^\circ$  ( $\underline{1}$ , 0.5;  $\underline{c}$ , 0.890 in ethanol), crystallising from the filtrate after 16 hours.

(-)-2-Octyl 2:4 dinitrophenyl sulphide

(+)-Octane-2-thiol (0.89 g.,  $\alpha_{5893}^{24} + 5.36^\circ$ ,  $\underline{1}$ , 0.5) and solutions of chloro-2:4-dinitrobenzene (1.24 g.) in ethanol (10 ml.) and sodium hydroxide (0.28 g.) in 50% aqueous ethanol (2 ml.) were heated under reflux for 10 minutes. The hot solution was filtered rapidly at the pump, (-)-2-octyl 2:4-dinitrophenyl sulphide (1.45 g.) m.p. 41-45°,  $[\alpha]_{5893}^{16} - 36^\circ$  ( $\underline{1}$ , 2;  $\underline{c}$ , 2.836 in benzene),  $[\alpha]_{5893}^{16} - 41^\circ$  ( $\underline{1}$ , 2;  $\underline{c}$ , 2.456 in ethanol) crystallising from the filtrate.

(±)-1-Phenylpropan-2-ol

Anhydrous iso-propanol (280 ml.) was heated under reflux with clean aluminium turnings (27 g.) and mercuric chloride (0.5 g.), the reaction being complete after 6

hours. To this warm solution, benzyl methyl ketone (41.5 g.) was added; the acetone formed was slowly distilled. After cooling to room temperature, the iso-propanol was removed by distillation at reduced pressure. The chilled solution was poured slowly, with vigorous stirring, into ice-cold 50% sulphuric acid (600 ml.). The whole was filtered at the pump, neutralised with potassium carbonate and ether-extracted. The extract was dried ( $K_2CO_3$ ) and evaporated; distillation of the product at reduced pressure gave ( $\pm$ )-1-phenylpropan-2-ol (30 g.), b.p.  $108-112^\circ/18$  mm.  $n_D^{18}$  1.5205.

( $\pm$ )-1-Methyl-2-phenylethyl hydrogen phthalate

( $\pm$ )-1-Phenylpropan-2-ol (115 g.) was added to a solution of phthalic anhydride (125 g.) in dry pyridine (130 ml.). After heating on a steam-bath for 4.5 hours, when its internal temperature was  $90-95^\circ$ , the reaction mixture was chilled and poured, with stirring, into 6N hydrochloric acid (500 ml.) and excess crushed ice. The solid ester was washed free of pyridine with dilute hydrochloric acid, water-washed and air-dried. There was obtained ( $\pm$ )-1-methyl-2-phenylethyl hydrogen phthalate (150 g.) m.p.  $112-115^\circ$ . [Pickard and Kenyon (41) record m.p.  $113-4^\circ$ .]

(+)- and (-)-1-Phenylpropan-2-ol

Method of Kenyon, Phillips, Pittman and Cochinaras (33) and Pickard and Kenyon (41) and Phillips (42).

(±)-1-Methyl-2-phenylethyl hydrogen phthalate (149 g.) was dissolved in boiling acetone (1500 ml.), anhydrous brucine (206.5 g.) being cautiously added in small quantities. On cooling of the clear solution, the alkaloidal salt crystallised in spherical clusters of needles. Four crystallisations of this crop (185 g.), m.p. 130-140°, from acetone, gave optically pure brucine (+)-1-methyl-2-phenylethyl phthalate (70.5 g.), m.p. 151-153°.

Evaporation of the filtrate, from the preparation of the brucine salt, gave a crop (165 g.), m.p. 73-83°. Three crystallisations of this crop from acetone gave brucine (-)-1-methyl-2-phenylethyl phthalate (135.5 g.), m.p. 85-7°. [Kenyon et al. (33) record m.p.s. 153° and 83° respectively].

Decomposition of the brucine salts

Brucine (+)-1-methyl-2-phenylethyl phthalate (2.5 g.) was shaken with 3N hydrochloric acid (1.5 ml.) and 50% aqueous ether (20 ml.). The aqueous layer was separated and thrice ether extracted: the combined extracts were washed free of acid and desiccated (Na<sub>2</sub>SO<sub>4</sub>).

The ether was evaporated at reduced pressure, and the (+)-1-methyl-2-phenylethyl hydrogen phthalate, an oil, dried to constant weight (0.86 g.) in vacuo over phosphoric oxide for 10 days. It had  $[\alpha]_{5893}^{20} + 48.0^{\circ}$ ,  $[\alpha]_{5461}^{18} + 57.8^{\circ}$  (1, 2; c, 4.225 in chloroform).

From brucine salt crystallised four times further there was obtained hydrogen phthalate of identical specific rotatory power.

By the identical procedure, brucine (-)-1-methyl-2-phenylethyl phthalate (3.0 g.) was decomposed to (-)-1-methyl-2-phenylethyl hydrogen phthalate (0.85 g.),  $[\alpha]_{5893}^{20} - 47.3^{\circ}$ ,  $[\alpha]_{5461}^{20} - 57.3^{\circ}$  (1, 2; c, 4.262 in chloroform).

[Kenyon et al. (33) record  $[\alpha]_{5893} + 44.5^{\circ}$   $[\alpha]_{5461} + 53.0^{\circ}$ ;  $[\alpha]_{5893} - 44.7^{\circ}$ ,  $[\alpha]_{5461} - 53.2^{\circ}$  in chloroform].

#### (+)-1-Phenylpropan-2-ol

Brucine (+)-1-methyl-2-phenylethyl phthalate (44.5 g.) was shaken with 3N hydrochloric acid (27 ml.) and 50% aqueous ether (300 ml.). The separated aqueous layer was thrice ether extracted, the combined extracts washed free of acid and the ether evaporated at reduced pressure, giving oily (+)-hydrogen phthalate ester. This oil was warmed with 5N sodium hydroxide (40 ml.)



and steam passed through the solution. The aqueous distillate was saturated with potassium carbonate, four times ether extracted the combined extracts dried with potassium carbonate, and allowed to stand over sodium sulphate. The ether was evaporated at reduced pressure, and distillation of the product yielded (+)-1-phenylpropan-2-ol (6.8 g.), b.p.  $104^{\circ}/15$  mm.  $\alpha_{5893}^{19} + 13.60^{\circ}$ ,  $\alpha_{5461}^{19} + 16.48^{\circ}$  (1, 0.5),  $n_D^{20}$  1.5210,  $n_D^{25}$  1.5190.

[Pickard and Kenyon (41) record b.p.  $125^{\circ}/25$  mm.,  $n_D^{20}$  1.5190,  $\alpha_{5893}^{20} + 26.2^{\circ}$ ,  $\alpha_{5461}^{20} + 31.88^{\circ}$  (1, 1).

Phillips records (42)  $n_D^{25}$  1.5194,  $\alpha_{5461}^{16} + 32.76^{\circ}$  (1, 1).

Kenyon et al. (33) record  $\alpha_{5461}^{16} + 8.17^{\circ}$  (1, 0.25).]

#### (-)-1-Phenylpropan-2-ol

Similar decomposition of brucine (-)-1-methyl-2-phenylethyl phthalate (136 g.) gave (-)-1-phenylpropan-2-ol (20.0 g.) b.p.  $116-7^{\circ}/23$  mm.,  $\alpha_{5893}^{23} - 26.24^{\circ}$ ,  $\alpha_{5461}^{23} - 31.6^{\circ}$  (1, 1),  $n_D^{20}$  1.5204,  $n_D^{25}$  1.5182.

[Phillips (42) records  $\alpha_{5461}^{16} - 30.9^{\circ}$  (1, 1).

Kenyon et al. (33) record  $\alpha_{5893}^{14} - 6.82^{\circ}$ ,  $\alpha_{5461}^{14} - 8.08^{\circ}$  (1, 0.25).]

#### (±)-1-Methyl-2-phenylethyl toluene-p-sulphonate

Powdered toluene-p-sulphonyl chloride (25.75 g.) was added slowly, with stirring, to a solution of (±)-1-

phenylpropan-2-ol (18.43 g.) in dry pyridine (13 ml.). The reaction mixture was water-extracted after standing at room temperature for 2 days. The ester was crushed, washed free of pyridine with dilute hydrochloric acid, washed with water and air-dried. There was obtained ( $\pm$ )-1-methyl-2-phenylethyl toluene-p-sulphonate (35.3 g.), m.p. 86-9°. This compound when pure had m.p. 90°.

( $\pm$ )-S-1-Methyl-2-phenylethylthiuronium toluene-p-sulphonate

( $\pm$ )-~~S~~-1-Methyl-2-phenylethyl toluene-p-sulphonate (14.5 g.) and thiourea (3.8 g.) were heated under reflux in ethanol (10 ml.) for 1.5 hours. The hot solution was immediately chilled in an ice-salt bath, vigorous scratching precipitating ( $\pm$ )-S-1-methyl-2-phenylethylthiuronium toluene-p-sulphonate, (13.9 g.), m.p. 180-181° after two crystallisations from ethanol.

[Found: C, 55.80; H, 6.25; S, 17.60.

$C_{17}H_{22}O_3N_2S_2$  requires C, 55.70; H, 6.05; S, 17.50.]

( $\pm$ )-1-Phenylpropane-2-thiol

( $\pm$ )-S-1-Methyl-2-phenylethylthiuronium toluene-p-sulphonate (12.2 g.) and quinol (0.1 g.) were placed in a flask fitted with reflux condenser, stirrer and nitrogen inlet. The apparatus was filled with nitrogen, and 6N sodium hydroxide (25 ml.) was added with stirring. After 45 minutes at 60.65°, the flask was chilled, and the

solution acidified to Congo Red with 3N hydrochloric acid. The solution was thrice ether-extracted; the extracts were washed with water, and dried ( $\text{Na}_2\text{SO}_4$ ) in nitrogen with quinol (0.3 g.) added as antioxidant. The ether was evaporated in a slow stream of nitrogen, quinol (0.3 g.) having been added; distillation at reduced pressure gave (±)-1-phenylpropane-2-thiol (4.1 g.), b.p.  $106-8^\circ/18$  mm.,  $n_D^{20}$  1.5448,  $[\text{R}]_{5893}$  48.08 (calc. 48.04).

[Found: S, (i) 20.70; (ii) 20.90.  $\text{C}_9\text{H}_{12}\text{S}$  requires 21.0%.]

Mercury (±)-1-Methyl-2-phenylethyl mercaptide

(±)-1-Phenylpropane-2-thiol (0.42 g.) in ethanol (2 ml.) was added to a solution of mercuric cyanide (0.4 g.) in water (40 ml.). After 2 minutes at room temperature, the solution was chilled, when the mercaptide precipitated. Two crystallisations from 50% chloroform-ethanol gave Mercury (±)-1-methyl-2-phenylethyl mercaptide (0.16 g.), m.p.  $88-9^\circ$ .

[Found: C, 43.20; H, 4.40.  $\text{C}_{18}\text{H}_{22}\text{S}_2\text{Hg}$  requires C, 43.00; H, 4.60%.]

(±)-1-Methyl-2-phenylethyl 2:4-dinitrophenyl sulphide

(±)-1-Phenylpropane-2-thiol (0.87 g.) in ethanol (2 ml.), chloro-2:4-dinitrobenzene (1.32 g.) in

ethanol (4 ml.) and sodium hydroxide (0.3 g.) in 50% aqueous ethanol (4 ml.) were heated under reflux for 10 minutes. The hot solution was rapidly filtered at the pump, (±)-1-methyl-2-phenylethyl 2:4-dinitrophenyl sulphide (1.68 g.), m.p. 87-89° crystallising from the cold filtrate. After two crystallisations from ethanol it (1.08 g.) had m.p. 93-4°.

[Found: N, 8.90; S, 10.15.  $C_{15}H_{14}O_4N_2S$  requires N, 8.80, S, 10.05%].

(+)-1-Methyl-2-phenylethyl toluene-p-sulphonate

Powdered toluene-p-sulphonyl chloride (22.8 g.) was added slowly, with stirring, to a solution of (+)-1-phenylpropan-2-ol (16.2 g.,  $[\alpha]_{5893}^{19} + 13.6^\circ$ ,  $d_4^{20}$ , 0.5) in dry pyridine (94 ml.). The reaction mixture was water-extracted after standing at room temperature for 60 hours. The ester was crushed, washed free of pyridine with dilute hydrochloric acid, water-washed and air-dried. There was obtained (+)-1-methyl-2-phenylethyl toluene-p-sulphonate (30 g.), m.p. 67.5-68°,

$[\alpha]_{5893}^{20} + 25.2^\circ$  ( $d_4^{20}$ , 2;  $d_4^{20}$ , 4.999 in chloroform).

[Phillips (42) records m.p. 94°;  $[\alpha]_{5893}^{19} + 24.97^\circ$  ( $d_4^{20}$ , 2;  $d_4^{20}$ , 5.068 in chloroform).

This melting point, 94°, recorded for the (+)-sulphonate is probably erroneous, and, from the present work, seems to refer to the (±) compound,

m.p. 90 °].

(-)-1-Methyl-2-phenylethyl toluene-p-sulphonate

Similarly reaction of toluene-p-sulphonyl chloride (27.7 g.) with (-)-1-phenylpropan-2-ol (19.7 g.,  $[\alpha]_{5893}^{23} - 26.24^\circ$ , 1, 1) in dry pyridine (11.5 ml.), gave (-)-1-methyl-2-phenylethyl toluene-p-sulphonate (37.4 g.), m.p. 62.5-64.5°  $[\alpha]_{5893}^{24} - 22.9^\circ$  (1, 2; c, 5.173 in chloroform).

(+)-S-1-Methyl-2-phenylethylthiuronium toluene-p-sulphonate

(+)-1-Methyl-2-phenylethyl toluene-p-sulphonate (29 g.,  $[\alpha]_{5893}^{20} + 25.2^\circ$ ) and thiourea (7.6 g.) were heated under reflux in ethanol (36.5 ml.) for 1.5 hours. The hot solution was immediately chilled to  $-10^\circ$ , crystallisation occurring on vigorous scratching. Filtration, washing several times with anhydrous ether, and air drying, gave (+)-S-1-methyl-2-phenylethylthiuronium toluene-p-sulphonate (30.7 g.),  $[\alpha]_{5893}^{20} + 4.3^\circ$  (1, 2; c, 4.976 in ethanol).

(-)-S-1-Methyl-2-phenylethylthiuronium toluene-p-sulphonate

Similarly, reaction of (-)-1-methyl-2-phenylethyl toluene-p-sulphonate (37 g.,  $[\alpha]_{5893}^{24} - 22.9^\circ$ ) with thiourea (9.7 g.) in ethanol (45 ml.) gave (-)-S-1-methyl-2-phenylethylthiuronium toluene-p-sulphonate (24.0 g.),

$[\alpha]_{5893}^{21} - 4.5^{\circ}$  (1, 2; c, 5.001 in ethanol).

(-)-1-Phenylpropane-2-thiol

(+)-S-1-Methyl-2-phenylethylthiuronium toluene-p-sulphonate (50 g.) and quinol (0.3 g.) were placed in a flask fitted with stirrer, reflux condenser and nitrogen inlet. The apparatus was filled with nitrogen, and 6N sodium hydroxide (50 ml.) was added with stirring. After 45 minutes at 60-65<sup>o</sup>, the chilled solution was acidified to Congo Red with 3N hydrochloric acid. The solution was thrice ether-extracted, and the combined extracts were washed with water and dried (Na<sub>2</sub>SO<sub>4</sub>) in nitrogen with quinol (0.3 g.) added as antioxidant. The ether was removed in a slow stream of nitrogen, and distillation at reduced pressure gave (-)-1-phenylpropane-2-thiol (13.2 g.), b.p. 111<sup>o</sup>/23 mm.,  $\alpha_{5893}^{23} - 13.46^{\circ}$ ,  $\alpha_{5780}^{24} 14.5^{\circ}$ ,  $\alpha_{5641}^{24} - 16.5^{\circ}$ ,  $\alpha_{4358}^{24} - 34^{\circ}$  (1, 1),  $n_D^{24} 1.5425$ .

[Found: C, 70.9; H, 8.3; S, (i) 20.8, (ii) 21.0. Calc. for C<sub>9</sub>H<sub>12</sub>S: C, 71.0; H, 7.9; S, 21.0%].

[Kenyon et al. (33) record b.p. 105-110<sup>o</sup>/16 mm.,  $[\alpha]_{5893} - 15.3^{\circ}$ ,  $n_D^{20} 1.5312$ .]

(+)-1-Phenylpropane-2-thiol

Similarly, decomposition of (-)-S-1-methyl-2-phenylethylthiuronium toluene-p-sulphonate (22.4 g.,  $[\alpha]_{5893}^{21} - 4.5^\circ$ ) gave (+)-1-phenylpropane-2-thiol (4.0 g.), b.p.  $104^\circ/17$  mm.,  $\alpha_{5893}^{17} + 6.08^\circ$ ,  $\alpha_{5780}^{19} + 6.26^\circ$ ,  $\alpha_{5461}^{19} + 7.31^\circ$ ,  $\alpha_{4358}^{19} + 14.6^\circ$  ( $\underline{1}$ , 0.5),  $n_D^{20}$  1.5450. [Found: S, 21.35%].

Mercury (-)-1-Methyl-2-phenylethyl mercaptide

(+)-1-Phenylpropane-2-thiol (0.95 g.,  $\alpha_{5893}^{17} + 6.08^\circ$ ,  $\underline{L}$ , 0.5) in ethanol (2 ml.) was added to a solution of mercuric cyanide (0.9 g.) in water (40 ml.). After 2 minutes at room temperature, the solution was chilled, when the mercaptide separated. After crystallisation from 50% chloroform-ethanol it (0.4 g.) had m.p.  $118-119^\circ$ ; further crystallisation gave Mercury (-)-1-methyl-2-phenylethyl mercaptide (0.24 g.), m.p.  $123.5-124.5^\circ$ ,  $[\alpha]_{5893}^{23} - 100^\circ$  ( $\underline{1}$ , 1;  $\underline{c}$ , 2.054 in chloroform).

Mercury (+)-1-Methyl-2-phenylethyl mercaptide

Similarly, (-)-1-phenylpropane-2-thiol (0.95 g.,  $\alpha_{5893}^{17} - 5.88^\circ$ ,  $\underline{1}$ , 0.5) gave Mercury (+)-1-methyl-2-phenylethyl-mercaptide (0.81 g.) m.p.  $117.5-118.5^\circ$ ,  $[\alpha]_{5893}^{22} + 88.3^\circ$  ( $\underline{1}$ , 0.5;  $\underline{c}$ , 4.458 in chloroform); after

two crystallisations from 50% chloroform-ethanol it had m.p.  $124^{\circ}$ ,  $[\alpha]_{5893}^{16} +100^{\circ}$  (l, 0.5; c, 3.258 in chloroform).

[Found: C, 43.20; H, 4.85.  $C_{18}H_{22}S_2Hg$  requires C, 43.00; H, 4.60%].

From (-)-1-phenylpropane-2-thiol ( $\alpha_{5893}^{23} -13.46^{\circ}$ , l, 1) there was obtained Mercury (+)-1-methyl-2-phenylethyl mercaptide having, after one crystallisation from 50% chloroform-ethanol m.p.  $122-123^{\circ}$ ,  $[\alpha]_{5893}^{22} +100^{\circ}$  (l, 1; c, 5.000 in chloroform).



SECTION II

The Optical Stability of Sulphides on Oxidation to  
Sulphones

The Optical Stability of Sulphides on Oxidation to Sulphones

The failure to obtain solid sulphides by addition of (+)- and (-)-1-phenylpropane-2-thiol to ω-nitrostyrene, suggested the oxidation of the oily sulphides to their corresponding sulphones, which would have higher melting points than the sulphides and would thus be expected to be crystalline solids. It should also be feasible to separate the diastereoisomeric sulphones by fractional crystallisation, the weight ratio of sulphones separated being equal to the weight ratio of sulphides present in the oily mixture.

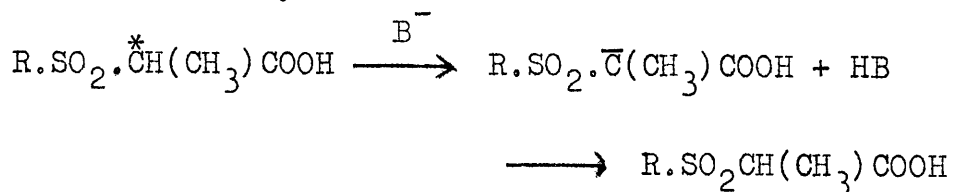
The most suitable method of oxidation was warming a glacial acetic acid solution of the sulphide with 34% hydrogen peroxide (47); these acidic conditions, however, might racemise the optically active sulphone.

This possibility arises from the work on optically active sulphones which is recorded in the literature (below). There is, however, an important difference between the sulphones hitherto investigated and the present sulphones: the former all have a carboxylic or sulphonic acid group adjacent to the asymmetric centre, whereas the latter do not. The presence of an acidic group was necessary for the resolution of the former

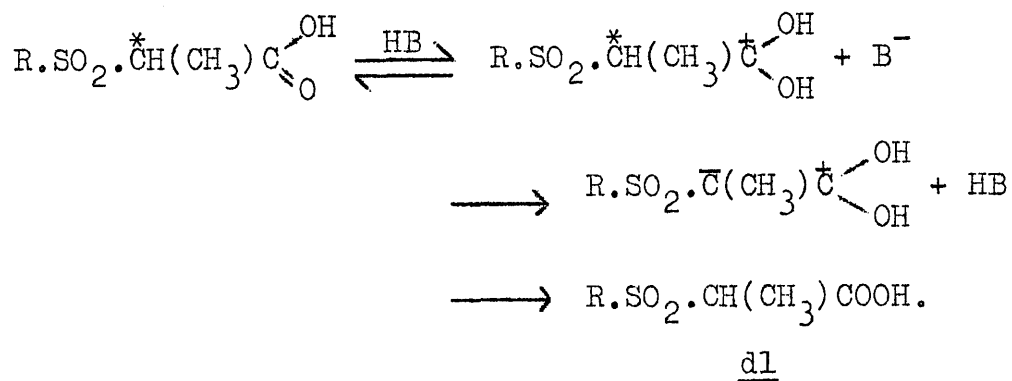
sulphones, whereas those of the present work arise by the oxidation of optically active thioethers.

Racemisation of optically active  $\alpha$ -sulphones, by acids and bases, was demonstrated by Ramberg and Hedlund (48) in 1934. These workers showed that  $\alpha$ -phenylsulphonyl propionic acid,  $\text{Ph}\cdot\text{SO}_2\cdot\text{CH}(\text{CH}_3)\cdot\text{COOH}$ , was racemised in acid and alkaline solution, and that the unimolecular racemisation was faster than the bromination of racemic sulphone under identical experimental conditions. The ratio of rates of racemisation to bromination were found to be almost identical for the  $\alpha$ -phenyl sulphone (1.08) and for the  $\alpha$ -ethyl sulphone (1.10) at  $25^\circ$ . Further work by Hedlund (49) on optically active  $\alpha$ -sulphones of sulphonic acids showed that acid catalysed racemisation does not occur, the base catalysed racemisation, however, proceeding at a rate ca. 50 times as fast as for the corresponding carboxylic acid sulphone. Ramberg and Hedlund (50) conclude that racemisation of the  $\alpha$ -sulphone in acid solution is caused by proton removal by a water molecule or by the acid anion.

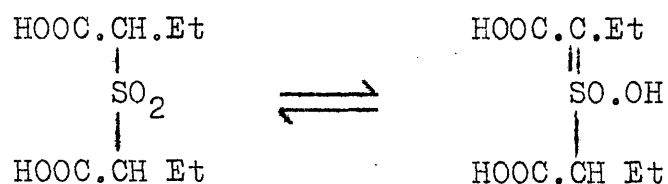
#### 1) Base Catalysed Racemisation



## 2) Acid Catalysed Racemisation



Backer and Meijer (51) and Ahlberg (52) show that optically active  $\alpha$ -sulphone-di-propionic acids racemise in aqueous solution, the latter worker also showing that the rate of racemisation decreased with increased molecular size of the acid. The following mechanism was proposed:



For the present work it was thus necessary to establish retention of configuration during oxidation, since any racemisation, partial or complete, disturbs the ratio of diastereoisomeric sulphones.

(-)-1-Methyl-2-phenylethyl 2:4-dinitrophenyl sulphone was prepared by oxidation of (-)-1-methyl-2-phenylethyl 2:4-dinitrophenyl sulphide with 34% hydrogen peroxide in glacial acetic acid at 100°. Recrystallisation

of the sulphone from ethanol indicated that a single compound was obtained from the oxidation, no change in melting point or specific rotation being observed.

The optical rotation of this sulphone, dissolved in dry acetic acid at  $100^{\circ}$ , was followed for eight hours, no change in rotation being observed. The specific rotation and melting point of the recovered sulphone were  $[\alpha]_{5893}^{17} - 32.8^{\circ}$ , and m.p.  $162^{\circ}$ , those values being close to those of the starting material  $[\alpha]_{5893}^{20} - 32.1^{\circ}$ , and m.p.  $166^{\circ}$ ; there was no depression of melting point on admixture with a pure specimen.

Experimental(-)-Methyl-2-phenylethyl 2:4 dinitrophenyl sulphide

(-)-1-Phenylpropane-2-thiol (1.95 g.,  $[\alpha]_{5893}^{17} - 5.88^{\circ}$ , 1, 0.5) in ethanol (5 ml.) and solutions of chloro-2:4-dinitrobenzene (2.6 g.) in ethanol (10 ml.) and sodium hydroxide (0.5 g.) in 50% aqueous ethanol (5 ml.) were heated under reflux for 10 minutes. The hot solution was rapidly filtered at the pump, (-)-1-methyl-2-phenylethyl 2:4-dinitrophenyl sulphide (3.2 g.), m.p.  $84^{\circ}$ , crystallising from the filtrate. Two crystallisations from absolute ethanol gave (1.9 g.), m.p.  $88^{\circ}$ ,  $[\alpha]_{5893}^{21} - 82.5^{\circ}$  (1, 0.5, c, 4.848 in acetone).

[Found: N, 8.85; S, 9.85.  $C_{15}H_{14}N_2O_4S$  requires N, 8.80; S, 10.05%].

(-)-1-Methyl-2-phenylethyl 2:4-dinitrophenyl sulphone

(-)-1-Methyl-2-phenylethyl 2:4-dinitrophenyl sulphide (1.2 g.,  $[\alpha]_{5893}^{21} - 82.5^{\circ}$ ), dissolved in glacial acetic acid (10 ml.), was warmed on a steam-bath for 1.5 hours with 34% hydrogen peroxide (5 ml.). From the cooled solution there was obtained (-)-1-methyl-2-phenylethyl 2:4-dinitrophenyl sulphone (0.5 g.), m.p.  $166^{\circ}$ ,  $[\alpha]_{5893}^{19} - 32.2^{\circ}$  (1, 0.5; c, 3.165 in acetone). On crystallisation of a portion from ethanol the physical properties remained unchanged.

[Found: S, 8.85; O, 27.30.  $C_{15}H_{14}N_2O_6S$   
requires S, 9.15; O, 27.40%].

The Optical stability of (-)-1-methyl-2-phenylethyl  
2:4-dinitrophenyl sulphone

The optical rotation of a solution of (-)-1-methyl-2-phenylethyl 2:4 dinitrophenyl sulphone (0.457 g.,  $[\alpha]_{5893}^{19} - 32.2^\circ$ ) in dry acetic acid (7.4 ml. at  $20^\circ$ ), maintained at  $100^\circ$  was observed over a period of 8.3 hrs,  $\alpha_{5893}^{100} - 0.62^\circ$ ;  $\alpha_{5893}^{100} - 0.60^\circ$   
t = 0 t = 8.3 hrs.

The hot solution was poured into ice-cold water (200 ml.), (-)-1-methyl-2-phenylethyl 2:4-dinitrophenyl sulphone (0.42 g.), m.p.  $162^\circ$ ,  $[\alpha]_{5893}^{17} - 32.8^\circ$  ( $\underline{1}$ , 0.5;  $\underline{c}$ , 5.010 in acetone) was recovered after 2.5 days. There was no depression of melting point on admixture with a pure specimen.

SECTION III

The Olefinic Addition Reactions of (+)-, (+)-, and (-)-  
1-Phenylpropane-2-thiol

The Alkylation Reactions of (+)-1-Phenylpropane-2-thiol



Asymmetric Synthesis

"Only asymmetry can beget asymmetry" was the view expressed by Japp (53) reviewing the fact that compounds containing an asymmetric centre obtained from natural products are usually optically active and that the synthesis of such compounds resulted in racemic products. He further expressed the view that "the production of single asymmetric molecules is the prerogative of life" (54).

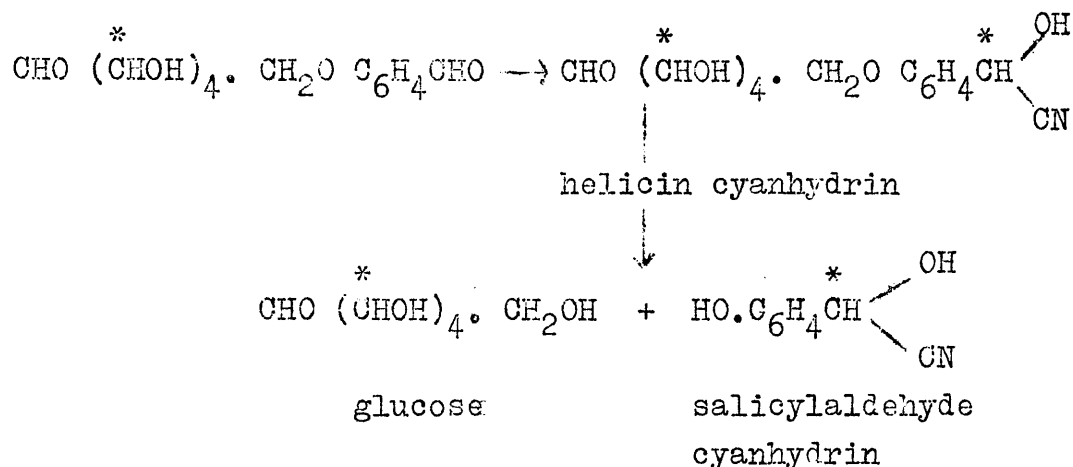
Pasteur and Van't Hoff shared the view that the use of external physical force such as circularly polarised light would achieve asymmetric synthesis.

The first such "Absolute Asymmetric Synthesis" was reported by Kuhn and Braun (55) who exposed ( $\pm$ ) - ethyl -  $\alpha$  - bromopropionate to dextra rotatory circularly polarised light, when a product of maximum rotation  $+ 0.05^\circ$  was obtained; similar irradiation with laevo-rotatory circularly polarised light gave a maximum rotation of  $-0.05^\circ$ .

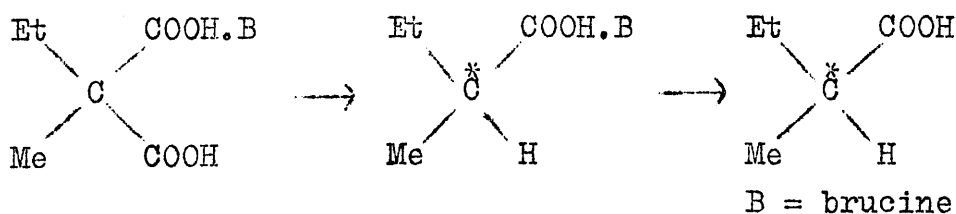
The classical definition of asymmetric synthesis was published by Marckwald (56) in 1904 "Asymmetric syntheses are such that, from compounds of symmetrical constitution, by the intermediate use of optically active substances, but without any analytical separation, optically active products result". This definition

applies to "Partial Asymmetric Synthesis" to distinguish it from "Absolute Asymmetric Synthesis" which is achieved by the use of an external dissymmetric physical agency.

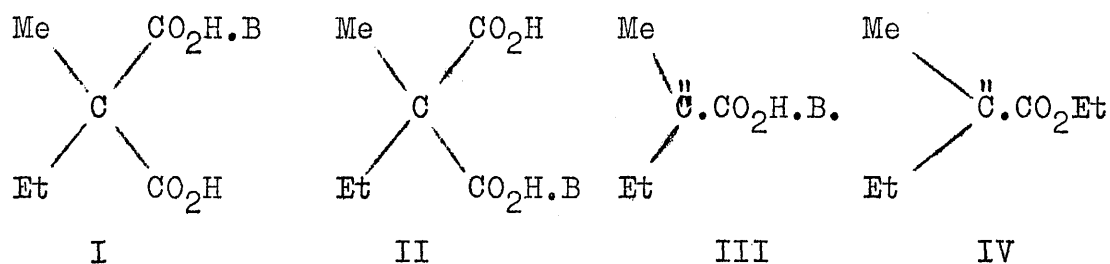
One of the first, but unsuccessful, attempted partial asymmetric synthesis was that of Fischer (57) who attempted the preparation of optically active salicylaldehyde cyanhydrin from helicin.



Isolation of the desired product was prevented by the hydrolysis of the intermediate. In 1904, Marckwald (58) claimed the first successful asymmetric synthesis by purely chemical means. Decarboxylation of the monobrucine salt of methylethylmalonic acid at 170° gave the brucine salt of methylethylacetic acid. Removal of the brucine gave (-)-methylethylacetic acid, 10% excess of the (-)-acid being present.



A more detailed explanation of this type of asymmetric synthesis has been put forward more recently by Kenyon and Ross. It was shown that decarboxylation of the dibrucine salt of ethylmethylmalonic acid gave 8.5-12.6% excess of (-)- $\alpha$ -methylbutyric acid (59) although decarboxylation of optically pure ethyl hydrogen (+)- and (-)-ethylmethylmalonate and their alkaloidal salts gave optically inactive ester (60). This is similar to the Marckwald reaction but the explanation of the formation of unequal amounts of (I) and (II), or differing rates of their decarboxylation, cannot account for the present results as there can be only one dibrucine salt.

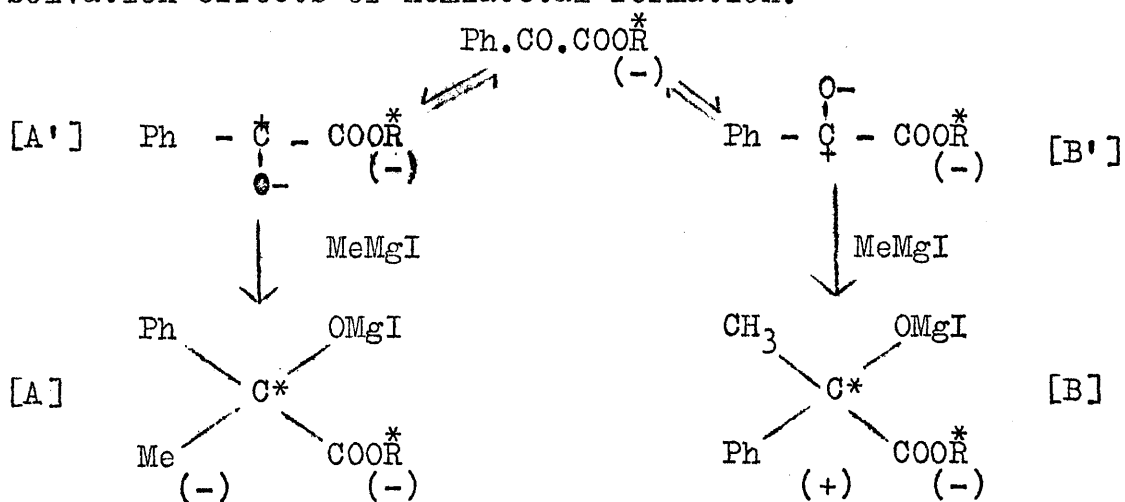


It is suggested that the carbanions (III) and (IV) are the intermediates in the above reactions; addition of  $\text{H}^+$  to (III) would give diastereoisomers, probably differing in rates of formation, whereas addition of  $\text{H}^+$  to (IV) would give enantiomers at the identical rate.

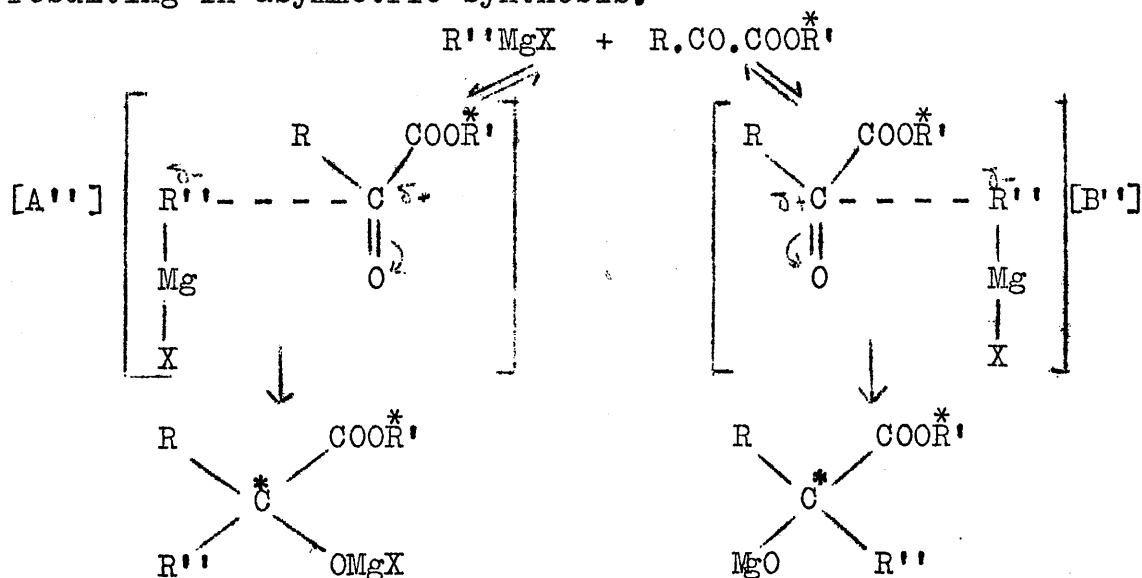
The year 1904 also saw the publication by McKenzie (61) of the first of a series of papers on partial



The following mechanism was proposed by McKenzie, based on Kortum's definition of Asymmetric Induction (65). This states that "asymmetric induction is the result of a force which coming from asymmetric molecules influences the configuration of a changeable molecule in such a manner that a formerly symmetric molecule becomes asymmetric". The formation of an excess of one acid isomer, and thus asymmetric synthesis, was primarily due to the existence of the benzoylformic ester as an unequal mixture of diastereoisomerides, in which the ketone group exhibits induced dissymmetry, the mutarotation which the ester exhibits in alcoholic solvents being connected with the attainment of equilibrium between the two forms [A'] and [B'] (below). Jamison and Turner (66) have, however, concluded that the mutarotation is due to solvation effects or hemiacetal formation.

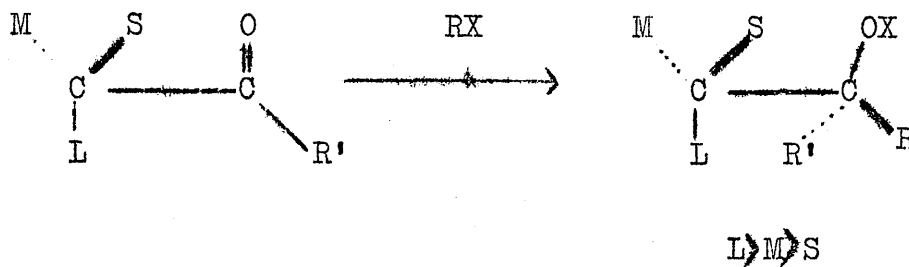


Reid and Turner (67) more recently have proposed an alternate mechanism for this reaction. These authors state that in the reaction between Grignard reagent and ketoester in ether, the two diastereoisomerides are formed in unequal quantities, but, since they are not interconvertible it is concluded that "mechanistic difference must be sought at the stage of the two corresponding transition states, from which they are formed irreversibly". The two transition states [A''] and [B''], below, formed reversibly from the reagents, must have different energies, since they are diastereoisomerides. This leads to the possibility of a reaction mechanism whereby the reaction with the lower activation energy is followed preferentially, resulting in asymmetric synthesis.



Cram and Elhafez (68) have proposed a rule to correlate and predict the stereochemical direction of asymmetric

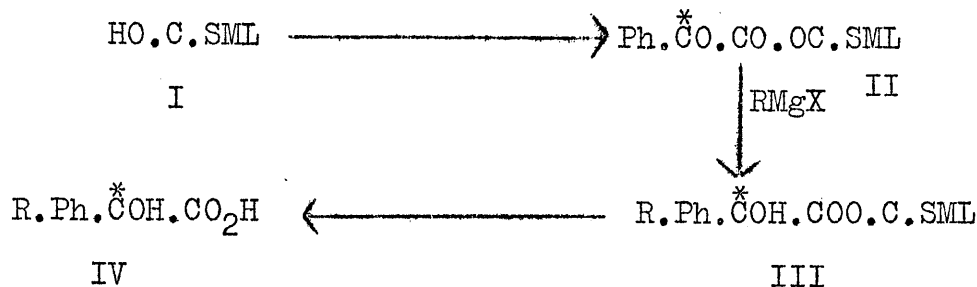
induction in reactions in which a new asymmetric centre is created adjacent to an old: "in non-catalytic reactions of the type shown (below), that diastereoisomer will predominate which would be formed by the approach of the entering group from the least hindered side of the double bond when the rotational conformation of the C - C bond is such that the double bond is flanked by the least two bulky groups attached to the adjacent asymmetric centre".



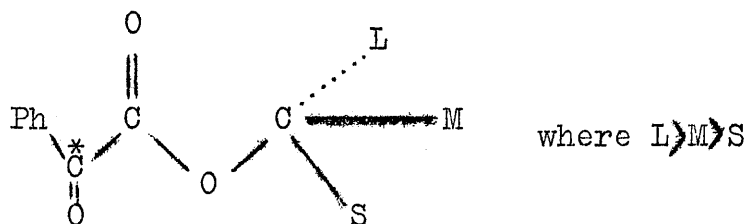
Thus in the addition of Grignard reagents or reduction with lithium aluminium hydride, the carbonyl oxygen atom, being coordinated with the metal atom  $MgX$  or  $AlH_3$ , becomes effectively the largest group and thus it orientates itself between S and M. The approach of the group R is then directed as would be expected, from the side of the molecule to which S is attached rather than M.

Prelog and his coworkers (69), on a similar basis of conformational analysis, have been able to relate the sign of rotation of the atrolactic acid produced in the

McKenzie asymmetric synthesis (page 55) with the configuration of the original asymmetric alcohol.



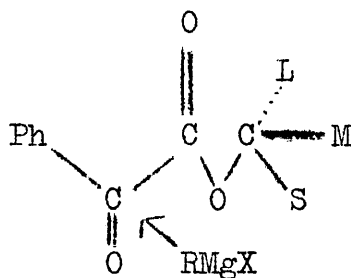
The most stable conformation of the phenylglyoxylic ester was considered to be



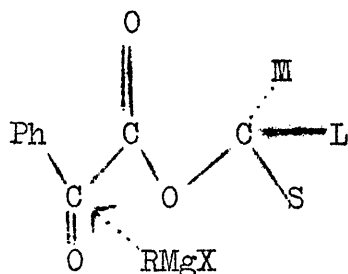
with the two carbonyl groups planar and anti to each other, with group S in the plane of the ester grouping and M and L lying in front of and behind respectively. It is proposed that the Grignard reagent, RMgX, would attack  $\overset{*}{\text{C}}$ , preferentially from the side on which the smaller substituent lies: thus the preferential attack will be as shown in (V), and in (VI), from the side of the smaller group M:







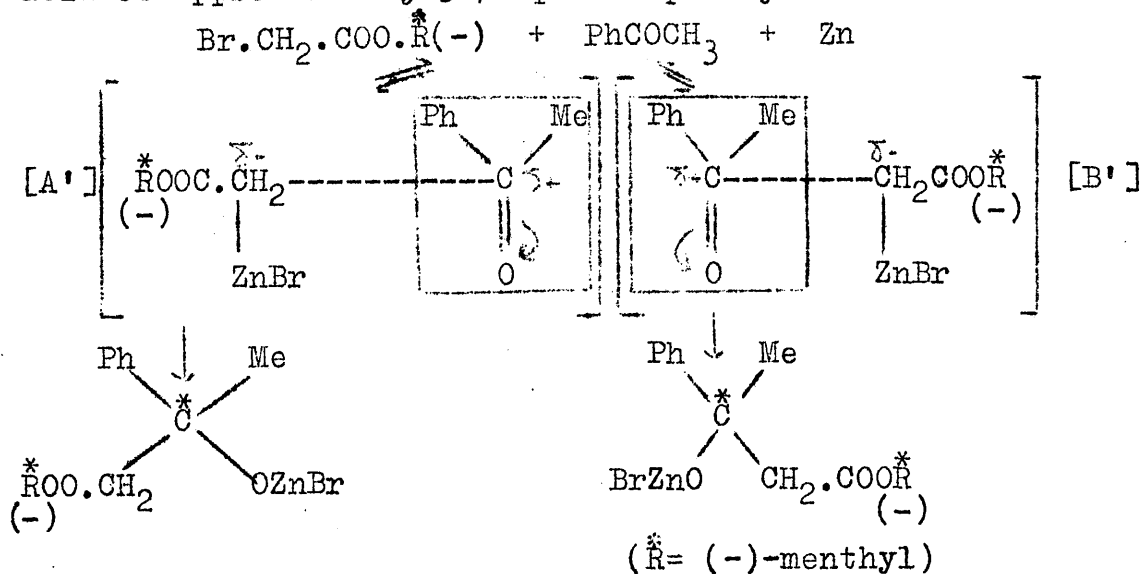
V



VI

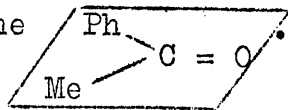
The results of thirty-seven reactions of this type, as studied by McKenzie and others, were tabulated; in certain instances the completeness of the hydrolysis of the intermediate (III) was brought into question; however it was concluded that thirty-five of the atrolactic acids had configuration as predicted by the rule.

Reid and Turner (67) have reported an asymmetric synthesis by the Reformatsky reaction. Reaction of (-)-menthyl bromoacetate with acetophenone in the presence of zinc gave (+)- $\beta$ -hydroxy- $\beta$ -phenylbutyric acid of approximately 30% optical purity.



$\text{Ph-C(=O)-Me} + \text{Zn} \rightarrow \text{[A] + [B]}$  [61]

The intermediates [A'] and [B'] are formed reversibly on the approach of the complex  $(-)\text{-}\overset{*}{\text{R}}\text{.COO.CH}_2\text{ZnBr}$  to the planar acetophenone

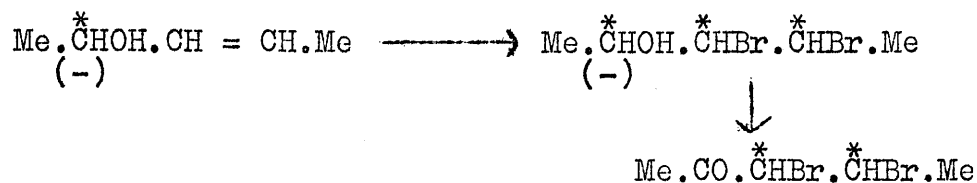


The two intermediates

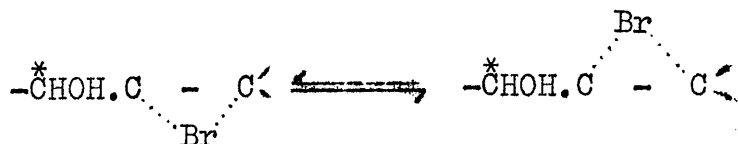
being diastereoisomerides possessing different energies, reaction will follow the path with the lower activation energy, a partial asymmetric synthesis resulting.

Metallic zinc was present in excess throughout the reaction, and it is now suggested by Arcus and Smyth (70) that much of the interaction, and particularly that leading to asymmetric synthesis, takes place at the zinc surface. The following mechanism would lead to a substantial degree of asymmetric synthesis: the molecule  $\text{Br}^- + \text{Zn.CH}_2\text{COO}\overset{*}{\text{R}}_{(-)}$  is absorbed at the zinc surface in a configuration determined by the menthyl group ( $\overset{*}{\text{R}}$ ); for minimum energy of activation, a molecule of acetophenone has to approach with carbonyl, methyl and phenyl groups in a definite relationship to the absorbed molecule. The new centre will then be formed with a preponderance of one configuration. This is an example of an asymmetric synthesis where there is no "fixed centre of asymmetry" in the carbonyl compound, the mechanism of reaction being inexplicable on the basis of induced asymmetry in the carbonyl group.

An asymmetric synthesis in which the intermediate asymmetric group was removed by oxidation was described by Kenyon and Partridge (71). Addition of bromine to (-)- $\alpha$ - $\delta$ -dimethylallyl carbonol gave (+)-methyl- $\alpha$ - $\beta$ -dibromopropyl carbinol which was oxidised to (+)-methyl- $\alpha$ - $\beta$ -dibromopropyl ketone.



It was also found that bromine addition to (+)- $\delta$ -phenyl- $\alpha$ -methylallyl alcohol at room temperature gave a mixture of two isomeric dibromocarbinols, oxidation yielding (+)- and (-)-1:2-dibromo-1-phenyl-3-butanone. The sign of rotation and the optical purity of the ketone was found to be dependent on the temperature at which addition occurred. A similar temperature effect was observed by Balfe, Kenyon and Waddan (72) on addition of bromine to (-)- and (+)-1-phenylpent-1-en-3-ol. The effect is explained as a variance in equilibrium between the two stereoisomerides of the intermediates formed by addition of the first bromine atom, the equilibrium controlling the relative proportions of dibromoalcohols formed on addition of the second bromine atom.

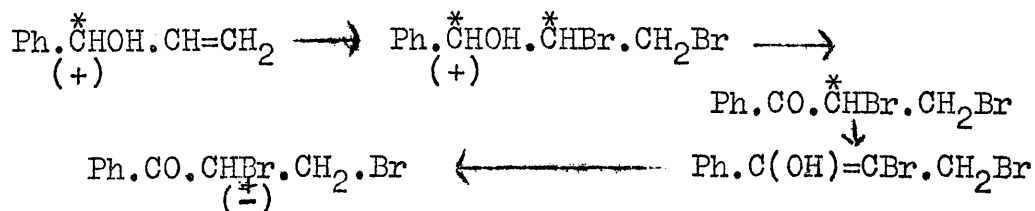


It is also shown that both atoms in the dibromoketone, obtained by oxidation of the dibromoalcohol, were giving rise to optical activity. Of the two asymmetric carbon atoms in the dibromoketone at least one must be giving rise to optical activity. If the second carbon atom were not giving rise to optical activity it would be racemic, and the ketone would be a mixture of diastereoisomerides which should be separable by fractional crystallisation.



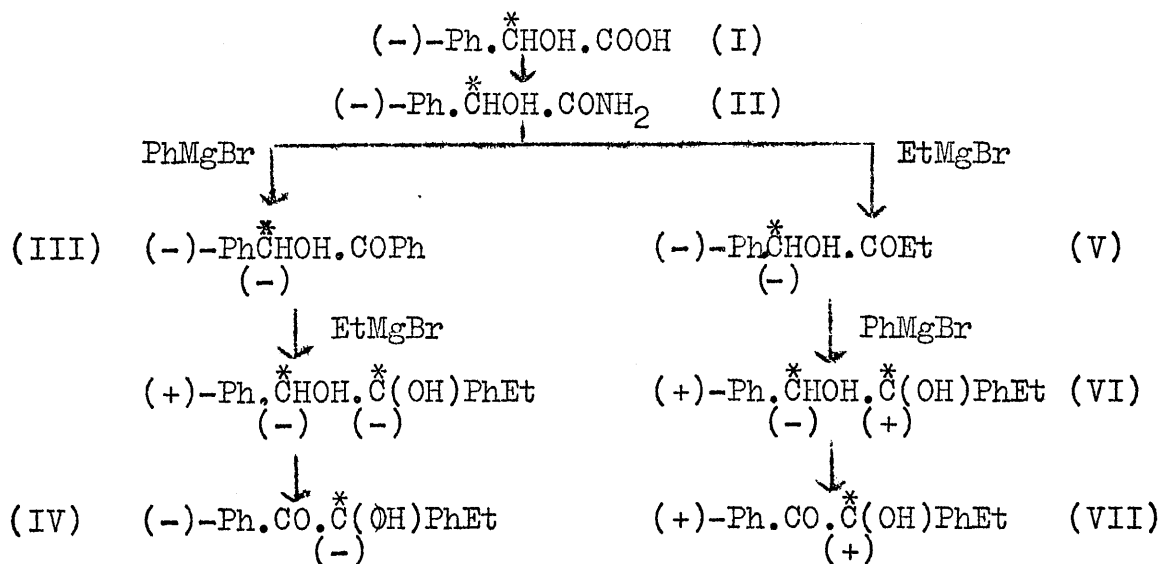
Since this separation was not achieved, the authors assume that both carbon atoms in the dibromoalcohol and its oxidation product, the dibromoketone, give rise to optical activity.

A similar series of reactions was carried out by Arcus and Strauss (73); addition of bromine to (+)-phenyl-vinyl carbinol and subsequent oxidation, however, yielded an optically inactive dibromoketone. It was postulated that the racemisation was due to keto-enol tautomerism, favoured by the phenyl group which permits conjugation of the enolic form.

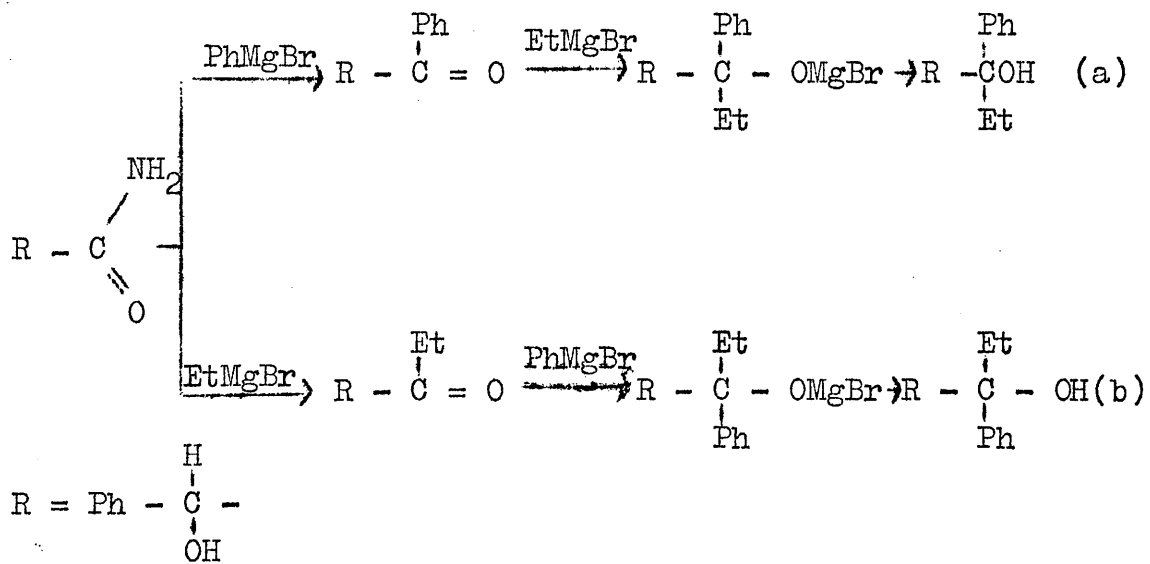


Similar removal of the original centre of asymmetry was the basis of an asymmetric synthesis described by Roger (74). Oxidation of (+)- $\alpha$ -ethylhydrobenzoin (VI), obtained by interaction of phenyl magnesium bromide and (-)-phenyl-propionyl carbinol (V), yielded (+)-ethylbenzoin (VII). Secondly, oxidation of (-)- $\beta$ -ethylhydrobenzoin obtained from (+)-benzoin and ethyl magnesium bromide also gave (+)-ethylbenzoin; he therefore assumed that commencing with (-)-benzoin (III), (-)-ethylbenzoin (IV) would be obtained. McKenzie and Wren (75) had previously obtained (-)-benzoin (III) from (-)-mandelamide (II), by reaction with phenyl magnesium bromide. Similarly, Roger (76) had prepared (-)-phenylpropionyl carbinol (V) from (-)-mandelamide (II) and ethyl magnesium bromide.

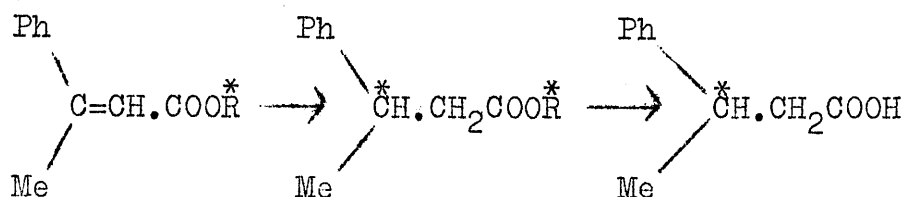
Thus the complete reaction scheme was:



Roger explained the reactions on the basis of induced asymmetry, optically pure products being obtained because the inducing and induced centres were directly linked, and not buffered as in McKenzie's experiments (page 55) where a smaller induction would be expected. That the same inducing force gave rise to both isomers of ethyl benzoin by following two different reaction routes was explained as being due to the variance in character of the phenyl and ethyl groups present in the ketone before reaction with the corresponding Grignard reagent. Partridge (77) suggested that the configurational difference of the ethylbenzoin was a necessary consequence of the order of addition of the phenyl and ethyl groups, the ethyl benzoin (a) and (b) being diastereoisomers.

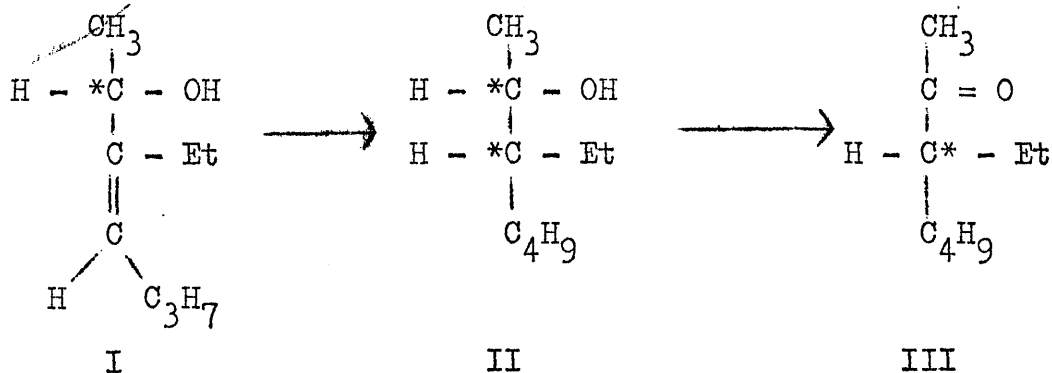


Vavon and Jakubowicz (78) achieved partial asymmetric synthesis by hydrogenating optically active esters of  $\beta$ -methylcinnamic acid using platinum black as catalyst, saponification of the saturated ester yielding optically active  $\beta$ -phenylbutyric acid.

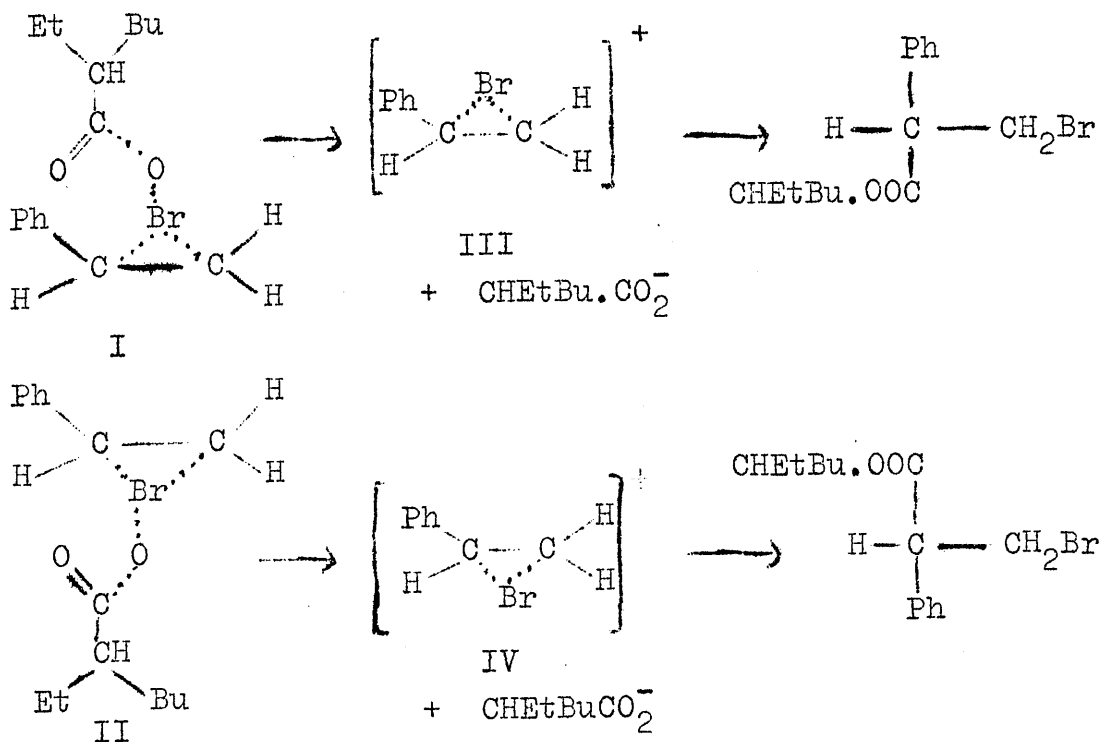


The highest degree asymmetric synthesis (20%) was obtained when R = (-)-menthyl.

Similarly, Arcus and Smyth (79) hydrogenated (+)- and (-)-ethylhept-3-en-2-ol (I), the (+)- and (-)-saturated alcohols (II) being oxidised to (-)- and (+)-3-ethylheptan-2-one (III) respectively. It is proposed that the asymmetric carbon atom controls the conformation in which the molecule is absorbed at the catalyst surface, the addition of hydrogen being asymmetric by reason of this circumstance.



Addition of an asymmetric reagent to an olefin, attempted by Abbott and Arcus (80), failed to give an optically-active product on removal of the original centre of asymmetry. (+)-2-Ethylhexoyl hypobromite reacted with styrene in carbon tetrachloride to give (+)-2-bromo-1-phenylethyl 2-ethylhexanoate which on alkaline hydrolysis gave ( $\pm$ )-phenylglycol. The authors conclude, from consideration of the most probable course of hydrolysis, that racemisation did not occur during this stage, and therefore that addition occurred symmetrically yielding the intermediates (III) and (IV) in equal quantities.



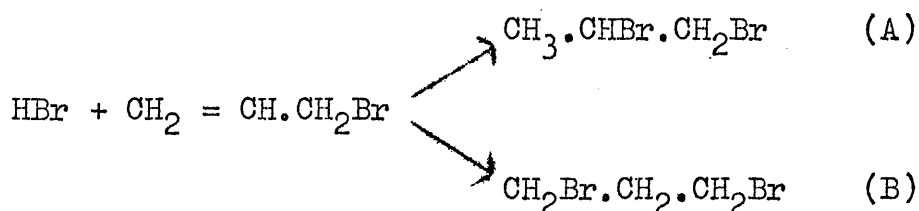
This result implies that there is no appreciable difference in the rates of formation of the diastereoisomeric intermediates (I) and (II).



Free Radical Addition to Monoethylenic Compounds

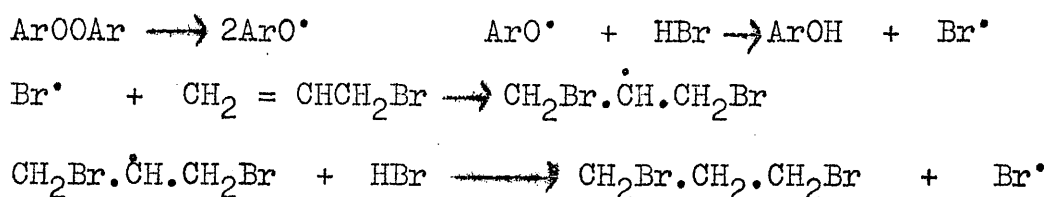
The steric course of an addition to olefins may take one of two alternative directions, "Normal" Markownikow, or "Abnormal" addition. It was not until the 1930's that the confusion existing over the formation of "abnormal" addition products from the addition reaction of hydrogen bromide to ethylenes was clarified. Kharasch and his coworkers showed that the anomalies which existed in reported addition reactions were due to impurities present in the reactants.

The course of addition of hydrogen bromide to allyl bromide was studied, the two courses of reaction, yielding different products, being determined.

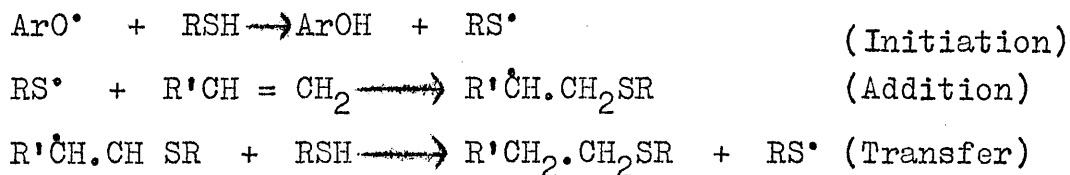


Kharasch and Mayo (81) established that the reaction followed the path (A) quantitatively when pure, freshly distilled reactants were employed, the reaction being carried out in the dark with the exclusion of air and peroxides. This constituted the "Normal" reaction. The alternative course (B) could be induced by addition of oxygen or peroxides or by use of old allyl bromide,

which had become peroxidised. Quantitative reaction by this course required 30 minutes compared to 10 days for the "Normal" addition. Many other instances of reversal of the mode of addition were investigated by Kharasch and his coworkers from 1933 onwards. An interpretation of the results was put forward independently by Hey and Waters (82) and Kharasch, Engelman and Mayo (83).



The "Abnormal" addition reactions are also initiated by photochemical means. The "Abnormal" addition of thiols to olefins was noted by Ashworth and Burkhardt (84), the necessity for peroxides being present having been shown by Jones and Reid (85). This led Kharasch, Read and Mayo (86) to propose the following radical chain mechanism involving neutral thiol radicals.



The interaction of thiols with unsaturated hydrocarbons was first reported by Posner (87) who reacted a number of olefins with thiophenol and benzyl thiol in acetic-sulphuric acid mixtures, addition of thiophenol

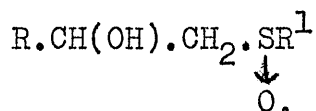
to styrene, in the absence of solvent, proceeding contrary to Markownikoff's rule. This reaction was confirmed by Ashworth and Burkhardt (84) who pointed out the catalytic activity of sunlight and the inhibition caused by addition of small amounts of piperidine. Later, Burkhardt (88) thought that the attack of thiol was by "sulphur in a positive ion or in an oxidising form" possibly as a free radical and possibly through a chain mechanism.

Ipatieff and his coworkers (89), found that "abnormal" addition of thiols to olefins occurred in the absence of catalysts, but that the presence of sulphuric acid reversed the orientation of the addition product and led to "normal" products, contrary to Posner's findings (87), discrepancies being found in numerous cases, due to isomerisation of certain hydrocarbons in acid solution in the presence of thiol.

"Normal" addition can also be induced by reaction in the presence of reducing agents such as hydroquinone (86). Reaction in the presence of sulphur, as ethyl tetrasulphide, also gives "normal" products (85). The activity of the reducing agents may be attributed to the disruption of the chain mechanism by reaction with the free radicals, or by reduction of the peroxides present, breaking the initiation process (90).

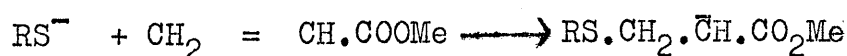
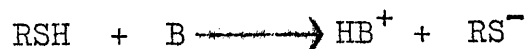
Addition of hydrogen sulphide to higher olefins with peroxide catalysts has been reported by Ipatieff et al. (89): Vaughn and Rust (91) have shown that ultra-violet irradiation is sufficient to cause addition to simple olefins. Shostatrovsky and his coworkers (92) find that the "abnormal" addition of thiols to vinyl ethers is slow using freshly distilled reactants, but that heating increases the rate of reaction and the overall yield.

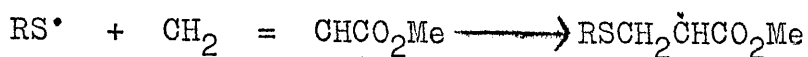
A point of practical importance has been recorded by Kharasch et al. (93) who have been shown that the homolytic addition of thiols to olefins is inhibited by oxygen, owing to formation of hydroxylated sulphoxides of the form:



Fuchs and Kharasch (94) have investigated the addition of thiols to methyl acrylate by both the homolytic and heterolytic (anionic or Michael) mechanisms: these workers found that reaction, in the presence of peroxide (homolytic) or of a strong base (heterolytic), yielded the identical product.

#### Heterolytic



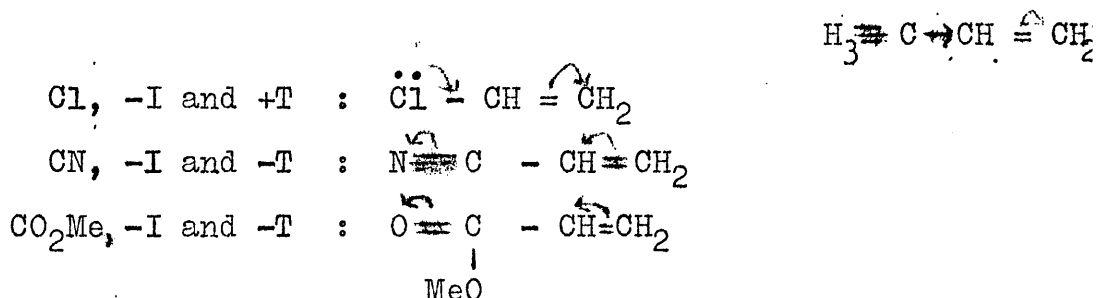
Homolytic

"Abnormal" peroxide catalysed addition of thiolacetic acid to  $\alpha,\beta$ -unsaturated carbonyl compounds has been described by Brown, Jones, and Pinder (95) who show that addition is exothermic and invariably occurs at the  $\beta$ -carbon atom to the carbonyl group. Addition of thiolacetic acid to acraldehyde and crotonaldehyde gave products characterised as their 2:4-dinitrophenylhydrazones, which were identical with compounds of proved structure, prepared by Catch, Cook, Graham and Heilbron (96) where the thioacetate group was in the  $\beta$ -position to the carbonyl group.

The Orientation of Free Radical Addition

An empirical rule proposed by Farmer (97) requires free radical attack exclusively at the most hydrogenated carbon atom. Reactions follow this empirical rule, orientation of the products from free radical attack being independent of the polar nature of R, and thus of the polarisation of the double bond in the olefin substrate  $RCH = CH_2$ , no change in orientation of the product being observed when  $R = Me$  or  $Cl$  and  $R = CN$  or  $CO_2Me$  (98). These groups vary markedly in electronic character:

Me, + I; and hyperconjugative electron release:

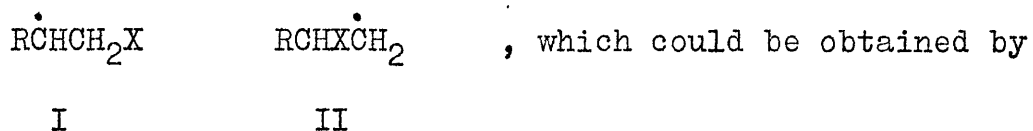


and will have different effects on the direction of polarisation of the double bond. Variation of R however leads to change in the rate of homolytic reaction,  $CH_3 \rangle CF_3$  which may be attributed to steric effects.

This rules out the theory of Waters (99) who regards halogen addition as attack by electrophilic halogen at the point of greatest electron density. Barton (100), however, suggests that free radicals attack preferentially

points of high differential electron density, differential in either direction with respect to the unsymmetrical unsubstituted system. Attack on the terminal  $\text{CH}_2$  group is in accord with steric factors, the terminal carbon atom being most favoured for attack. This explanation however is not generally applicable.

The most important factor influencing the orientation of addition is the relative stability of the intermediate radicals,



attack of HX on  $\text{RCH} = \text{CH}_2$  (101).

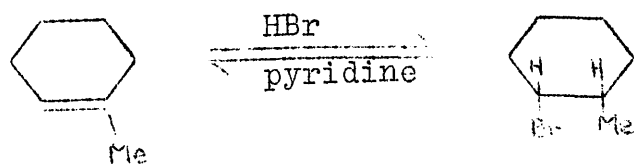
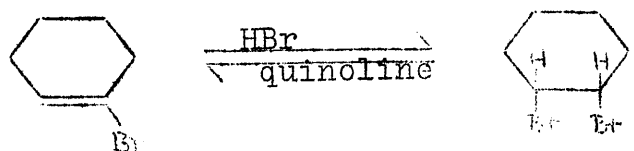
The preferred reaction path will be via the transition state involving the least energy increment. Generally the radical (I) will be more stable than (II) and a radical  $\text{R}_3\text{C}^\cdot$  will be more stable than either.

Thus it is seen that the theory of the orientation problem is not yet in a complete state.

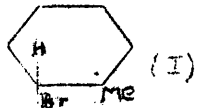
The Stereochemistry of Free Radical Additions

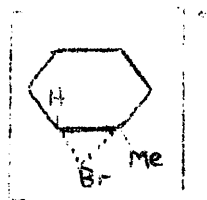
For several free radical additions to cyclic olefinic systems, where a possibility of cis - trans isomerisation is avoided, addition has been shown to be trans. Free radical hydrogen bromide addition to simple olefins is not stereospecific; the addition of atomic bromine is reversible (102) and promotes isomerisation more than addition. Abell, Aycock and Goering (103) have investigated the homolytic addition of hydrogen bromide to 1-bromocyclohexene; the two possible dibromocyclohexanes give different trans elimination products on reaction with quinoline, whereby discrimination can be made of the addition products. It was found that the reaction product was 100% cis - 1:2-dibromocyclohexane, indicating trans addition. In this case the cis isomer is the thermodynamically less stable compound, thus ruling out any cis-trans isomerisation.

Addition of hydrogen bromide to 1-methylcyclohexene is similar.





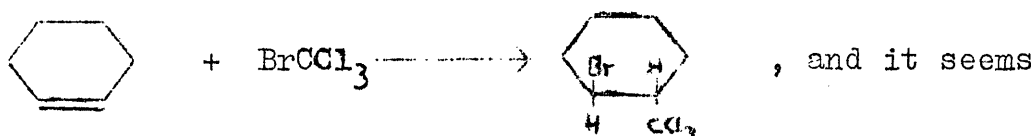
The intermediate radical  (I) might be expected to give a mixture of cis and trans isomers if the free radical has a planar structure with the methyl group coplanar with the ring; but evidently trans addition of the hydrogen bromide is favoured. Resonance between the unshared electron of the carbon radical and the unshared electrons of the bromine atom, giving rise to the intermediate of structure

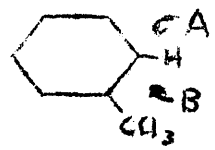


is invoked to explain why (I)

should react with hydrogen bromide in the direction remote from the bromine atom.

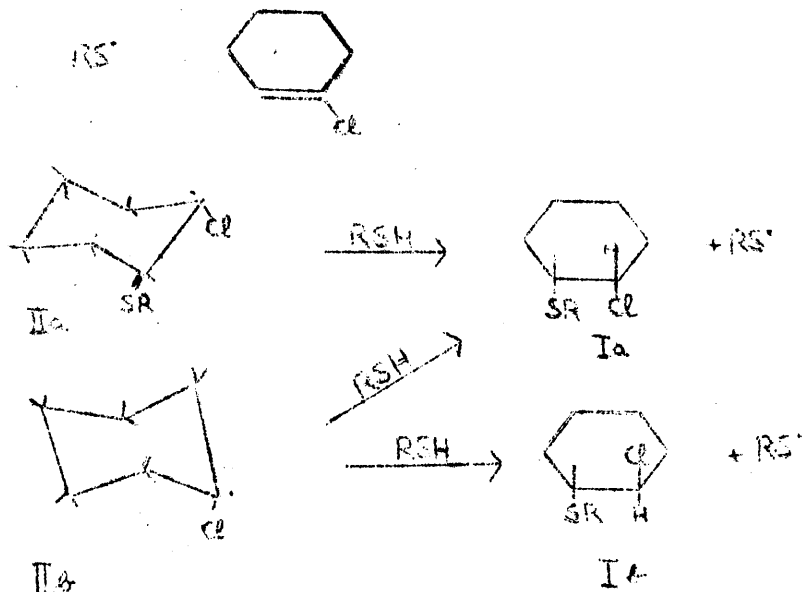
The trans addition of bromotrichloromethane to cyclohexene (104) has been discussed by Fawcett (105); the observed direction of elimination of hydrogen bromide from the adduct suggests trans addition of the bromine and trichloromethyl groups



probable that the bromotrichloromethane would approach the radical intermediate  from a position

(A) rather than position (B) in order to remain further removed from the  $\text{CCl}_3$  group. Abell et al. (103) discussing these results, show that from space models there is essentially no steric difference in approach by path (A) or (B) if the  $\text{CCl}_3$  group occupies the more thermodynamically stable equatorial position. As the trans - cyclohexanes are more stable than the cis isomers, the relative stabilities of the transition states corresponding to (A) and (B) (above) would be expected to lead preferentially to the trans isomer. Inasmuch as the trans addition of bromotrichloromethane to cycloalkenes may be a consequence of the relative stabilities of the possible products, it cannot be concluded that the addition of radicals to double bonds involves a required or preferred trans stereochemical course.

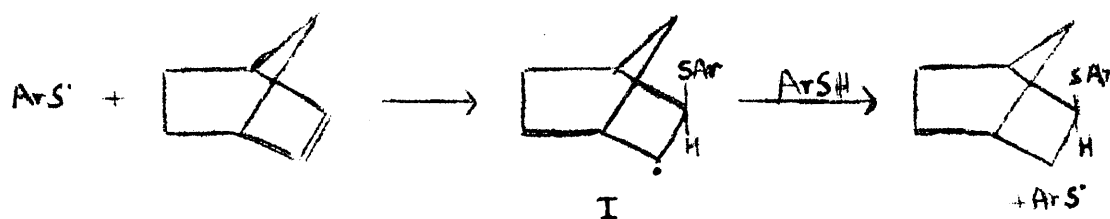
Free radical additions of thiols to 1-chlorocyclohexene have been investigated by Goering, Relyea and Larsen (106). It was found that the homolytic additions of thiols are not as stereospecific as are those of hydrogen bromide. However, in every example investigated, trans addition predominates, even though the cis - 1:2 - disubstituted cyclohexanes are thermodynamically less stable than the corresponding trans-isomer.



It seems likely that the initial conformation of the 2-substituted 1-chlorocyclohexyl radical, resulting from the addition of a radical to 1-chlorocyclohexene, will be the one in which the 2-substituent is in the axial position. Thus the first step of the chain reaction, presumably, results in the formation of (IIa). In this conformation there is an obvious steric advantage for the thiol addendum to approach the radical in the transfer stage so as to give the trans addition product (Ia). Thus if the transfer stage occurs before conformational equilibration of the intermediate radical, or if (IIa) is a more stable conformation than (IIb), a preferred trans addition would be expected. If the intermediate radical is converted in part to (IIb), both addition products would be expected since there is little or no steric advantage for the approach of the

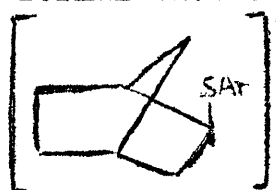
addendum so as to lead to trans addition. The authors conclude that the stereospecificity is dependant on the lifetime of the intermediate (IIa) which is consistent with the observed correlation between stereospecificity and ratio of addendum to substrate in each of three cases. At a high ratio of addendum to substrate, the rate of conversion of (IIa)  $\longrightarrow$  (Ia) is larger than at low ratios and there is less opportunity for (IIa) to undergo conformational interconversion to (IIb).

Cristol and Brindell (107) discuss the free radical addition of toluene-p-thiol to norbornylene, an exothermic reaction giving exclusively exo-norbornyl p-tolyl thioether.

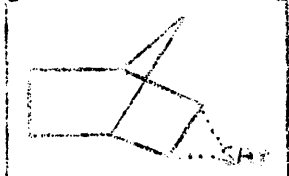


The reaction was unaccompanied by a Wagner-Meerwein type rearrangement as reported with the ionic reaction of bromine with norbornylene (108).

The authors state that their results do not require the formulation of an intermediate mesomeric radical



The results may be explained by reaction at only one position of

the bridged radical or more logically by means of the classical radical (I). The possibility also exists of a sulphur bridged radical of type  which could not be discussed on the evidence as presented.

The findings in the literature may be summarised as follows:

- (a) every example leads to predominatingly trans addition
- (b) there is no final agreement on mechanism; the types of olefin used for investigation permit explanation of trans addition on the lines of either:
  - (i) sterically stable intermediates of the three-membered ring type,
  - (ii) the conformation properties of cyclohexyl radicals.



at the  $\beta$ -position, due to the polarisation of the bond by the carbethoxy (or other electron-attracting) group.

Vorlander (110) found that Michael reactions are reversible, but that the forward reaction is generally exothermic, the reaction thus being favoured by low temperature conditions, a fact recorded by Michael in his original publication.

The kinetics of the Michael addition reaction have not been investigated to date, but the rate determining stage would be expected to be the attack of the anion on the  $\beta$ -carbon atom of the  $\alpha\beta$ -unsaturated molecule. This would be similar to the reaction between cyanide ion and  $\alpha\beta$ -unsaturated compounds where the rate controlling step is the attack of cyanide ion on the  $\beta$ -carbon atom (111).

It has been established by Ingold and Powell (112) that substituted alkyl or aryl groups at the beta carbon atom are inhibitory to addition due to a tendency to conjugate or hyperconjugate with the double bond. It follows that substituents of - I character would impede nucleophilic addition whereas + I substituents would accelerate addition assuming that no secondary conjugation effects occur with the substituent and the  $\alpha\beta$ -double bond.

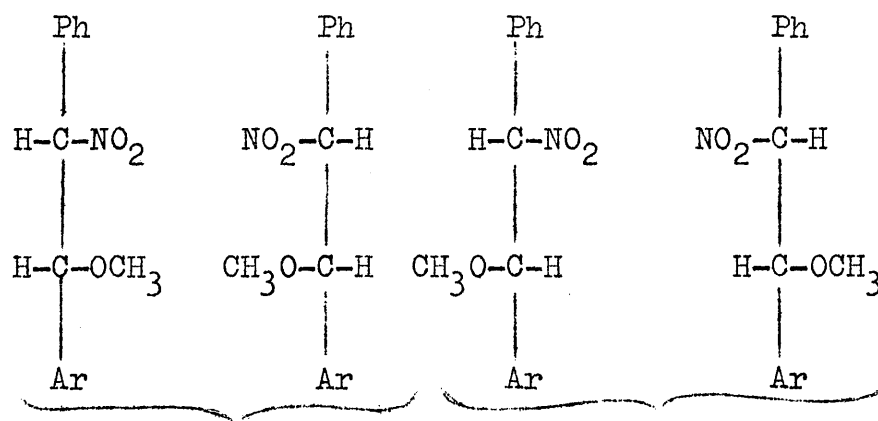
Numerous examples of base catalysed additions of thiols to olefins are recorded in the literature. Sodium alkoxides (113), piperidine (114), and benzyltrimethylammonium hydroxide (115) have been used as catalysts.





The Stereochemistry of Base-catalysed Olefin Addition.

The addition of methanol to substituted  $\alpha$ -nitrostilbenes has been discussed by Reichert and Kuhn (121). Addition of methanol to 4'-methoxy- $\alpha$ -nitrostilbene in the presence of potassium hydroxide gave rise to three products, the ration of yields of the addition products being dependent on the temperature at which the reaction was carried out. The main products were the two racemates:



Ar = p-methoxyphenyl

the subsidiary product being an isomer of the nitrostilbene.

The addition of methanol to 4':5' (presumably equals 3':4')-methylenedioxy- $\alpha$ -nitrostilbene gave two addition products together with a small amount of an isomer of the nitrostilbene. It was also determined that a fourth

compound could be isolated as a product when the reaction was carried out at a higher temperature. From the analysis data of this compound it was assumed that it was 4-(3:4-methylenedioxyphenyl)-3:5-diphenylisoxazole.

No evidence relating to the structure of the addition products was put forward.

#### Ascaridole



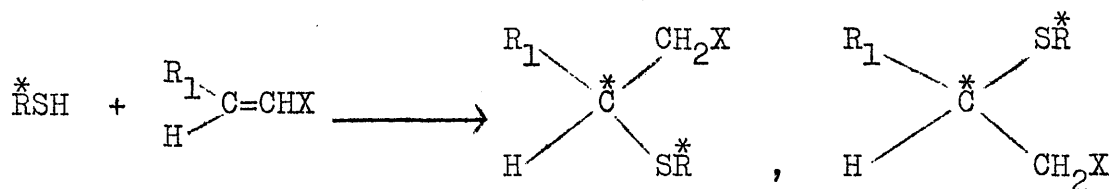
Ascaridole is a viscid oil, isolated from oil of chemopodium, with a strong tendency to decompose with explosive violence above 150° or in the presence of strong acids.

Ascaridole has been used extensively as a peroxidic initiator for free radical reactions, especially with thiol additions.

SECTION III aIntroductionThe Addition of Asymmetric Thiols to Olefins.

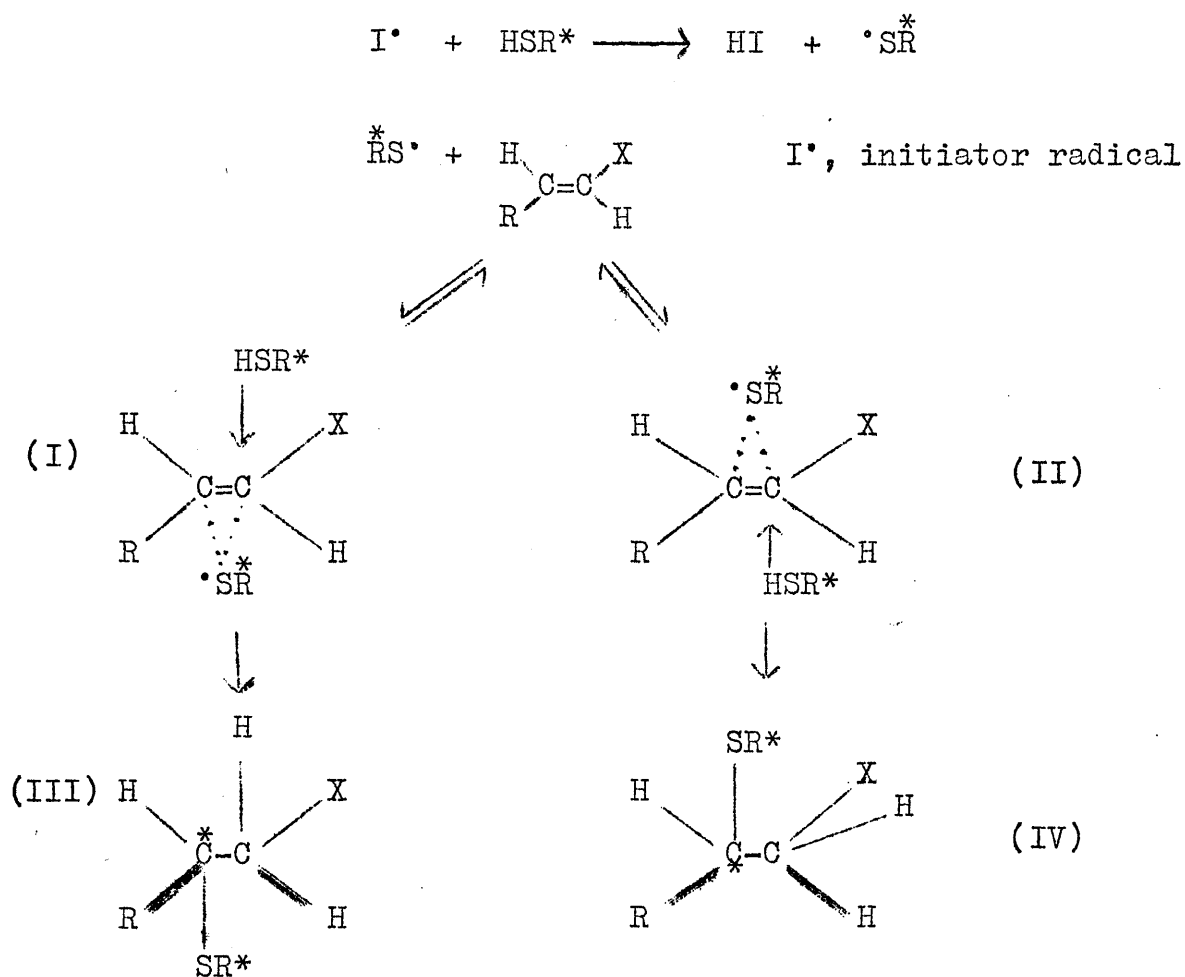
Asymmetric synthesis by addition of an optically active compound to an olefin has not been achieved. The addition of an asymmetric acyl hypobromite to styrene (Abbott and Arcus, page 67) did not proceed in a dissymmetric manner.

It was thought possible that an asymmetric thiol would add dissymmetrically to an olefin under the influence of the optically active centre in the thiol, resulting in the formation of two diastereoisomerides in unequal amounts.

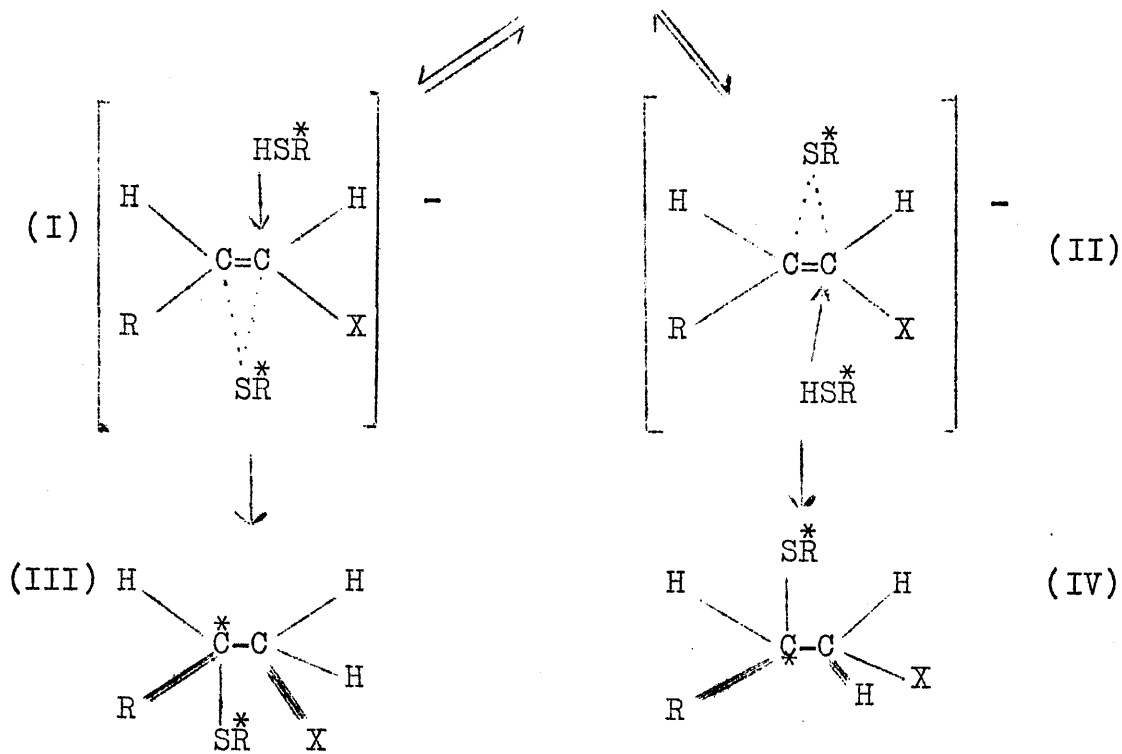
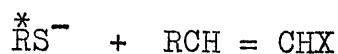
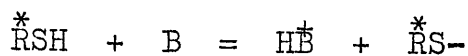


No practicable method was available for the removal of the original centre of asymmetry in the thiol, which necessitated demonstrating the extent of asymmetric synthesis by separation of the diastereoisomerides and determining their weight ratio.

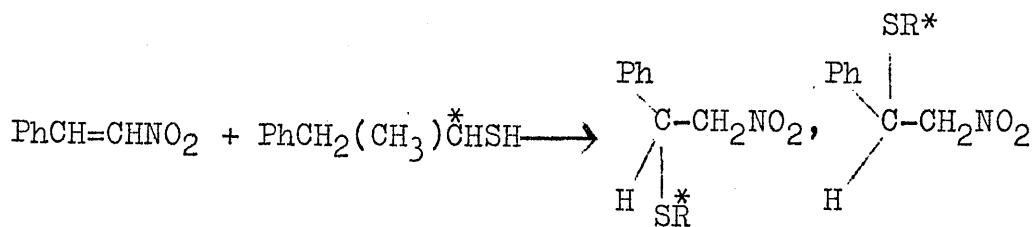
Asymmetric synthesis of this nature is necessarily caused by different activation energies for the transition states in the rate-controlling stages of the addition.



Similarly the base-catalysed addition is:



The rates of formation of (I) and (II) will be dependent upon the activation energies of the two stages, which would be expected to differ. The second stage, the reaction of asymmetric thiol molecules with the two intermediates, (I) and (II), at  $C_a$  to the group X, is necessarily an "inversion", the reactions being "predestined" to take this course; they will, however, proceed at different rates for the two intermediates. Assuming the concentration of (I) and (II) never to be large at any given time, these rates will be large compared to the rates of formation of (I) and (II).

Discussion of ResultsThe Addition of (+)-1-Phenylpropane-2-thiol to *w*-Nitrostyrene

Where  $\overset{*}{\text{R}} = \text{CH}_2\text{Ph} \cdot \overset{*}{\text{C}}\text{H}(\text{CH}_3)-$

Every group of compounds containing the same two asymmetric centres (each capable of two configurations) can be divided into two classes according as the centres have one or other of the two possible relationships to each other. For the present series of sulphides and sulphones these series are designated A and B, and the description of the present section is rendered easier by inserting from the beginning the configurational relationships which have been determined. The experimental basis for the assigned relationships is fully described below.

i) The addition of (+)-1-phenylpropane-2-thiol to *w*-nitrostyrene with peroxide catalyst yielded two diastereoisomeric (+)-2-nitro-1-phenyl-1'-benzyldiethyl sulphides of different crystal structure and melting point. From three experiments the diastereoisomerides,

colourless rhombs (A), m.p.  $76^{\circ}$ , and colourless rectangular plates (B), m.p.  $53.5^{\circ}$ , were obtained in weight ratio 58:42; 73:27 and 67:33%. The total yields of pure diastereoisomers from material from the addition reaction were 75%, 44% and 50% respectively, giving percentage-yield ratios of the two diastereoisomerides 43.5 : 31.5; 32 : 12, and 33.5 : 16.5, a preponderance of the higher-melting diastereoisomeride being observed in each reaction. The highest overall yield (75%) was obtained from the first addition reaction performed; in this experiment it was found that, over a period of months, the higher-melting diastereoisomeride separated completely from a solution of the mixture in light petroleum (b.p.  $40-60^{\circ}$ ), evaporation of the solvent thereafter yielding the almost pure lower-melting diastereoisomeride. Complete separation of this type was not found to be repeatable, the products from later additions always containing an intractable oil.

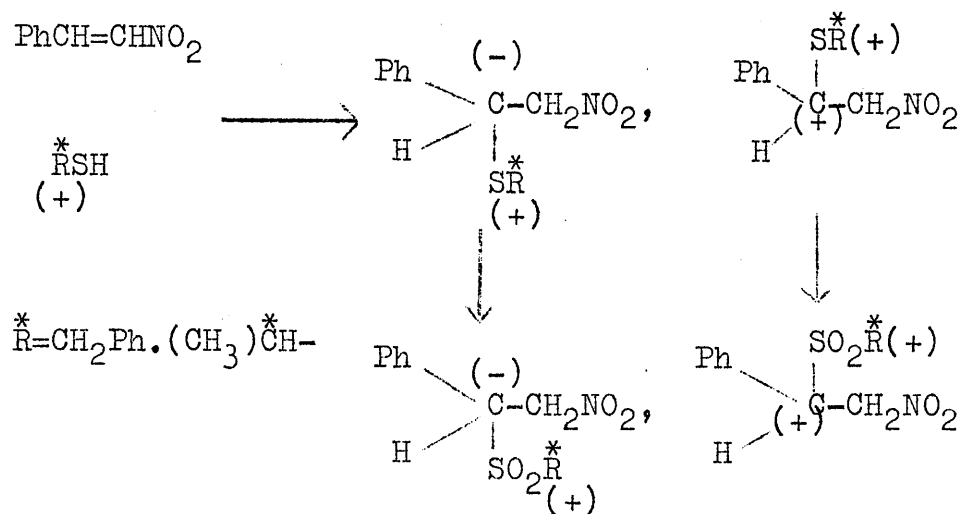
The (±)-sulphide-A, m.p.  $76^{\circ}$ , was oxidised smoothly in warm glacial acetic acid with 34% hydrogen peroxide and gave (±)-2-nitro-1-phenyl-1'-benzyldiethyl sulphone-A, colourless needles, m.p.  $117.5^{\circ}$ . Similar oxidation of the diastereoisomeric (±)-sulphide-B, m.p.  $53.5^{\circ}$ , gave the diastereoisomeric (±)-sulphone-B, colourless needles, m.p.  $111^{\circ}$ .

ii) The addition of freshly distilled ( $\pm$ )-1-phenyl-1-propane-2-thiol to w-nitrostyrene with piperidine catalyst yielded the two diastereoisomeric ( $\pm$ )-2-nitro-1-phenyl-1'-benzyldiethyl sulphides. These were obtained as colourless rhombs (A), m.p. 75-76° and rectangular plates (B), m.p. 52.5°, in a weight ratio of 68:32 with an overall yield of 34%. The percentage-yield ratio isolated was thus 23:11.

The diastereoisomeric sulphides, m.p. 75-76° and m.p. 52.5° were oxidised in warm glacial acetic acid with 34% hydrogen peroxide and gave diastereoisomeric ( $\pm$ )-2-nitro-1-phenyl-1'-benzyldiethyl sulphones, (A) m.p. 117°, and (B) m.p. 95-97°, the latter compound not being obtained in sufficient quantity to attain maximum purity. The mixed melting point of the ( $\pm$ )-sulphones-A from the peroxide- and piperidine- catalysed reactions was 116.5°.



The Addition of (+)-1-Phenylpropane-2-thiol to w-nitrostyrene



The signs on the right-hand side of the equation represent relative configurations.

The addition of 90% optically pure (+)-1-phenylpropane-2-thiol,  $[\alpha]_{5893}^{17} + 6.08^\circ (1, 0.5)$  to w-nitrostyrene with peroxide catalyst yielded an oil which failed to crystallise from solvents, and remained as an oil on prolonged refrigeration. Oxidation of this oil, on a small scale, with 34% hydrogen peroxide in warm glacial acetic acid gave a solid sulphone which was found to be optically stable in hot glacial acetic acid. The bulk of the oil was therefore oxidised by the same method, a mixture of sulphones contaminated with w-nitro-styrene being obtained. Fractional crystallisation from ethanol yielded (-)-2-nitro-1-phenyl-1'-benzyl-diethyl sulphone-A,  $[\alpha]_{5893}^{17} - 46.5^\circ$

(l, 0.5; c, 4.296 in acetone), m.p. 140° and (+)-2-nitro-1-phenyl-1'-benzyl-diethyl sulphone-B,  $[\alpha]_{5893}^{21} + 74.6^\circ$  (l, 0.5; c, 2.332 in acetone), mp. 79-83° respectively, together with two crops both containing w-nitrostyrene one crystalline and one a mixture of oil and crystals. Vacuum sublimation of the crystalline crop at 50°/1 mm. for 1 hour gave a sublimate of w-nitrostyrene leaving the sulphone as residue. The latter material was "plated" for 24 hours, a crystalline mixture of sulphone and w-nitrostyrene remaining. Vacuum sublimation at 50°/1 mm. for 38 hours gave a sublimate of w-nitrostyrene, the residue after washing with ice-cold ethanol yielded (-)-sulphone-A, m.p. 120-121°,  $[\alpha]_{5893}^{20} - 40.7^\circ$  (l, 0.5; c, 2.064 in acetone).

The weight-ratio of diastereoisomeric sulphones was calculated from the specific rotations of the individual crops isolated in the fractionation utilising the maximum values of the specific rotations of the pure (+)- and (-)-sulphones, +89° and -46.5° respectively. The numerical value of the specific rotation of the (+)-sulphone-B, which was not obtained optically pure in the present fractional crystallisation, was taken as that of its enantiomer which was isolated in a pure state from similar reactions of the enantiomeric thiol.

If the diastereoisomeric sulphone of specific rotation P is present as a fraction x of the mixture and its

diastereoisomer has specific rotation Q, then the specific rotation R of the mixture will be given by the equation:

$$Px + Q(1-x) = R$$

<u>Crop</u>	<u>Weight</u>	<u>[<math>\alpha</math>]<sub>5893</sub></u>	<u>Weight of diastereoisomerides</u>	
			(+)-	(-)-
A	1.27 g.	zero	0.44 g.	0.83 g.
B	0.18 g	-9.0°	0.05 g.	0.13 g.
C	0.23 g.	-24.9°	0.04 g.	0.19 g.
D	0.07 g	-44.0°	0.01 g.	0.06 g.
E	0.40 g.	zero		
F	1.10 g.			
E'	0.14 g.	zero	0.05 g.	0.09 g.
F'	0.05 g.	-40.7°	0.002 g.	0.048 g.

Total weight present in reaction product:

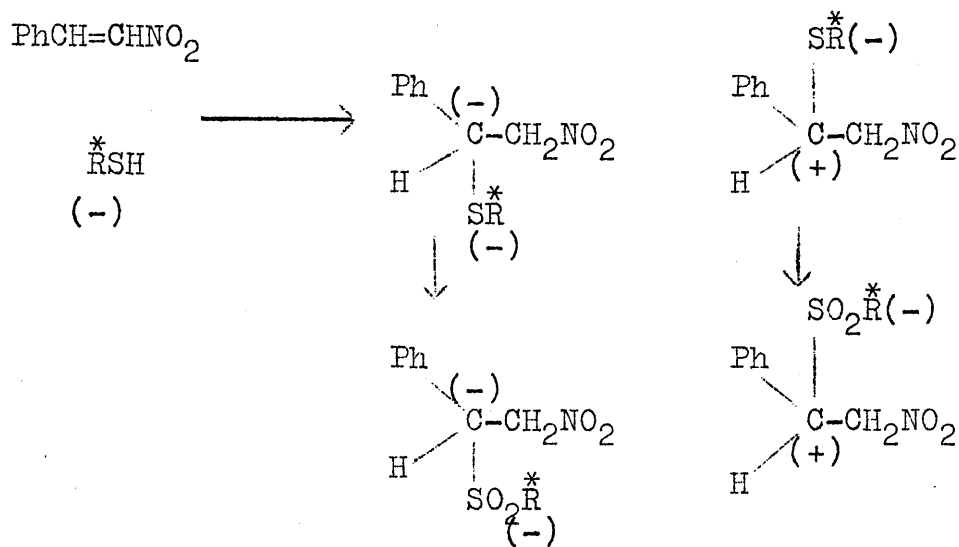
(-)-sulphone-A, 1.35 g.

(+)-sulphone-B, 0.59 g.

These calculations, made for each crop of mixture of diastereoisomeric sulphones obtained, gave a weight-ratio for (-)-A to (+)-B-sulphone of 69.6:30.4. The overall yield for the reaction was calculated as the amount of product obtained initially minus the quantity of

w-nitrostyrene known to be present, as obtained from the vacuum sublimation and subsequent characterisation. Therefore the overall yield for the reaction was  $[3.60 - (0.26 + 0.20)] \text{ g.} = 3.14 \text{ g.}$  The total weight of "proven" sulphones present was 1.94 g., the percentage yield of diastereoisomeric sulphones thus being 61.7%. Therefore the percentage yield of (-)-sulphone-A in the reaction product was 42.9 and that of the (+)-sulphone-B, 18.8%.

The Addition of (-)-1-Phenylpropane-2-thiol to w-nitrostyrene



The signs on the right-hand side of the equation represent relative configurations.

1) The peroxide-catalysed addition of (-)-1-phenylpropane-2-thiol,  $[\alpha]_{5893}^{23} - 13.46^\circ$  (l, 1) to w-nitrostyrene gave as product an oil. It was oxidised with 34% hydrogen peroxide in warm glacial acetic acid solution and gave a semi-solid product, crystallisation of which from ethanol gave a crop (4.7 g.), m.p. 116-118°,  $[\alpha]_{5893}^{20} - 22.8^\circ$  (l, 0.5; c, 5.432 in acetone), of a mixture of diastereoisomeric sulphones; evaporation of the filtrate yielded an oil (2.9 g.) which partially solidified after 4 months. Fractional crystallisation of the former crop gave (+)-2-nitro-1-phenyl-1'-benzyl-diethyl sulphone-A, colourless needles, m.p. 139.5°,  $[\alpha]_{5893}^{20} + 47.0^\circ$  (l, 0.5; c, 5.016 in

acetone) and (-)-2-nitro-1-phenyl-1'-benzyl-diethyl sulphone-B (not quite pure), m.p. 85-86°,  $[\alpha]_{5893}^{20} - 89.5^\circ$  (l, 0.5; c, 5.320 in acetone) respectively.

The partially solidified oil after "plating" for 24 hours gave crystalline material, m.p. 41.5-44.5°,  $[\alpha]_{5893}^{21} - 0.48^\circ$  (l, 0.5; c, 4.570 in acetone). Vacuum sublimation of this mixture (three experiments) at 50°/ 1 mm. for 28 hours showed it to contain 61% w-nitrostyrene, and there was obtained (-)-sulphone-B, m.p. 100.5-102.5°,  $[\alpha]_{5893}^{20} - 89.0^\circ$  (l, 0.5; c, 2.514 in acetone), which remained after shaking the residue from the sublimation with ice-cold ethanol.

With reference to the mixture, above, which has  $[\alpha]_{5893}^{21} - 0.48^\circ$ , if c is the concentration of sulphone, then  $\frac{100 \times 0.48}{0.5 \times \underline{c}} = -89$ , whence c = 1.079. The actual concentration, c, of material for the rotation was, however, 4.570, whence the percentage content of (-)-sulphone-B was 23.6%. The weight-ratio of diastereoisomeric sulphones was calculated from the specific rotation of the solid crop (4.7 g.),  $[\alpha]_{5893}^{20} - 22.8^\circ$ , based on the values +46.5° and -89° as the maximum specific rotations of the (+)- and (-)-sulphone respectively. This calculation showed that the mixture (4.7 g.) contained (+)-sulphone-A, 2.30 g. and (-)-sulphone-B, 2.40 g. The oil (2.9 g.) contains (-)-sulphone-B, 23.6%, i.e. 0.68 g.

Therefore the ratio  $\frac{(-)\text{-sulphone-B}}{(+)\text{-sulphone-A}} = \frac{3.08}{2.30} = \frac{57}{43}$

The overall yield calculated as  $\frac{\text{"proven" sulphone}}{\text{product less } \underline{w}\text{-nitrostyrene}}$

$$= \frac{5.38}{4.7 + 2.9 - \frac{61 \times 2.9}{100}} = \frac{5.38}{5.83} = 92\%$$

Therefore the percentage of (+)-sulphone-A present was 39.6% and that of the (-)-sulphone-B was 52.4%.

2) The piperidine catalysed addition of (-)-1-phenylpropane-2-thiol,  $\alpha_{5893}^{23} - 13.46^\circ$  (1, 1) also gave an oil which was oxidised to give a semi-solid product. This material was crystallised from ethanol and gave a crop (3.71 g.), m.p. 119-120°,  $[\alpha]_{5893}^{21} + 4.1^\circ$  (1, 0.5; c, 4.912 in acetone); evaporation of the filtrate gave an oil (2.31 g.),  $\alpha_{5893}^{20} - 4.50^\circ$  (1, 2; c, 11.545 in acetone) which did not solidify after 4 months.

Fractional crystallisation of the crop (3.71 g.) from ethanol gave (+)-2-nitro-1-phenyl-1'-benzyl-diethyl sulphone-A, m.p. 140°,  $[\alpha]_{5893}^{22} + 46.0^\circ$  (1, 0.5; c, 5.046 in acetone) and (-)-2-nitro-1-phenyl-1'-benzyl-diethyl sulphone-B, m.p. 102.5°,  $[\alpha]_{5893}^{20} - 89.5^\circ$  (1, 0.5; c, 2.478 in acetone) respectively.

The oil which could not be induced to crystallise failed to yield any solid sulphone either by vacuum sublimation or by separation of the residue on an aluminium oxide column.

By calculation based on the maximum specific rotations of the diastereoisomeric sulphones,  $+46.5^\circ$  and  $-89.0^\circ$  respectively, the main crop of mixed sulphones (3.71 g.)  $[\alpha]_{5893}^{21} + 4.1^\circ$ , contained 2.60 g., 69% (+)-sulphone-A and 1.11 g., 31% (-)-sulphone-B.

The oil which could not be characterised, had  $[\alpha]_{5893}^{20} - 4.5^\circ$  (1, 2; c, 11.545 in acetone). If, for the purpose of calculating the sign of rotation of the major sulphone product, the oil is assumed to contain (-)-sulphone-B,  $[\alpha]_{5893} - 89^\circ$ , then the solution which had an overall concentration c = 11.545 will have a concentration of this body, c' = 2.528, i.e. 21.9% of (-)-sulphone-B. Thus the weight of (-)-sulphone-B present in the oil (2.31 g.) is 0.51 g.

On the basis of this calculation, which gives the maximum possible weight of (-)-sulphone-B present in the oil, the weight-ratio of (+)-sulphone-A to (-)-sulphone-B cannot be less than

$$\frac{2.60}{1.11 + 0.51} = \frac{61}{39} \cdot$$

The maximum overall yield of sulphone will therefore be

$$\frac{4.22}{3.71 + 2.31 - 0.51} = 76\%,$$

whence the percentage-ratio of sulphones present is 46.4 : 29.6.

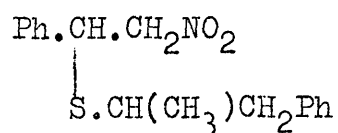


The Stereochemistry of the Addition of (+)-1-Phenylpropane-  
2-thiol to w-Nitrostyrene

1) The Structure of the Sulphides

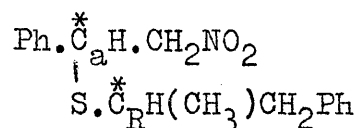
No depression of mixed melting points of specimens of ( $\pm$ )-sulphide-A, m.p.  $76^{\circ}$  and  $75-76^{\circ}$ , and of ( $\pm$ )-sulphide-B m.p.  $53.5^{\circ}$  and m.p.  $52.5^{\circ}$ , from the peroxide- and piperidine-catalysed additions respectively, was observed, indicating that the diastereoisomers, obtained from the same reactants but with different catalysts, were identical. Also, there was no depression of melting point on admixture of the sulphones obtained by oxidising the higher-melting diastereoisomeric sulphides obtained from the peroxide- and piperidine-catalysed additions.

Evidence in the literature (Cason and Wanser, page 83) shows that thiols add to w-nitrostyrene in the beta position to the nitrogroup in the presence of piperidine; further evidence by Kharasch and Fuchs (page 71) shows that addition of thiols to an activated olefin occurs in the same position with peroxide and base catalysts. It may thus be concluded that the sulphides isolated are diastereoisomerides of ( $\pm$ )-2-nitro-1-phenyl-1'-benzyl-diethyl sulphide:

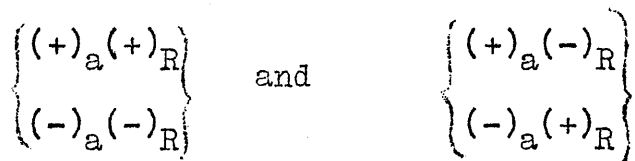


2) Qualitative infra-red analysis of solutions of the (+)-sulphides-A and -B, m.p. 76° and m.p. 53.5° in cyclo-hexane, showed that the two compounds were closely similar, from which it may be concluded that the two sulphides are diastereoisomers and not structural isomers formed by attack of the thiol radical on different carbon atoms of the w-nitrostyrene.

The inactive diastereoisomeric sulphides have structure



and will be racemic mixtures of composition:



### Asymmetric Synthesis

The addition of (+)-1-phenylpropane-2-thiol to w-nitrostyrene, yielding two diastereoisomeric sulphides, indicates that addition to the olefin is not unilateral. Experimentally, the higher-melting isomer was isolated in the greater amount from both the peroxide- and piperidine-catalysed reactions.

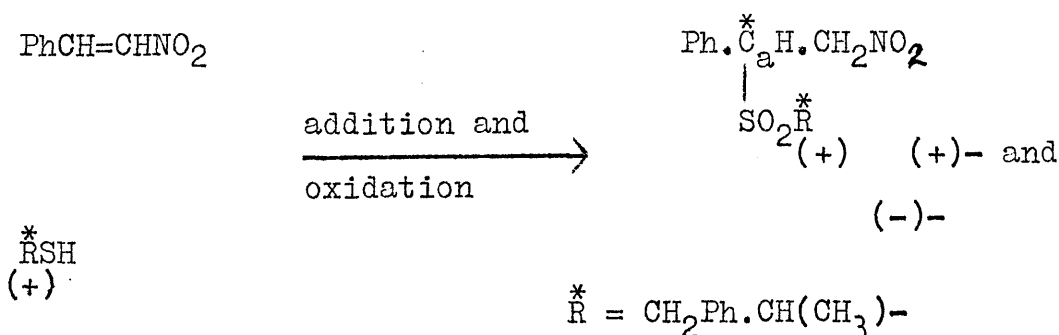
The significance of the relative yields of the sulphides is discussed below, together with further data.

The Stereochemistry of the Addition of (+)- and (-)-1-Phenylpropane-2-thiol to w-Nitrostyrene.

1) The Structure of the Sulphides

The mixed melting point of (+)-sulphone-A, m.p. 139.5°,  $[\alpha]_{5893}^{20} + 47.0^\circ$ , obtained from the peroxide-catalysed addition of (-)-1-phenylpropane-2-thiol, and (+)-sulphone-A, m.p. 140°,  $[\alpha]_{5893}^{22} + 46.0^\circ$ , obtained from the piperidine-catalysed addition of the same thiol, was 139.5°. A mixture of the specimens of (-)-sulphone-B, m.p. 100.5-102.5°,  $[\alpha]_{5893}^{20} - 89.0^\circ$ , and m.p. 102.5°,  $[\alpha]_{5893}^{20} - 89.5^\circ$ , obtained from the peroxide- and piperidine-catalysed additions, respectively, had m.p. 101.5-102.5°. It is therefore concluded that the two diastereoisomerides obtained from the peroxide- and piperidine-catalysed additions are identical.

2) Configuration of the Optically Active Sulphones, and thence of the Optically Inactive Sulphides and Sulphones.



[ (+)- and (-)- denote signs of rotation].

The addition of (+)-1-phenylpropane-2-thiol to w-nitrostyrene, and oxidation of the product, gave rise to (+)- and (-)-diastereoisomeric sulphones, from which it may be concluded that the contribution of the new asymmetric carbon atom,  $C_a$ , to the rotatory power of the compound as a whole, will be (+)- in the former sulphone and (-)- in the latter sulphone. The (+)-sulphone will thus have a steric configuration  $[(+)_a(+)_R]$  and the (-)-sulphone will have a steric configuration  $[(-)_a(+)_R]$ . Similarly the (+)- and (-)-sulphones obtained from the addition of the enantiomorphic (-)-thiol will have steric configurations  $[(+)_a(-)_R]$  and  $[(-)_a(-)_R]$  respectively.

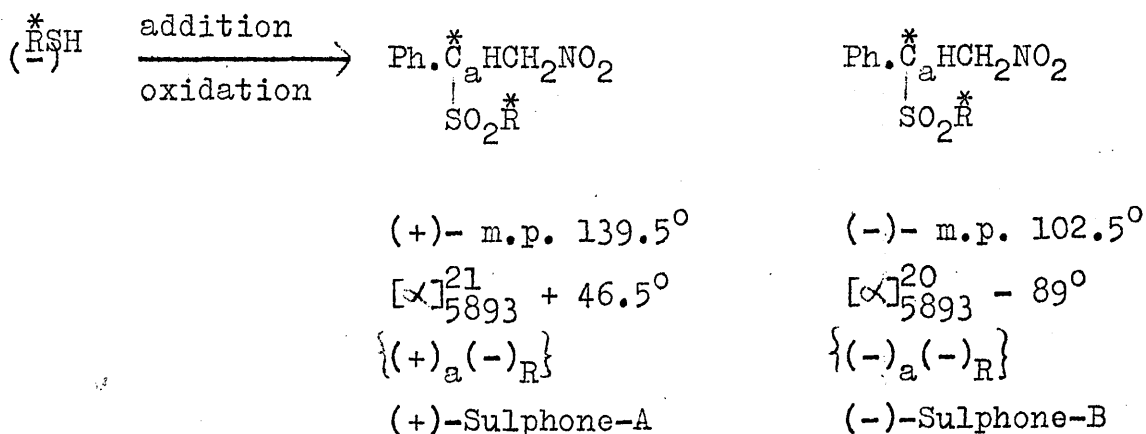
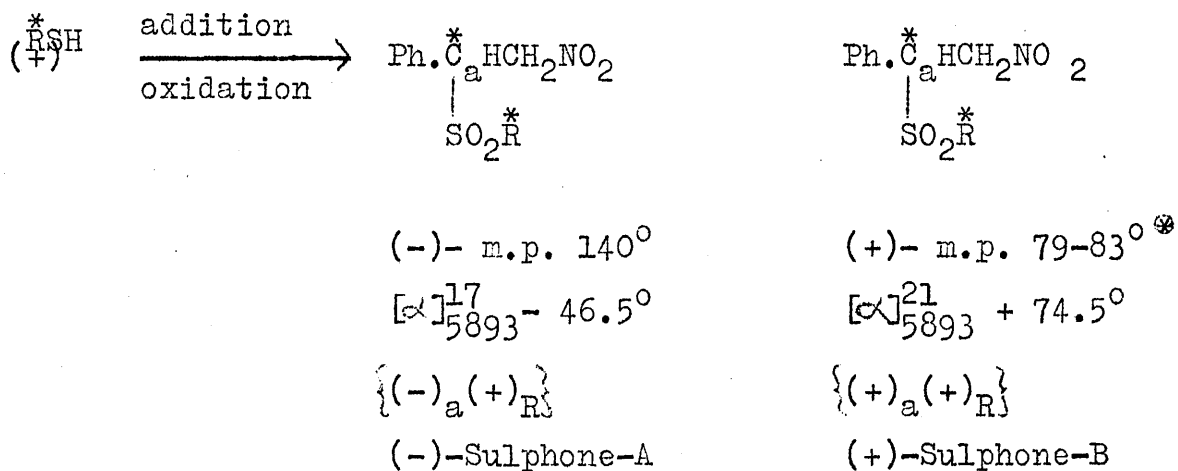
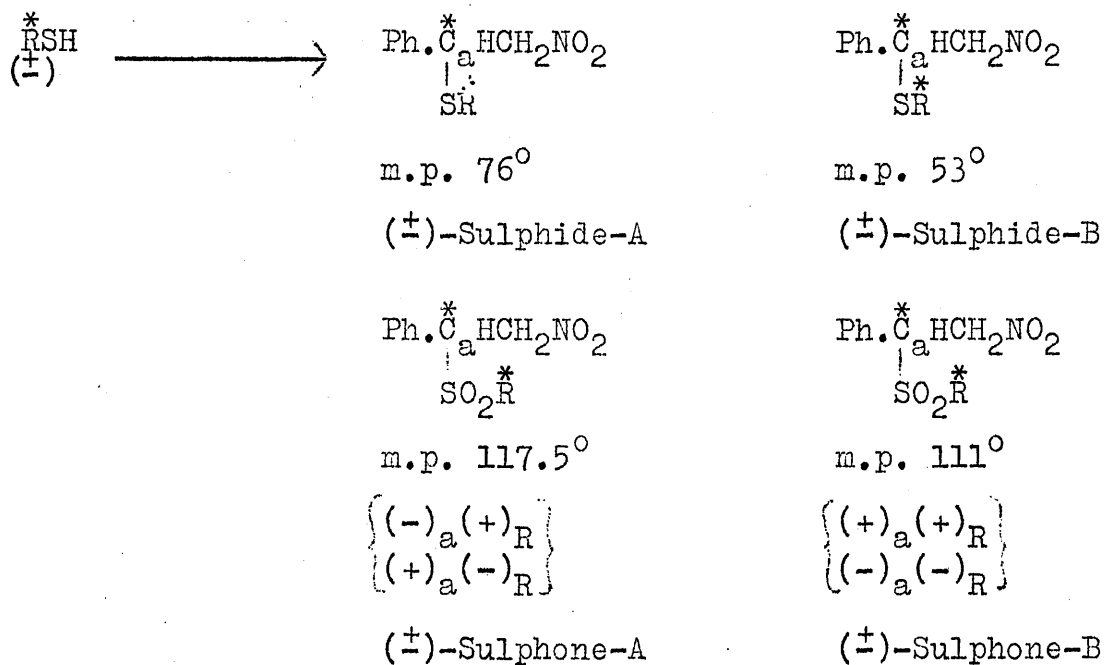
The optically inactive 50% mixture of (+)-sulphone, m.p.  $139.5^\circ$ ,  $[\alpha]_{5893}^{20} + 47.0^\circ$ , derived from (-)-1-phenylpropane-2-thiol, and (-)-sulphone, m.p.  $140^\circ$ ,  $[\alpha]_{5893}^{17} - 46.5^\circ$ , derived from the enantiomorphic (+)-thiol, had m.p.  $117-118^\circ$ . A mixture of this material with (+)-sulphone, m.p.  $117.5^\circ$ , obtained by oxidation of the (+)-sulphide-A m.p.  $76^\circ$ , had m.p.  $117-117.5^\circ$ . It may thus be concluded that this (+)-sulphone is a mixture of (+)-sulphone and (-)-sulphone of steric configurations  $[(+)_a(-)_R]$  and  $[(-)_a(+)_R]$  respectively, and hence the steric configuration of this (+)-sulphone is to be represented as  $\left\{ \begin{array}{l} (+)_a(-)_R \\ (-)_a(+)_R \end{array} \right\}$ . It is this group of compounds which has been referred to throughout as series A.

The inability to obtain optically pure (+)-sulphone from the addition of (+)-1-phenylpropane-2-thiol prevented the carrying out of a similar series of mixed melting points for the ( $\pm$ )-sulphone, m.p. 111<sup>o</sup>, the configuration of which, however, is made virtually certain by the characterisation of the other ( $\pm$ )-sulphone, and to the (+)-, and (-)-, and ( $\pm$ )-sulphones of this B-series are assigned the configurations  $[(+)_{\text{a}}(+)_{\text{R}}]$ ,  $[(-)_{\text{a}}(-)_{\text{R}}]$ , and  $\left\{ \begin{array}{l} (+)_{\text{a}}(+)_{\text{R}} \\ (-)_{\text{a}}(-)_{\text{R}} \end{array} \right\}$  respectively. The complete reaction scheme is set out in Table 1.

The configurations of the two ( $\pm$ )-sulphides of the Table are the same as those of the sulphones to which they give rise. (The optically active sulphides were oils and have therefore been omitted.)

The evidence obtained from the present work is insufficient to determine the absolute configuration of the new asymmetric centre,  $C_{\text{a}}$ , in any of the compounds prepared. The determination of the absolute configuration of  $C_{\text{a}}$  would necessitate the removal of the original centre of asymmetry at  $C_{\text{R}}$  and the relating of the compound thus obtained with compounds of known configuration. Of the methods recorded in the literature for the cleavage of sulphides,  $\text{RSR}'$ , most lead to a mixture of products while those which are elimination reactions would lead to removal of asymmetry at  $C_{\text{a}}$  rather than at  $C_{\text{R}}$ .

Addition of (+)-, (+)- and (-)-1-Phenylpropane-2-thiol  
to w-Nitrostyrene



[Rotations in acetone.]

\* Not completely free from the other diastereoisomer]

TABLE 2

Percentage-yield Ratios.

<u>Thiol</u>	<u>catalyst</u>	<u>RSR'</u>		
		A-m.p. 76°	B-m.p. 53°	
(±)	ascaridole	(i)	43.5%	31.5%
		(ii)	32%	12%
		(iii)	33.5%	16.5%
	piperidine	(iv)	23%	11%
		<u>RSO<sub>2</sub>R'</u>		
		A-m.p. 140°	B- m.p.	
(+)	ascaridole	42.9%	18.8% (79-83)	
(-)	ascaridole	39.6%	52.4% (102.5°)	
(-)	piperidine	[43.4%]	[29.6%]( " )*	

greater  
proportion

\* [see page 98 ]

The conclusions which are deduced from the data of Table 2 are as follows:

1) In every experiment both diastereoisomeric (A and B) sulphides, or sulphones, were isolated. The addition of 1-phenylpropane-2-thiol to w-nitrostyrene is, therefore, not unilateral but such that the two diastereoisomeric transition states (p.87) are formed in substantial

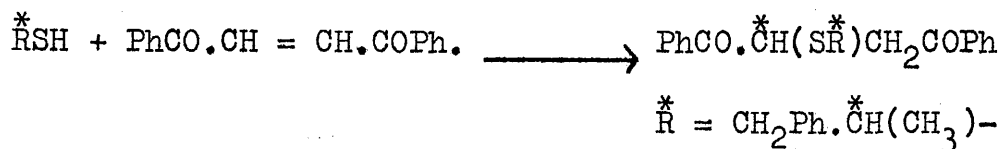
amount in both free radical and Michael addition.

2) The mode of separation by crystallisation and sublimation, and of the evaluation of the composition of mixtures by use of the rotatory powers in the experiments where optically active thiol was employed, have been described in detail above. The higher-melting and less soluble A-series has been isolated, or its presence deduced from rotatory powers, in the greater amount in all instances except the (-)-thiol-ascaridole addition. In this instance, in which an exceptionally large quantity of solid optically active (mixed) sulphones was isolated, it is deduced that the B-isomer was present in the greater amount. This experiment then, though giving an exceptional result was also one in which the total sulphone isolated and/or deduced was exceptionally large. Viewing the results of the free radical addition as a whole, in the light of this last circumstance, it cannot be certainly concluded that the A-configuration is in fact formed in the greater quantity, and the safest conclusion appears to be that by free radical addition the two diastereo-isomeric series ( A and B ) are formed in approximately equal amount.

With regard to the Michael addition with (-)-thiol the values of Table 2 are minimal for A and maximal for B



(see description above, p.99); it therefore appears reasonably certain that dissymmetric addition has occurred, and that the A-configuration predominates.

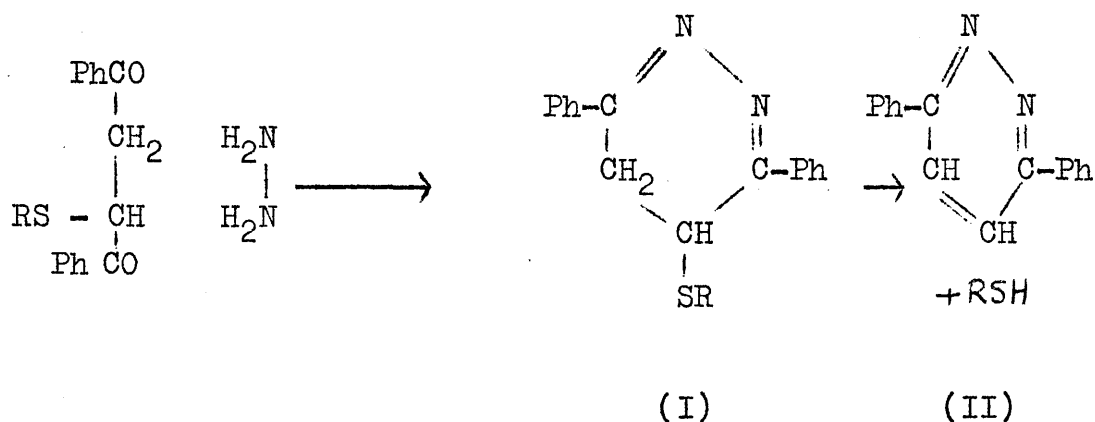
Additions to trans-1:2-Dibenzoyl ethylenea) (+)-1-Phenylpropane-2-thiol

The addition of (+)-1-phenylpropane-2-thiol to trans-1:2-dibenzoyl ethylene with peroxide catalyst gave an oil which partially crystallised from ethanol to give (+)-1:2-dibenzoyl-1'-benzyldiethyl sulphide, which, after further recrystallisation, had m.p. 87.5°, and an intractable oil. The weight ratio of solid sulphide to oil in each of three additions was 46:54; 39:61; 36:64. These values do not take into account an indeterminate quantity of solid sulphide which remained dissolved in the oil.

Attempts to prepare a crystalline 2:4-dinitrophenyl-hydrazone and semicarbazone of the oil failed.

An attempt to prepare (+)-4-(1-methyl-2-phenylethyl-mercapto)-3:6-diphenylhydropyridazine (I), by reaction of the sulphide (oil) with hydrazine hydrate, gave 3:6-diphenyl-pyridazine (II), although a sulphur containing compound was formed initially. Crystallisation of the initial product from hot chloroform-ethanol was

accompanied by a strong odour of thiol. It is concluded that, as shown, elimination of thiol takes place.



The reaction between hydrazine hydrate and trans-1:2-dibenzoylthane has been described by Paal and Dencks (122). The final product of the reaction was found to be 3:6-diphenylpyridazine, formed from the dihydro compound (not isolated in a pure state nor characterised) when it was air-dried or recrystallised by atmospheric oxidation.

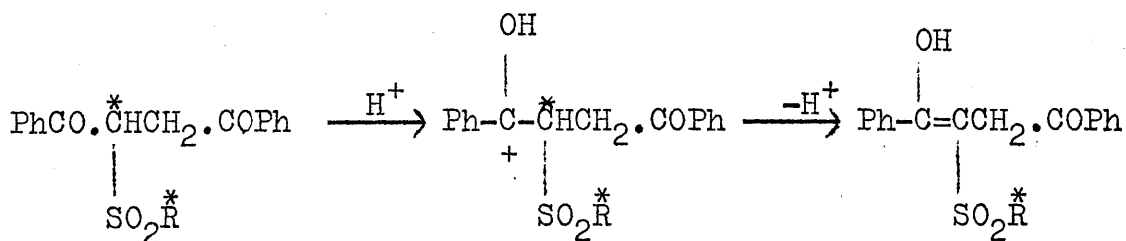
However, although a proof in the form of solid derivatives was not obtained, it is considered that the oil is mainly a (+)-sulphide diastereoisomeric with the (+)-sulphide of m.p. 87.5°. Definite proof was then sought by oxidation of the sulphides to the corresponding sulphones.

b) Benzyl Thiol

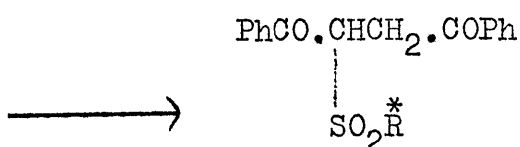
i) Addition of benzyl thiol to trans-1:2-dibenzoylethylene, with peroxide catalyst, gave an 85% yield of 1:2-dibenzoylethyl benzyl sulphide, m.p. 99°.

The Oxidation of the Sulphidesa) Cold solution

Oxidation of (+)-1:2-dibenzoyl-1'-benzyl-diethyl sulphide, both the oil and the solid, in cold glacial acetic acid solution with 34% hydrogen peroxide, gave rise to a single sulphone, the specimens having m.p. 122.5-123° and m.p. 119-120° respectively, and mixed m.p. 122°. The fact that the same sulphone is obtained from the two different sulphides suggests that racemisation of the new asymmetric centre occurs, caused by tautomeric hydrogen shifts in the acid solution:



enol, new  
centre race-  
mised.



most stable diastereo-  
isomer appears as product.

Thus a single diastereoisomeric racemic sulphone appears from either diastereoisomeric racemic sulphide.

ii) Oxidation of 1:2-dibenzoylethyl benzyl sulphide in cold glacial acetic acid with 34% hydrogen peroxide gave a good yield of 1:2-dibenzoylethyl benzyl sulphone, m.p. 175.5°.

b) Hot solution

i) The oxidation of (+)-1:2-dibenzoyl-1'-benzyldiethyl sulphide (oil and solid) with 34% hydrogen peroxide in hot acetic acid gave trans-1:2-dibenzoylethylene, identified by mixed melting points, in 54% and 50% yields respectively. [100% decomposition of the sulphides yields 61% trans-1:2-dibenzoylethylene.] It was not found possible to characterise the second, water-soluble, decomposition product, which presumably was (+)-1-methyl-2-phenylethyl sulphonic acid.

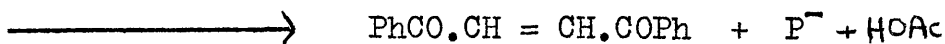
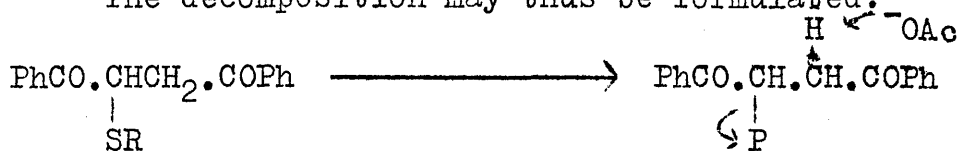
ii) Similar oxidation of 1:2-dibenzoylethyl benzyl sulphide gave a mixture of 1:2-dibenzoylethyl benzyl sulphone (40% yield) and trans-1:2-dibenzoylethylene, which was characterised by mixed melting point. The water-soluble decomposition product was not characterised.

The following facts were observed in the investigation of the decompositions on oxidation in hot acetic acid solution:

- a) ( $\pm$ )-1:2-Dibenzoyl-1'-benzyldiethyl sulphide (solid) and 1:2-dibenzoylethyl benzyl sulphide are both stable in hot acetic acid, recovery being 82% and 92% respectively.
- b) ( $\pm$ )-1:2-Dibenzoyl-1'-benzyldiethyl sulphone and 1:2-dibenzoylethyl benzyl sulphone are both stable in hot acetic acid, recovery being 76% and 88% respectively.
- c) The above sulphones are both stable in hot acetic acid-hydrogen peroxide solution, recovery being 53% and 90% respectively.

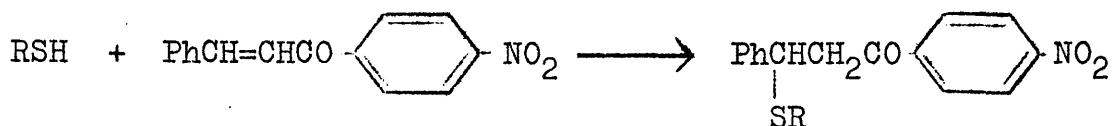
From this data it is concluded that the decomposition occurs at a stage intermediate to the formation of the sulphone by an undetermined mechanism. An attempt to prepare 1:2-dibenzoylethyl benzyl sulphoxide by oxidation of the sulphide with the theoretical quantity of 34% hydrogen peroxide failed, the original sulphide, benzyl thiol (detected by odour) and trans-1:2-dibenzoyl-ethylene being recovered.

The decomposition may thus be formulated:



where R = PhCH<sub>2</sub>- or CH<sub>2</sub>Ph. $\overset{*}{\text{C}}\text{H}(\text{CH}_3)$ -

and P = partially (?) oxidised -SR

Additions to 4'-Nitrochalkonei) Benzyl Thiol

The peroxide catalysed addition of benzyl thiol to 4'-nitrochalkone gave a high yield of 1-phenyl-2-(p-nitrobenzoyl)-ethyl benzyl sulphide, m.p. 87°.

ii) (+)-1-Phenylpropane-2-thiol

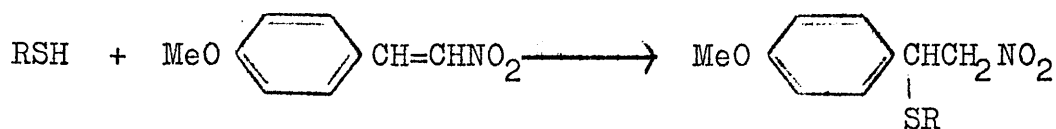
a) The attempted addition of (+)-1-phenylpropane-2-thiol to 4'-nitrochalkone with peroxide catalyst in benzene solution, maintained just below its boiling point, failed, 4'-nitrochalkone (70%) being recovered.

b) Addition of (+)-1-phenylpropane-2-thiol to 4'-nitrochalkone in the absence of solvent gave a considerable quantity of impure (+)-2-(p-nitrobenzoyl)-1-phenyl-1'-benzyl-diethyl sulphide. Fractional crystallisation of this material from cyclo-hexane, which was accompanied by decomposition of the sulphide, yielded one isomer, m.p. 81-82°, only.

No stereochemical interpretation can be deduced for this addition reaction owing to the decomposition which occurred in the attempt to purify the product; only one of the two possible diastereoisomeric sulphides was

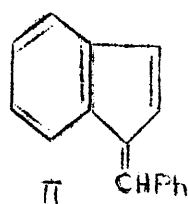
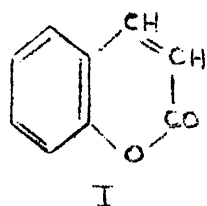
isolated, and it in a final yield too low to permit an assertion that it is the major addition product.

Addition to p-Methoxy-w-nitrostyrene



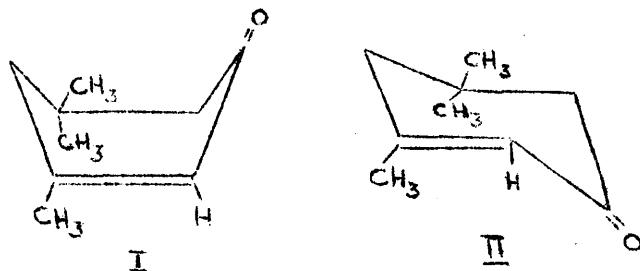
The addition of (+)-1-phenylpropane-2-thiol to p-methoxy-w-nitrostyrene, with peroxide and piperidine as catalyst, gave rise to an oil. Attempts to oxidise this oil with hydrogen peroxide in glacial acetic acid gave a red intractable tar.



The Attempted Addition to Coumarin and Benzylideneindene

- a) Addition of (+)-1-phenylpropane-2-thiol and benzyl thiol to coumarin (I), with peroxide and with piperidine catalyst, did not occur. The ethylenic bond in this compound undergoes the Michael reaction with some "reactive" compounds such as malonic ester and cyanoacetamide but is unreactive towards ethyl acetoacetate. The failure to achieve addition cannot be attributed to steric causes, the molecule (I), being flat. The heterocyclic ring in coumarin, however, is a semi-aromatic structure, which would possibly account for its lack of reactivity towards the thiols.
- b) (+)-1-phenylpropane-2-thiol failed to add to benzylideneindene (II), an unhindered flat molecule, in the presence of peroxide catalyst. No explanation for the failure of the addition is advanced for this compound, whose class (the fulvenes) are generally reactive.

The Attempted Addition to iso-Phorone



From (+)-1-phenylpropane-2-thiol and iso-phorone, with peroxide catalyst, no addition compound was obtained; the product, which had a strong odour of both reactants, distilled almost completely within the boiling point range of the reactions. Examination of scale models shows that in the boat (I) and chair (II) forms steric hindrance occurs either above or below the plane of the molecule, respectively, the "free" side, however, still being slightly hindered by the hydrogen atoms of the methyl group at C<sub>5</sub>. No simple explanation can be put forward for the complete failure of the reaction.

SECTION IIIaEXPERIMENTAL(+)-2-Nitro-1-phenyl-1'-benzyldiethyl sulphides

w-Nitrostyrene (2.38 g.) and ( $\pm$ )-1-phenylpropane-2-thiol (2.38 g.) were heated in nitrogen at 100° for 5 hours with ascaridole (1 drop). The hot reaction mixture was cooled in ice, followed by freezing at -80°, a glass being formed. Addition of light petroleum (b.p. 40-60°) caused crystallisation: recrystallisation of the product (1.78 g.), m.p. 66-70°, from the same solvent yielded (+)-2-nitro-1-phenyl-1'-benzyldiethyl sulphide-A (1.2 g.), m.p. 73-76°. Further crystallisation gave colourless rhombs, m.p. 76° [Found: C, 67.95; H, 6.35; N, 4.85; S, 10.30.  $C_{17}H_{19}NO_2S$  requires C, 67.75; H, 6.35; N, 4.65; S, 10.70%]. From the last two filtrates there were obtained crops: 0.16 g., m.p. 72-74.5° and 0.13 g., m.p. 49.5-52.5°.

Evaporation of the main filtrate gave an oil (2.1 g.) which partially crystallised to give a product (0.6 g.), m.p. 40.5-42.5°. After crystallisation from ethanol it (0.34 g.) had m.p. 49.5-51.5°, and on further crystallisation gave (+)-2-nitro-1-phenyl-1'-benzyldiethyl sulphide-B, colourless rectangular plates, m.p. 53.5° [Found: C, 67.70; H, 6.35; N, 4.50; S, 10.55%].

Overall yield of sulphides, 44%.

The addition was repeated, w-nitrostyrene (2.65 g.) and (+)-1-phenylpropane-2-thiol (2.65 g.) being reacted as above. Fractionation of the reaction product gave the two diastereoisomeric sulphides, A, m.p. 76° (1.1 g.) and B, m.p. 53.5° (0.52 g.). Overall yield of sulphides, 50%

The addition of w-nitrostyrene (0.38 g.) and (+)-1-phenylpropane-2-thiol (0.38 g.) under conditions as above, carried out as a preliminary trial preparation, gave the following yields of diastereoisomerides:

A, 0.11 g., m.p. 72-74°, and 0.22 g., m.p. 73-76°

B, 0.24 g., m.p. 51.5-52.5°

Overall yield of sulphides, 75%.

2) w-Nitrostyrene (2.2 g.) and freshly distilled (+)-1-phenylpropane-2-thiol (2.2 g.) were heated in nitrogen at 100° for 4.2 hours with freshly distilled piperidine (3 drops). The resulting oil, which could not be induced to crystallise by freezing, was washed with cold methanol, a crop (0.57 g.), m.p. 65° being obtained. Slow evaporation of the solvent gave two further crops: 0.13 g., m.p. 67-69°, and 0.47 g., m.p. 65-67°. These three crops were combined (1.17 g.) and crystallised from ethanol, yielding colourless rhombs (0.61 g.), having m.p. 75-76°, and mixed melting

point with the diastereoisomeride-A, m.p.  $76^{\circ}$ , obtained from the peroxide-catalysed addition,  $74-76^{\circ}$ . From the combined filtrates there was obtained the other diastereoisomeride (0.3 g.), m.p.  $52.5^{\circ}$ , mixed melting point with the diastereoisomeride-B, m.p.  $51.5-53.5^{\circ}$ , from the peroxide-catalysed addition,  $52.5^{\circ}$ .

Overall yield of sulphides, 34%.

(+)-2-Nitro-1-phenyl-1'-benzyldiethyl sulphones

[1) Oxidation of the (+)-sulphides from the peroxide-catalysed addition.]

a) (+)-2-Nitro-1-phenyl-1'-benzyldiethyl sulphide-A, m.p.  $76^{\circ}$ , (0.5 g.) dissolved in glacial acetic acid (6 ml.) was warmed on a steam-bath for 5 minutes with 34% hydrogen peroxide (3 ml.). The acetic acid solution was frozen to  $-80^{\circ}$  and allowed to warm slowly to room temperature, a crop (0.33 g.), m.p.  $114-115^{\circ}$  being obtained. Three crystallisations from ethanol gave (+)-2-nitro-1-phenyl-1'-benzyldiethyl sulphone-A, colourless needles, m.p.  $117.5^{\circ}$  [Found: O, 19.34; S, 9.60.  $C_{17}H_{19}NO_4S$  requires O, 19.20; S, 9.60%]. The acetic acid solution was diluted with water (250 ml.); a further crop (0.08 g.), m.p.  $108.5-113^{\circ}$  was obtained.

b) (±)-2-Nitro-1-phenyl-1'-benzyl-diethyl sulphide-B, m.p. 53.5°, (0.35 g.) dissolved in glacial acetic acid (6 ml.) was warmed on a steam-bath for 5 minutes with 34% hydrogen peroxide (3 ml.). The solution was frozen to -80° and allowed to warm slowly to room temperature, a crop (0.15 g.), m.p. 100-100.5° being obtained. Two crystallisations from ethanol gave (±)-2-nitro-1-phenyl-1'-benzyl-diethyl sulphide-B, colourless needles, (0.08 g.), m.p. 111° [Found: S, 9.55%]. Dilution of the acetic acid solution with water (250 ml.) gave a further crop (0.06 g.), m.p. 97.5-100.5°. Oxidation of both diastereoisomerides was unaccompanied by decomposition to w-nitrostyrene.

[2) Oxidation of the (±)-sulphides from the piperidine-catalysed addition.]

a) (±)-2-Nitro-1-phenyl-1'-benzyl-diethyl sulphide-A, m.p. 75-76°, (0.5 g.) dissolved in warm acetic acid (6 ml.) was shaken with a solution of 34% hydrogen peroxide (3 ml.) in glacial acetic acid (5 ml.); the whole was allowed to stand overnight in a melting ice-salt bath. The crop obtained (0.28 g.) had m.p. 104.5-105.5°. This was crystallised from excess methanol, and yielded (±)-sulphide-A, m.p. 117°. Mixed melting point with the (+)-sulphide-A (1a), m.p. 117.5°, was 116.5°.

The acetic acid solution was diluted with water (250 ml.); a further crop (0.17 g.), m.p. 109-111° was obtained.

b) Similar oxidation of the (+)-sulphone-B, m.p. 52.5°, (0.28 g.) gave a very small yield of impure (+)-sulphone-B, m.p. 95-97°.

(+)- and (-)-2-Nitro-1-phenyl-1'-benzyldiethyl sulphide

m-Nitrostyrene (3.12 g.) and (+)-1-phenylpropane-2-thiol (3.14 g.,  $\alpha_{5893}^{17} + 6.08^\circ$ , l, 0.5) were heated in nitrogen at 100° for 6 hours with ascaridole (2 drops). The product could not be induced to crystallise by freezing at -80° for 6 hours nor would it crystallise from ethanol, methanol and light petroleum (b.p. 40-60° and 60-80°). Refrigeration for 7 months also failed to crystallise the product.

(+)- and (-)-2-Nitro-1-phenyl-1'-benzyldiethyl sulphone

Non-racemisation on Oxidation

The oily sulphide (0.1 to 0.2 g.) dissolved in glacial acetic acid (3 ml.) was warmed on a steam-bath for 10 minutes with 34% hydrogen peroxide (3 ml.). The hot solution was diluted with ice-cold water (25 ml.) and allowed to stand. Crystallisation of the precipitate from ethanol gave (-)-2-nitro-1-phenyl-1'-benzyldiethyl sulphone, m.p. 128-130°,  $\alpha_{5893}^{18} - 15^\circ$  (l, 0.5; c, 1.194

in acetone) [Found: N, 4.50; S, 9.60.  $C_{17}H_{19}NO_4S$  requires N, 4.20; S, 9.60%]. This sulphone (0.06 g.) was dissolved in hot glacial acetic acid (5 ml.) and maintained at  $100^\circ$  for 15 minutes. The hot solution was diluted with cold water (25 ml.); the sulphone (0.05 g.), m.p.  $125-128^\circ$ ,  $[\alpha]_{5893}^{18} - 16^\circ$  ( $\underline{l}$ , 0.5;  $\underline{c}$ , 1.006 in acetone) was recovered.

The oily sulphide (5.62 g.) dissolved in glacial acetic acid (30 ml.) was warmed on a steam-bath with 34% hydrogen peroxide (20 ml.) for 10 minutes. The hot solution was cooled and poured into cold water (1 litre). The solid product (3.6 g.) was fractionally crystallised from ethanol, the following crops being obtained:

<u>Crop</u>	<u>Weight</u>	<u>m.p.</u>	$[\alpha]_{5893}^{17}$	( $\underline{l}$ , 0.5; in acetone)
A	1.27 g.	$122-123^\circ$	zero	( $\underline{c}$ , 4.808)
B	0.18 g.	$116-120^\circ$	$-9.02^\circ$	( $\underline{c}$ , 2.216)
C	0.23 g.	$129^\circ$	$-24.9^\circ$	( $\underline{c}$ , 2.172)
D	0.07 g.	$133-133.5^\circ$	$-44.0^\circ$	( $\underline{c}$ , 1.004)
E	0.40 g.			
F	1.10 g.			

Crops E and F were pale yellow, containing w-nitrostyrene.



Crystallisation of crop A (1.0 g.) from ethanol gave (-)-2-nitro-1-phenyl-1'-benzyl-diethyl sulphone-A, (0.33 g.), colourless needles, m.p.  $140^{\circ}$ ,  $[\alpha]_{5893}^{17} - 46.5^{\circ}$  ( $\underline{1}$ , 0.5;  $\underline{c}$ , 4.296 in acetone), [Found: O, 19.25; S, 9.30.  $C_{17}H_{19}NO_4S$  requires O, 19.20; S, 9.60%], as the less soluble fraction, and a crop (0.12 g.), colourless needles, m.p.  $79-83^{\circ}$ ,  $[\alpha]_{5893}^{21} + 74.6^{\circ}$  ( $\underline{1}$ , 0.5;  $\underline{c}$ , 2.332 in acetone) by crystallisation of crops obtained by evaporation of the filtrates from the main fractionation.

Crop E (0.40 g.) was vacuum sublimed at  $60-62^{\circ}/0.5$  mm. for 1 hour, w-nitrostyrene (0.26 g.), m.p.  $52.5-53.5^{\circ}$ , mixed m.p.  $54.5-55.5^{\circ}$ , being obtained as sublimate. The residual sulphone, crop E' (0.14 g.), m.p.  $119-120^{\circ}$  was optically inactive.

Crop F (1.10 g.), a mixture of crystals and oil, was "plated" for 24 hours, crystalline material (0.32 g.),  $[\alpha]_{5893}^{21} - 0.25^{\circ}$  ( $\underline{1}$ , 0.5;  $\underline{c}$ , 6.396 in acetone) being obtained. Vacuum sublimation of this crop (0.30 g.) at  $50^{\circ}/1$  mm. for 28 hours gave w-nitrostyrene (0.20 g.), m.p.  $54.5-55.5^{\circ}$ , mixed m.p.  $53.5-55.5^{\circ}$ , as sublimate. The residue was shaken with ice-cold ethanol (2 ml.) and gave crop F', (-)-sulphone-A (mainly), (0.05 g.), m.p.  $120-121^{\circ}$ ,  $[\alpha]_{5893}^{20} - 40.7^{\circ}$  ( $\underline{1}$ , 0.5;  $\underline{c}$ , 2.064 in acetone).

(+)- and (-)-2-Nitro-1-phenyl-1'-benzyl-diethyl sulphide

w-Nitrostyrene (5.33 g.) and (-)-1-phenylpropane-2-thiol (5.33 g.,  $[\alpha]_{5893}^{23} - 13.46^{\circ}$ , l, 1) were heated in nitrogen at  $100^{\circ}$  for 6 hours with ascaridole (3 drops). The reaction mixture was allowed to stand at room temperature for 3 days, and then frozen at  $-80^{\circ}$  for 1 day, no solidification occurring.

(+)- and (-)-2-Nitro-1-phenyl-1'-benzyl-diethyl sulphone

The oily sulphide (10.6 g.) dissolved in glacial acetic acid (60 ml.) was warmed on a steam-bath with 34% hydrogen peroxide (40 ml.) for 5 minutes, when effervescence occurred. The hot solution was immediately chilled to  $-15^{\circ}$ , and poured into ice-cold water (1 litre). The solid product was filtered at the pump, washed with water, air-dried and crystallised from ethanol. There was obtained Crop A (4.7 g.) m.p.  $116-117^{\circ}$ ,  $[\alpha]_{5893}^{20} - 22.8^{\circ}$  (l, 0.5; c, 5.432 in acetone) and on evaporation of the filtrate, Crop A' (2.9 g.), containing a mixture of w-nitrostyrene, (-)-sulphone and a brown oil.

Fractionation of Crop A (4.7 g.) from ethanol gave (+)-2-nitro-1-phenyl-1'-benzyl-diethyl sulphone-A (1.60 g.), colourless needles, m.p.  $139.5^{\circ}$ ,  $[\alpha]_{5893}^{20} + 47.0^{\circ}$  (l, 0.5; c, 5.016 in acetone), [Found: O, 19.00; S, 9.15%] and the diastereoisomeric (-)-sulphone-B (0.28 g.), m.p.  $85-86^{\circ}$ ,  $[\alpha]_{5893}^{20} + 89.5^{\circ}$  (l, 0.5; c, 5.320 in acetone).

Crop A' (2.84 g.) was plated for 24 hours, solid (1.87 g.) being obtained. Vacuum sublimation of small portions of this solid at 50°/ 1 mm. for 28 hours gave the following data:

	Weight of mixture	<u>w</u> -Nitrostyrene sublimate		Residue weight	
		weight	m.p.		mixed m.p.
1)	0.30 g.	0.19 g.	52.5-54.5°	52.5-55.5°	0.07 g. (1
2)	0.32 g.	0.22 g.	54.5-55.5°	54.5-55.5°	0.08 g. (2
3)	0.47 g.	0.28 g.	54.5-55.5°	53.5-55.5°	0.18 g. (3

	m.p.	$[\alpha]_{5893}^{19}$
1)	101.5-103.5°	-89.0° ( <u>l</u> , 0.5; <u>c</u> , 2.514 in acetone) at 20°
2)	100.5-102.5°	
3)	99.5-102.5°	-89.1° ( <u>l</u> , 0.5; <u>c</u> , 2.644 in acetone) at 21°

Vacuum sublimation of Crop A' (0.32 g.) at 100-140°/ 1 mm. for 30 hours gave a crop (0.29 g.) which on vacuum sublimation at 50°/1 mm. gave w-nitrostyrene (0.20 g.), m.p. 54.5-55.5°, mixed m.p. 53.5-55.5°, and, after "plating" and washing with ice-cold ethanol, a residue of (-)-sulphone-B (0.09 g.), m.p. 95.5-97°  $[\alpha]_{5893}^{19} - 83°$  (l, 0.5; c, 0.778 in acetone).

(+)- and (-)-2-Nitro-1-phenyl-1'-benzyl-diethyl sulphone

w-Nitrostyrene (4.38 g.) and (-)-1-phenylpropane-2-thiol (4.39 g.,  $[\alpha]_{5893}^{23} - 13.46^{\circ}$ , 1, 1) were heated in nitrogen at  $100^{\circ}$  for 6.25 hours with piperidine (4 drops). The product, an oil, was dissolved in glacial acetic acid (75 ml.) and warmed on a steam-bath with 34% hydrogen peroxide (30 ml.) in glacial acetic acid (39 ml.) until slight effervescence occurred. The solution was allowed to stand at room temperature for 10 minutes and diluted to 1 litre with ice-cold water. The solid product obtained was washed with water, air-dried and crystallised from ethanol. There was obtained Crop A (3.71 g.), m.p.  $119-120^{\circ}$ ,  $[\alpha]_{5893}^{21} + 41^{\circ}$  (1, 0.5; c. 4.912 in acetone); evaporation of the filtrate gave an oil (2.31 g.),  $[\alpha]_{5893}^{20} - 4.50^{\circ}$  (1, 2; c. 11.545 in acetone) which did not solidify after 3 months.

Fractional crystallisation of Crop A (3.71 g.) from ethanol gave (+)-2-nitro-1-phenyl-1'-benzyl-diethyl sulphone-A (1.57 g.), m.p.  $139.5^{\circ}$ ,  $[\alpha]_{5893}^{22} + 46.0^{\circ}$  (1, 0.5; c. 5.046 in acetone) and the diastereoisomeric (-)-2-nitro-1-phenyl-1'-benzyl-diethyl sulphone-B (0.12 g.), m.p.  $102.5^{\circ}$ ,  $[\alpha]_{5893}^{20} - 89.5^{\circ}$  (1, 0.5; c. 2.478 in acetone), [Found: O, 18.75; S, 9.15%]. Mixed melting point  $101.5-102.5^{\circ}$  with (-)-sulphone-B, m.p.  $100.5-102.5^{\circ}$  from the peroxide-catalysed addition of (-)-thiol.

The oil (0.77 g.) was vacuum sublimed at 58-61°/0.6 mm. for 4 hours and at 110-112°/0.6 mm. for 1.75 hours. The sublimate (0.14 g.), m.p. 49.5-51.5° was identified as w-nitrostyrene, it having mixed melting point 51.5-53.5°. The remaining unsublimed material, a brown oil, dissolved in benzene, was chromatographed on an aluminium oxide column. An eluate of benzene (2 litres) yielded no solid material. The top quarter of the column, which was yellow-brown in colour, was carefully removed from the dry column, and extracted in a Soxhlet apparatus for 2 hours with acetone. The concentrated acetone solution was optically inactive; evaporation of the solvent gave a brown oil (0.16 g.). The lower, colourless, section of the column was similarly extracted for 2 hours with acetone. The concentrated acetone solution was optically inactive; evaporation of the solvent gave a brown oil (0.19 g.). [Total recovery: 64%].

(+)-1:2-Dibenzoyl-1'-benzyl-diethyl sulphide

trans-1:2-Dibenzoyl-ethylene (3.63 g., m.p. 111°) and (+)-1-phenylpropane-2-thiol (2.43 g.) were heated at 100° in nitrogen for 6.25 hours with ascaridole (2 drops). The resultant oil was crystallised from ethanol, and gave a crop (2.3 g.), m.p. 80-81°. One crystallisation of this crop from light petroleum (b.p. 40-60°) and one crystallisation from ethanol gave (+)-1:2-dibenzoyl-1'-benzyl-diethyl sulphide (1.27 g.), colourless rhombs, m.p. 87.5° [Found: C, 76.80; H, 6.35; S, 7.95. C<sub>25</sub>H<sub>24</sub>O<sub>2</sub>S requires C, 77.30; H, 6.20; S, 8.25%]. Evaporation of the filtrates gave a further crop (0.37 g.), m.p. 84-85° and an oil (3.2 g.) which could not be induced to crystallise.

Addition of (+)-1-phenylpropane-2-thiol to trans-1:2-dibenzoyl-ethylene under the same conditions as described above, followed by fractionation gave:

<u>(+)-thiol</u>	olefin	products <u>solid</u>	<u>oil</u>
2.86 g.	4.43 g.	1.42 g., m.p. 87-88°;	2.65 g.
2.15 g.	3.33 g.	2.17 g., m.p. 80-81°;	2.75 g.

Small scale attempts to prepare the 2:4-dinitro-phenylhydrazone and semicarbazone of the sulphide (oil) failed to yield crystalline products.

The Attempted Preparation of 4-(1-Methyl-2-phenylethyl-  
mercapto)-3:6-diphenylhydropryridazine

(+)-1:2-Dibenzoyl-1'-benzyldiethyl sulphide, oil, (0.4 g.) dissolved in glacial acetic acid (5 ml.) was warmed on a steam-bath for 5 minutes with 100% hydrazine hydrate (4 drops). The solution was diluted to 15 ml. with water and air aspirated for 10 minutes. The solid product after crystallisation (0.27 g.) had m.p. 130-135° and contained sulphur. Crystallisation from chloroform-ethanol (1:5) gave a product m.p. 215-217° which did not contain sulphur. Further crystallisation yielded 3:6-diphenyl-pyridazine, m.p. 223-223.5°.

[Paal and Dencks (122) record m.p. 221-222°]

The Oxidation of (+)-1:2-Dibenzoyl-1'-benzyldiethyl  
sulphide

a) Oily sulphide

i) (+)-1:2-Dibenzoyl-1'-benzyldiethyl sulphide (2.72 g.) dissolved in glacial acetic acid (20 ml.) was warmed on a steam-bath for 10 minutes with 34% hydrogen peroxide (10 ml.), and chilled to 0°. There was obtained a crop (0.41 g.), yellow needles, m.p. 103.5-105.5° which after two crystallisations from ethanol had m.p. 109-110°, mixed m.p. 111-112° with trans-1:2-dibenzoylethylene. The acetic acid solution was poured into cold water (500 ml.) and allowed to stand for several days, a crop

(0.9 g.) being obtained. This crop after two crystallisations had m.p. 107.5-108.5°, mixed m.p. 110° with trans-1:2-dibenzoyl-ethylene. Evaporation of the aqueous filtrate on a steam-bath gave a charred solid (ca. 1 g.) which was not characterised.

ii) (+)-1:2-Dibenzoyl-1'-benzyl diethyl sulphide (2.23 g.) dissolved in glacial acetic acid (10 ml.) was allowed to stand at room temperature for 16 hours with a solution of 34% hydrogen peroxide (4 ml.) in glacial acetic acid (10 ml.). The solution, from which an oil had separated, was warmed on a steam-bath for 2 minutes until the solution became homogeneous and was immediately poured into cold water (1 litre). The solution was filtered after 1 month, a crop (1.93 g.), a mixture of white and yellow crystals being obtained. Fractional crystallisation from excess methanol gave (+)-1:2-dibenzoyl-1'-benzyl diethyl sulphone (1.2 g.), m.p. 116°. Two crystallisations from methanol gave colourless rhombs (0.8 g.), m.p. 122.5-123° [Found: O, 15.15; S, 7.55.  $C_{25}H_{24}O_4S$  requires O, 15.25; S, 7.60%].



b) Solid sulphide, m.p. 87.5°

i) (±)-1:2-Dibenzoyl-1'-benzyldiethyl sulphide (0.68 g.) dissolved in glacial acetic acid (4.5 ml.) was warmed on a steam-bath for 30 minutes with 34% hydrogen peroxide (3 ml.). The hot solution was poured into cold water (500 ml.) and allowed to stand for 2 days, a solid product (0.37 g.) being obtained. Crystallisation from ethanol gave trans-1:2-dibenzoyl-ethylene (0.17 g.), m.p. 108-109.5°, mixed m.p. 108.5°. Evaporation of the aqueous filtrate at reduced pressure gave a charred solid (0.35 g.), containing sulphur, which could not be characterised.

ii) To a cooled solution of (±)-1:2-dibenzoyl-1'-benzyldiethyl sulphide (0.25 g.) in glacial acetic acid (10 ml.) was added to a solution of 34% hydrogen peroxide (1.5 ml.) in glacial acetic acid (3 ml.). The solution was chilled in an ice-bath and allowed to warm to room temperature overnight. The solution was poured into water (150 ml.) and allowed to stand. The pale yellow solid obtained was crystallised from methanol and gave a crop (0.12 g.) m.p. 115-116°. Crystallisation from methanol gave m.p. 118-119.5°, mixed m.p. 118-119° with the sulphone obtained by oxidation of the oily sulphide. Further crystallisation from methanol gave product (0.05 g.) m.p. 119-120°, mixed m.p. 122°.

The Stability of (+)-1:2-Dibenzoyl-1'-benzyldiethyl sulphide

(+)-1:2-Dibenzoyl-1'-benzyldiethyl sulphide (0.5g.) dissolved in glacial acetic acid (10 ml.) was warmed on a steam-bath for 1 hour. The hot solution was poured into ice-water (50 ml.) and allowed to stand for several days. The product (0.41 g.) had m.p.  $86^{\circ}$ , mixed m.p.  $86-87^{\circ}$  with a specimen of pure sulphide, m.p.  $87.5^{\circ}$ .

The Stability of (+)-1:2-Dibenzoyl-1'-benzyldiethyl sulphone

- i) (+)-1:2-Dibenzoyl-1'-benzyldiethyl sulphide (0.25 g.) dissolved in glacial acetic acid (12 ml.) was warmed on a steam-bath for 1.5 hours. The hot solution was poured into cold water (40 ml.) and allowed to stand for 2 days, 0.22 g. of product, m.p.  $117-119^{\circ}$ , being obtained. Crystallisation from methanol gave the sulphone (0.19 g.), m.p.  $121-122^{\circ}$ , mixed m.p.  $122^{\circ}$ .
- ii) (+)-1:2-Dibenzoyl-1'-benzyldiethyl sulphone (0.19 g.) dissolved in glacial acetic acid (8 ml.) was warmed on a steam-bath for 20 minutes with 34% hydrogen peroxide (2 ml.). From the diluted solution (50 ml.) there was obtained unchanged sulphone (0.10 g.), m.p.  $120-121^{\circ}$ , mixed m.p.  $121-122^{\circ}$ .

1:2-Dibenzoylethyl benzyl sulphide

Benzyl thiol (4.0 g.) and trans-1:2-dibenzoylethylene (7.6 g.) were heated in coal-gas at 100° for 5.5 hours with ascaridole (2 drops). The partially solidified product was crystallised from ethanol and gave a crop (9.9 g.), m.p. 97.5-98.5°. Two crystallisations from ethanol gave 1:2-dibenzoylethyl benzyl sulphide (7.7 g.), m.p. 99° [Found: C, 76.50; H, 5.55; S, 8.70.  $C_{23}H_{20}O_2S$  requires C, 76.60; H, 5.60; S, 8.90%].

The Oxidation of 1:2-Dibenzoylethyl benzyl sulphide

i) 1:2-Dibenzoylethyl benzyl sulphide (4.0 g.) dissolved in glacial acetic acid (30 ml.) was warmed on a steam-bath with 34% hydrogen peroxide (20 ml.) for 10 minutes. From the cooled solution there was obtained a crop (2.66 g.) of white and yellow crystals. Fractionation of this product from ethanol gave four crops: (1.1 g.), m.p. 173.5-174.5°; (0.65 g.), m.p. 175.5°; (0.40 g.), m.p. 97.5-98.5°; (0.40 g.), m.p. 101.5-103.5°. Further crystallisation of the former two crops gave 1:2-dibenzoylethyl benzyl sulphone, m.p. 175.5°, [Found: C, 70.50; H, 5.30; S, 8.25.  $C_{23}H_{20}O_4S$  requires C, 70.40; H, 5.15; S, 8.15%].

The latter two crops when crystallised from ethanol gave trans-1:2-dibenzoylethylene, m.p. 108.5-111°, mixed m.p. 110-112°.

The acetic acid solution was poured into water (360 ml.), the whole being slowly evaporated on a steam-bath. The residual solid was dissolved in methanol, boiled with decolourising charcoal, filtered, and the solution evaporated. The brown deliquescent residue (ca. 1 g.) was found to contain sulphur but could not be characterised.

ii) 1:2-Dibenzoyl ethyl benzyl sulphide (1.0 g.) was dissolved in warm glacial acetic acid (15 ml.) and allowed to cool to room temperature. The addition of 34% hydrogen peroxide (3.5 ml.) precipitated the unreacted sulphide m.p. 95.5-96.5°, mixed m.p. 97.5-98.5°. The precipitated sulphide and the filtrate were combined, glacial acetic acid (5 ml.) was added, and the solution warmed on a steam-bath for 2 minutes when complete solution occurred. The solution was immediately chilled in ice-water and allowed to stand overnight, slowly warming to room temperature; 1:2-dibenzoyl ethyl benzyl sulphone (0.9 g.), m.p. 165° crystallised. On recrystallisation from ethanol the sulphone (0.77 g.) had m.p. 175.5°.

The Attempted Preparation of 1:2-Dibenzoylethyl benzyl sulphoxide

i) Hydrogen peroxide (34%, 0.6 ml., the theoretical quantity) was added with shaking to a solution of 1:2-dibenzoylethyl benzyl sulphide (2.3 g.) in warm glacial acetic acid (10 ml.). The solution was filtered after 1 hour and gave a product (0.64 g.), m.p.  $86^{\circ}$ ; this after crystallisation from ethanol, had m.p.  $98.5^{\circ}$ , alone and when mixed with 1:2-dibenzoylethyl benzyl sulphide. The filtrate was diluted to 50 ml. with water after 3 hours at room temperature. The solution was ether-extracted, the ether was evaporated and the partially solidified residue, which had a strong odour of benzyl thiol, crystallised from methanol. The crystalline material was identified as trans-1:2-dibenzoylethylene, m.p.  $107-108^{\circ}$ , mixed m.p.  $110-111^{\circ}$ .

ii) 1:2-Dibenzoylethyl benzyl sulphide (1.0 g.) was dissolved in warm glacial acetic acid (15 ml.) and cooled to  $45^{\circ}$ . Hydrogen peroxide (34%, 0.3 ml., the theoretical quantity) in glacial acetic acid (1 ml.) was added to this solution, the whole being kept at  $45-50^{\circ}$  for 5 minutes, when a yellow colour developed. The solution was poured into water (100 ml.) and filtered after 16 hours. The product was crystallised

from ethanol and had m.p.  $97-98^{\circ}$ , mixed m.p.  $98.5-99^{\circ}$  with 1:2-dibenzoylethyl benzyl sulphide.

The Stability of 1:2-Dibenzoylethyl benzyl sulphide.

1:2-Dibenzoylethyl benzyl sulphide (1.0 g.) dissolved in glacial acetic acid (10 ml.) was warmed on a steam-bath for 2 hours. The hot solution was diluted with water (15 ml.) and filtered after 2 days. The product (0.97 g.) had m.p.  $95.5^{\circ}$ , mixed m.p.  $98.5^{\circ}$ .

The Stability of 1:2-Dibenzoylethyl benzyl sulphone

i) 1:2-Dibenzoylethyl benzyl sulphone (0.34 g.) dissolved in glacial acetic acid (10 ml.) was warmed on a steam-bath for 2 hours. The hot solution was diluted with water (15 ml.) and filtered after 2 days. The product had m.p.  $171.5^{\circ}$ , mixed m.p.  $172.5^{\circ}$ .

ii) 1:2-Dibenzoylethyl benzyl sulphone (0.65 g.) dissolved in glacial acetic acid (10 ml.) was warmed on a steam-bath for 20 minutes with 34% hydrogen peroxide (2 ml.). The hot solution was diluted with water (40 ml.) and allowed to stand, solid product (0.59 g.), m.p.  $168-169^{\circ}$  being recovered. After crystallisation from methanol, the sulphone had m.p.  $173.5-174.5^{\circ}$ , mixed m.p.  $175.5^{\circ}$ .

1-Phenyl-2-(p-nitrobenzoyl)-ethyl benzyl sulphide

Benzyl thiol (1.0 g.) and 4'-nitrochalkone (2.05 g., m.p. 149-150°) were heated in coal-gas at 100° for 5.3 hours with ascaridole (2 drops). The reaction mixture, on cooling and crystallisation from light petroleum (b.p. 40-60°) gave a crop (2.55 g.), m.p. 81-82°. Three further crystallisations from excess ethanol gave 1-phenyl-2-(p-nitrobenzoyl)-ethyl benzyl sulphide (0.8 g.), m.p. 87° [Found: N, 3.70; S, 8.50.  $C_{22}H_{19}NO_3S$  requires N, 3.80; S, 8.05%].

(+)-2-(p-Nitrobenzoyl)-1-phenyl-1'-benzyldiethyl sulphide

i) (+)-1-Phenylpropane-2-thiol (2.27 g.) and 4'-nitrochalkone (3.77 g.) dissolved in benzene (50 ml.) were heated in nitrogen at 78° for 6.25 hours with ascaridole (3 drops). On cooling, there was obtained a crop (2.6 g.), m.p. 148°, containing no sulphur, mixed m.p. 147-149° with 4'-nitrochalkone. The recovered 4'-nitrochalkone was heated under reflux with the benzene solution filtrate for 11 hours, together with ascaridole (3 drops). From the cooled solution there was obtained a crop (2.6 g.), m.p. 143.5°, containing no sulphur, mixed m.p. 146-149° with 4'-nitrochalkone.

ii) (±)-1-Phenylpropane-2-thiol (5.05 g.) and 4'-nitrochalkone (8.42 g.) were heated in nitrogen at 100° for 6 hours with ascaridole (4 drops). The oil which was obtained on cooling was dissolved in warm ethanol, two crops (9.95 g.), m.p. 48-49° and (2.05 g.), m.p. 48.5-50.5° crystallising from the cold solution. Two crystallisations of the former crop from methanol (decomposition occurring when the solution was heated) gave (5.0 g.), m.p. 54.5°. Four crystallisations from warm cyclohexane gave (±)-2-(p-nitrobenzoyl)-1-phenyl-1'-benzyldiethyl sulphide (0.65 g.) white fluffy needles, m.p. 81-82° [Found: C, 71.10; H, 5.90; S, 7.80. C<sub>24</sub>H<sub>23</sub>NO<sub>3</sub>S requires C, 71.15; H, 5.70; S, 7.90%].

The Attempted Preparation of (±)-2-Nitro-1-(p-methoxy-phenyl)-1'-benzyldiethyl sulphide

i) p-Methoxy-w-Nitrostyrene (3.44 g.) and (±)-1-phenylpropane-2-thiol (2.92 g.) were heated in nitrogen at 100° for 11.5 hours with ascaridole (3 drops). The product, an oil, resisted crystallisation from solvents and by prolonged refrigeration. Small scale oxidation of this oil with 34 % hydrogen peroxide in glacial acetic acid gave a red intractable tar.



ii) p-Methoxy-w-nitrostyrene (2.3 g.) and (±)-1-phenylpropane-2-thiol (1.93 g.) were heated in nitrogen at 100° for 4 hours with piperidine (2 drops). The product, an oil, resisted crystallisation from solvents and by prolonged refrigeration.

This oil, dissolved in glacial acetic acid (10 ml.), was stirred with 34% hydrogen peroxide (5 ml.). Glacial acetic acid (15 ml.) was added, and the solution warmed on a steam-bath for 10 minutes, to dissolve the oil which had separated; the solution was poured into cold water (500 ml.), from which an orange-red tar separated.

The Attempted Addition of Benzyl thiol to Coumarin

i) Coumarin (2.14 g.) and benzyl thiol (1.84 g.) were heated in coal-gas at 118° for 5 hours with ascaridole (3 drops). The reaction mixture was allowed to stand for 7 days, a crop (1.32 g.), m.p. 68-69° being obtained after being washed with light petroleum (b.p. 40-60°); the washings were added to the filtrate, from which a second crop (0.35 g.) m.p. 66-68° was precipitated. These crops had mixed m.p.s 69-70° and 66-69° respectively with coumarin (m.p. 70°), and contained no sulphur.

ii) Coumarin (2.26 g.) and benzyl thiol (1.94 g.) were heated in coal-gas for 5.3 hours with piperidine (2 drops). The cooled reaction mixture gave a crop (0.62 g.), m.p.  $61^{\circ}$ , which had m.p.  $67^{\circ}$  after crystallisation from ethanol. From the reaction filtrate there was obtained a second crop (0.93 g.), m.p.  $65-67^{\circ}$ . This crop had m.p.  $68-69^{\circ}$  after crystallisation from ethanol. Neither of these crops contained sulphur, and both had mixed m.p.  $67-68^{\circ}$  with coumarin.

The Attempted Addition of (+)-1-Phenylpropane-2-thiol to Coumarin

i) Coumarin (1.63 g.) and (+)-1-phenylpropane-2-thiol (1.70 g.) were heated in nitrogen at  $90^{\circ}$  until solution occurred. Ascaridole (2 drops) was added, and the solution heated at  $100^{\circ}$  for 5 hours. The reaction mixture was allowed to stand for 2 days, partial crystallisation occurring. The reaction mixture was washed with light petroleum (b.p.  $40-60^{\circ}$ ) and filtered at the pump, a crop (1.2 g.), m.p.  $65^{\circ}$  being obtained. This crop contained no sulphur and had mixed m.p.  $67-70^{\circ}$  with coumarin.

ii) Coumarin (1.03 g.) and (+)-1-phenylpropane-2-thiol (1.08 g.) were heated in nitrogen at 90° until solution occurred. Piperidine (2 drops) was added, and the solution heated at 100° for 2.4 hours, and for a further 15 minutes at 150°. The reaction mixture was cooled and washed with ethanol, a crop (0.8 g.), m.p. 66-67° being obtained. This crop contained no sulphur and had mixed m.p. 66-69° with coumarin.

The Attempted Addition of (+)-1-Phenylpropane-2-thiol to Benzylideneindene

Benzylideneindene (2.76 g.) and (+)-1-phenylpropane-2-thiol (2.06 g.) were heated in nitrogen at 100° for 3.75 hours with ascaridole (2 drops). On cooling the reaction mixture, a crop (1.6 g.), m.p. 80°, was obtained. Crystallisation from methanol gave a product having m.p. 86-87°, mixed m.p. 88° with benzylideneindene (m.p. 89°).

The Attempted Addition of (+)-1-Phenylpropane-2-thiol to iso-Phorone

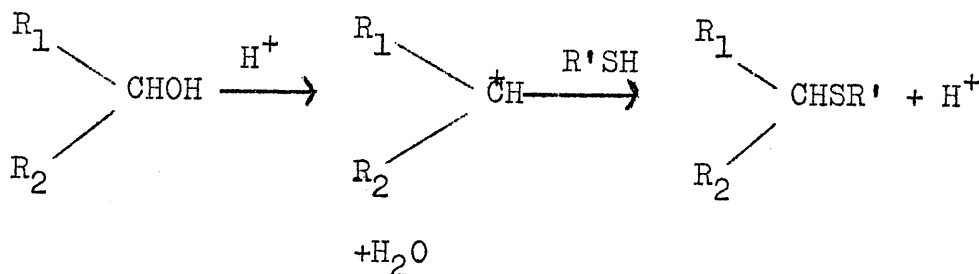
iso-Phorone (1.60 g., b.p. 103°/ 24 mm.) and (+)-1-phenylpropane-2-thiol (1.60 g.) were heated in nitrogen at 100° for 4.5 hours with ascaridole (2 drops). The reaction mixture, which remained liquid on chilling,

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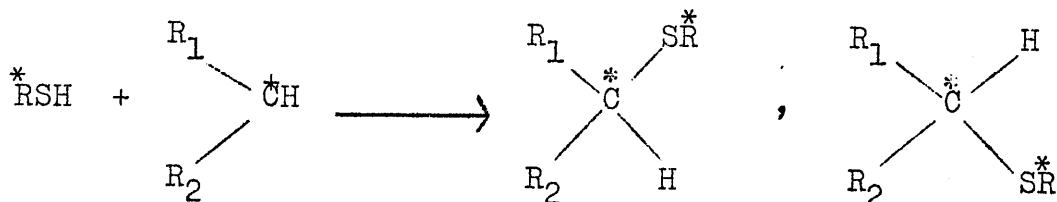
distilled entirely at 100-120° / 25 mm., leaving  
only a very small quantity of high boiling residue.

SECTION IIIb.Asymmetric AlkylationIntroduction

It has been shown by Kenyon and his coworkers that carbinols which undergo alkyl-oxygen fission react with thiols, under conditions assisting fission, to form sulphides:

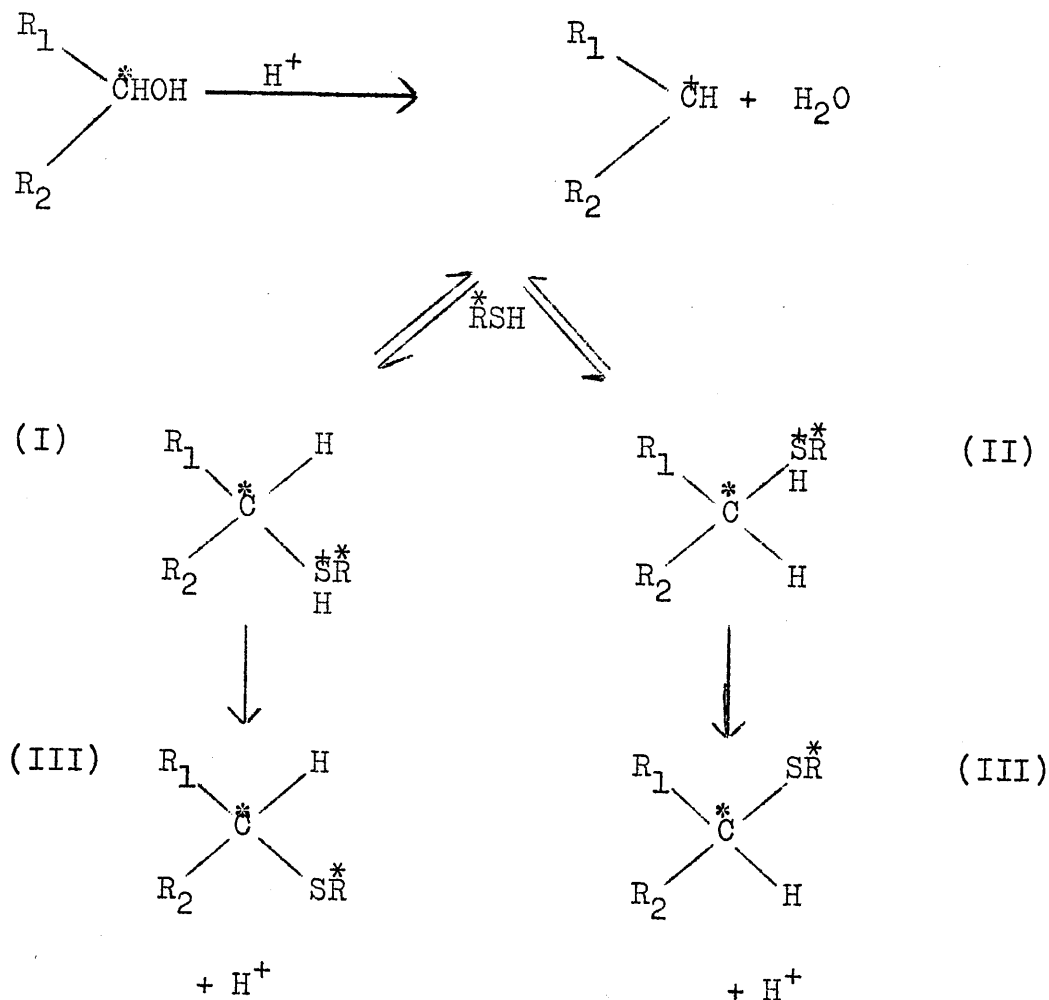


It was thought that alkylation of an asymmetric thiol with a carbon cation derived from a dissymmetric carbinol would give rise to diastereoisomeric sulphides:



and that they might be formed in significantly different amounts.

The mechanism of alkylation will be as follows:

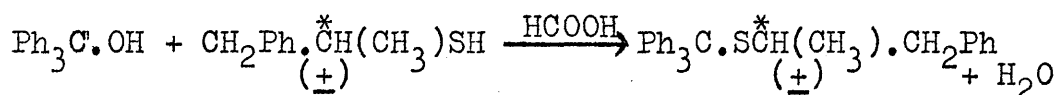


The formation of the intermediates (I) and (II) is probably the rate controlling stage of the reaction, and since (I) and (II) are diastereoisomeric, their activation energies would be expected to differ. If the energies of activation are different, then reaction would be expected to proceed by the path requiring the lowest energy increment, and would thus lead to unequal amounts of the diastereoisomeric sulphides (III) and (IV).

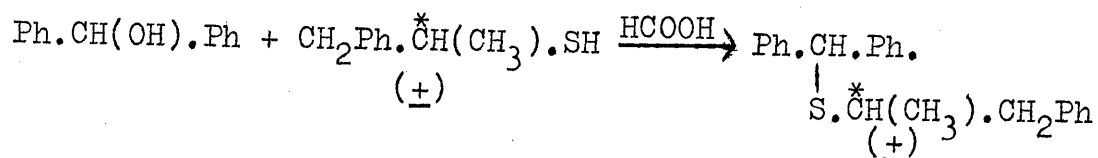
### Discussion of Results

Alkylations of (+)-1-phenylpropane-2-thiol with six carbinols have been attempted; four reactions gave rise to solid products, two reactions gave oils as products. Four alkylation reactions were carried out with (+)-carbinols (as distinct from symmetrical carbinols), solid products being obtained from two of these, the data on the weight-ratio of sulphides, however, being insufficient to demonstrate the occurrence or definite absence of asymmetric synthesis.

### Alkylation with Triphenyl Methanol

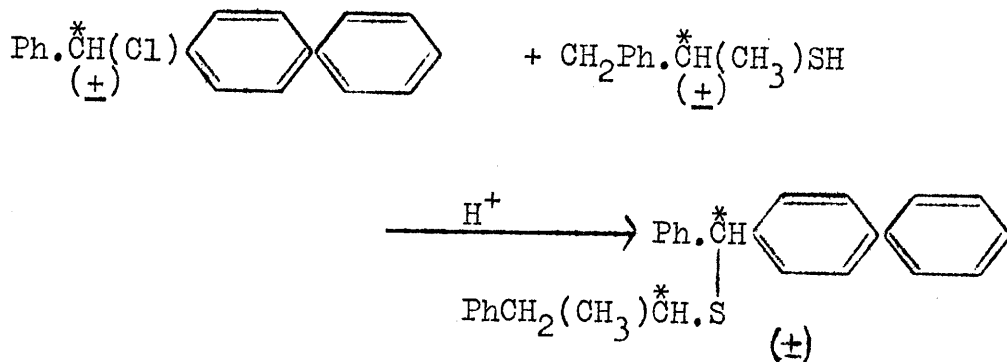


This alkylation reaction was carried out in order to find suitable conditions for further alkylations. Fractional crystallisation of the reaction product gave (+)-1-methyl-2-phenylethyl triphenylmethyl sulphide, m.p. 118-118.5°, together with small quantities of triphenylmethane, m.p. 78-89°.

Alkylation with Benzhydrol

Reaction of benzhydrol with (+)-1-phenylpropane-2-thiol in formic acid gave a low-melting sulphide which proved too soluble for purification by crystallisation.

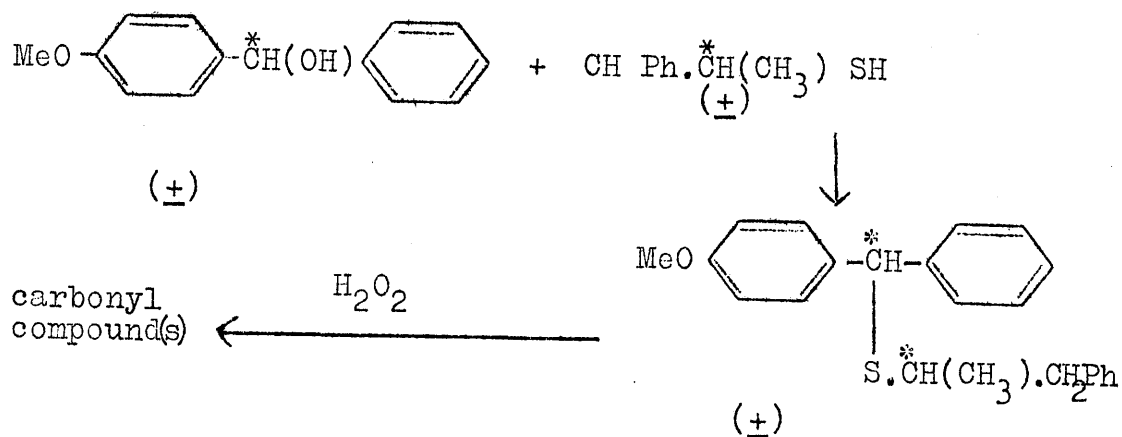
Oxidation of this sulphide with hydrogen peroxide in glacial acetic acid yielded a crystalline sulphone, m.p. 138.5°.

Alkylation with (+)-Diphenylphenylmethyl Chloride

Reaction of (+)-diphenylphenylmethyl chloride with (+)-1-phenylpropane-2-thiol in warm formic acid gave rise to a semi-solid from which (+)-1-methyl-2-phenylethyl diphenylphenylmethyl sulphide, m.p. 105-105.5°, was obtained, together with an oil which contained sulphur.

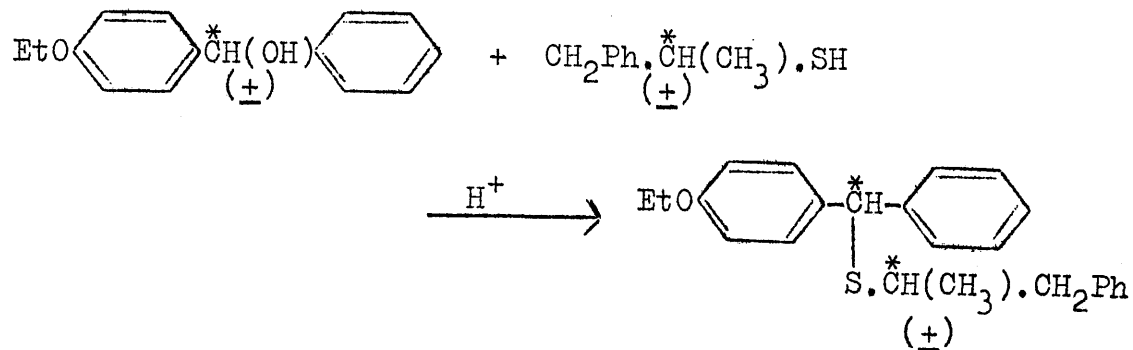




Alkylation with (+)-p-Methoxybenzhydrol

Reaction of (+)-p-methoxybenzhydrol with (+)-1-phenylpropane-2-thiol in cold or warm formic acid and cold glacial acetic acid gave an oil, possibly the sulphide, which could not be induced to crystallise.

The oxidation of this oil in warm glacial acetic acid with 34% hydrogen peroxide gave an intractable red tar, whereas similar oxidation at room temperature gave a carbonyl compound, or mixture of compounds, whose 2:4-dinitrophenyl-hydrazone had m.p. 224-226° (uncorr.).

Alkylation with (+)-p-Ethoxybenzhydrol

The formic acid catalysed reaction of (+)-p-ethoxybenzhydrol with (+)-l-phenylpropane-2-thiol in chloroform gave an oil which could not be induced to solidify. Oxidation of part of this oil with 34% hydrogen peroxide in warm glacial acetic acid gave an intractable red tar.

SECTION IIIbEXPERIMENTAL(+)-1-Methyl-2-phenylethyl triphenylmethyl sulphide

To a solution of triphenylmethanol (3.2 g.) in 90% formic acid (10 ml.) was added (+)-1-phenylpropane-2-thiol (1.75 g.). After 45 minutes' warming on a steam-bath, the reaction mixture was poured into ice and water. Fractional crystallisation of the product (2.5 g.) gave (+)-1-methyl-2-phenylethyl triphenylmethyl sulphide (1.1 g.), m.p. 118-118.5° [Found: C, 85.15; H, 6.70; S, 7.80.  $C_{28}H_{27}S$  requires C, 85.25; H, 6.65; S, 8.15%], together with triphenylmethane (0.7 g.), m.p. 78-89°, which was not purified.

(+)-1-Methyl-2-phenylethyl benzhydryl sulphide

To a solution of benzhydrol (1.22 g.) in warm 90% formic acid (25 ml.), in a nitrogen atmosphere, was added (+)-1-phenylpropane-2-thiol (1.75 g.). After 45 minutes' warming on a steam-bath, the reaction mixture was poured into ice-cold water (200 ml.). The product, (1.10 g.), m.p. 33-35°, solidified after several days but could not be purified by recrystallisation.

(+)-1-Methyl-2-phenylethyl benzhydryl sulphone

(+)-1-Methyl-2-phenylethyl benzhydryl sulphide (0.57 g.), dissolved in glacial acetic acid (5 ml.), was warmed on a steam-bath for 10 minutes with 34% hydrogen peroxide (3 ml.), glacial acetic acid (8 ml.) being added to keep in solution the oil which had formed. The solution was chilled to  $-80^{\circ}$  and slowly warmed to room temperature, a crop (0.42 g.), m.p.  $119-120^{\circ}$  being obtained. Crystallisation from ethanol gave (+)-1-methyl-2-phenylethyl benzhydryl sulphone (0.30 g.), m.p.  $138.5^{\circ}$  [Found: O, 9.70; S, 9.45.  $C_{22}H_{22}O_2S$  requires O, 9.15; S, 9.15%].

(+)-1-Methyl-2-phenylethyl diphenylphenylmethyl sulphide

(+)-Diphenylphenylmethyl chloride (0.85 g.) was added to a solution of (+)-1-phenylpropane-2-thiol (0.50 g.) in 99% formic acid (10 ml.). After 5 minutes' warming on a steam-bath, the solution was poured into ice-water. The resulting semi-solid was filtered and fractionally crystallised from methanol. Two crystallisations from ethanol gave (+)-1-methyl-2-phenylethyl diphenylphenylmethyl sulphide (0.16 g.), m.p.  $105-105.5^{\circ}$  [Found: S, 7.85.  $C_{26}H_{26}S$  requires S, 8.10%], an oil being obtained from the filtrate.

(+)-1-Methyl-2-phenylethyl p-dimethylaminobenzhydryl sulphide

(+)-p-Dimethylaminobenzhydrol (4.62 g.) and (+)-1-1-phenylpropane-2-thiol (3.08 g.) were heated under reflux in chloroform (14 ml.) for 3 hours. The solution was frozen at  $-80^{\circ}$  for 15 minutes, no crystallisation occurring. 99% formic acid (3 drops) was added to the solution which was heated under reflux for 3 hours. The chloroform was evaporated slowly at room temperature, the last traces in vacuo. The oil which remained partially solidified after several hours, and was fractionally crystallised from methanol, two diastereoisomers being separated: (+)-1-methyl-2-phenylethyl p-dimethylaminobenzhydryl sulphide-A (2.10 g.), m.p.  $103-103.5^{\circ}$  [Found: N, 3.95; S, 8.75.  $C_{24}H_{27}NS$  requires N, 3.90; S, 8.90%] and sulphide-B (2.25 g.), m.p.  $65.5^{\circ}$  [Found: N, 3.80; S, 9.00%], the latter being the more soluble fraction.

The Attempted Preparation of (+)-1-Methyl-2-phenylethyl p-methoxybenzhydryl sulphide and sulphone

i) (+)-p-Methoxybenzhydrol (1.4 g.) was added to a warm solution of (+)-1-phenylpropane-2-thiol (1.0 g.) in 90% formic acid (40 ml.). The solution was poured into ice-water after 15 minutes'warming on a steam-bath.

The resulting oil resisted crystallisation by standing, freezing, and from solvents.

The oil dissolved in glacial acid (10 ml.) was warmed for 30 minutes on a steam-bath with 34% hydrogen peroxide ( 5 ml.). The solution was diluted to 250 ml., a dark red intractable oil being formed.

ii) (+)-p-Methoxybenzhydrol (1.4 g.) and (+)-l-phenylpropane-2-thiol (1.0 g.) were allowed to stand for 20 hours at room temperature in 99% formic acid ( 9 ml.). The solution was poured into water, an intractable oil being formed which resisted crystallisation. Small scale oxidation as above gave an intractable red tar.

iii) (+)-p-Methoxybenzhydrol (1.76 g.) and (+)-l-phenylpropane-2-thiol (1.26 g.), dissolved in glacial acetic acid (10 ml.) containing concentrated sulphuric acid (1 drop), were allowed to stand at room temperature for 1 day. The solution was poured into water and allowed to stand; the oil which formed was frequently washed with ice-cold water, but no solidification occurred during three weeks.

This oil was dissolved in cold glacial acetic acid (10 ml.), 34% hydrogen peroxide ( 2 ml.) in glacial acetic acid (10 ml.) being added. After standing at room temperature for 2 days, the solution was diluted

with water (100 ml.). The oil which formed was ether-extracted; evaporation of the ether gave a residual oil of aldehydic odour; addition of 2:4-dinitrophenylhydrazine in methanol precipitated a 2:4-dinitrophenylhydrazone, m.p. 224-226<sup>0</sup> (uncorr.).

The Attempted Preparation of (+)-1-Methyl-2-phenylethyl p-ethoxybenzhydryl sulphide and sulphone.

(+)-p-Ethoxybenzhydrol (3.0 g.) and (+)-1-phenylpropane-2-thiol (2.0 g.) were heated under reflux in chloroform ( 5 ml.) and 99% formic acid ( 2 drops) for 7 hours. The chloroform was allowed to evaporate slowly, an oil remaining. This oil was shaken repeatedly with water but did not solidify after 2 months.

Oxidation on a small scale in acetic acid solution with 34% hydrogen peroxide gave an intractable red tar.



### Summary and Conclusions

Two possible methods for the preparation of optically active thiols have been investigated:

- a) resolution of a (+)-thiuronium cation by an optically active acid, followed by decomposition to thiol;
- b) conversion of an optically active halide or reactive ester into a thiuronium salt and thence into the thiol.

(+)-2-Octylthiuronium (+)-camphor-10-sulphonate has been prepared, but fractional crystallisation did not effect resolution into the diastereoisomeric salts.

(+)-2-Bromo-octane has been converted, by reaction with thiourea, into the thiuronium bromide, and thence into (-)-octane-2-thiol.

(+)-1-Methyl-2-phenylethyl toluene-p-sulphonate, on reaction with thiourea, gave the thiuronium toluene-p-sulphonate; this salt, on decomposition with alkali, yielded (-)-1-phenylpropane-2-thiol.

From a consideration of the literature, a mechanism is proposed in which thiourea and the alkyl bromide or sulphonate undergo a bimolecular reaction, with, at least for the above sulphonate, a high degree of inversion of configuration of the asymmetric carbon atom.

1-Phenylpropane-2-thiol has been used to investigate two types of dissymmetric reaction (potential asymmetric syntheses). The first is its addition to olefins of such

structure that a new asymmetric centre is formed. Addition of (+)-, (+)-, and (-)-1-phenylpropane-2-thiol to w-nitrostyrene has been investigated: the two possible diastereoisomeric (+)-sulphides, (+)-sulphones, (-)-sulphones and (+)-sulphones have been isolated, and their properties and proposed configurative relationships are set out in Table 1.

Both the free radical and base-catalysed additions have been investigated; from the additions both diastereoisomeric products were isolated, whence these reactions are not sterically unilateral. Consideration of the quantitative data leads to the tentative conclusion that the quantities of diastereoisomers formed are approximately equal in free radical addition, but that dissymmetric addition occurs in the base-catalysed reaction.

The oxidation of sulphides to sulphones, above, was effected by hydrogen peroxide in glacial acetic acid. (-)-1-Methyl-2-phenylethyl 2:4-dinitrophenyl sulphone has been found to be optically stable in glacial acetic acid at 100° for 8 hours, indicating that this solvent is unlikely to alter diastereoisomeric ratios.

Addition of (+)-1-phenylpropane-2-thiol to trans-1:2-dibenzoylethylene gave a crystalline and an oily sulphide, both of which on oxidation gave the same sulphone. It is considered that the sulphides are diastereoisomers, and that enolisation (involving the carbonyl group next to the new asymmetric centre) during oxidation leads to a common sulphone.

It has been found that, while oxidation of sulphides, prepared by addition of (+)-1-phenylpropane-2-thiol and benzyl thiol to trans-1:2-dibenzoylethylene, with cold hydrogen peroxide and glacial acetic acid yields the corresponding sulphones, the hot reagent gives trans-1:2-dibenzoylethylene; it is concluded that an intermediate oxidation product undergoes an elimination reaction to yield the olefin.

Addition of (+)-1-phenylpropane-2-thiol to 4'-nitrochalkone gave (+)-2-(p-nitrobenzoyl)-1-phenyl-1'-benzyl-diethyl sulphide (one isomer); the corresponding sulphide from benzyl thiol has also been prepared.

The second class of reactions investigated is the alkylation, via a carbonium cation, of (+)-1-phenylpropane-2-thiol by asymmetric arylmethanols, whereby two diastereoisomeric sulphides,  $\text{CH}_2\text{Ph}.\overset{*}{\text{C}}\text{HMe}.\text{S}.\overset{*}{\text{C}}\text{HRR}'$ , may be formed in different amounts.

(+)-1-Methyl-2-phenylethyl triphenylmethyl sulphide, and the diphenylmethyl sulphide (converted into sulphone) have been prepared in order to ascertain reaction conditions.

One isomer of (+)-1-methyl-2-phenylethyl p-diphenyl-phenylmethyl sulphide, and two isomers of (+)-1-methyl-2-phenylethyl p-dimethylaminodiphenylmethyl sulphide, have been isolated, the latter compounds in nearly equal amount.

Notes on Experimental

- i) Melting points are corrected.
- ii) Analyses by Dr.A.Bernhardt, Mülheim (Ruhr), Germany.
- iii) Addition reactions (Section IIIa) were carried out in firmly corked pyrex tubes, immersed in a constant temperature bath
- iv) Nitrogen was deoxygenated (Fieser's solution).

Acknowledgements for Chemicals.

iso-Phorone: Messrs Howards, Ilford.

trans-1:2-Dibenzoylethylene: National Aniline Division,  
Allied Chemical & Dye Corporation,  
New York, U.S.A.

(+)-Diphenylphenylmethyl chloride: Dr.C.E.Searle.



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