ON THE CHEMISTRY OF NON-AROMATIC THIOPHEN DERIVATIVES

A thesis presented by

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Finally, I can hardly begin to thank Jacqui for her constant affection, inspiration and companionship in the course of this work.

To my father.

INDEX.

ABSTRACT.

The scope of some new reactions of sulphones and sulphoxides of interest in organic synthesis is reviewed.

Some synthetic approaches to 2,5-dihydrothiophen and its derivatives are described. These compounds are assessed as starting materials in biotin synthesis. A novel ring opening of cyclic sulphonium salts is investigated.

Syntheses of various 3,4-disubstituted tetrahydrothiophen derivatives is investigated. The NMR spectra of these compounds and their sulphoxides are analysed. Cis- and trans-fused cyclic ureas related to biotin are isolated using azido-compounds as intermediates.

The isolation of dimers of thiophen-1-oxides is discussed, and structures assigned to these compounds from spectroscopic data. The resemblance between thiophen-1-oxides and cyclopentadiene derivatives is discussed, and the synthesis of adducts of the former with cyclopentadiene described.

Some unusual reduction reactions of 3-methoxy-2-sulpholene and 2-sulpholene are observed, and discussed in the light of mechanisms of reduction of sulphones. 3-sulpholene and its methylated derivatives are observed to undergo a facile ring opening reaction in the prescence of alkyl-lithiums, to give lithium salts of butadienylsulphinic acids. These were alkylated to sulphones which gave δ-addition products with amines, a reaction of possible synthetic use in natural product synthesis.

Scientific truth is the remotest of mistresses, she hides in strange places, she is attained by tortuous and laborious roads, but she is always there! Win to her and she will not fail you; she is yours and mankind's forever. She is reality, the one reality I have found in this strange disorder of existence. She will not sulk with you, nor misunderstand you, nor cheat you of your reward upon some petty doubt. You cannot change her by advertisement or clamour, or stifle her in vulgarities. Things grow under your hands as you serve her, things that are permanent as nothing else is permanent in the whole life of man. That, I think, is the peculiar satisfaction of science and its enduring reward...

(H.G. Wells)

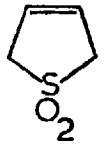
REVIEW

A man will turn over half a library to make one book.

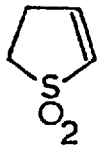
(Dr. Johnson)

NOTE.

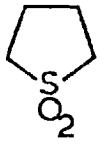
Throughout this thesis, the following names are used for reduced thiophen derivatives.



3-sulpholene



2-sulpholene



sulpholan

thiolan

The terms "sulphinyl" and "sulphonyl" are used for the groups -SO- and $-SO_2-$ respectively. Where necessary, these groups are written $\rangle S\text{-}O$ and $\rangle S\langle^{O}_{O}$ in a conventional sense; no indication of the sulphur-oxygen bond order is implied by the use of such structures.

The symbol "E" is used in structural formulae to denote the ester function $-CO_2Me$ or $-CO_2Et$.

1. INTRODUCTION.

"Sulphoxides still retain an unshared electron pair; hence the sulphoxide group does not have a strong attraction for electrons and it does not 'activate' hydrogen in the alpha position." (W.O. Ranky and D.C. Nelson in "Organic Sulphur Compounds", Pergamon Press, 1961, p.170)

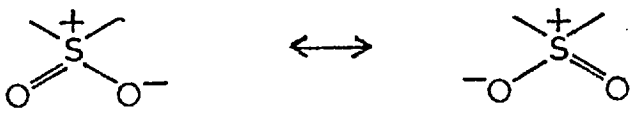
"The recently published statement that the sulphoxide group is not electron withdrawing because of the presence of an unshared electron pair at the sulphur atom is erroneous... The sulphoxide function exerts a lesser acidifying effect on an adjacent methylene group than the sulphone group, and for this reason, some investigators were led to the conclusion that the effect of the sulphoxide group was null." (H.H. Szmant, ibid., p.165)

These two statements, five pages apart in the same book, express eloquently the confusion and obscurity surrounding the chemistry of sulphoxides until recently. The structure and properties of sulphones were somewhat better understood in 1961, but apart from the Ramberg-Bäcklund reaction, were little used in synthesis. Development of reliable syntheses of sulphoxides, and the discovery of the spectacular solvent effects of DMSO, have led to the realization of numerous powerful synthetic tools which use sulphur compounds as reagents for the preparation of sulphur-free compounds. Methods using sulphoxides and sulphones have usually depended upon the acidities of protons α to a sulphinyl or sulphonyl group (pK_a 31 and 28 respectively) and the generation of the

conjugate base - "sulphinyl-" or "sulphonyl ylids" - in the presence of strong bases. Uses of sulphinyl ylids, especially that derived from DMSO, have been reviewed by Durst[1]; of especial interest is the generation, by reaction of the conjugate base of DMSO (dimsyl sodium) with esters, of ß-ketosulphoxides and the exceptionally large number of functional groups accessible from these versatile intermediates, e.g. methyl ketones, α-ketoacids, 1,2-diols, α-hydroxyacids, glyoxals and many others[2]. The relative ease of abstraction of the α-protons from sulphones has led to the preparation of numerous α-metallated, α-alkylated and α-halogenated derivatives of sulphones[3]. ß-ketosulphones are more readily alkylated than simple sulphones or ß-ketosulphoxides and examples of their use have been reported[4]. In this present review, it is intended to select some recent synthetic uses of sulphoxides and sulphones, which use the sulphur function in ways other than purely as an activating group. Many of the more unusual applications perhaps deserve to be better known.

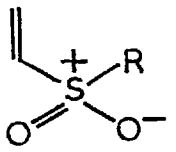
2. STRUCTURE OF THE SULPHONYL GROUP.

Koch and Moffitt[5], and more recently de-Jong and Janssen[6], have elucidated the structure of the sulphonyl group using molecular orbital methods. They concluded (a) that the sulphur atom was tetrahedrally hybridised and that both S-O bonds had considerable (ca. 85%) π-character; canonical forms (1) and (2) are convenient representations.

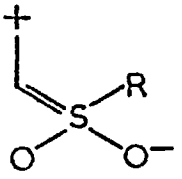


(1) (2)

(b) that conjugation involving α,β-unsaturated sulphones fell into two categories. Case I - type "donor-acceptor" conjugation (4) resulted in no change of S-O bond order or length relative to the "unconjugated" form (3); Case II - type "ketonic" conjugation involved direct interaction between the carbon-carbon π system and the sulphur-oxygen π system (5).



(3)



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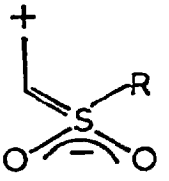
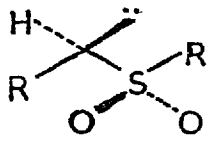


(5)

For acyclic sulphones, where the carbon 2p orbitals may be coplanar with the C-S-C plane, only Case I conjugation is observed; for cyclic sulphones, where the carbon 2p orbitals are constrained to be orthogonal to the C-S-C plane, ketonic Case II conjugation may also occur. This treatment is in accord with various physical measurements (bond lengths, bond angles, etc.)[7].

So far, all is clear. Confusion reigns, however, when discussing the chemical properties of sulphones, as there is great difficulty in separating alleged conjugative effects from the large inductive or field effect of the sulphonyl group. An examination of the chemistry of sulphonyl carbanions or ylids is illustrative. The earlier literature has been admirably surveyed by Cram[8], who concluded that the slow rate of exchange of protons α to a tetraalkylammonium group relative to those α to a trialkylsulphonium group was evidence for d-orbital interaction by second-row elements, similar to Case I conjugation in sulphones. Cram also estimated from Hammett σ-constants that for methylsulphinyl and methylsulphonyl

groups, inductive and resonance effects in aromatic systems were of equal strengths for both groups. This has recently been shown to be in error[9], the methylsulphonyl group possessing about 80% "inductive character" and the methylsulphinyl group almost 100% "inductive character", using new quantities $\mathcal{F}$ and $\mathcal{R}$, the field and resonance constants for a particular group. Two conclusions can thus be drawn, that inductive effects are at least as important as resonance effects in the chemistry of sulphones, and probably a great deal more important. Secondly, it is known that sulphones with an asymmetric α-carbon atom retain this chirality upon proton abstraction[10]; in the earlier literature[8] there is ample evidence that ability to adopt an electrostatically favourable conformation has much influence upon the acidity of the α-protons in a sulphone; sulphones which can adopt conformation (6) are more acidic than those which cannot. In either case, a pyramidal carbanion is preferred.

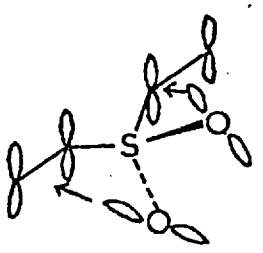


(6)

Otherwise, there is no objection to bridgehead anions α to a sulphonyl group, i.e. Bredt's rule does not apply, in contrast to the corresponding carbonyl system. These facts imply that classical ketonic or Case II resonance plays little part in stabilizing these carbanions. It is also well known that sulphones readily form α,α'-dicarbanions[11]. All of this illustrates the limitations of drawing analogies between carbonyl and sulphonyl group chemistry, which on almost every point are different. Note should be taken of ab initio molecular orbital calculations on the hypothetical

hydrogen sulphonyl carbanion ($HSO_2CH_2^-$) which show that it is quite unnecessary to invoke d-orbital stabilization (Case I conjugation) to explain its observed properties (e.g. asymmetry)[12]. More experimental evidence will be quoted below, but we may sum up the position as follows. First, that inductive effects are sufficient to explain most of the chemistry of the sulphonyl group; secondly, that most resonance effects observed are of Case I type and are in no way comparable to conjugation in carbonyl systems; thirdly, "d-orbital participation" is often invoked with great facility but with little evidence. Clark[13] has noted that M.O. calculations "should caution organic chemists in particular against the indiscriminate use of pictorial explanations using d-orbitals. These may look very nice on paper...but they often have little scientific foundation."

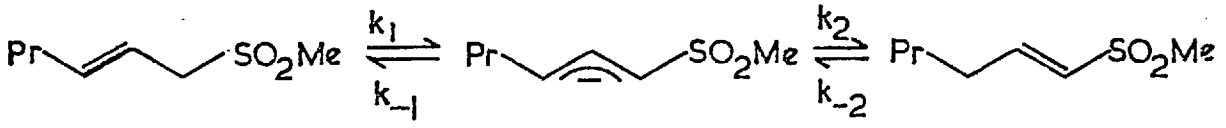
Some further examples of the absence of conjugation involving sulphonyl groups will now be noted. Thermochemical studies[14] of various α,β-unsaturated sulphones show a slight (ca. 4kcal) stabilization over the β,γ-isomers. Photoelectron spectroscopic evidence[15] is claimed to demonstrate the existence of spiroconjugation[16] in divinyl sulphones of type (7) where the p-orbitals of the oxygen atoms can interact with the carbon π system. The effect, however, is reckoned to be weak compared to the inductive effect.



(7)

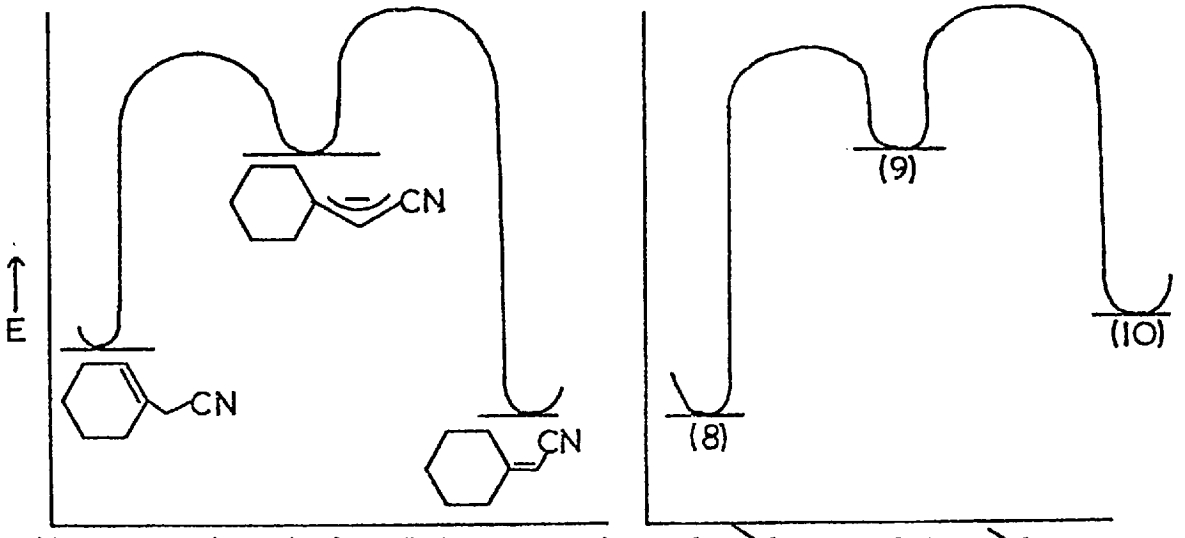
Much kinetic work has been done on the properties of α,β-unsaturated sulphones. In acyclic systems, O'Connor

and Lyness[17] have shown that the ß,γ-isomer (8) is favoured over the α,ß-isomer (10) by a factor of 99:1 at equilibrium.



(8) (9) (10)

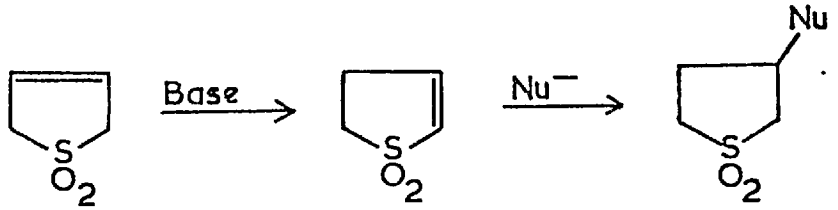
These authors conclude that thermodynamic stabilities of the isomers are purely determined by the large -I effect of the sulphonyl group and sulphur d-orbital resonance is negligible. Broaddus[18] has examined the energy profile for the inter-conversion of (8) and (10) and concludes that, despite the reversal of the ground state energies of the isomers, such systems are exactly parallel to the classic α,ß- and ß,γ-unsaturated nitrile equilibria studied by Ingold[19].



In the unsaturated sulphone series, $k_1 > k_2$, and $k_{-1} > k_{-2}$; the same situation occurs for the unsaturated nitrile with the important distinction that in the sulphone series, kinetic protonation of the intermediate anion (9) gives the most stable isomer, while in the nitrile series, it gives the least stable isomer.

Further chemical evidence for non-conjugative interaction

between a π-system and a sulphonyl group is provided by kinetic studies of the addition of bromine to α,ß-unsaturated sulphones. Bromination is slow and the rate is unaffected by acid catalysis and bromide ion[20]; comparison of rates of addition to the α,ß- and ß,γ -isomers shows that the ß,γ-addition is faster, though there is evidence that inductive deactivation still persists[21]. These results are quite different to those obtained for typical α,ß-unsaturated carbonyl or nitro systems, and the only influence of the sulphonyl group detectable seemed to be a strong -I effect. Deactivation of the double bond is also observed in 3-sulpholene (11), which reacts sluggishly with iodine isocyanate and other electrophiles[22], but which readily gives various 3-substituted sulpholans (13) by base-catalysed addition of nucleophiles to the intermediate α,ß-isomer, 2-sulpholene (12).



(11) (12) (13)

It therefore appears that, whatever the nature of the interaction between the double bond and the sulphonyl group, α,ß-unsaturated sulphones are strongly activated towards Michael-type addition of nucleophiles[23, 24, 25].

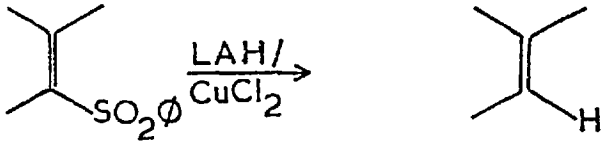
3. SYNTHESIS AND THE SULPHONYL GROUP.

The synthetically useful functions of the sulphonyl group may be classified as:- (1) an activating group; (2) a leaving group; (3) a sterically bulky group.

(1) The role of the sulphonyl group in activating (a) adjacent methylene groups, (b) double bonds towards nucleophilic

additions, has been discussed above.

(2) Since sulphinic acids (RSO_2H) are moderately strong (pK_a *ca.* 3×10^{-2})[26], the sulphinate anion RSO_2^- is a reasonably good leaving group, particularly in the highly favoured intramolecular nucleophilic displacements; likewise, it may be removed by E2 elimination, or more often a reductive cleavage, e.g. with sodium amalgam[27]. These methods give a choice of generating a single or double bond linkage. Recently, Truce[28] has shown that alkyl-aryl sulphones are readily cleaved to an aryl thiol and an aliphatic hydrocarbon in lithium-methylamine solutions, if proton sources are excluded. Cleavage of dialkyl sulphones under similar conditions has also been observed[29]. The mechanism of these cleavages, whether radical or carbanionic, is uncertain. Lithium aluminium hydride has also been used to cleave vinyl sulphones to an olefin in a stereospecific manner[30].

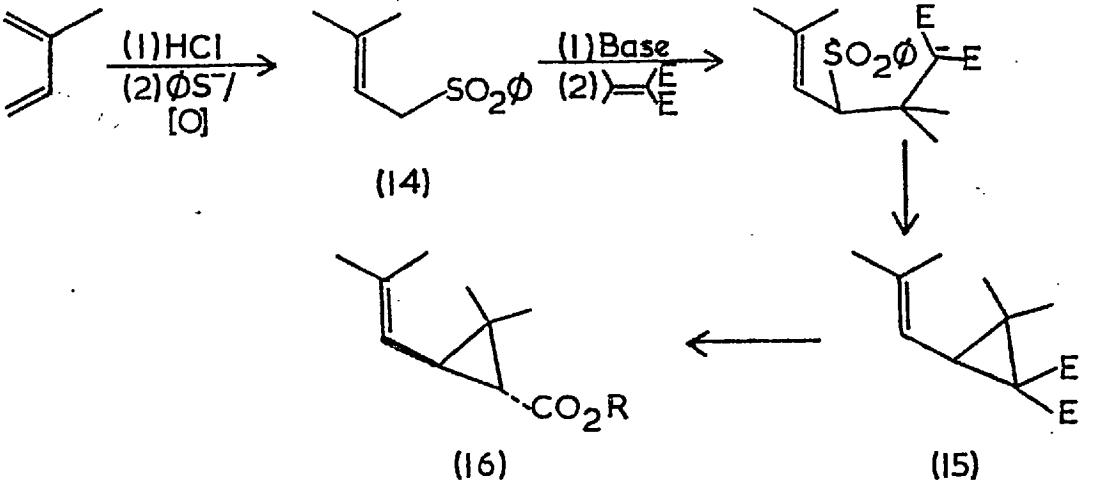


Sulphur-free compounds are also obtained from sulphones by extrusion of the sulphur dioxide fragment, as discussed below in Section 5.

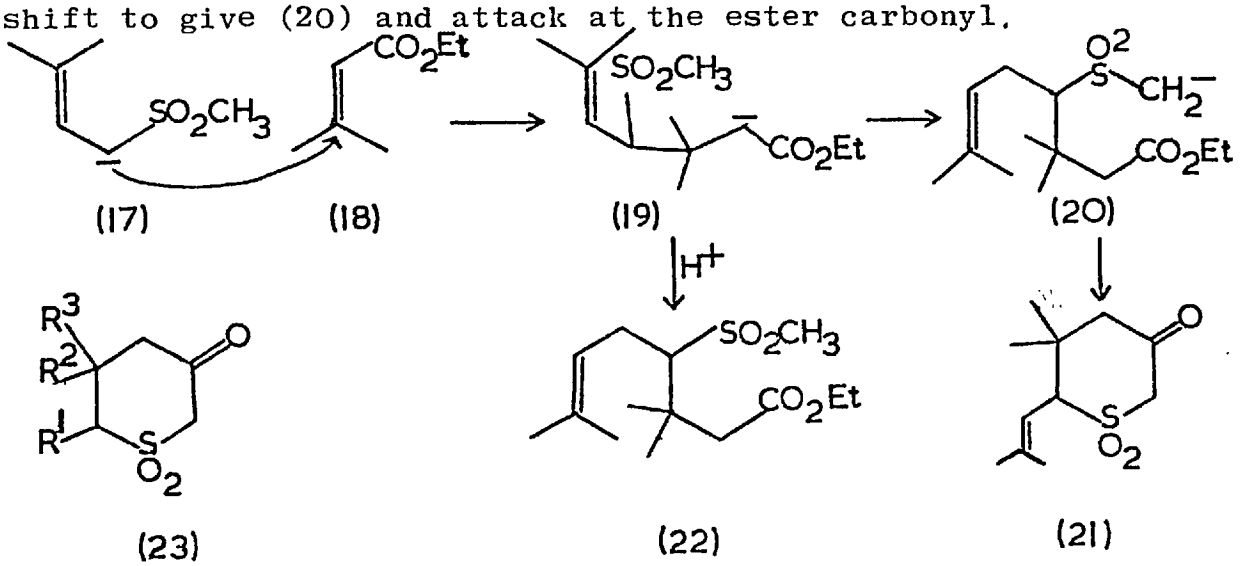
(3) The steric bulk of the sulphonyl group is usually cited as the reason for the reluctance of α-halogenosulphones to partake in nucleophilic displacements[31]. The free energy barrier to rotation in substituted ethanes is reckoned by Eliel to be about 3kcal. for the sulphonyl substituent.

4. SYNTHETICALLY USEFUL REACTIONS OF THE SULPHONYL GROUP.

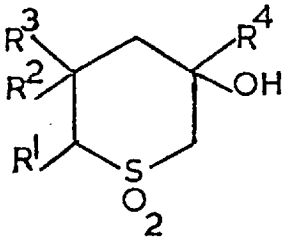
An aryl sulphone has been used in a neat synthesis of chrysanthemic acid[32]. The useful isoprene "synthon" (14) was prepared from isoprene via the hydrogen chloride addition product. The addition of the anion of the sulphone (14) to isopropylidenemalonic ester in a 1,4-fashion, followed by an intramolecular displacement to give the diester (15), afforded chrysanthemic acid (16; R=H) on hydrolysis and decarboxylation.



With α,ß-unsaturated aldehydes and ketones, sulphonyl ylids usually give only 1,2-products[33], but Michael addition appears to be favoured with α,ß-unsaturated esters. In parallel work, Martel[34] found that the anion (17) with senecioic ester (18) gave the heterocycle (21) by Michael addition, a prototropic shift to give (20) and attack at the ester carbonyl.



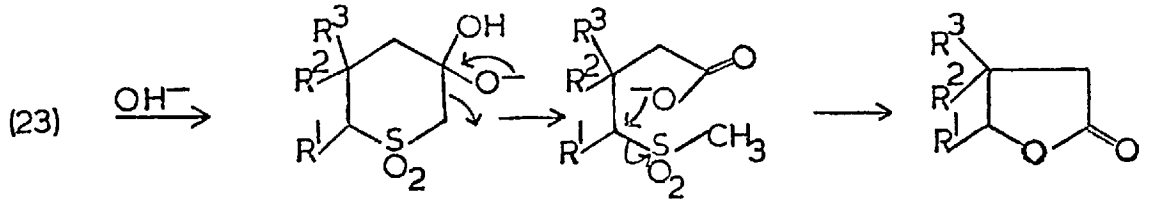
This scheme was easily generalized to prepare compounds of type (23); α,ß-unsaturated aldehydes were also found to undergo this reaction, giving alcohols of type (24).



(24)

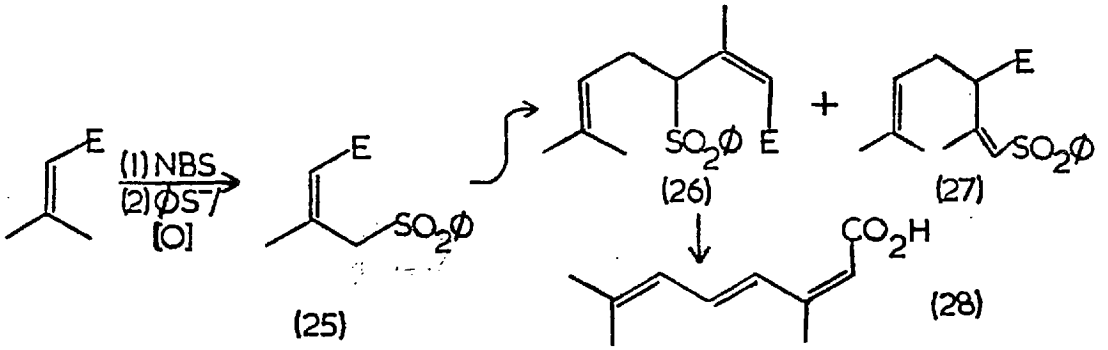
This proves that the correct sequence of events is 1,4-addition followed by attack at the carbonyl group. The intermediate (22) may also be isolated by kinetic protonation of (19). However, the ratio of 1,4- to 1,2-initial adduct is somewhat dependent upon the nature of the substituents; e.g. for compound (23; R^1=CH_3, R^2=H, R^3=Ø), formation of the 1,2-adduct is the initial step. The effect of cuprous salts[36] upon the course of the reaction was not investigated.

This reaction was used to prepare chrysanthemic acid ethyl ester (17; R=Et) directly and stereospecifically from sulphone (14) and ester (18). A further bonus for this reaction was the preparation of γ-lactones in high yield from (23) and sodium hydroxide[35].

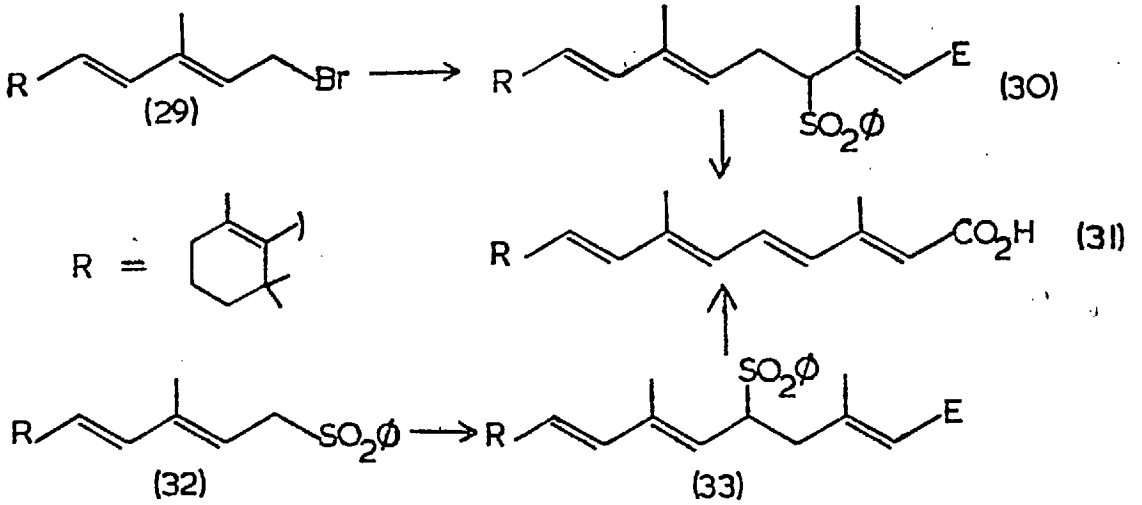


A similar combination of properties of sulphones has been exploited by Julia in a synthesis of terpenoids using a "head to tail" coupling of isoprene units[37]. The isoprene synthon (25) could easily be alkylated by ß,ß-dimethylallyl bromide to give a mixture of (26) and (27) in the ratio 9:1.

This predominance of (26) is not unexpected, in view of our discussion on p.15, where it was shown that kinetic quenching of the intermediate anion (11) gave the most stable ß,γ-isomer. (26) is readily converted, by hydrolysis and elimination, to (28). Thus it is possible to couple isoprene units "head to tail" via a double bond.



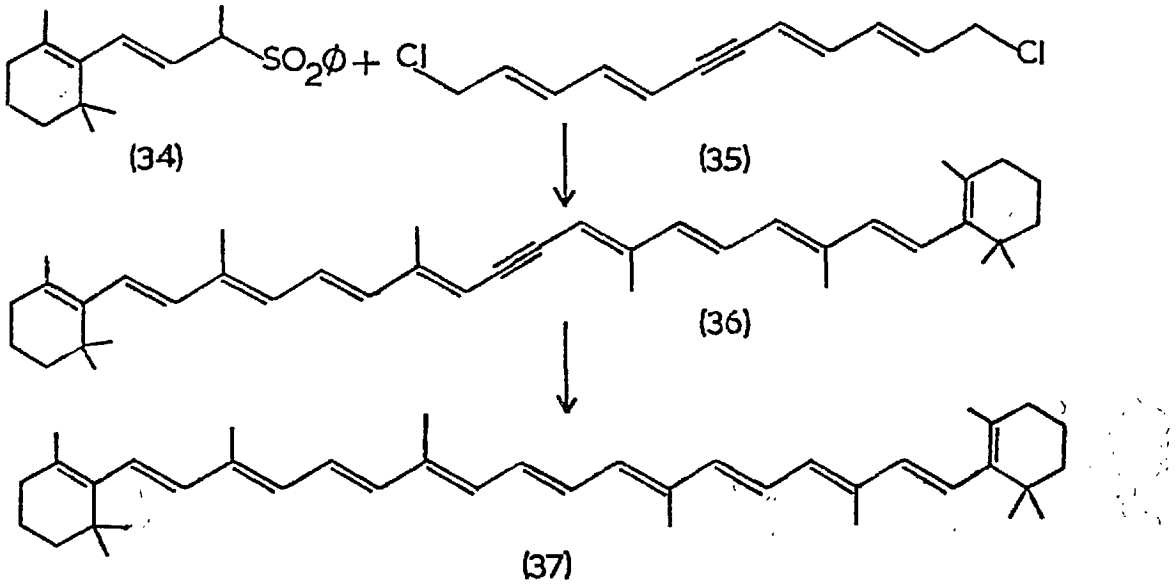
The scope of this reaction was demonstrated by a short synthesis of Vitamin A[38]. The synthon (25) was alkylated with bromide (29) (from ß-ionone) to give a mixture of α- and γ-alkylated isomers. Hydrolysis and elimination of the α-isomer (30) gave a modest yield of all-trans-Vitamin A (31).



A much improved yield was obtained by "reversing" the roles of the components, and alkylation of sulphone (32) gave (33) in 90% yield, convertible to Vitamin A in 80% yield.

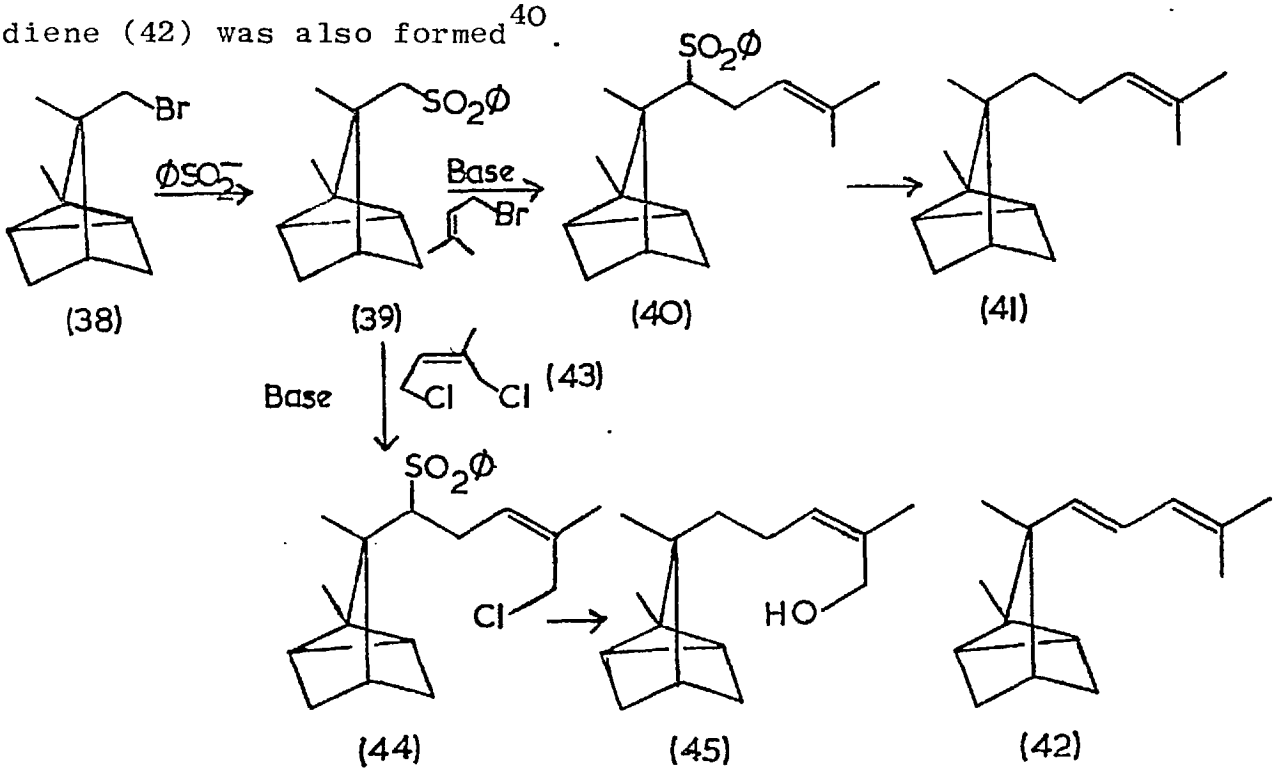
A very similar route to carotenoids has been developed

using sulphone (34). When alkylated with the polyenyne (35), the intermediate (36) is obtained directly, which is reduced to ß-carotene (37) in good yield[39].



(34) (35) (36) (37)

Another application in the field of terpene synthesis is illustrated by the synthesis of α-santalene and its derivatives. Treatment of optically active bromide (38) with sodium benzenesulphinate gave sulphone (39). This was alkylated to (40); reduction of this with sodium amalgam gave a 90% yield of optically pure α-santalene (41). A small amount of diene (42) was also formed[40].

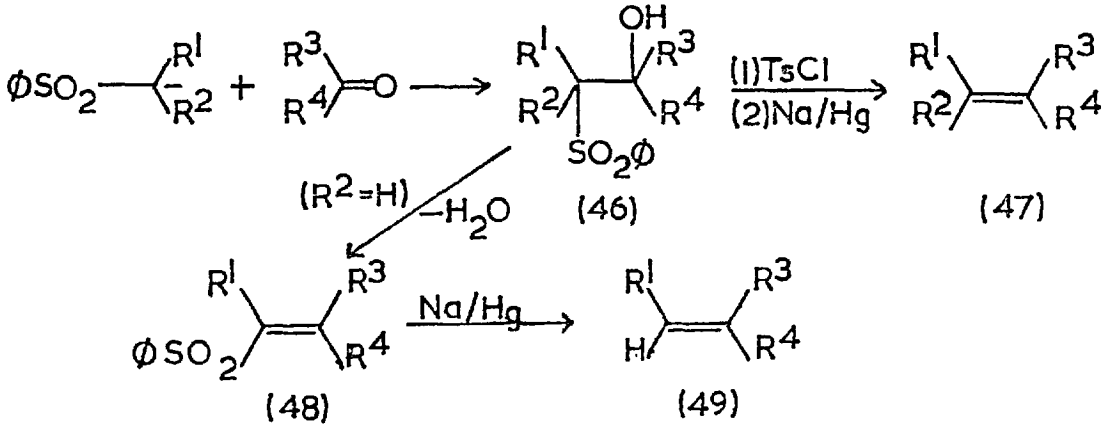


(38) (39) (40) (41) (43) (44) (45) (42)

Previous syntheses of santalene derivatives have been non-stereospecific, e.g. by more laborious chain-lengthening sequences from (38).

Using synthon (39), (+)-α-santalol was made in good yield by regiospecific alkylation with (43) to give only (44). Subsequent hydrolysis and reduction readily gave optically pure α-santalol (45).

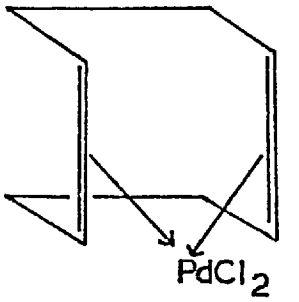
An extension of the coupling reaction to give an olefin has been described. Sulphonyl ylids readily give ß-hydroxy-sulphones (46) with carbonyl compounds[33, 41], which can be easily dehydrated to α,ß-unsaturated sulphones (48)[42]. This property lends itself to the synthesis of olefins of any desired substitution pattern.



Treatment of hydroxysulphones (46) with tosyl chloride followed by reductive elimination leads to a tetrasubstituted olefin (47)[43], whereas trisubstituted olefins (49) are available directly by dehydration of (46) to α,ß-unsaturated sulphones (48) followed by reduction[30]. The stereochemical course of this reaction remains to be elucidated.

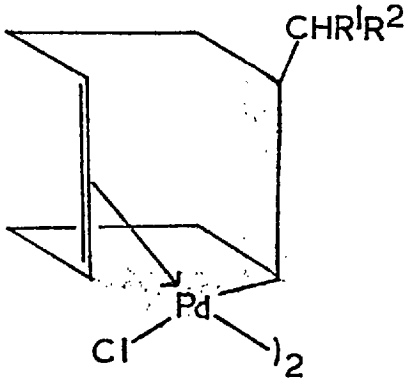
A very interesting method of converting a trisubstituted olefin into a tetrasubstituted olefin has been achieved using the palladium chloride complex of cycloocta-1,5-diene (COD) (50). This readily adds nucleophiles to give adducts

such as (51; $R^1=R^2=CO_2H$). However with the lithium salt of the conjugate base of phenyl methyl sulphone, a mixture of products comprising (51; $R^1=SO_2\phi$, $R^2=H$), (52) and (53) is obtained; with the corresponding sodium salt, only (52) and (53) are formed[44].

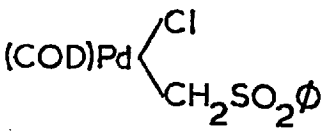


(COD)$PdCl_2$

(50)



(51)

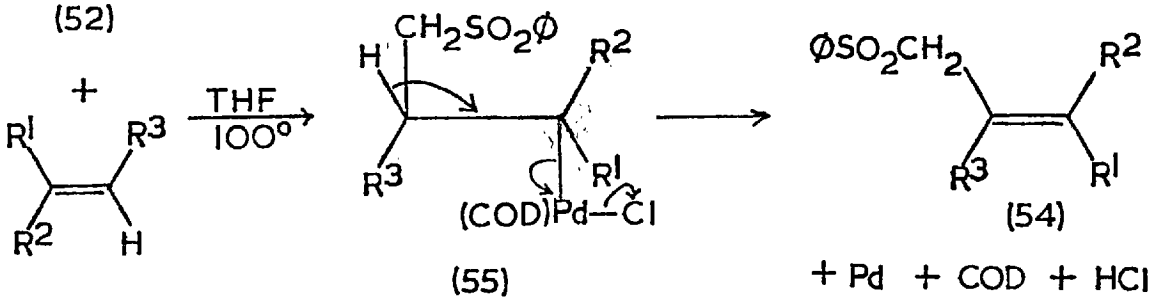


(52)

(COD)$Pd(CH_2SO_2\phi)_2$

(53)

(53) is readily converted to (52) by dilute hydrochloric acid; both complexes are stable to air and moisture. If (52) is reacted with a trisubstituted olefin, palladium metal is deposited and a ß,γ-unsaturated sulphone (54) is obtained.



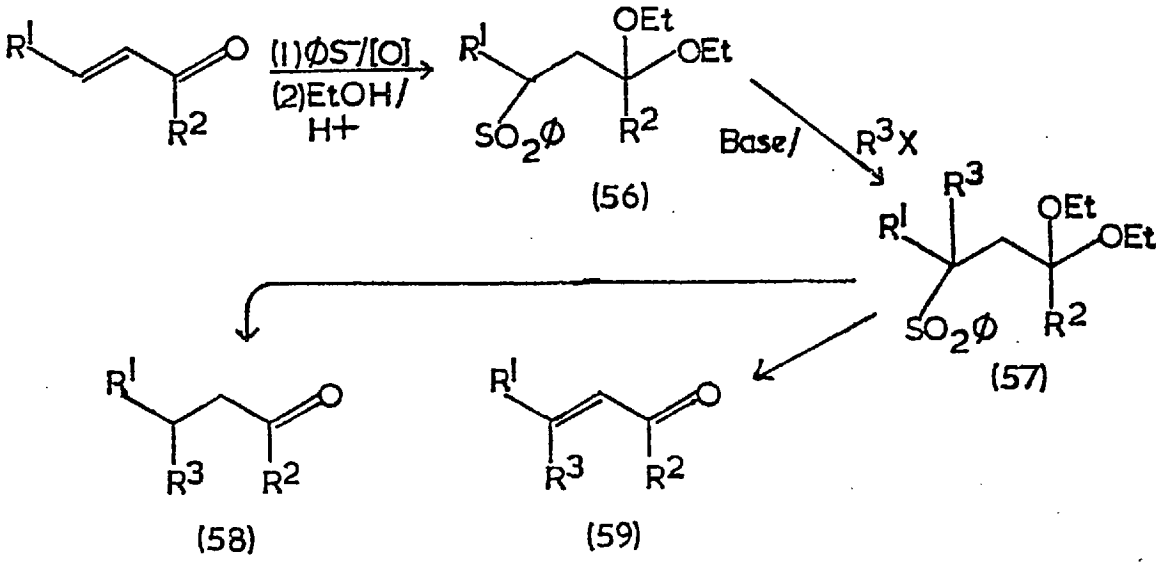
(55)

+ Pd + COD + HCl

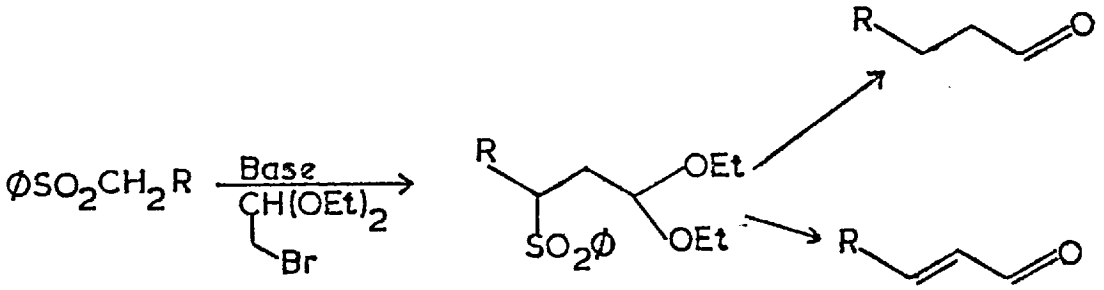
More highly substituted sulphones are, in principle, useable, and the product (54) can easily be reduced to a tetra-substituted olefin. If the postulated intermediate (55) does indeed collapse via a ß-elimination process, stereochemical control should be possible; indeed, some stereospecificity is already observed. The critical step, as far as the stereochemistry is concerned, is whether addition of (52) to the olefin proceeds via an electrophilic or a radical process. This has yet to be ascertained; as the reagent (52) effects

such an unusual transformation, further work is called for.

A sulphonyl group can be used to prepare ß-alkylated ketones, saturated or α,ß-unsaturated[45]. An α,ß-unsaturated carbonyl compound is converted to the sulphone (56), which is readily alkylated to (57). This can either be reduced and hydrolysed to give the ß-alkylated ketone (58) or eliminated to give the ß-alkylated α,ß-unsaturated compound (59).

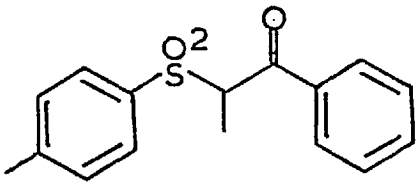


Using bromoacetal, this method can be used in reverse to generate aldehydes.

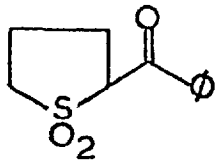


The use of the sulphonyl group in stereochemical control has been undervalued. One of the first observations of the sulphonyl group in this role was by Truce[42] who prepared various asymmetric ß-hydroxysulphones from sulphonyl ylids and carbonyl compounds; no stereoselectivity was observed

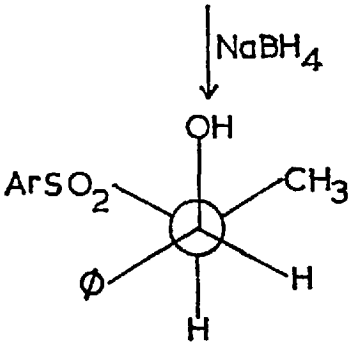
during the 1,2-addition. However, reduction of the ß-keto-sulphones (60) and (61) with sodium borohydride gave the respective threo alcohols (62) and (63) with 97% specificity.



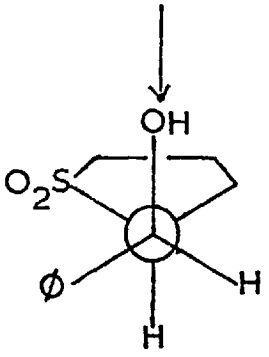
(60)



(61)

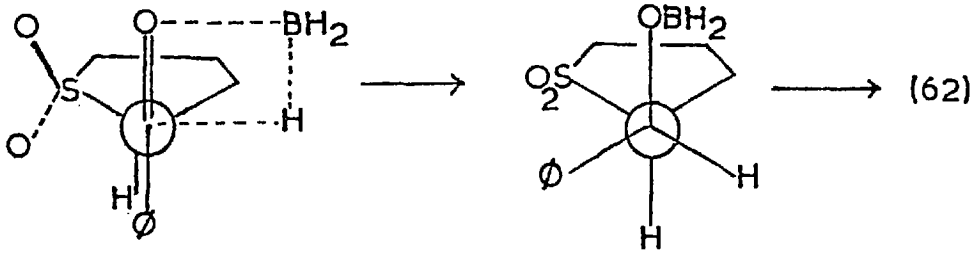


(62)



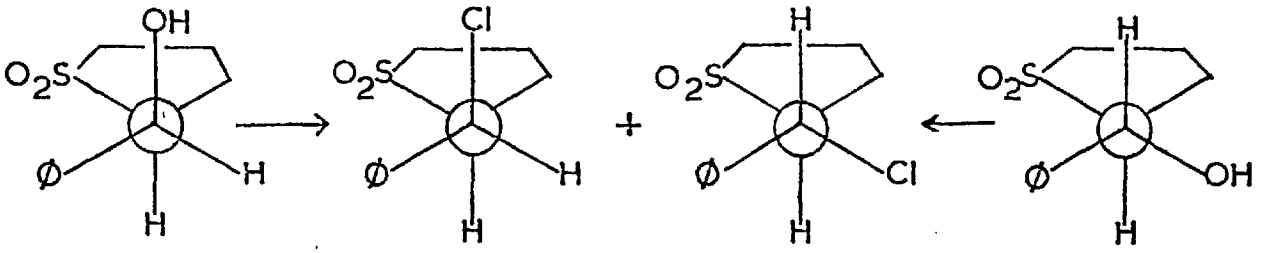
(63)

This finding was readily rationalized by considering the transition states, e.g. (64), which is the only such state which does not result in serious steric interference by the sulphonyl group, in accordance with the rule of steric control of asymmetric induction[46].



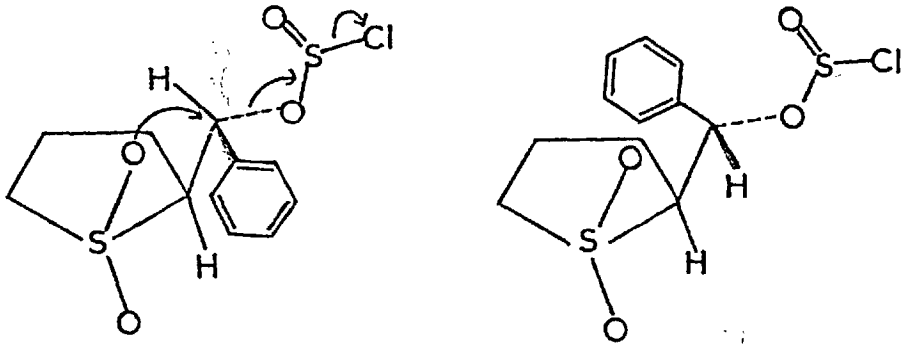
(64)

An unusual case of sulphonyl participation was observed by Truce in the reaction of the erythro isomer (65) of alcohol (63), with thionyl chloride. Whereas the threo-alcohol (63) gave a 1:1 mixture of threo:erythro chlorides (66) and (67); erythro-alcohol (65) specifically gave only erythro-chloride (67).



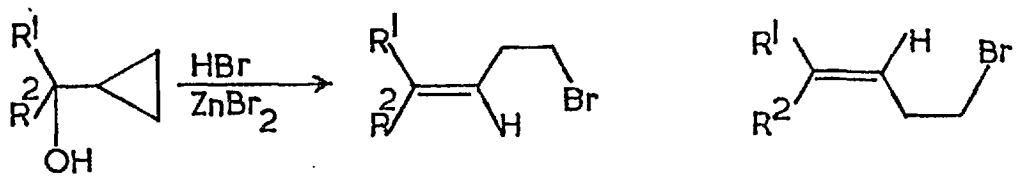
(63) (66) (67) (65)

This was explained by sulphur-oxygen bond participation during the collapse of the intermediate chlorosulphite ester. In the erythro-case, (68), a conformation of the chlorosulphite ester may be adopted, without steric crowding, to enable the S-O bond to participate. In the threo-case, (69), adoption of such a conformation requires the aromatic ring to sit on top of the sulpholan ring, causing severe steric strain, as well as restricting the ability of the aryl group to stabilize the developing carbonium ion as the chlorosulphonyl group leaves.



(68) (69)

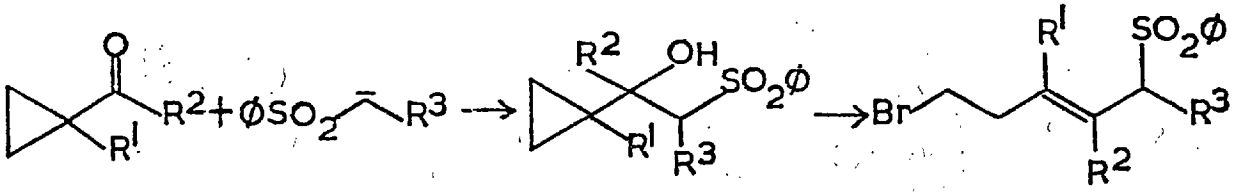
The bulky properties of the sulphonyl group have been brilliantly exploited by Julia in an elegant extension of his own stereospecific synthesis of disubstituted olefins[47] from α-cyclopropylcarbinols (70).



(70) (71) (72)

This synthesis works very well if R^1 is much larger than R^2, e.g. if R^1=alkyl, R^2=H, then olefin (72) is overwhelmingly preferred. Extension of the method to trisubstituted olefins usually fails, mixtures of isomers (71) and (72)[48] being obtained, unless R^1 has a much greater steric requirement than R^2.

The sulphonyl group can be used as a temporary agent for increasing the bulk of the alkyl group R^1 in this reaction. Reaction of a sulphonyl ylid with cyclopropyl methyl ketone gives the carbinols (73). These were readily rearranged to the bromides (74) with hydrogen bromide and zinc bromide; stereospecificity was almost 100% in most cases[49].

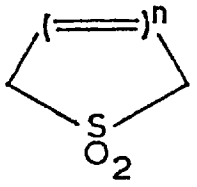


(73) (74)

The E-isomer[50] was favoured over the Z-isomer in all cases, except where R^1=R^3=H, R^2=dimethylallyl, when a 9:1 mixture of E:Z was obtained. It seems, therefore, that the group $\emptyset SO_2CH_2$- can compete favourably with the ß,ß-dimethylallyl group as regards bulk.

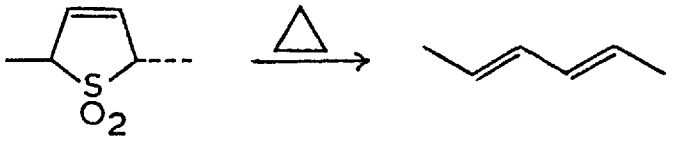
5. LOSS OF SULPHUR DIOXIDE FROM UNSATURATED SULPHONES.

The fragmentation of small- and medium-ring sulphones is a reaction of great synthetic and mechanistic importance. The role of sulphones in the Ramberg-Bäcklund olefin synthesis has been reviewed[51] and some aspects of the chemistry of medium-ring unsaturated sulphones (75) will be dealt with here.

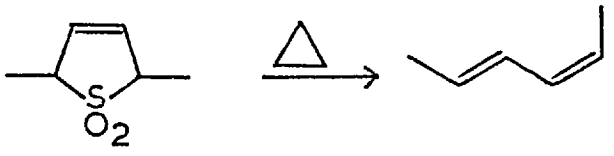


(75)

The earlier literature on formation of compounds (75; n=1), or sulpholenes, from dienes and sulphur dioxide has been reviewed[52]. A vast number of dienes have been used in this reaction yet only recently has the process been rigorously shown to be stereospecific[53]. Cis- and trans-2,5-dimethyl-sulpholenes (76) and (77) were shown to give hexadienes on pyrolysis, consistent with a disrotatory (suprafacial) ring opening, with a specificity of at least 99.9%. It is not surprising that this reaction has been used to make pure diene stereoisomers.

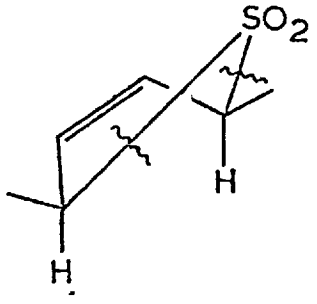


(76)



(77)

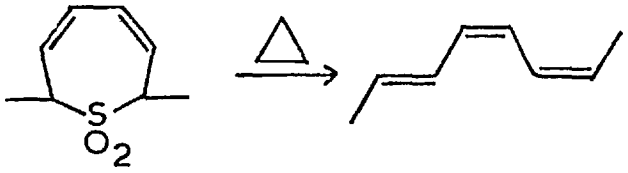
A transition state such as (78) is envisaged[54] (cis-isomer shown).



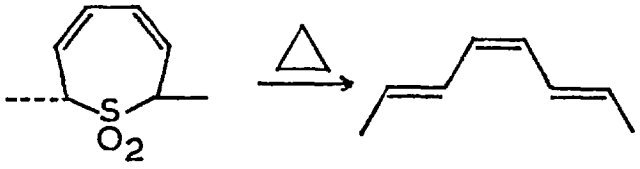
(78)

Further mechanistic studies [55] showed that the corresponding 2,7-dimethyldihydrothiepin dioxides (79) and (80) gave

trienes consistent with the expected concerted conrotatory (antarafacial) ring opening, on pyrolysis, with about 97% specificity.

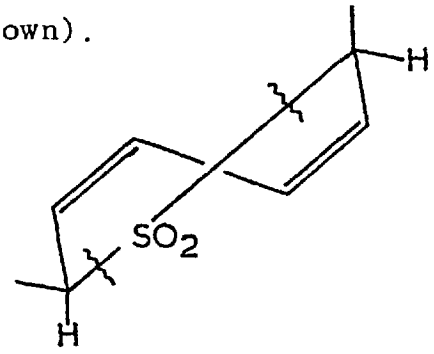


(79)



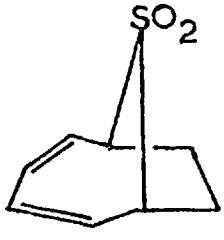
(80)

In this case, a transition state (81) was postulated[54] (cis-isomer shown).



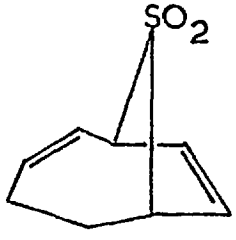
(81)

An interesting consequence of the apparent concertedness of the reaction was demonstrated by the extremely slow rate of fragmentation of (82) which is constrained to undergo a suprafacial elimination, which is thermally forbidden for this system. However, for the isomer (83), for which the easily attained suprafacial mode is allowed, fragmentation is rapid.



(82)

Rate 1



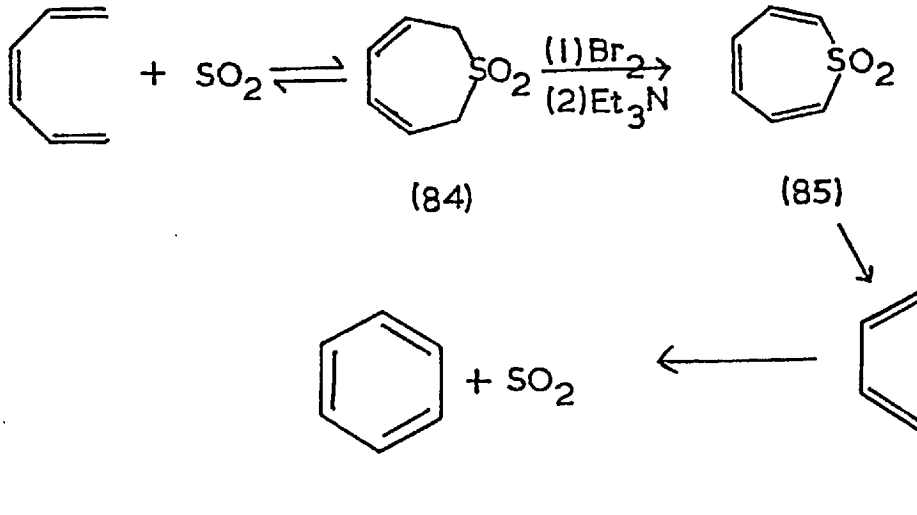
(83)

6×10^4

In the same way, cycloocta-1,3,5-triene can only add sulphur dioxide to give (83); no (82) was detected[57].

We may safely conclude from all the classic hallmarks of a concerted reaction (reversibility, specificity, etc.) that the major constraint operating in these fragmentations is orbital symmetry conservation. Mock[56], however, more cautiously states that all the data indicate is that a synchronous pathway is more favoured by ca. 10kcal. over a sequential pathway, and that radical or polar character in these extrusions cannot be ruled out; he states that[54] "our working definition of concertedness is an observational one; the reservation is made that considerable non-synchronicity in the order of bond-breaking is compatible with experimental observation."

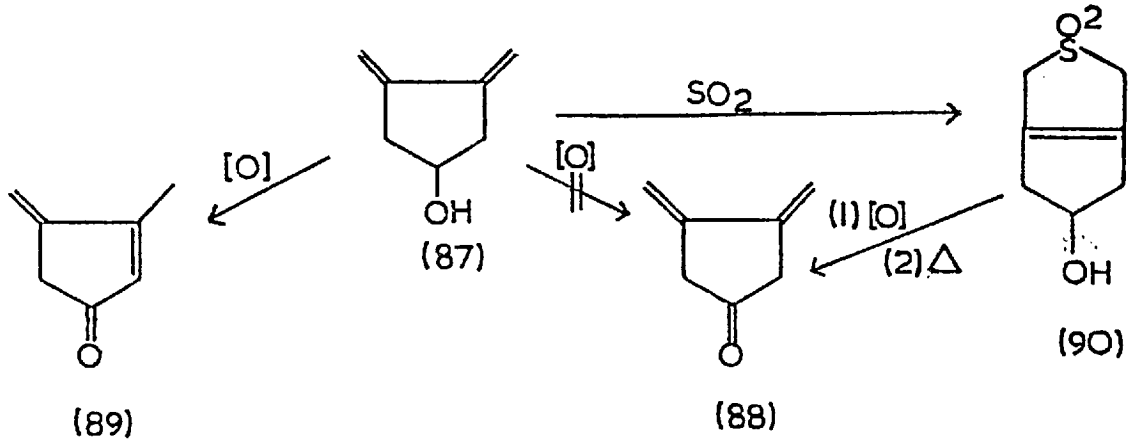
Although the addition of sulphur dioxide to dienes is well known, addition to trienes was not observed until quite recently, when hexatriene reacted with sulphur dioxide at room temperature to give dihydrothiepin dioxide (84) in good yield, the triene being regenerated upon heating the adduct to 150°.



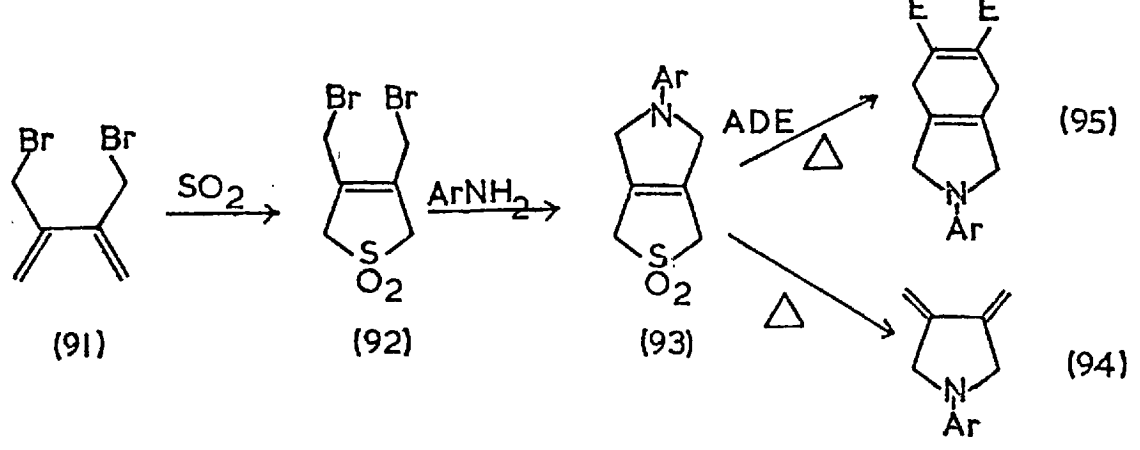
(84) was converted to thiepin dioxide (85), which showed the expected lack of aromaticity. On heating, (85) gave the

ring-closed product (86), "benzene episulphone", as an unstable intermediate which spontaneously gave benzene and sulphur dioxide. The synthetic possibilities for SO_2 additions to trienes are limited, since starting materials are not readily obtained pure; also attempts to make the adducts (79) and (80) directly from the octatrienes failed[55].

In contrast, the scope of uses for sulpholenes (75; n=1) is large. Sulpholene formation is a useful protective method for the often unstable 1,3-diene moiety. For example, the dimethylenecyclopentane (87) could not be oxidised to ketone (88) without rearrangement to (89); the adduct (90) was cleanly oxidised and the diene system readily regenerated[59].

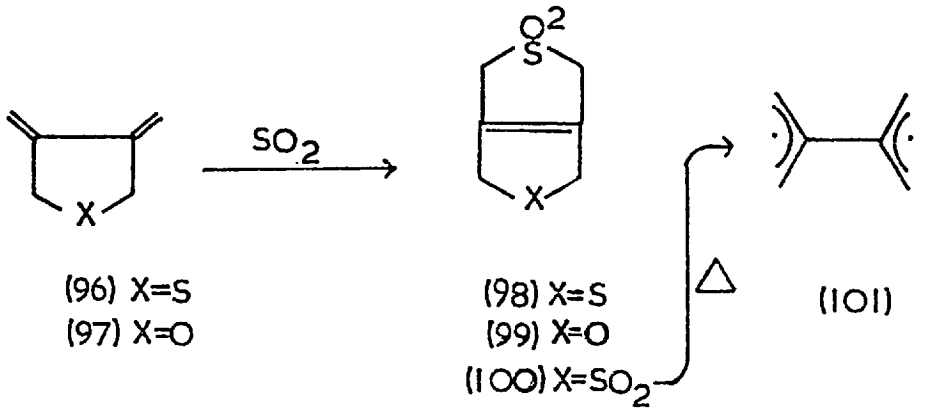


The unstable allylic dibromide (91) is best stored as its crystalline adduct (92)[50]. This is a useful precursor to 3,4-dimethylenepyrrolidine (94), by cyclization with an amine to (93) and subsequent extrusion to give (94)[61].



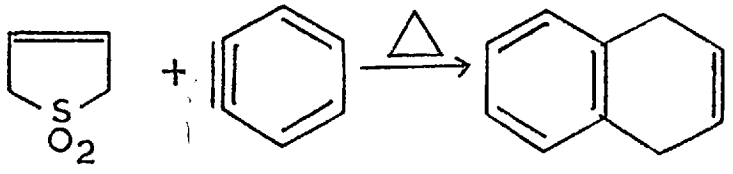
Compounds of type (94) are useful precursors of various pharmaceuticals, via Diels-Alder reactions of the diene system. A good yield of adduct is obtained by direct pyrolysis of (93) in the presence of the dienophile, rather than by direct use of the unstable diene (94). With acetylenedicarboxylic ester, adduct (95) is formed[62].

3,4-Dimethylenetetrahydrothiophen (96) and the corresponding furan derivatives (97) are also highly unstable[63] and are best stored as the adducts (98) and (99).



The sulphone (100) should fragment to give the tetramethyleneethane diradical (101), a species of considerable theoretical interest[64].

The use of the sulphur dioxide adduct to "mask" unstable dienes is exemplified by the trapping of benzyne with butadiene generated from 3-sulpholene to give the dihydronaphthalene (102) in low yield[65].

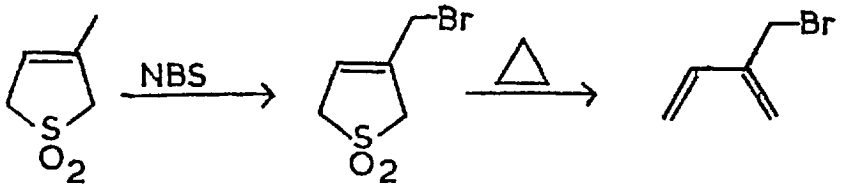


(102)

Free butadiene gave no adduct; kinetic studies show that the sulphur dioxide moiety is not involved in the transition

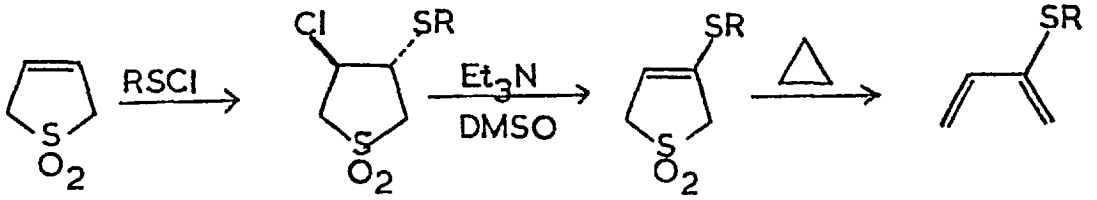
state. It is conjectured that the diene is generated in the cisoid form. Considering the success of the examples quoted above, it is surprising that more use has not been made of other sulphur dioxide-masked dienes.

Functional alterations to sulpholenes are a convenient route to many unstable dienes. The isoprene synthon (104) is made from isoprene sulphone (103)[66].



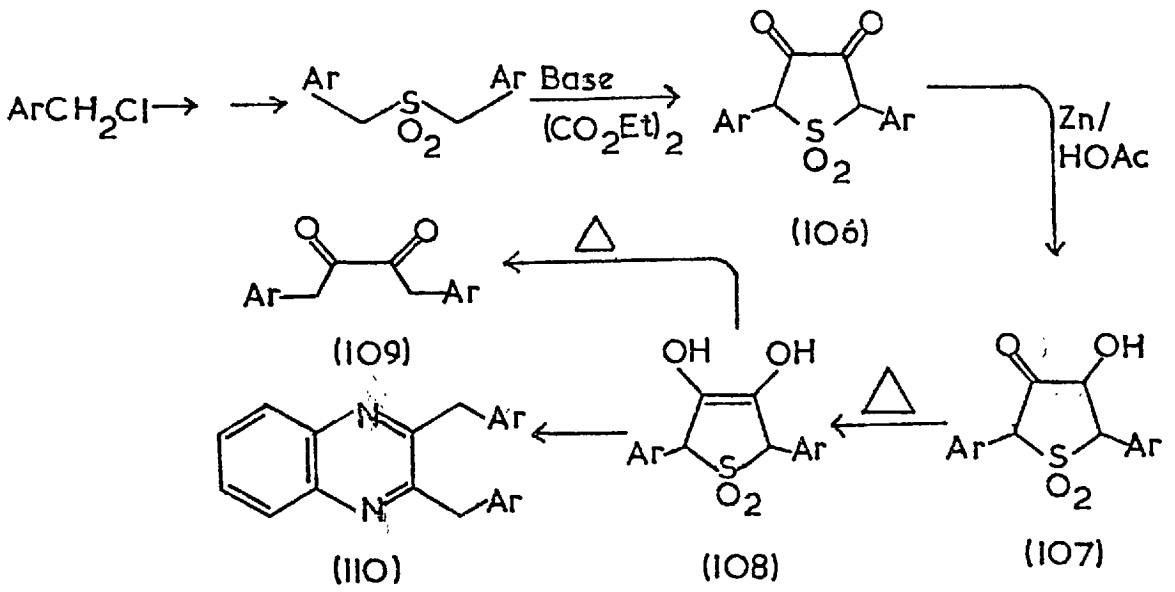
(103) (104)

The butadienyl sulphides (105) were made from the adduct of 3-sulpholene and a sulphenyl halide[67].



(105)

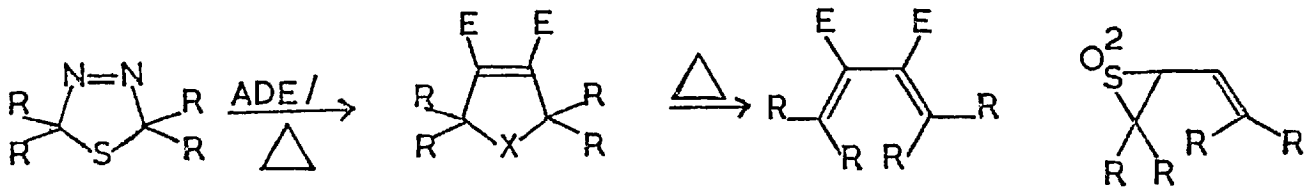
An ingenious synthesis of 1,4-diarylbutane-2,3-diones from benzyl halides has been developed[68]. The 3,4-dioxosulpholan (106) was readily synthesised, and was reduced to the hydroxyketone (107). This ring-opened in the presence of sodium acetate and acetic acid to give the dione (109). Direct reaction of (107) with o-phenylenediamine gave the quinoxaline (110).



The presence of both acid and base was necessary for clean decomposition of (107), presumably due to promotion of enolization of (107) to (108); the dione is in fact isolated as a mixture of the mono- and di-enol forms (111) and (112).

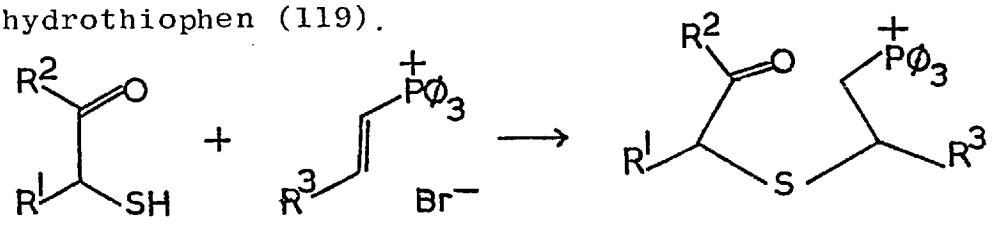
(111) (112)

Sulpholenes synthesised independently of diene-sulphur dioxide additions have been made. The 2,5-dihydrothiophen-3,4-dicarboxylic esters (113), from (114) and acetylene dicarboxylic ester, gave sulphones (115) on oxidation[67]. These fragment thermally to give an excellent and stereo-specific yield of the dienes (116).

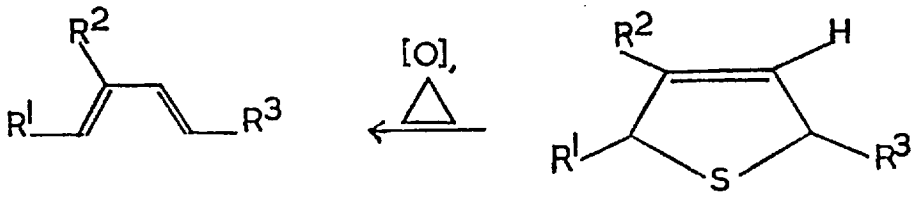


Interestingly, these authors showed that photolysis of (115), which from orbital symmetry considerations, should give the conrotatory (antarafacial) product, proceeded to give mixtures of stereoisomers, indicating a stepwise reaction. Episulphones (117) were invoked as intermediates, but not isolated; however, photolysis of the sulphides (113) gave the corresponding vinylepisulphides as the major product[70].

Another route to dihydrothiophenes, from 2-mercapto-ketones[71] and 2-mercaptoaldehydes[72] has been reported. The monomeric mercaptocarbonyl compound is added to vinyl-triphenylphosphonium bromide and the adduct (118) cyclized with base, via an intramolecular Wittig reaction, to the dihydrothiophen (119).

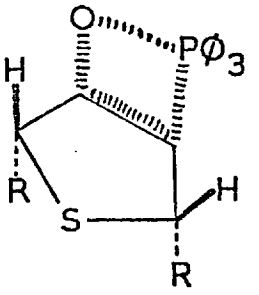


(118)



(120) (119)

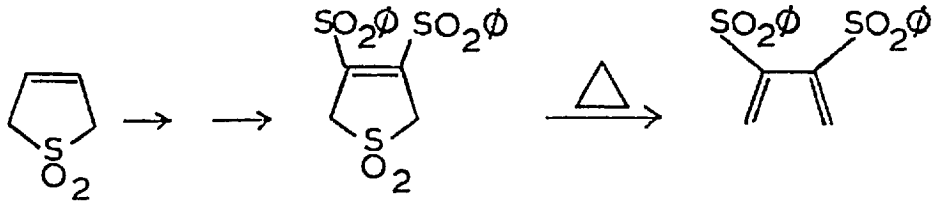
Oxidation and thermolysis of (119) gave dienes (120). Unfortunately, the formation of (119) is only partly stereo-specific; e.g. if R^1=Me, R^2=H, R^3=Et, the cis-isomer of (119) is favoured by a factor of only 4:1 over the trans-isomer. This is ascribed to avoidance of steric hindrance in the transition state, where the substituents prefer to be trans to the betaine ring in (121)[73].



(121)

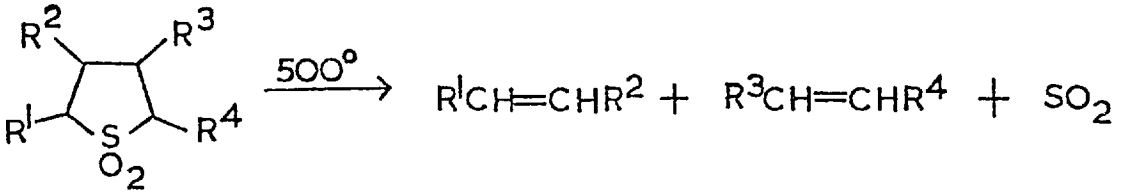
If the specificity of this synthesis could be improved, a major obstacle to the use of the Diels-Alder reaction in synthesis - i.e. the limited availability of dienes of known stereochemistry - would be removed[74].

A recent example of synthesis with sulpholenes is the preparation of the bis-arylsulphonylbutadiene (123) by decomposition of the sulpholene (122), itself prepared from 3-sulpholene by a multistep process[75].



(122) (123)

Sulpholans (124) fragment at elevated temperatures to two molecules of olefin and sulphur dioxide[76].

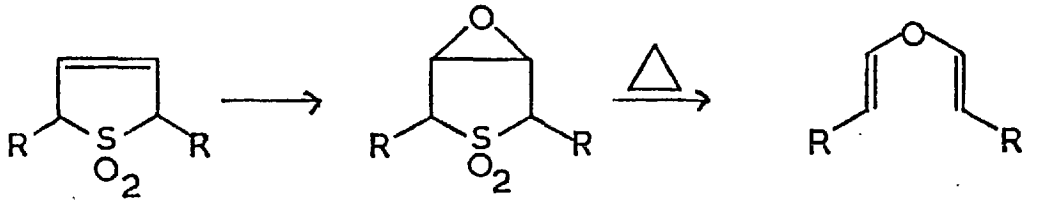


(124)

It has now been proved that this reaction, applied to cis- and trans-2,3-dimethylsulpholan (124; R^1=R^2=Me, R^3=R^4=H), gives, in both cases, a mixture of cis- and trans-2-butenes, and is thus non-concerted, though the nature of the mechanism

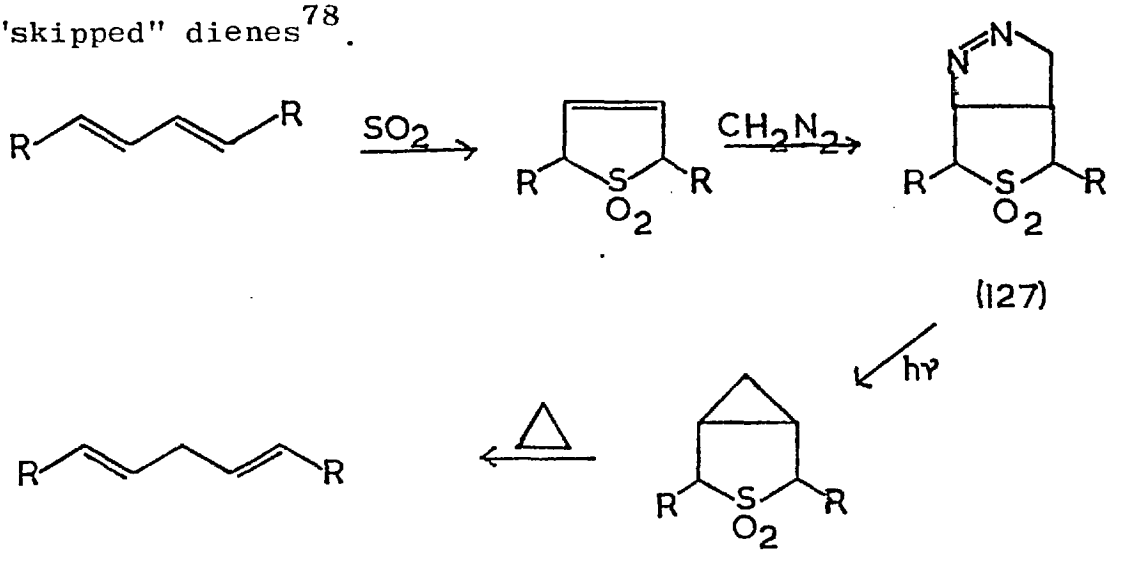
(whether radical or polar) is still in doubt[77].

In contrast, the saturated sulpholans (125) undergo facile and stereospecific elimination[78] to give divinyl ethers (126).



(125) (126)

The bicyclic sulphones (128), made by photolysis of the pyrazoline adduct (127), were smoothly converted to 1,4-dienes (129), thus providing an excellent synthesis of "skipped" dienes[78].

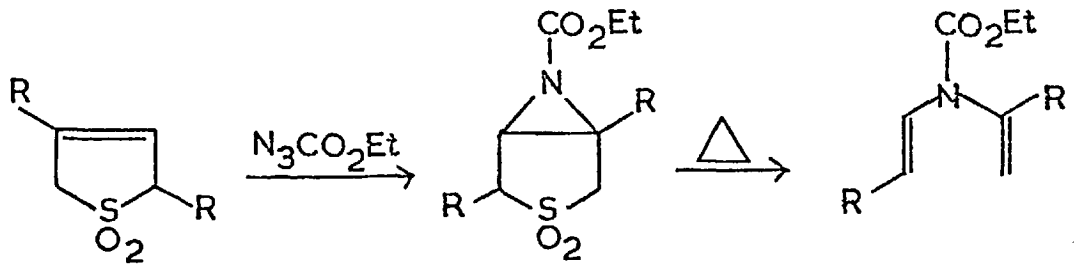


(127)

(129) (128)

This reaction is also stereospecific; thus a [σ2s + σ2s + σ2s] cheleotropic dissociation is indicated. These examples emphasize the well-known "double-bond character" of small rings.

Recently, this method has been applied to the synthesis of divinylamine derivatives (131), made from adducts (130) as shown[79]. This reaction is also stereospecific and hence probably concerted.

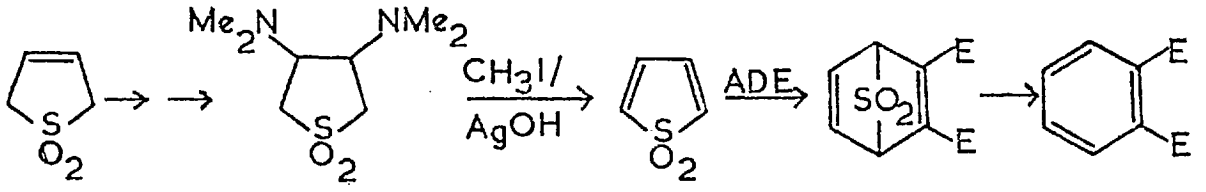


(130) (131)

So far, none of these reactions have been exploited in the dihydrothiepin dioxide (84) series, nor have possible applications in the preparation of large-ring heterocycles or ring-expanded carbocycles from bicyclic sulphones, attracted any attention.

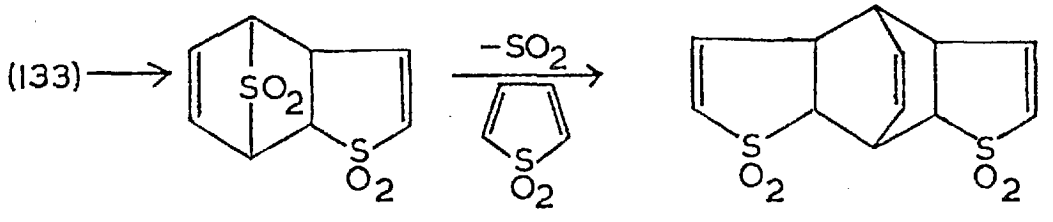
6. THIOPHEN-1,1-DIOXIDE AS A ROUTE TO SULPHUR-FREE COMPOUNDS.

A versatile, though underrated class of Diels-Alder dienes is thiophen-1,1-dioxide and its derivatives[80]. The parent compound (133) is made from sulpholene via Hoffmann elimination from the diamine (132)[81]. This can be trapped with dienophiles, usually with subsequent loss of the sulphonyl bridge; for instance, the adduct with acetylene dicarboxylic ester readily gives dimethyl phthalate.



(132) (133) (134)

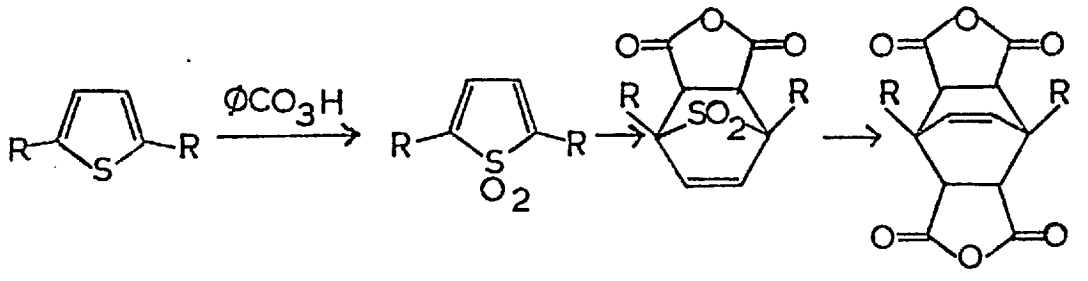
Thiophen-1,1-dioxide (133) cannot be isolated pure; it is stable in solution and removal of solvent results in dimerization to (135) and some trimerization to (136)[82].



(135) (136)

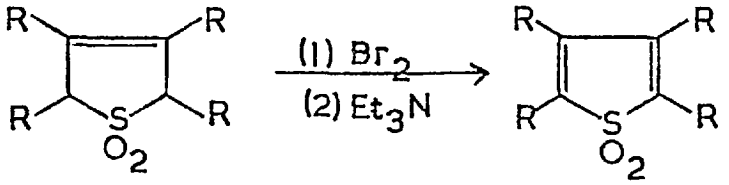
By analogy with certain M.O. calculations on antiaromatic systems such as the cyclopentadienones[83], it has been concluded[84] that this facile dimerization and high Diels-Alder activity in general, is due to a reduced energy gap between the highest occupied and lowest unoccupied molecular orbitals of the diene system (HOMO and LUMO respectively). The transition state for dimerization is now stabilized by effective mixing of these orbitals. Bulky 2,5-substituents stabilize the dioxide, presumably due to steric inhibition of dimerization[84]. Polychlorinated derivatives of (133) are also stable and isolable[85], probably due to the +M effect of the substituents. A recent semiquantitative CNDO treatment of thiophen-1,1-dioxide[86] shows that, compared to thiophen, the C2-C3 bond is shortened and the C3-C4 bond is lengthened in the dioxide, corresponding to a change from a delocalised to a semilocalised system with corresponding loss of aromaticity.

The preparation of the parent dioxide is given above. A more general method is oxidation of substituted thiophens, which often give stable dioxides (137). These give mono- and bis-adducts (138) and (139) with maleic anhydride[87].

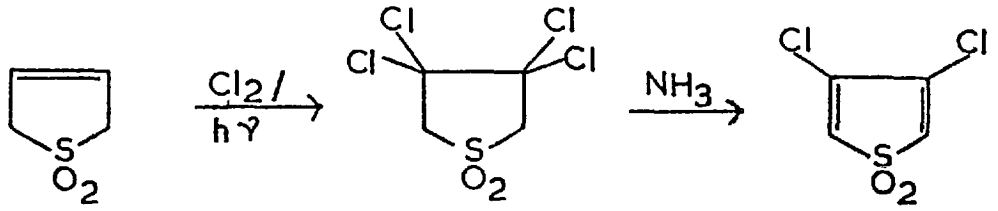


(137) (138) (139)

A very general preparative method is bis-elimination from suitably substituted sulpholans, easily available from sulpholenes.

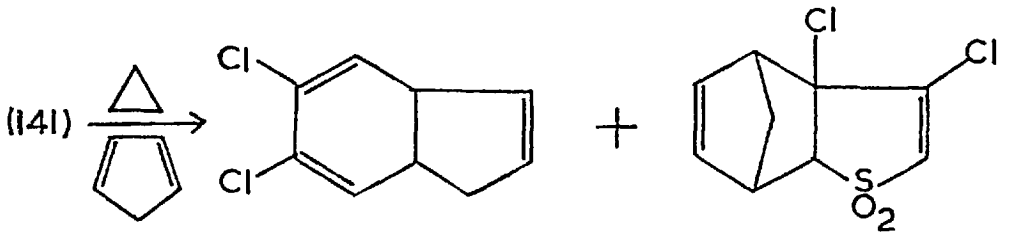


This has been used to make 3,4-dichlorothiophen dioxide (141) from tetrachlorosulpholan (140)[88].



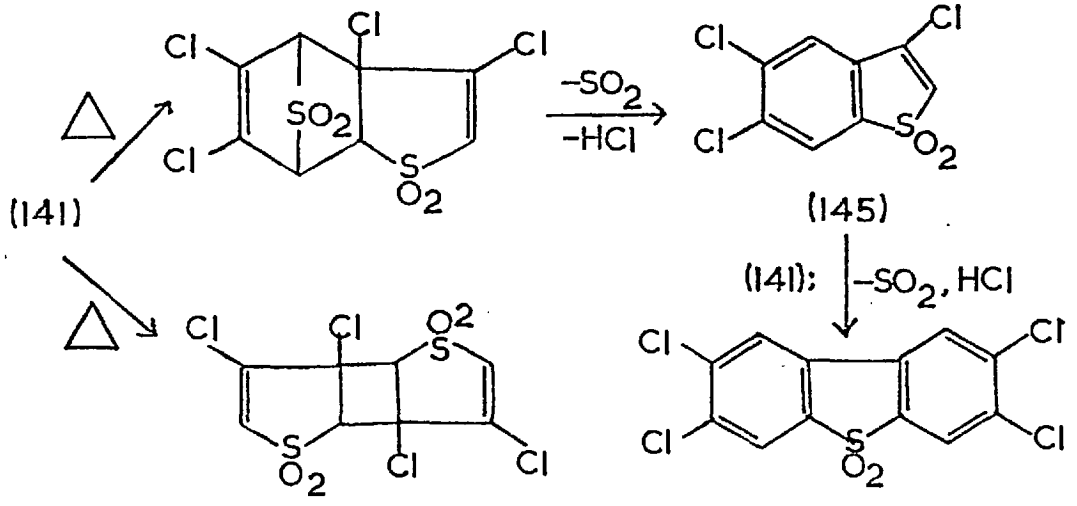
(140) (141)

(141) gave adducts with maleic anhydride [of type (138) and (139)]. With cyclopentadiene, it gave a mixture of adducts, resulting from anomalous reaction both as a diene (142) and as a dienophile (143).



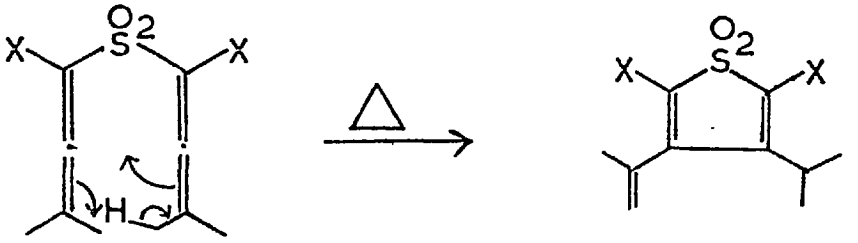
(142) (143)

It also appeared to dimerize in a [2 + 2] fashion, furnishing (144) as well as the expected [4 + 2] products (145) and (146).



(144) (146)

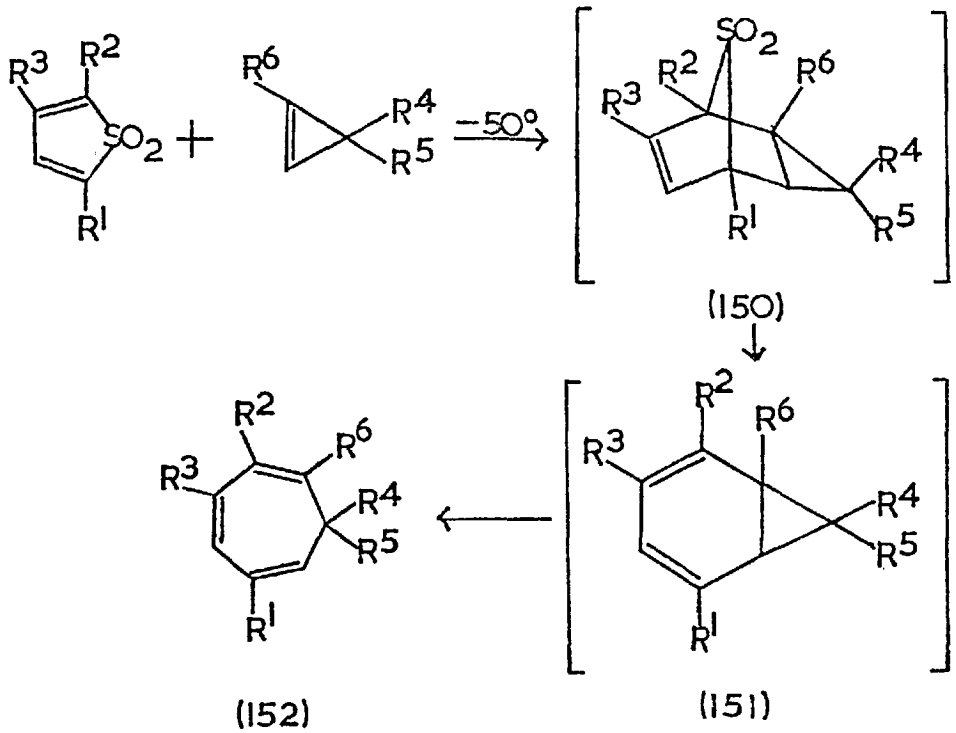
A new and potentially useful preparation of unsymmetrical 3,4-disubstituted thiophen dioxides has been accomplished[89] by thermal ring-closure of the diallenic sulphone (147) to give the 3-isopropenyl-4-isopropyl derivative (148). The 2,5-dibromo derivative (149) was made similarly.



(147)

(148) X= H
(149) X=Br

The analogies of the reactions of thiophen dioxides to those of cyclopentadienones ("cyclones") are very strong[90]. The thiophen dioxides are often more stable and more accessible than the corresponding cyclones; and their activity as dienes, followed by elimination of the sulphonyl bridge from the resulting adducts (the counterpart of the ready loss of the carbonyl bridge in cyclone adducts) rivals that of the cyclones. However, so far, the most useful synthesis involving thiophen dioxides has been a new preparative method for cycloheptatrienes (152) free of isomers, a difficult feat using conventional methods. A cyclopropene is reacted with a thiophen dioxide; the initial adduct (150) and the caradiene (151) were not observed in the NMR at -60°. The cycloheptatriene (152) was then obtained cleanly and in good yield[91].

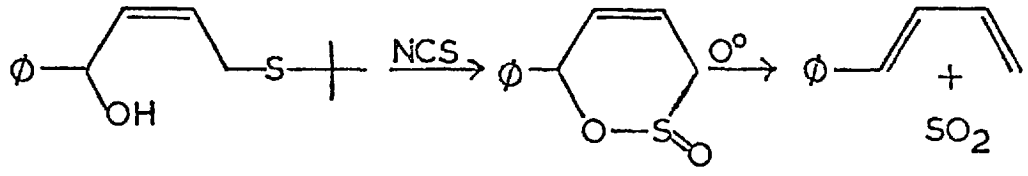


(150)

(152) (151)

The only limitation appears to be avoidance of excessive steric crowding in the transition state leading to (150).

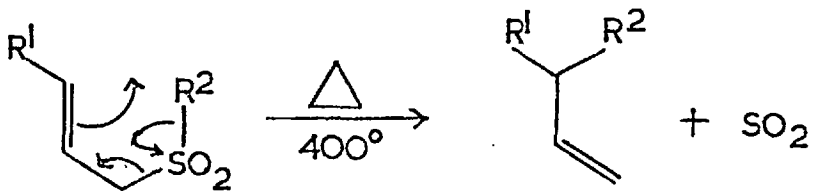
Two fragmentation reactions have been noted which bear a strong formal resemblance to sulpholene fragmentations. The internal sulphinate ester (154), made from sulphide (153), has been shown to decompose readily and stereospecifically at 0° to a diene and sulphur dioxide[92]. This appears to be a concerted process.



(153) (154)

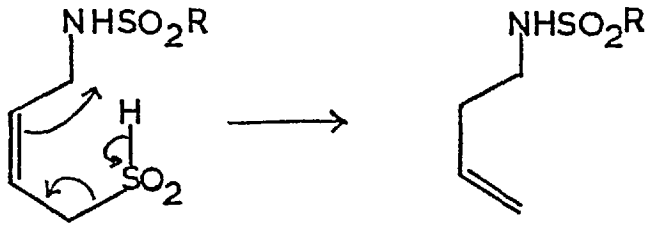
A comprehensive and stimulating survey of the whole field of pericyclic reactions[93] by Hendrickson led him to the discovery of the acyclic analogue of the sulpholene fragmentation. Allylic sulphone (155) underwent a thermal rearrangement to the olefin (156) by a formally concerted

process[94].



(155) (156)

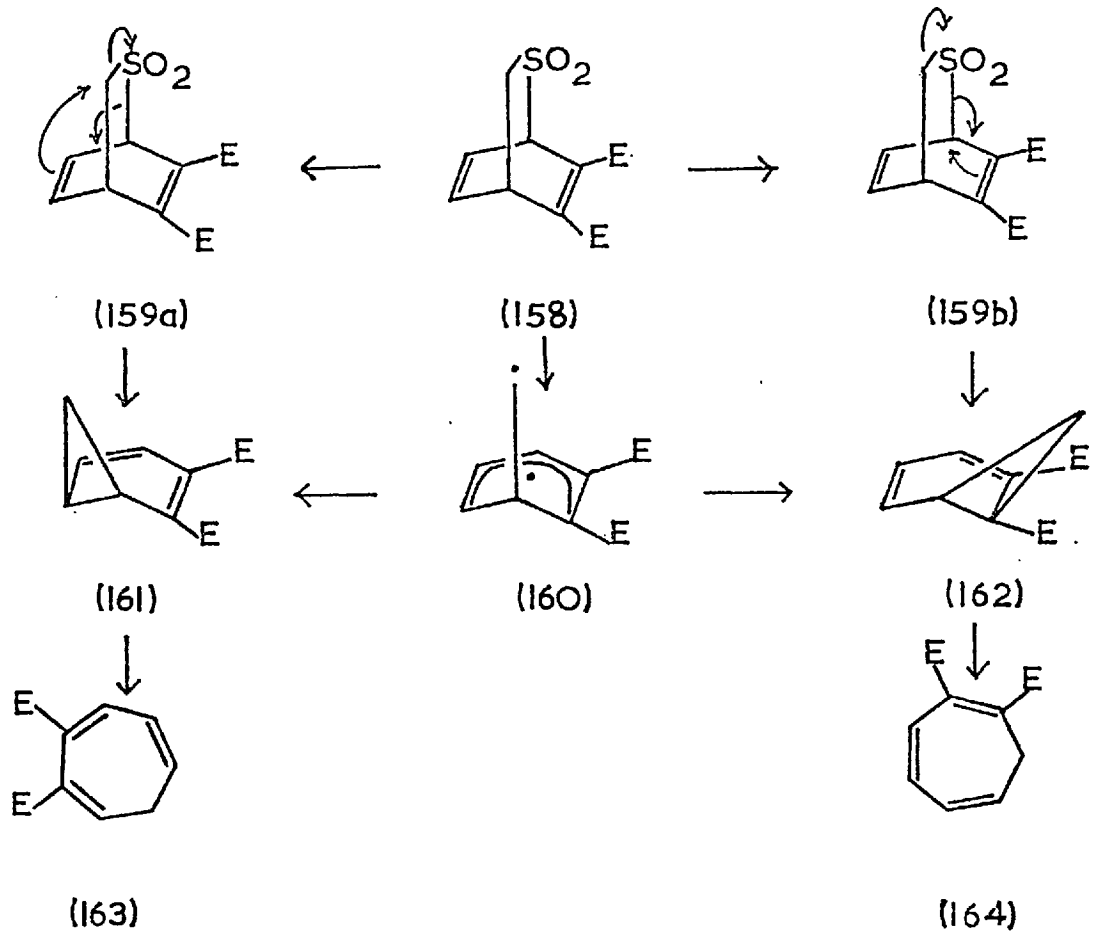
A closely analogous and very facile rearrangement has been observed for free allylic sulphinic acids (157)[95].



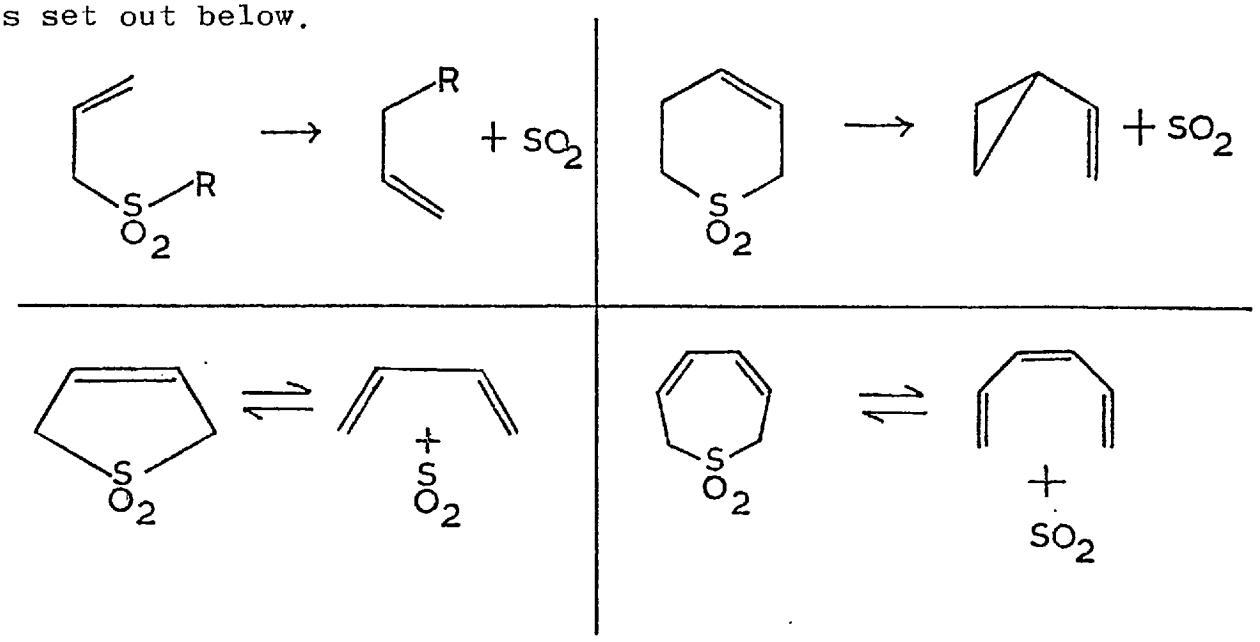
(157)

The reaction is not observed with the salts of the acids; according to kinetic and other data, the reaction is concerted and occurs via the usual cyclic transition state[96].

The homo-analogue of the sulpholene fragmentation has also been observed, though it is debatable whether it is a concerted process[97]. The bicyclic sulphone (158) gave a mixture of the cycloheptatrienes (163) and (164) via the norcaradienes (161) and (162) as intermediates. No chemical evidence was adduced to distinguish between a concerted [$\pi 2a + \sigma 2a + \sigma 2s$] mechanism (159) or a radical intermediate (160), both of which could give rise to the observed products[98].

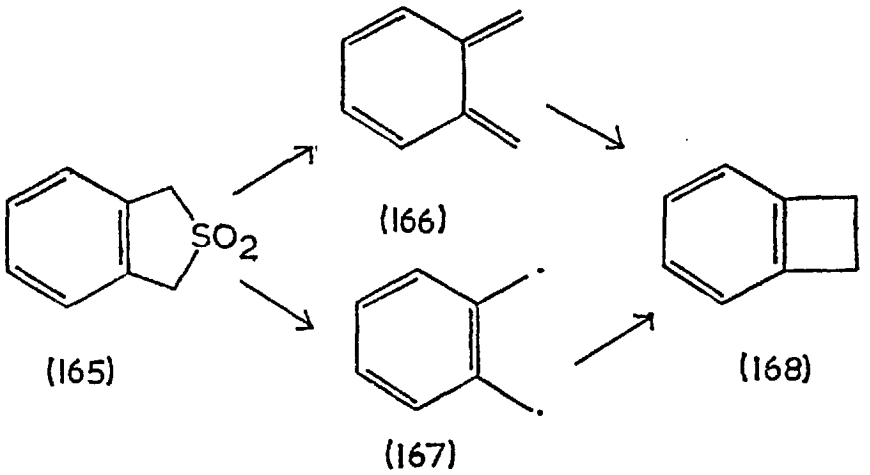


We can thus summarize these fragmentations into a family, as set out below.

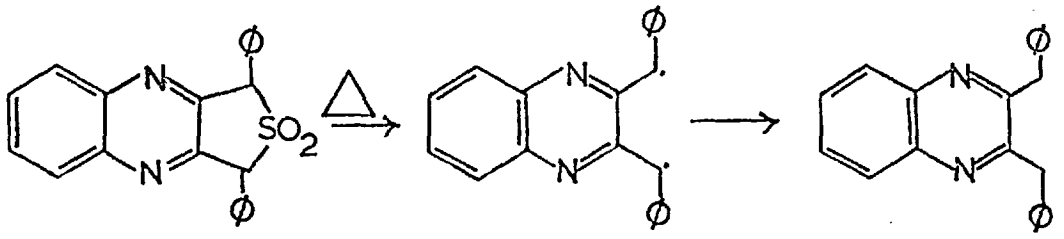


There is a vast chemistry of various more or less non-concerted fragmentations of "sulpholene-like" species, a few of which will be alluded to here. Most consist of

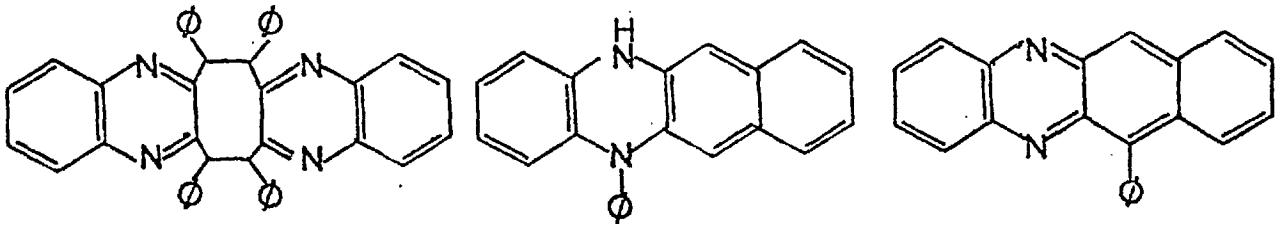
sulpholene rings [c]-fused to aromatic systems, where a concerted fragmentation of the sulpholene moiety is energetically unfavourable, due to disruption of the aromatic system. Much work has been done by Cava[99] on dihydrobenzo[c]thiophen dioxides (165) which give benzocyclobutenes (168) in good yield upon thermolysis. The relative contribution of the o-quinonedimethide (166) or the diradical (167) to the course of this, and the reverse, reaction is a matter of controversy and is in any case dependent upon the nature of the substrate.



In more complex systems in which formation of an o-quinonedimethide intermediate is not possible, a host of products resulting from the operation of the radical mechanism is observed. The quinoxaline (169) when thermolysed gives a mixture of four products; (170) arising from hydrogen abstraction from the solvent; (171) arising from radical cyclization onto the adjacent aryl group; a rearranged product (172); and a dimer (173)[100].

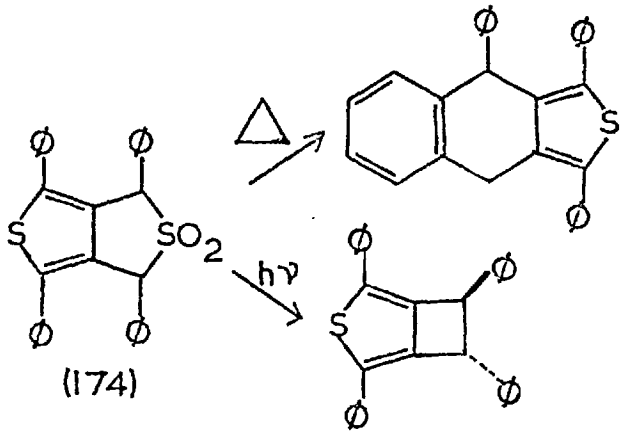


(169) (170)



(173) (172) (171)

With the thienothiophen (174), thermolysis gives a radical cyclization product (175); photolysis gives the thienocyclobutane (176)[101].



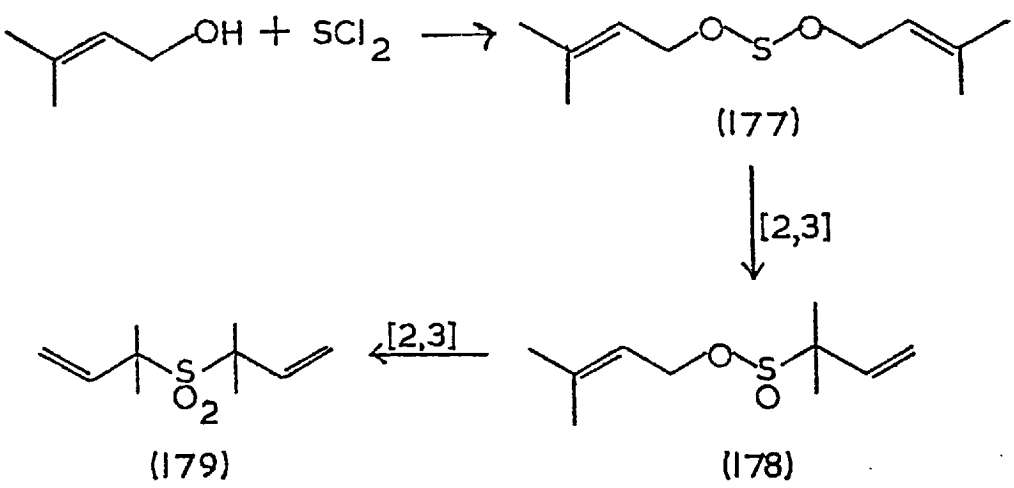
(175)

(174)

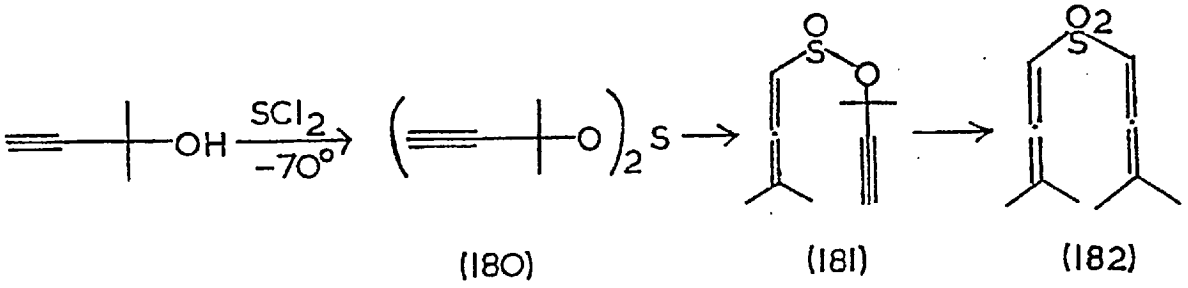
(176)

7. ALLYLIC SULPHINATE ESTER-SULPHONE REARRANGEMENT.

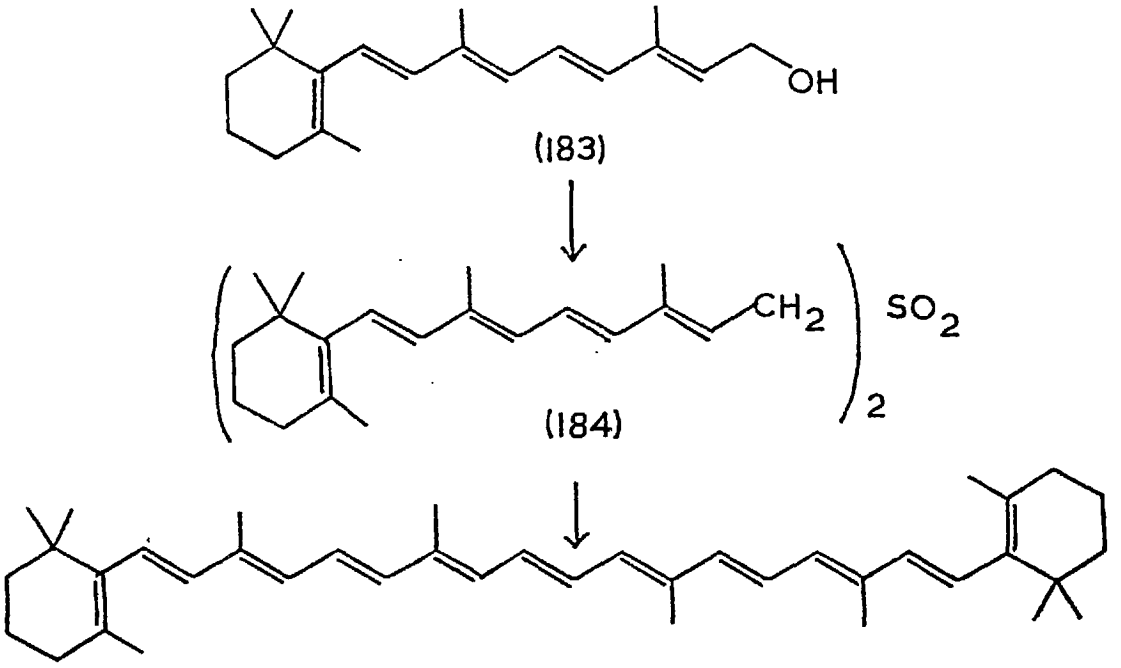
As a final word on sulphones, an important synthesis of allylic sulphones has come to light[102]. The reaction of sulphur dichloride and allylic alcohols gives initially a sulphoxylate (177), rapidly rearranging to a sulphinate ester (178) and finally the sulphone (179), probably via a sequence of [2,3]-shifts.



This has been applied to the synthesis of diallenic sulphones, of interest as precursors to thiophen dioxides (p.41). The propargylic sulphoxylate (180) rapidly rearranged to the allenic sulphinate (181) at -70° by a [2,3]-shift; refluxing in chloroform gave the diallenic sulphone (192)[89]. This was cyclized to thiophen dioxide (148) as previously described.



Büchi[103] has observed that mixtures of geometrical isomers result when suitably substituted allylic alcohols are used in this reaction, possibly due to isomerization of the sulphone rather than any lack of concertedness in the rearrangement. The reaction was used to prepare sulphone (184) from the Vitamin A derivative (183); this was converted to ß-carotene (185) in moderate yield by a Ramberg-Bäcklund rearrangement.



(183)

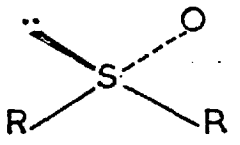
(184)

(185)

New methods of replacing the sulphonyl group by a double bond, to supplant the Ramberg-Bäcklund reaction, are currently attracting interest. Ring-contraction of sulpholans to cyclobutenes with Grignard reagents[104] or butyl-lithium and lithium aluminium hydride[105] is proving a fruitful entry into this strained small-ring system. It is probable that such methods can be extended into acyclic systems[105].

8. STRUCTURE OF SULPHOXIDES.

Sulphoxides are structurally similar to sulphones in many respects; the sulphur atom is again tetrahedrally hybridised with a lone pair at one apex (186).



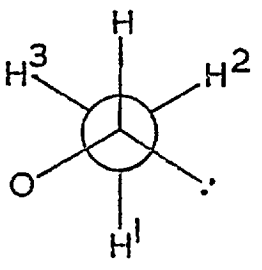
(186)

The barrier to inversion is large (ca. 20kcal.) and sulphoxides are thus easily obtained optically active. This

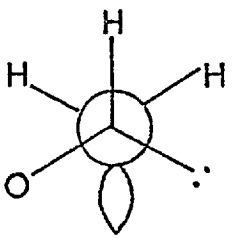
asymmetric property of the sulphinyl group is a characteristic of much sulphoxide chemistry.

The question of bonding in sulphoxides is still in a state of flux. It is fairly clear that the sulphur-oxygen bond is highly polar with little double bond character; the oxygen atom appears to be more nucleophilic than the sulphur atom[106], despite a recent assertion[107] that sulphur is the site of protonation of sulphoxides in "magic acid". This marked basicity of sulphoxides is in contrast to the almost total lack of nucleophilicity of sulphone oxygens.

The question of conjugation involving the sulphinyl group is likewise unsettled. The comparative study of the field or resonance effects, referred to in connection with sulphones[9] (p.13), seems to indicate a zero contribution to resonance effects of the sulphinyl group in aromatic systems. A recent non-empirical self-consistent field M.O. calculation on the hypothetical hydrogen methyl sulphoxide ($HSOCH_3$) and its anion (a model for that of DMSO)[108], indicated that (a) there was a total absence of any d-orbital effects and (b) that the α-protons in $HSOCH_3$ were diastereotopic; the acidities of the methyl protons in (187) followed the order $H^1 > H^2 > H^3$, i.e. the carbanion (188) was preferred, arising from the proton bisecting the sulphur-oxygen bond - lone pair angle is most acidic.

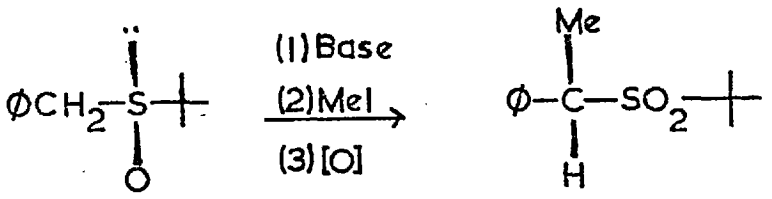


(187)



(188)

The carbanion formed by abstraction of an α-proton from a sulphoxide retains its initial configuration, making possible asymmetric synthesis by induction. If an optically active sulphoxide (189) is used in an alkylation reaction, the product (190) is optically pure[109].

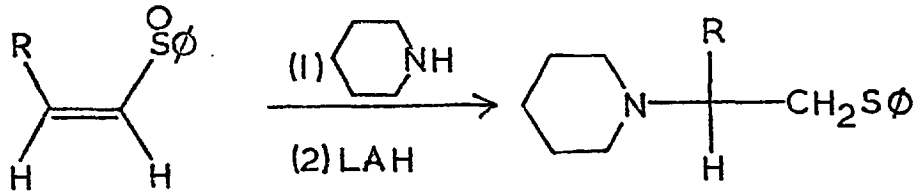


(189) (190)

The M.O. treatment referred to above has been criticized for neglect of solvation factors which apparently affect the relative acidities of the α-protons[110]. However, confirmatory evidence for the M.O. theory is also available[111]. We may sum up by saying that (a) the effect of resonance in the chemistry of the sulphoxide group is negligibly small; (b) the diastereotopic nature of the α-protons is indubitable, but M.O. theory, while discounting d-orbital participation, is not sufficiently realistic to explain fully the course of reactions in solution.

The chemical evidence for the above assertions is similar to that already cited for sulphones. Broaddus[112] and O'Connor[17] have shown that α,β-unsaturated sulphoxides are thermodynamically less stable than the β,γ-isomers, and that the energy profile for the equilibration of these isomers is very similar to that for the corresponding sulphone system[18]. Like sulphones, the double bond of α,β-unsaturated sulphoxides is reasonably activated towards nucleophilic attack. The

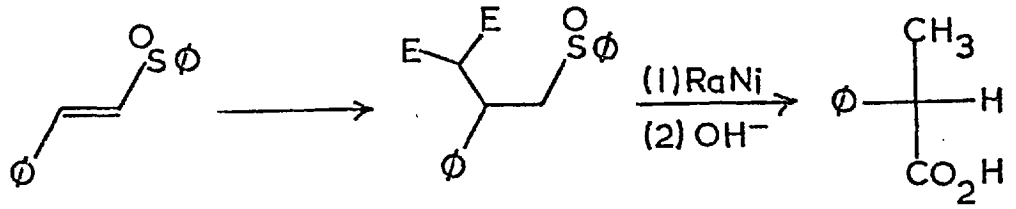
sulphoxide function exerts an asymmetric influence in such additions; optically active sulphoxide (191) gave adduct (192) with piperidine, of optical purity 74%[113].



(191) (192)

This can be rationalized by assuming that thermodynamic control operates; since the relation of the piperidine moiety to the developing carbanion on the α-carbon is fixed on conformational grounds, and the configuration of the carbanion relative to the sulphoxide function is fixed on electronic grounds, then the sulphinyl group can control the approach of the incoming nucleophile in a thermodynamically controlled situation.

The addition of the sodium salt of malonic ester to optically active sulphoxide (193) gave the adduct (194) convertible to the (-)-3-phenylbutyric acid (195) in 95% optical yield[114].

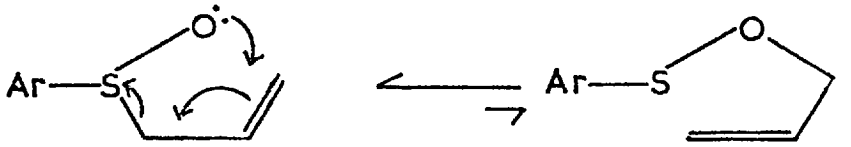


(193) (194) (195)

9. REARRANGEMENT OF SULPHENATE ESTERS.

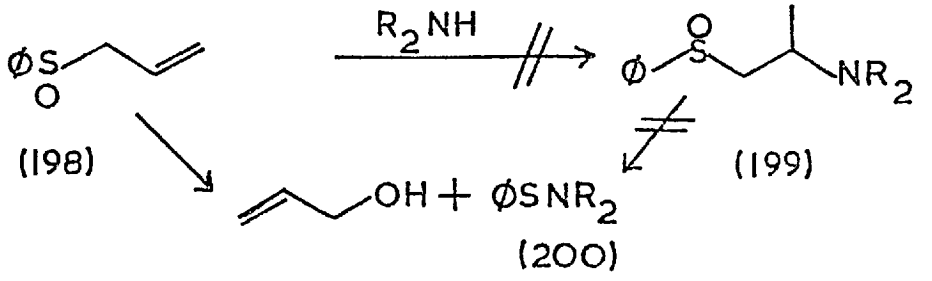
A reaction of great synthetic use in recent years has been the [2,3]-sigmatropic rearrangement of allylic sulphenate

esters. This was discovered by Mislow during a study of thermal racemization of benzylic and allylic sulphoxides. The racemization of the former was shown to be a radical process[115]. This was not the case for allyl-p-tolyl sulphoxide (196), as racemization required a very low activation energy and a high entropy of activation. The equilibration between (196) and the isomeric sulphenate ester (197) was assumed to occur, leading to loss of optical activity.



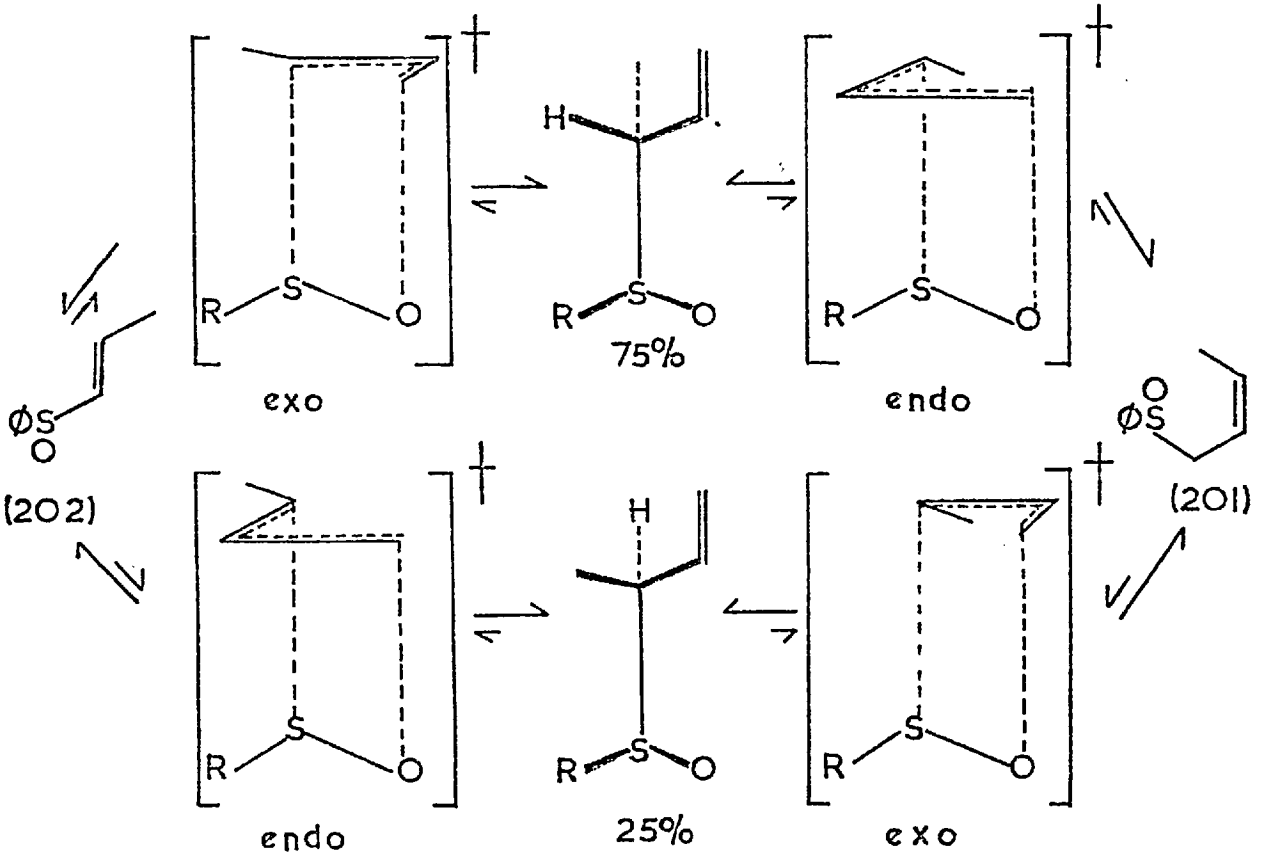
(196) (197)

Stirling[117] obtained an anomalous product from sulphoxide (198) and piperidine. None of the expected Michael adduct (199) (from isomerization and Michael addition) was obtained, but only allyl alcohol and the benzenesulphenamide (200). This was interpreted in the light of the equilibrium between sulphoxide (198) and the isomeric sulphenate ester, which, although present in vanishingly small concentration at equilibrium, is readily decomposed irreversibly using thiophilic reagents (secondary amines, triphenyl phosphite) and the equilibrium can thus be displaced in favour of the allylic alcohol.



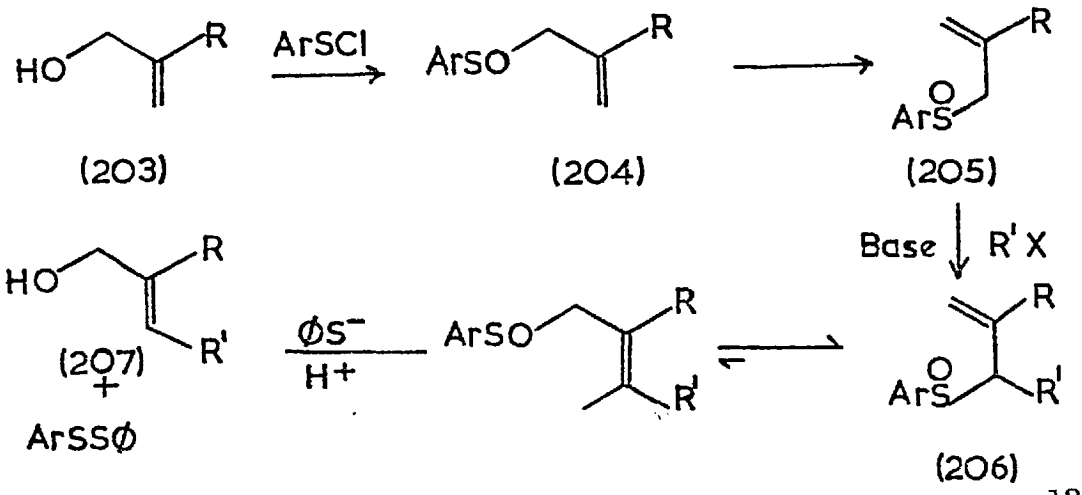
(198) (199) (200)

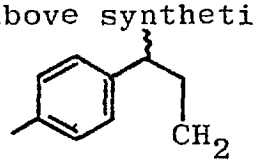
The kinetics of this reaction, and the effects of solvent and structure on reaction rates, have been studied by Mislow[118]. Rautenstrauch[119] has rearranged the cis- and trans-benzenesulphenate esters (201) and (202) and has found the reaction to be stereospecific; that product arising from a less hindered exo-transition state being preferred by a factor of 3:1.

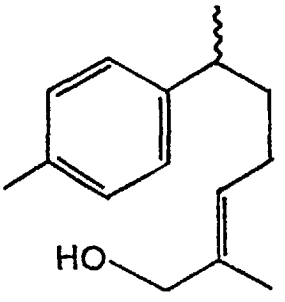


The applications of this reaction have been fruitful. Grieco has developed a stereospecific olefin synthesis which effectively transforms a 1,1-disubstituted olefin into a 1,1,2-trisubstituted olefin[120]. Allylic alcohols of type (203) are converted to the sulphenate (204) with p-toluene-sulphenyl chloride. This immediately gives allylic sulphoxide (205) at room temperature which is then alkylated to (206) (cf. alkylation of the similar sulphones, pp. 11 and 20). Treatment of (206) with a thiophilic reagent gives the allylic

alcohol (207) with a new substituent. The process is claimed to be entirely stereospecific.

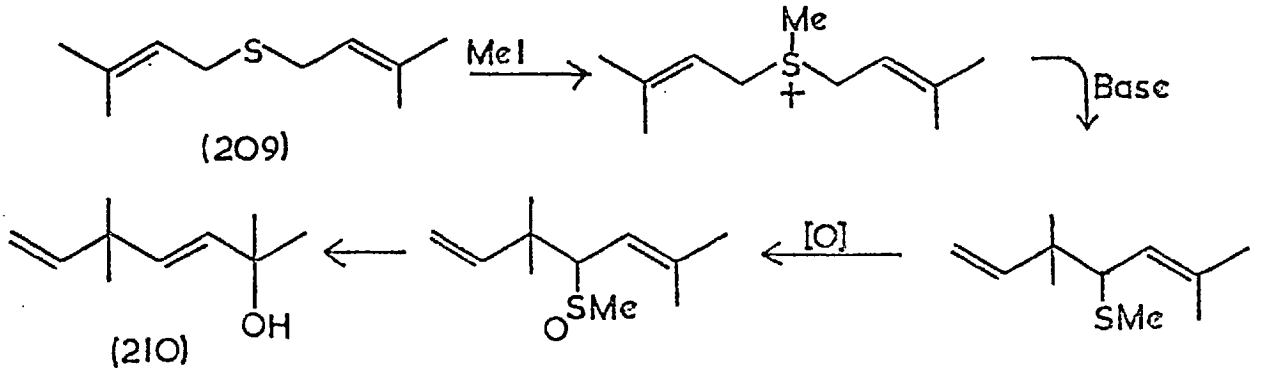


This was applied to the synthesis of (±)-nuciferol (208)[121] where the above synthetic scheme was carried out with $R=CH_3$, $R' =$  , which proceeded in 50% yield from the ß-methylcinnamic acid starting material.

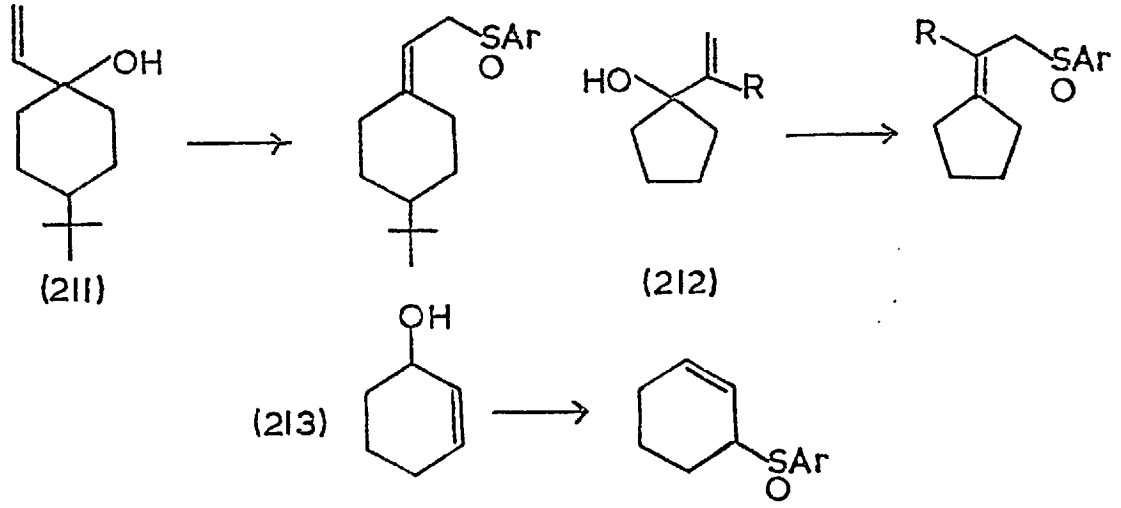


(208)

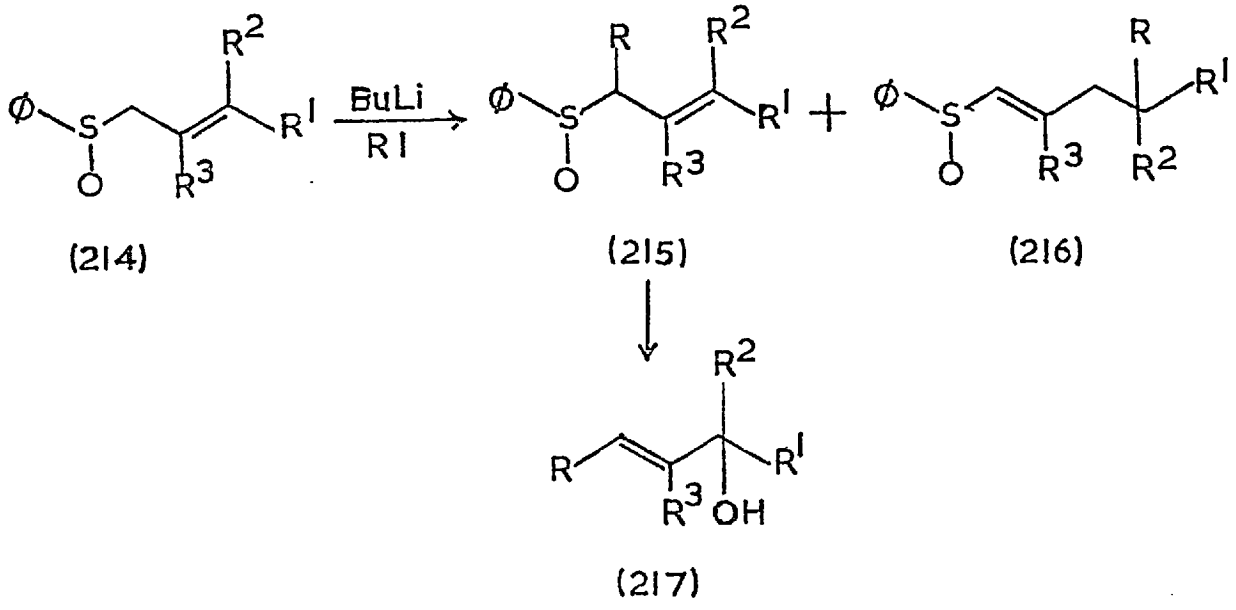
Evans[122] has neatly combined the properties of sulphonium ylids and those of sulphenate esters in a synthesis of yomogi alcohol (210) from the allylic sulphide (209) via the sequence shown below.



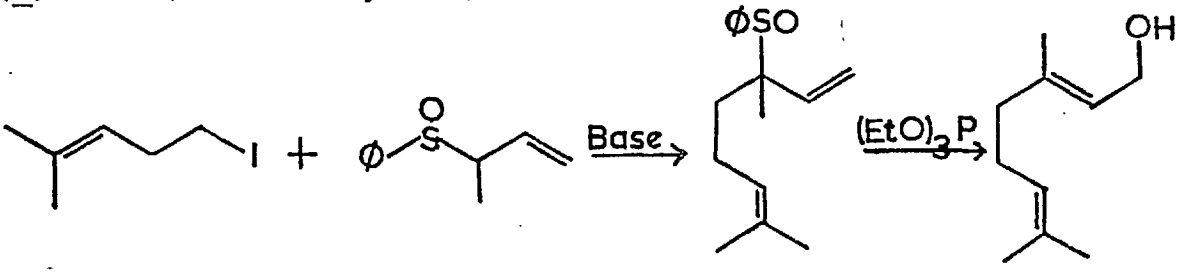
Evans has also completed an extensive study of the scope of this rearrangement. He found that exo- and endocyclic alcohols (211), (212) and (213) all undergo rearrangement with equal facility; the reaction was found to be reversible in all cases in the presence of thiophiles. Triethyl phosphite was seen to be particularly efficient[123].



A critical study of Grieco's[120, 121] work has shown that, besides α-alkylated products (206) a variable amount of γ-alkylation also occurs[124]. Compounds of type (214) were studied and the α/γ ratio (215)/(216) determined. Obviously, the greater the yield of γ-alkylation, the lower the yield of desired alcohol (217).



In cyclic cases, [e.g. (213)], α/γ was very high. With acyclic compounds (214) more variable yields of γ-products were found, despite the great prediliction of allylic sulphoxides for α-proton exchange[18]. The size of the α/γ ratio did not have any obvious rationale for a given substrate and alkylating agent, and was unaffected by solvent. In general, high α/γ ratios seem favoured by (a) R^1, $R^2 \neq H$; (b) $R=CH_3$ rather than any larger alkyl group. In another study[125], the stereospecificity of the rearrangement was rigorously established. Compounds of type (214) ($R^1=R^2=H$, $R^3=CH_3$) were found, after alkylatation and rearrangement, to give the E-isomer (217) with a specificity of 95%. To exemplify all these findings, a synthesis of geraniol (218) was undertaken. In the alkylation step, the α/γ ratio was 2.3; the rearrangement gave 90% geraniol (E) and 10% nerol (Z) in 55% overall yield.



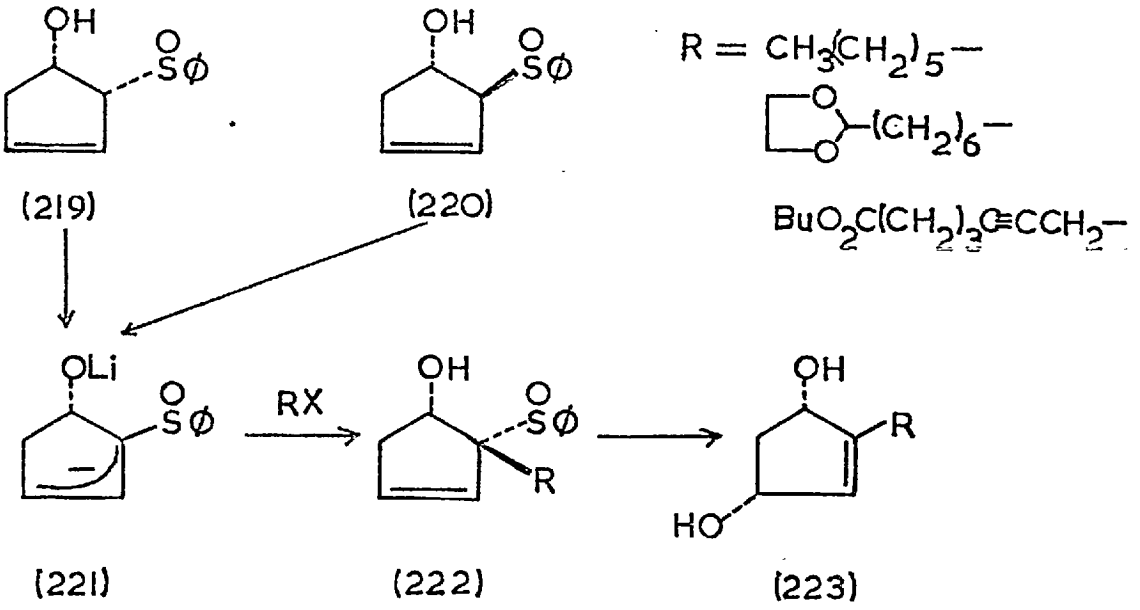
(218)

One may conclude that the synthesis is very useful for cyclic sulphoxides and reasonable for acyclic substrates as far as specificity in both steps is concerned. The main disadvantages are the unpredictable α/γ values and the low nucleophilicities of the sulphinyl carbanions, necessitating the use of very reactive alkyl halides.

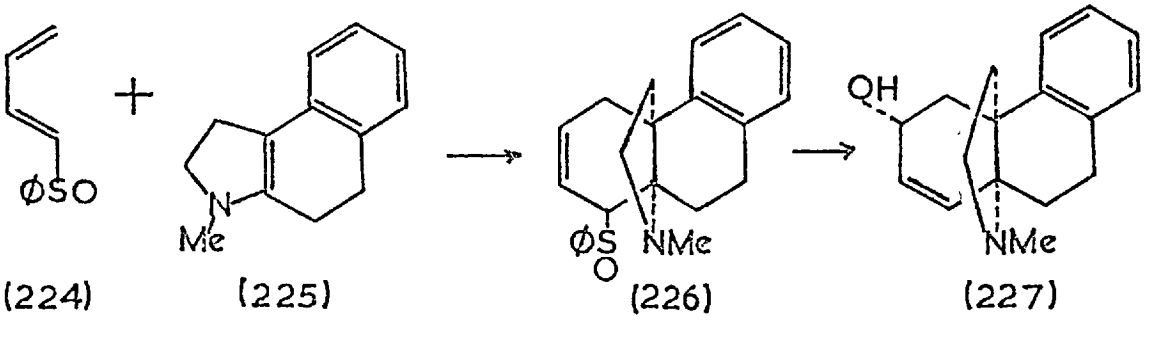
A mechanistic study[126] indicates the course of desulphurization of sulphenate esters by phosphites is similar to the

well-known Michaelis-Arbusov deoxygenation of peroxides by these reagents.

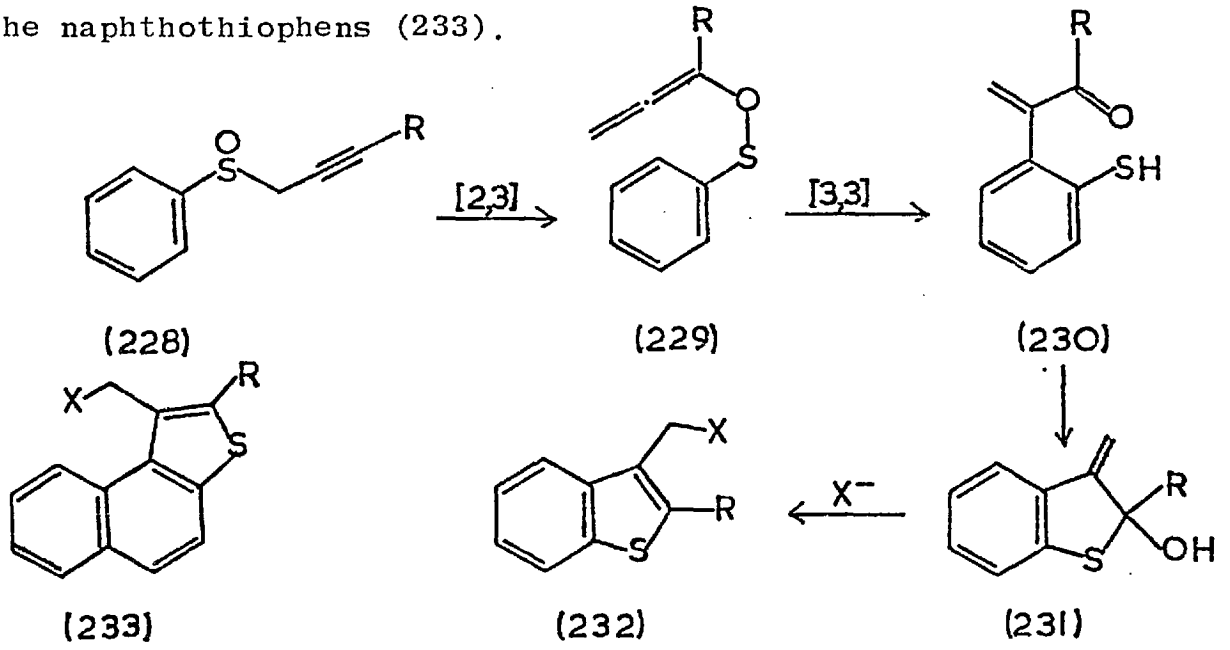
The high specificity of the alkylation/rearrangement with compounds of type (212) has found use in a prostoglandin synthesis[127]. Either cis- or trans-hydroxysulphoxides (219) and (220) are available from cyclopentadiene. Both isomers gave the same alkylated product (222), though whether the sulphinyl carbanion (221) is planar is doubtful. Rearrangement gave (223), a useful precursor of prostoglandins E and F, with correct stereochemistry.



An ingenious application of this rearrangement was the generation of the allylic sulphoxide through a Diels-Alder reaction. The dienyl sulphoxide (224) and the enamine (225) gave the adduct (226), which on rearrangement gave the allylic alcohol (227), an entry into the hasubanan alkaloid system[128].

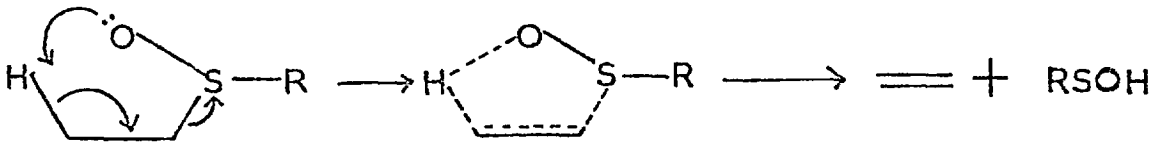


Finally, an elegant synthesis of benzo- and naphtho[b]-thiophens using the rearrangement of acetylenic sulphoxides, has been reported[129]. The readily-available sulphoxide (228) readily rearranges to give the allenic sulphenate (229) which gives the thiol (230) by a [3,3]-shift. Cyclization and aromatization then follow. The intermediate (231) can be detected in the absence of nucleophiles, and decomposed to the benzo[b]thiophen (232) by an appropriate nucleophile. The conversion of (228) to (232) may be accomplished in one pot in high yield. The synthesis is easily adapted to give the naphthothiophens (233).



10. PYROLYSIS OF SULPHOXIDES.

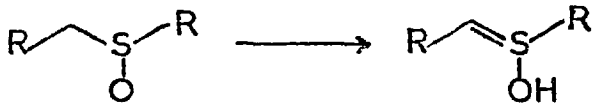
To complete this account of sulphoxides, let us survey the use of an overlooked reaction - the pyrolytic elimination of sulphenic acids from sulphoxides with a ß-proton. The reaction was discovered by Cram[130], who found it was a stereospecific syn-elimination, analogous to the known eliminations of acetates, xanthates, etc., and he proposed a cyclic transition state mechanism (234).



(234)

The reaction was found to proceed at a lower temperature than was necessary for acetates, and sulphoxides with ß-aryl substituents eliminated more readily than simple aliphatic sulphoxides[131]. DMSO as solvent was shown to give good yields with aliphatic sulphoxides[132].

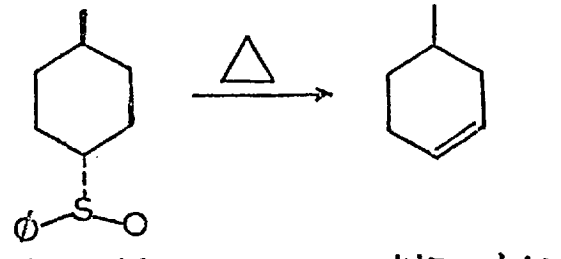
Other products have been observed during pyrolysis, for example, aldehydes and sulphides[133]. These were postulated to arise from the "enolized" form of the sulphoxide (235), a suggestion which, in the light of our discussion on the structure of sulphoxides, does not seem likely.



(235)

A base-catalysed elimination of sulphenate anion from sulphoxides has been observed[134], but has not found any synthetic application.

A very interesing application of this pyrolysis has been the elimination of the optically active sulphoxide (236) to give 4-methylcyclohex-1-ene of 70% optical purity[135].

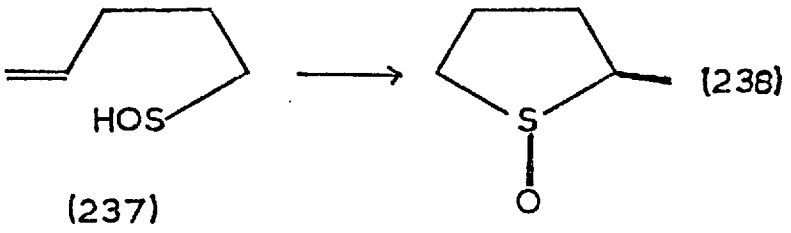


(+)R or (−)S (+)R or (−)S

(236)

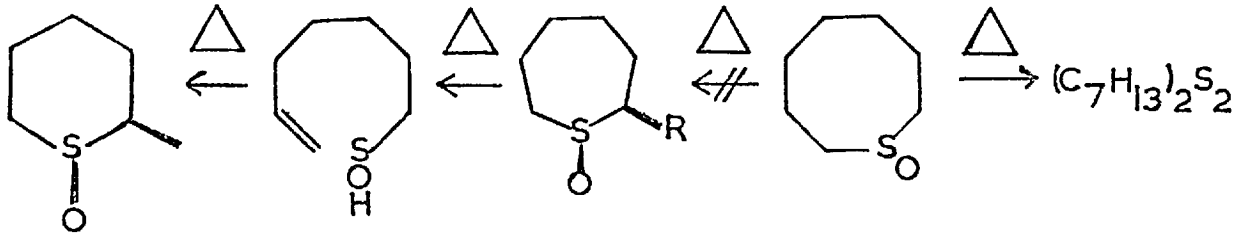
The stereochemistry of elimination from steroidal sulphoxides has also been examined[136].

The reverse reaction, i.e. addition of a sulphenic acid to a double bond, has been observed in intramolecular cases. It is stereospecific and appears to proceed via a five membered cyclic transition state[137], similar to the elimination reaction. The sulphenic acid (237) spontaneously cyclizes to give the cis-2-methylthiolan-1-oxide (238) specifically.



(237) (238)

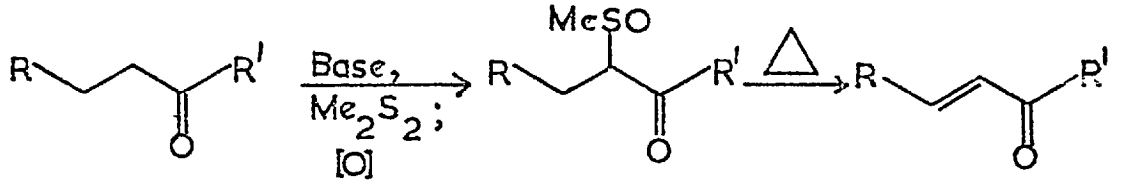
This provides an attractive route for stereospecific preparation of substituted thiolan-1-oxides. Similar processes have been observed in large-ring sulphoxides. If the ring is large enough to allow a five membered cyclic transition state, elimination occurs followed by side-reactions of the sulphenic acids thus formed[138]. The thiepan-1-oxide (239; R=H) rapidly forms cis-2-methylthiophan-1-oxide (241) by recyclization of the intermediate sulphenic acid (240).



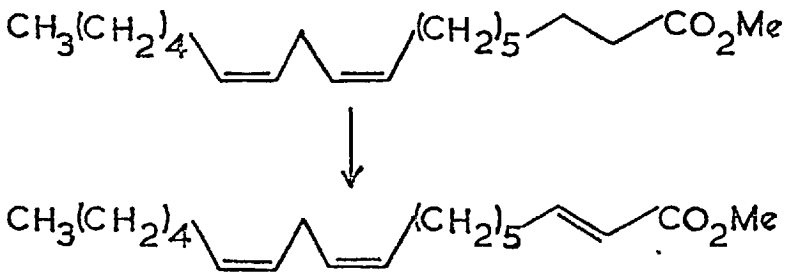
(241) (240) (239) (242) (243)

Thiocan-1-oxide (242) gives no ring-contracted product (239; R=CH_3). The decomposition of (242) is slow compared to side reactions of the pyrolysis products and only a mixture of isomeric acyclic unsaturated disulphides (243) is obtained.

The best synthetic use of the pyrolysis reaction has been made by Trost. A large variety of α,ß-unsaturated carbonyl compounds (ketones, esters, lactones, etc.) have been obtained[139] by "sulphenation" of the enolate of a carbonyl compound with dimethyl disulphide. Oxidation of the resulting α-methylthiocarbonyl compound and pyrolysis of the sulphoxide thus formed at 110° gave the unsaturated compounds in yields of 70-90%.



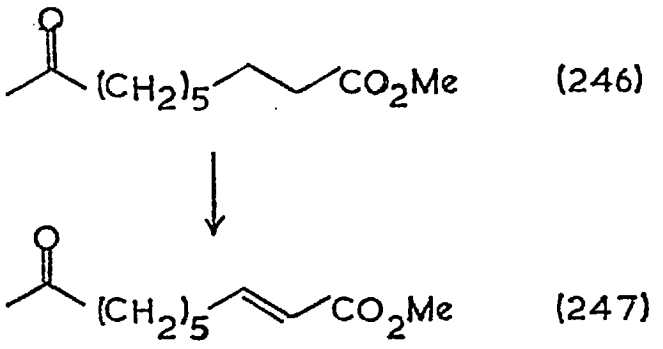
Trans-isomers appear to result; this fact was used in a synthesis of queen's substance and the pollen attractant of honey bees[140]. Linoleic ester (244) was subjected to the above synthetic scheme and the α,ß-unsaturated ester (245), the ester of the pollen attractant, was formed.



(244)

(245)

Similarly, ketoester (246) (from azelaic acid monoester) was transformed cleanly into the queen's substance (247).

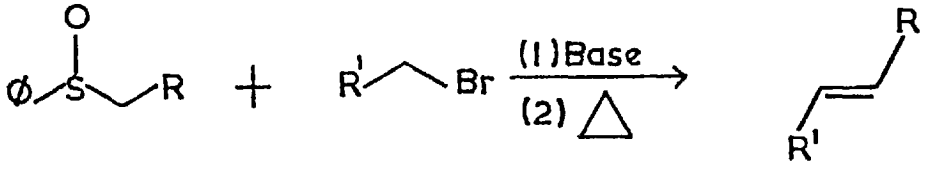


(246)

(247)

The presence of the α-carbonyl group enables the pyrolysis of such compounds as α-methylthiocarbonyl compounds to take place at lower temperatures than with unactivated sulphoxides.

A synthesis of functionalized olefins has been developed which offers great promise[141]. An α-substituted sulphoxide (248) is alkylated by a primary alkylating agent and the product decomposed by raising the temperature of the reaction mixture to reflux, affording trans-olefin (249) in a one-pot procedure.

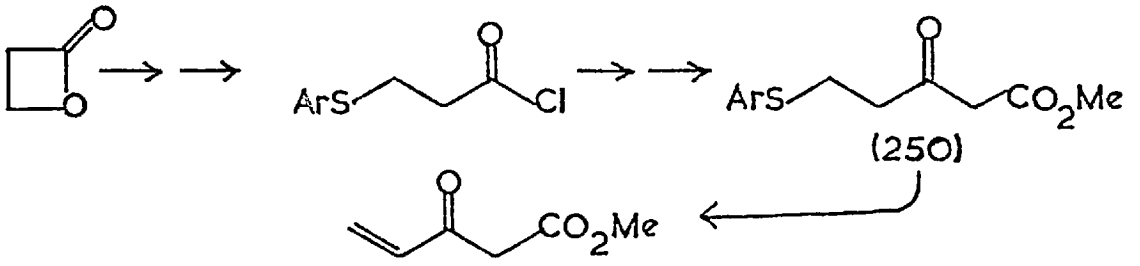


(248) (249)

The reaction has been investigated for R=Ar, SAr, SOAr, CN, so a variety of α,ß-unsaturated functions are available by a mild, one-pot method in high (50-90%) yield.

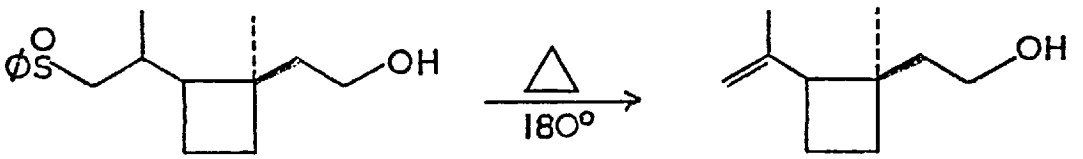
Other applications include the preparation of the terpene synthon (251). The ketoester (250), prepared as indicated, was oxidised and pyrolysed to give (251) in 75% overall yield. This useful compound is only available with some

difficulty by other routes[142].



(251)

Finally, a sulphoxide elimination formed a key step in the total synthesis of the bol-weevil sex attractant, grandisol (252). The isopropenyl group was introduced, without any isomerization, by a sulphoxide pyrolysis[143].



(252)

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DISCUSSION AND

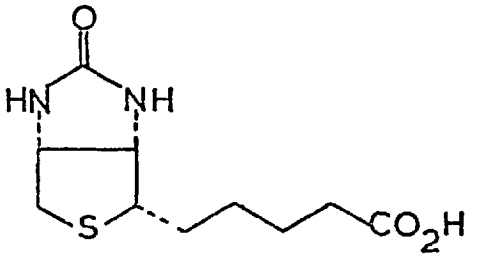
RESULTS

Preach not because you have to say something, but because you have something to say.

(Richard Whateley)

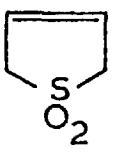
1. INTRODUCTION.

(+)-Biotin (1), Vitamin H, plays an important role in *in vivo* carboxylation-decarboxylation reactions[1, 2] and, as a growth factor in plants, is of great technical importance.

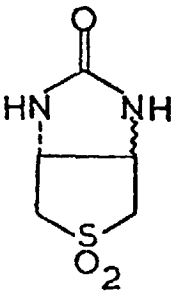


(1)

Of the numerous total syntheses of biotin[3], to date the most commercially viable has been the route of Goldberg and Sternbach[4] which starts from fumaric acid. An attractive alternative starting material appeared to be 3-sulpholene (2), made commercially from butadiene and sulphur dioxide, which has a double bond as a "handle" for the 3,4-positions, and which is activated in the 2-position by the sulphonyl group. A method was devised[3] whereby *cis*- or *trans*-fused cyclic ureas of type (3) could be made stereospecifically and in high yield from sulpholene.



(2)

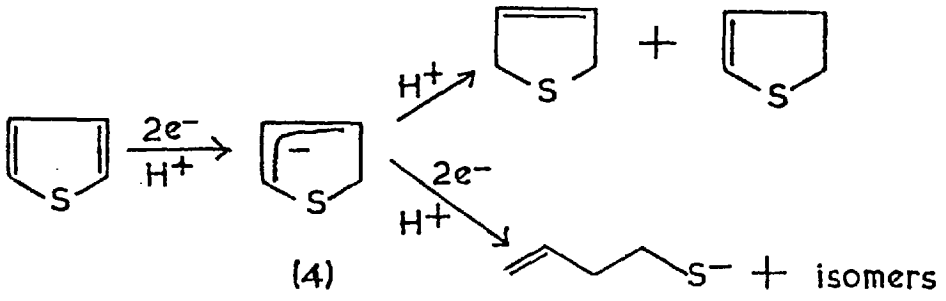


(3)

The principal drawback of this approach was the great difficulty of reduction of the resulting sulphones under mild conditions. The impetus for the work described in this thesis was the investigation of the sulphide or sulphoxide analogues of (2) as suitable starting materials for the synthesis of biotin-like molecules, where difficulties involving reduction were not envisaged.

2. DIHYDROTHIOPHEN CHEMISTRY.

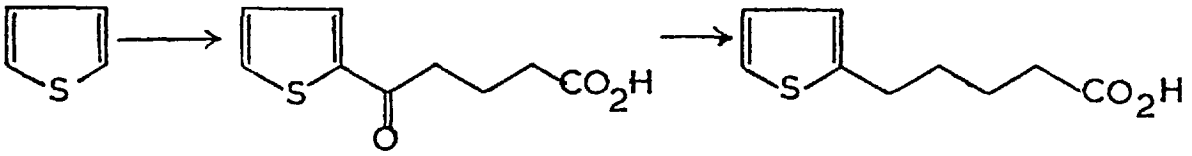
Most of the existing syntheses of dihydrothiophens are unsatisfactory; the earliest synthesis was accomplished[5] by reduction of thiophens by sodium and liquid ammonia. This gives very low yields, a mixture of the 2,3- and 2,5-dihydrothiophen isomers, and a large quantity of acyclic unsaturated thiols, arising from ring-opening of the intermediate anion (4) (Scheme 1).



Scheme 1.

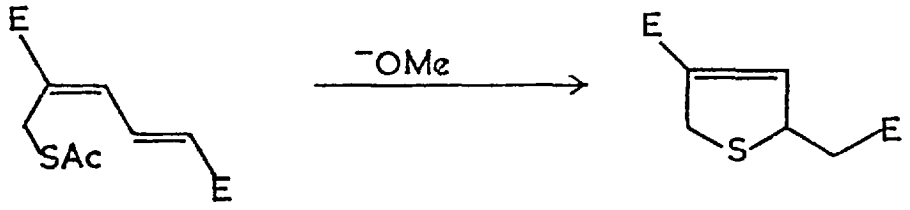
It was considered, however, that 2-alkylthiophens might be reduced more cleanly. The acid (6) was therefore synthesized from thiophen and glutaric anhydride with an aluminium chloride catalyst, followed by reduction of the resulting ketoacid (5) by hydrazine and potassium hydroxide. Attempted reduction of this acid with sodium or lithium in liquid ammonia gave mixtures of saturated products and starting

material; no vinylic protons were observed in the NMR, and this method was not pursued further.



(5) (6)

A synthesis of functionalized dihydrothiophens was reported, using an intramolecular Michael addition. The thiolacetate (7) was hydrolysed to generate the thiolate anion which spontaneously cyclized to the dihydrothiophen (8)[6].

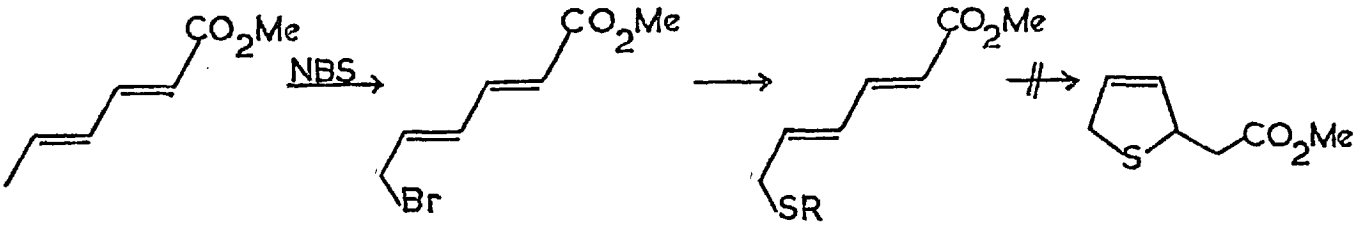


(7) (8)

An attempt was made to apply this method in the sorbic acid series (Scheme 2). Bromination[7] of trans, trans-methyl sorbate (9) proceeded only with difficulty without solvent at 120° with N-bromosuccinimide. At higher temperatures, only tars were obtained. The bromination did not give reproducible results; on distillation, unreacted methyl sorbate was obtained, as well as fractions containing a complexity of allylic methyl signals in the NMR, suggesting vinylic bromination is a favourable reaction under the harsh conditions used. The yield of allylic bromide (10) was low, and it is probable that high yield procedures previously

reported give mixtures of allylic and vinylic bromides[8].

Scheme 2.

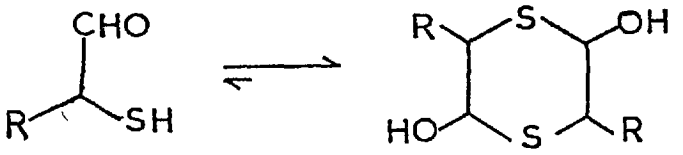


(9) (10) (11) R=Ac (12) R=H (13)

Treatment of (10) with potassium thiolacetate in DMF gave the thiolacetate (11), after chromatographic purification, as a yellow, evil-smelling oil. Hydrolysis of (11) with methanolic hydrogen chloride gave a complex mixture, amongst which the thiol (12) could be detected as an upfield triplet in the NMR, slowly exchanging with D_2O. No signals attributable to the dihydrothiophen (13) were observed; although cis-trans isomerization was a possible process, especially at the NBS stage, the known instability of any isomers of sorbic acid, with respect to the all-trans compound[9], makes such an isomerization thermodynamically unlikely.

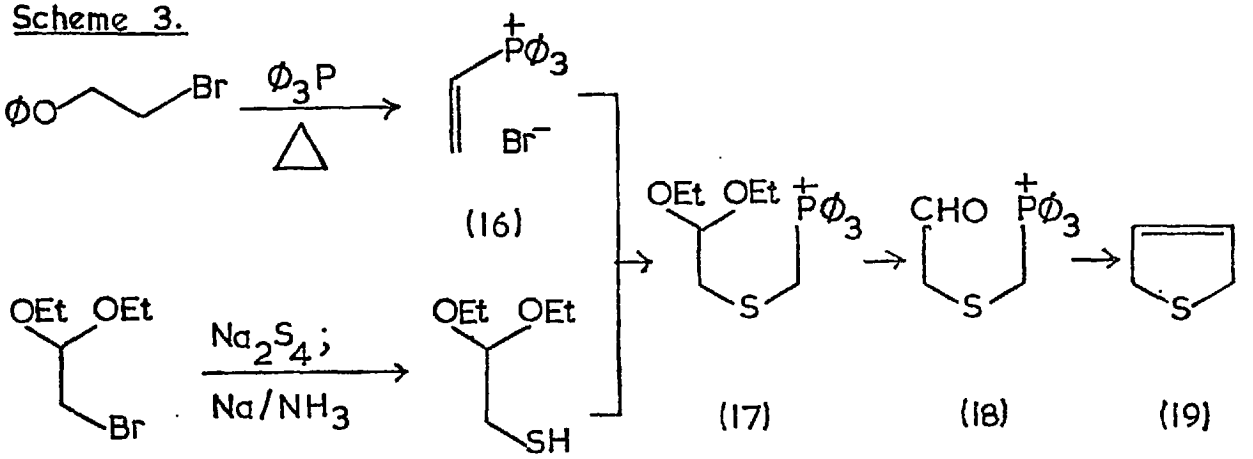
In the Review section, a dihydrothiophen synthesis, using an intramolecular Wittig reaction, was described. This appeared useful for the preparation of 3-substituted dihydrothiophens from α-mercaptoketones. Since α-mercaptoaldehydes exist entirely in the dimeric 2,5-dihydroxy-1,4-dithian form (14), this synthesis was adapted using mercaptoacetal (15) from bromoacetal by formation of a tetrasulphide and reductive cleavage[10]; vinyltriphenylphosphonium bromide (16) was prepared from 2-phenoxyethyl

bromide[12] (Scheme 3).



(14)

Scheme 3.

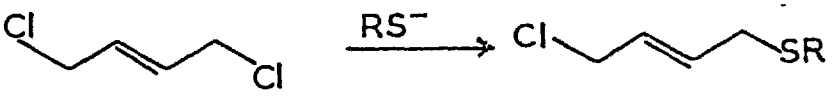


(15)

Addition of one drop of triethylamine to a mixture of (15) and (16) in methylene chloride gave the adduct (17) exothermally. This could be hydrolysed to the free aldehyde (18) by 2N hydrochloric acid in THF. These phosphonium bromides were water-soluble syrups which would not crystallize; an aqueous solution of tetraphenylboron sodium, when added to an aqueous solution of these salts, gave a crystalline precipitate of the tetraphenylboron complex which was suitable for characterization. Aldehyde (18) was treated with pyridine and triethylamine to give dihydrothiophen (19) in poor yield (Scheme 3). Subsequently, an adaption of this synthesis was published which uses the dimers (14) directly in a one-pot procedure, which gives fair yields[13]. However, the route from mercaptoacetal was not suited to the

preparation of (19) in quantity.

Trans-1,4-dichlorobut-2-ene (20) is a commercially available substance which seemed to offer opportunities as a starting material. Treatment of this compound with one equivalent of a sulphur nucleophile gave compounds (21) and (22) (from thiolate anions in methanol) and (23) (from potassium thiolacetate in DMF). A small amount of starting material and 1,4-disubstituted compound made purification of these products by distillation or chromatography difficult, so they were characterized as the isothiuronium picrates. Compounds (21)-(23) are unpleasant-smelling oils which are vinylogues of the sulphur mustards, though they apparently show little physiological activity.



(21) R = $C_4H_9^n$
(22) R = ϕCH_2
(23) R = Ac
(24) R = H

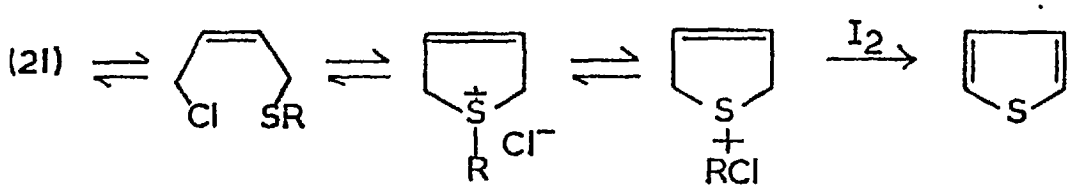
(20)

Thiolacetate (23) yielded the thiol (24) upon hydrolysis with methanolic hydrogen chloride, as an evil-smelling oil, very subject to aerial oxidation. Upon standing, it formed a solid polymer. Treatment with base did not effect any cyclization to (19).

It was hoped that, if an equilibrium could be set up between (21) and its cis-isomer, then removal of the cis-isomer by formation of cyclized products such as (25) and (19) by a sequence which was irreversible, or nearly so, should result in clean decomposition of the sulphide (21).

At temperatures up to 150°, (21) was recovered unchanged after prolonged pyrolysis in a sealed tube. However, if a trace of iodine was added, NMR analysis of the product showed a clean conversion to thiophen and n-butyl chloride occurred at 150°, with very little tar formation. It was not certain whether the iodine was acting as a cis-trans isomerization catalyst, or as a dehydrogenating agent. Use of free radicals as catalysts (galvinoxyl or diphenylpicryl hydrazide) gave no conversion, so the latter function of the iodine would seem more likely. In that case, the irreversible step is a dehydrogenation, which perhaps indicates that all the other equilibria were well over to the left under the conditions used. (Scheme 4).

Scheme 4.



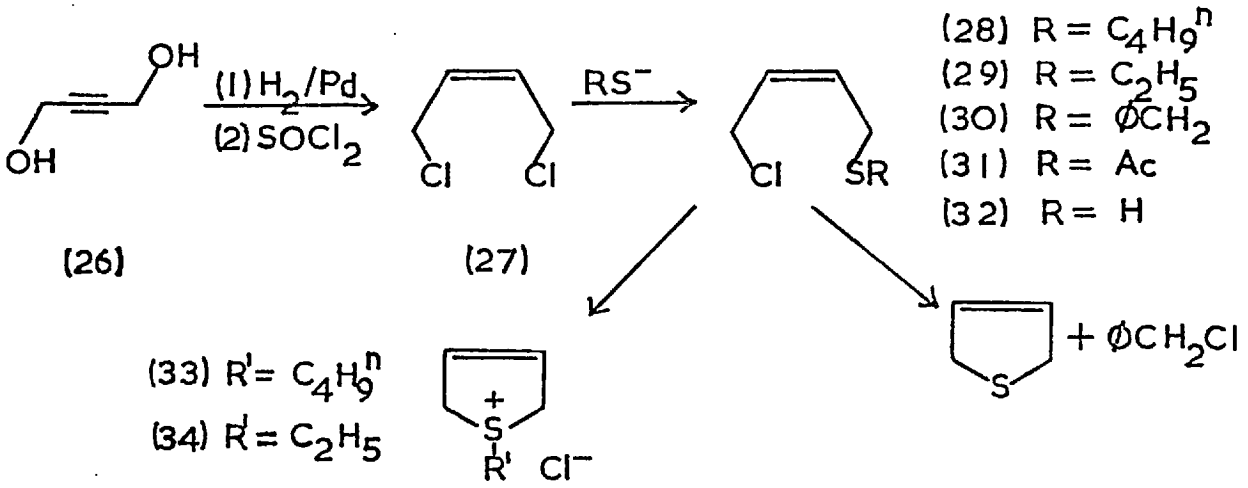
(25)

Pyrolysis of the benzyl derivative (22) in toluene or DMF, without an iodine catalyst, gave some dihydrothiophen (19) and benzyl chloride, reflecting the comparative readiness of the presumed S-benzyl intermediate (25) to dissociate. The reaction in this case, however, was much less clean than the pyrolysis of (21). The reaction products were easily identified by NMR.

Bromination of (21) to allow free rotation/cyclization gave an unstable yellow solid addition product with one mole of bromine, which rapidly decomposed to a red tar with evolution

of hydrogen bromide.

Attention was next directed at the cis-isomers of (21), etc. Cis-1,4-dichlorobut-2-ene (27) was made from the readily available butyne-1,4-diol (26) by catalytic hydrogenation and treatment of the product with thionyl chloride. Reaction of (27) with various sulphur nucleophiles gave the same series of compounds as before (Scheme 5).



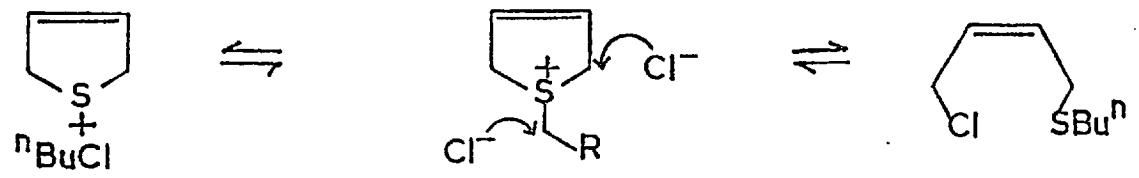
Scheme 5.

Dealing with the thiolacetate (31) first, hydrolysis as before gave the thiol (32). This was unstable and rapidly decomposed to tars. Treatment of (32) with triethylamine or pyridine failed to effect cyclization to the dihydrothiophen' (19), but gave only polymers.

Despite this result, the cis-stereochemistry of this series of products was in little doubt, as the NMR normally showed a pair of overlapping triplets in the vinylic region, unlike the highly complex pattern observed with the trans-isomers. Furthermore, the isothiuronium picrate of thiolacetate (31) had a different melting point and crystalline form compared to the trans-derivative. Most convincingly, the alkyl sulphides (28) and (29) cyclized rapidly and spontaneously

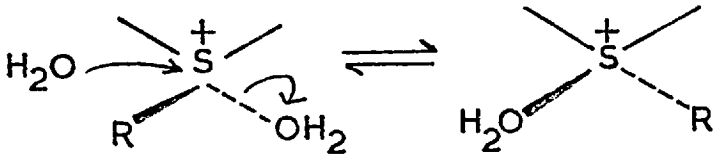
at room temperature to give the colourless, crystalline, deliquescent dihydrothiophenium salts (33) and (34). These were characterized as the non-deliquescent tetraphenylborate complexes. With the benzyl compound (30) no cyclic salt formation was observed, but only a slow decomposition with dihydrothiophen (19) and benzyl chloride being observed among the products. This supports the assignment of such salts as (33) as intermediates in the pyrolysis of the trans-sulphides.

In the NMR spectrum of the sulphonium salt (33) recorded in deuteriochloroform, the vinylic protons are very weakly coupled to the methylene protons, and resonate as a broadened singlet. This absence of coupling is observed in the sulphone (2) and the sulphide (19), in both of which the vinylic and methylene protons resonate as a sharp singlet; this fact was useful for detecting (19) in complex mixtures. The methylene protons in (33), α to the tetrahedral sulphonium centre, are non-equivalent and appear as a broadened AB quartet with a typical geminal coupling of 16Hz. Unaccountably, this pattern collapsed to a much more tightly-coupled multiplet when the spectrum was recorded in D_2O. The energy barrier to inversion of sulphonium salts is large, especially when carbon-sulphur bond fission is required. For this reason, optically active sulphonium salts may be isolated. In this case, in D_2O, the greater mobility of the chloride counterion could perhaps allow inversion to occur rapidly by attack of Cl^- on the n-butyl group or upon the ring methylene (Scheme 6).

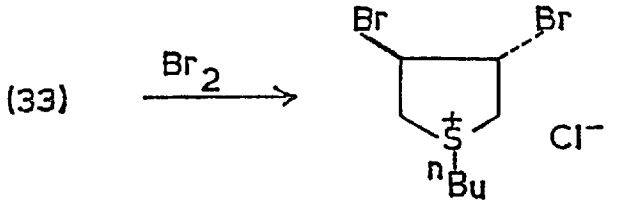


Scheme 6.

Whether this could result in the observed spectrum is difficult to predict. The methylene multiplet in D_2O is quite sharply resolved, so that if exchange occurs, it is fast on the NMR timescale. This sharpness of resolution would count against any type of solvent effect, such as solvation followed by S_N2 inversion as shown, as this would give rise to a broadened singlet resonance.

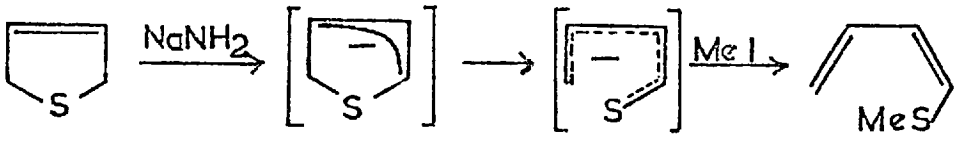


The salt (33) readily added bromine to give the dibromide (35). Attempts at nucleophilic displacement by amines upon these bromine atoms were unsuccessful, as were attempts to form the bromohydrin from (33). Since these compounds are not amenable to chromatographic techniques, and are difficult to extract from aqueous solution, their synthetic uses were thus limited.



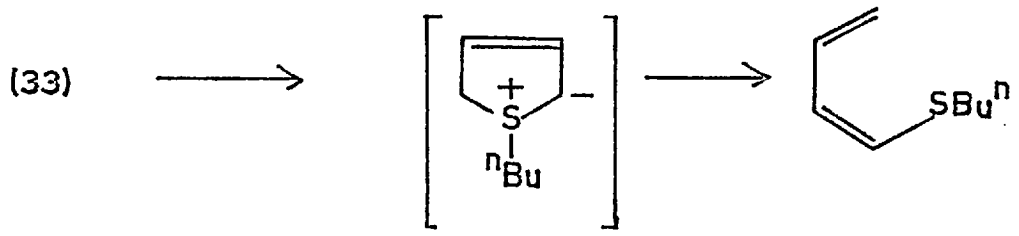
(35)

It has been observed that 2,5-dihydrothiophen undergoes a ring-opening reaction with sodamide in liquid ammonia[14]. The anion (36) could not be detected as such, but the acyclic form (37) was trapped as the butadienyl sulphide (38).



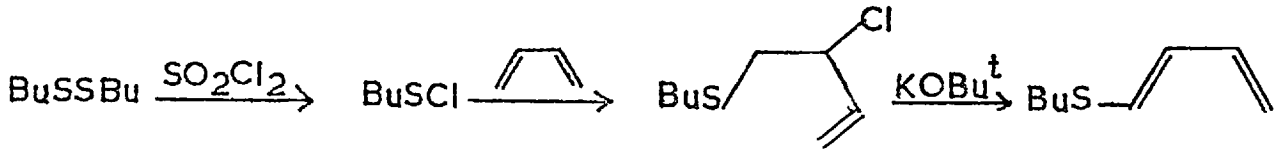
(36) (37) (38)

A fragmentation reaction has been observed for 2,5-blocked dihydrothiophenium salts[15]; the unblocked compound (33), in which the methylene protons are much more strongly activated than in (19), gave the dienyl sulphide (40) when treated with basic ion-exchange resin in methylene chloride, through the intermediacy of the ylid (39).



(39) (40)

Trans-dienyl sulphides can be obtained by addition of thiols to enynes, but a more convenient synthesis of authentic trans-isomer of (40) involved addition of n-butylsulphenyl chloride (41) to excess butadiene to give the mono-Markownikov adduct (42)[16], which was dehydrohalogenated to (43) (Scheme 7).



(41) (42) (43)

Scheme 7.

The separate identity of (40) and (43) was difficult to establish. Both dienes (40) and (43) exhibited intense UV

absorptions at ca. 286nm. Despite a report to the contrary[17], both were surprisingly unreactive towards the usual electron-poor dienophiles. Diene (40) eventually produced a mixture of acetophenone and butanethiol, when heated neat in methyl vinyl ketone. Initial adduct formation is rapidly followed by decomposition to these products. The R_f values and G.L.C. retention times of (40) and (43) were too similar to prove conclusively that they were indeed different compounds. In their NMR spectra, both had similar, though in this case, significantly different, 2-proton multiplets at ca. δ5, highly characteristic of terminal methylene groups. The complexity of the other vinylic signals makes analysis very tentative, but the more complex spectrum of (43) supports the cis-trans assignment. In (40), H^1 appears to resonate as a broad singlet, as $J_{1,2}$ would be expected to be small. A consistent, though tentative, analysis is set out below in Table 1.

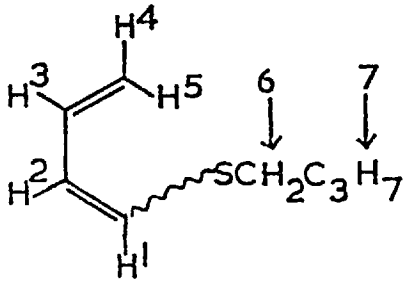
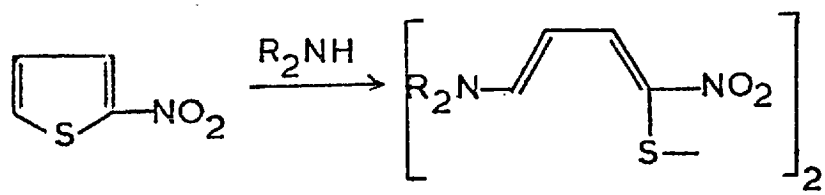


TABLE 1.

Cis-isomer, (40)		Trans-isomer, (43)		Proton
Shift, δ	Area	Shift, δ	Area	
6.20-6.90	1H, m	6.3-7.1	1H, m	3
6.06	1H, bs	6.15	1H, d; $J_{1,2}$=9Hz	1
6.12	1H, d; $J_{2,3}$=5Hz	6.18	1H, dd; $J_{2,3}$=6Hz	2
5.10-5.40	2H, m	4.8-5.3	2H, m	4,5
2.69	2H, t	2.83	2H, t	6
0.7-2.1	7H, m	0.8-2.0	7H, m	7

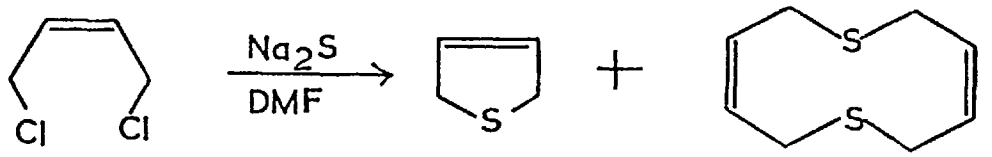
The IR spectra of both isomers were very similar, and gave few clues to a positive assignment of stereochemistry.

If, as seems at least possible, the cis-isomer is obtained from (33), then the ring-opening is presumably concerted. This forms a very interesing supplement to the concerted fragmentations of sulpholenes discussed in the Review section (p.27). It is notable that recent work on the ring-opening of 2-nitrothiophen[18] with amines to give dienyl disulphides (44), which proceeds via a dihydrothiophenium intermediate, gives exclusively products with the Z-configuration of (44), corresponding to the cis-configuration assigned to (40). Since the simplified spectral data of (44) leave no room for doubt about the stereochemistry, it seems likely that the ring-opening of the cyclic sulphonium salts is indeed synchronous.



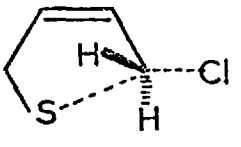
(44)

Treatment of the cis-dichloro-compound (27) with sodium sulphide in DMF, gave reasonable (30%) yields of the 2,5-dihydrothiophen (19), isolated by steam distillation. Also isolated in the later stages of this distillation were some white crystals. These showed a one-proton triplet at δ5.46 and a two-proton doublet at δ3.12 in the NMR, and analysed correctly for $C_8H_{12}S_2$; its melting point was similar to a tetrahydrodithiecin (45) isolated from the reaction of (27) and cis-but-2-ene-1,4-dithiol[19]. The compound was thus identified as (45).

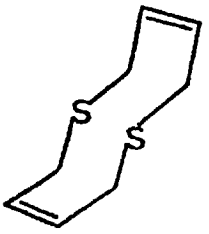


(19) (45)

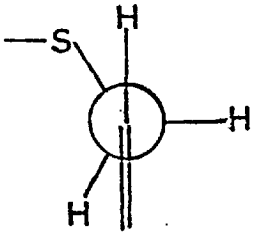
Although this provides a convenient synthesis of (19), a rubber-like polymer is the major product of the reaction, a surprising result in view of the apparently favourable stereochemistry. However, Eschenmoser has found several cases[20] where exocyclic S_N2 reactions at tetrahedral carbon atoms which can proceed through formally attractive 5- or 6-membered transition states, are none the less forbidden, apparently due to the inability of the incoming nucleophile, the carbon atom and the leaving group to attain collinearity; such reactions tend to occur intermolecularly. Quite possibly, this is the situation in this case, when the conformational rigidity of the double bond and the steric size of the sulphur atom may be unfavourable. The preference of the thiol (32) for polymerization rather than cyclization, in the presence of base, may be due to this cause. It is noteworthy that the more flexible 1,4-dichlorobutane system cyclizes very readily with no polymer formation.



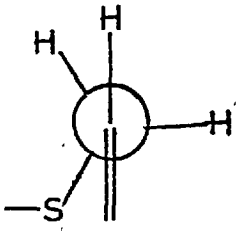
The NMR spectrum of (19) shows no coupling between the methylene and vinylic protons, both of which resonate as singlets. The coupling observed in (45) appears to be a conformational effect[21], as (45) exists in an extended conformation (46), in which the methylene and vinylic protons have the relative conformation (47), as opposed to conformation (48) in dihydrothiophen (19).



(46)

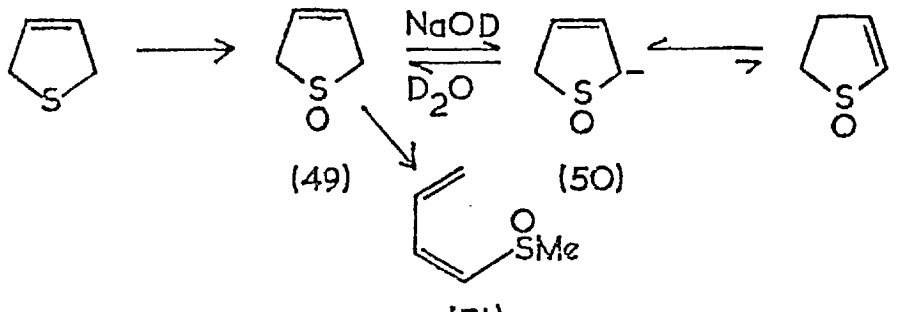


(47)



(48)

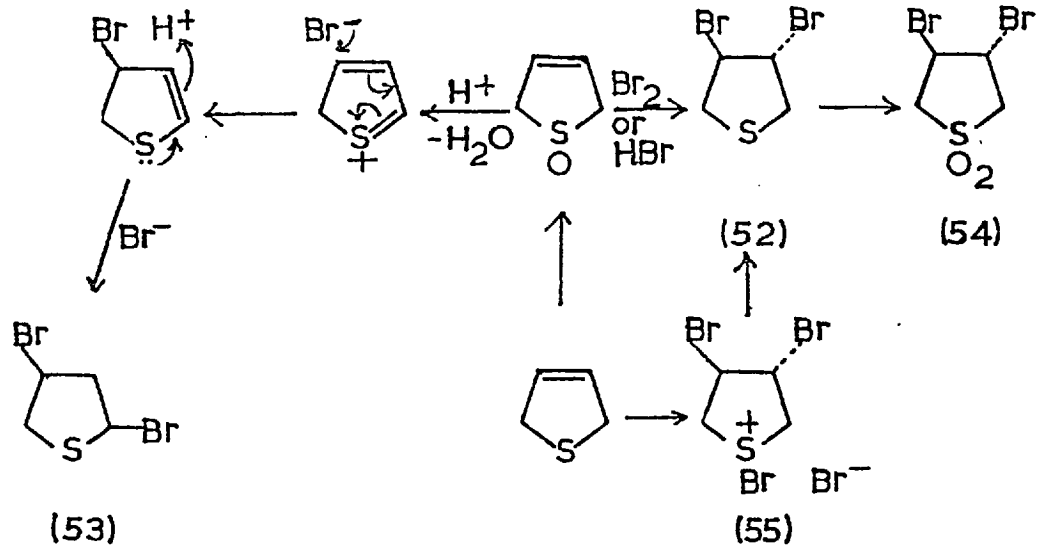
Sulphide (19) is readily oxidised to the sulphoxide (49) by hydrogen peroxide in acetone. In (49), the α-protons appear as an AB quartet due to the tetrahedral nature of the sulphinyl group; the vinylic protons again resonate as a singlet. The methylene protons in (49) should be relatively acidic, being doubly activated by the sulphinyl group and the double bond. In $NaOD/D_2O$, the methylene signal rapdily disappeared, but the vinylic resonance remained unchanged, hence no equilibration of the α,β- and β,γ-unsaturated sulphoxide isomers was occuring. This is in agreement with the proven stability of the β,γ-isomer in the acyclic case[22].



Attempts were made to alkylate (49) in the α-position, in the light of these findings. Since in rigid systems, the acidities of the two α-methylene protons are different (p.48) a stereospecific reaction was predicted. With sodium hydride in THF, an anion was formed which was quenched with methyl iodide. A polar product with a strong UV absorption and an NMR spectrum similar to butadienyl sulphides (40) and (43), was isolated, so it was concluded that a rapid ring-opening of the intermediate ylid (50) had occurred, as with the sulphonium salts, and the product was assigned the structure (51). In support of this, the product had a strong absorption at $1040cm^{-1}$ in its IR spectrum, characteristic of the S-O stretching frequency. The ambident sulphenate and sulphinate anions are sulphur, rather than oxygen, nucleophiles with a "soft" alkylating agent such as methyl iodide[23]. With a "hard" alkylating agent, e.g. dimethyl sulphate, the O-alkylated products (esters) are obtained.

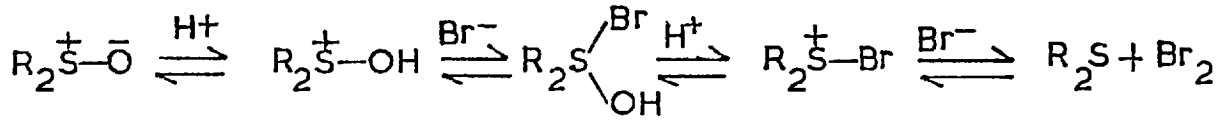
Reaction of (49) with bromine yields a non-polar product; the same product is formed using anhydrous hydrogen bromide. this was previously identified as 3,4-dibromothiolan (52)[24]. Since hydrogen bromide gave the same product as bromine, an acid-catalysed Pummerer-type rearrangement process was expected, to give, finally, the 2,4-dibromo derivative (53). The mechanism is indicated in Scheme 8.

Scheme 8.



However, oxidation of the bromide obtained from the action of bromine upon the sulphoxide gave authentic trans-3,4-dibromosulpholan (54), according to IR, melting point and mixed melting point evidence. Since only the trans-isomer is formed, the brominating agent in the case of hydrogen bromide is probably molecular bromine arising from oxidation of hydrogen bromide by the sulphoxide. Bromine is formed in this way through a complex of equilibria[25] (Scheme 9).

Scheme 9.



Two explanations are possible to account for the reduction of sulphoxide (49) during bromination. Either presence of hydrogen bromide in the bromine used give rise to the deoxygenated product (52) when bromine is employed; or a redox process involving bromine and the sulphoxide group is involved.

The NMR spectrum of (52) is very similar to that of sulphone (54), showing a distorted ABX pattern for the

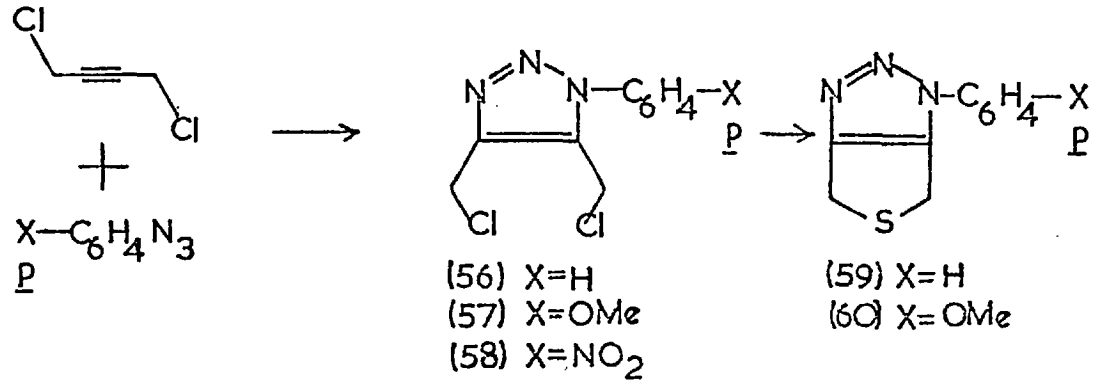
methylene protons, later found to be highly characteristic of trans-3,4-disubstituted thiolans. The dibromide (52) was more readily prepared from dihydrothiophen by addition of two moles of bromine to give the bromosulphonium bromide complex (55) followed by debromination with sodium bisulphite. This material was identical to that obtained from sulphoxide (49). Some properties of this dibromide will be discussed in the next section.

The addition of electrophiles to the double bond of (19) or (49) was not a synthetically useful process. Both were inert to iodine isocyanate, presumably due to the large -I effect of the sulphur function; (19) was also inert to 1,3-dipolar reagents such as aryl azides[26]. Reaction of either compound with oxidising electrophiles, such as HOBr, gave a multiplicity of products; the number of possible side reactions with such reagents (e.g. oxidations, Pummerer rearrangements, α-bromination, etc.) is legion.

A final effort at using 2,5-dihydrothiophen derivatives as a route to 3,4-disubstituted thiolans was made by synthesis of a fused thiophen-triazole (thienotriazole) nucleus. This hitherto unreported system was approached by addition of aryl azides to 1,4-dichlorobut-2-yne to give triazoles (56)-(58) in good yield. Treatment of these with sodium sulphide gave cyclized products (59) and (60) from (56) and (57). Attempted cyclization of (58) gave rise to various by-products, probably involving reduction of the nitro group by the sodium sulphide. The cyclized products were non-crystalline and impure, and were identified by mass spectroscopy. All attempts at crystallization of the

products failed, and they were not studied further (Scheme 10).

Scheme 10.

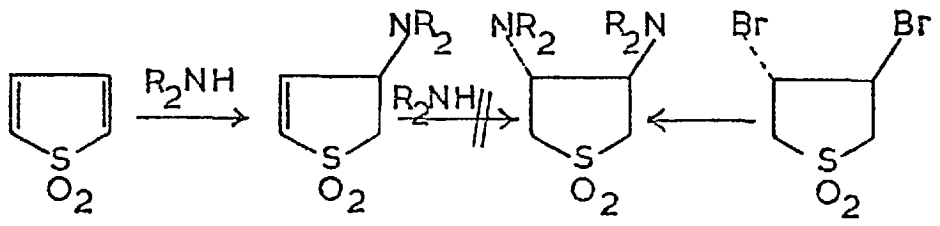


3. TETRAHYDROTHIOPHEN (THIOLAN) CHEMISTRY.

Thiolans are usually made by ring-closure of 1,4-dichlorobutane derivatives, as reduction of thiophens is rarely successful; however, a recent ionic reduction has been reported using triethylsilane/trifluoroacetic acid mixture as an ionic hydrogenating agent[27].

3,4-Dibromosulpholans undergo nucleophilic displacements with great ease[28]. This is normally attributed to an elimination/Michael addition sequence, and indeed the intermediate unsaturated sulphones may often be isolated[29]. An anomaly is the amine (62), readily formed from thiophen-1,1-dioxide (61) and dimethylamine, which shows no tendency to add a second molecule of amine[30] (Scheme 11).

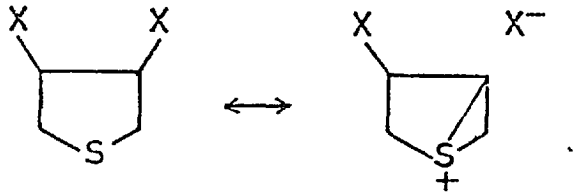
Scheme 11.



(61) (62) (63) (54)

The trans-diamine (63) is obtained from the trans-dibromide

(54), possibly via an aziridinium species[29]. The corresponding sulphide (52) was expected to be much less reactive since (a) the lower acidity of the α-protons would make elimination difficult; (b) in any case, α,ß-unsaturated sulphides prefer electrophilic addition; (c) the only other form of assistance is through episulphonium forms such as (64) which thermodynamically would be expected to make a negligible contribution.



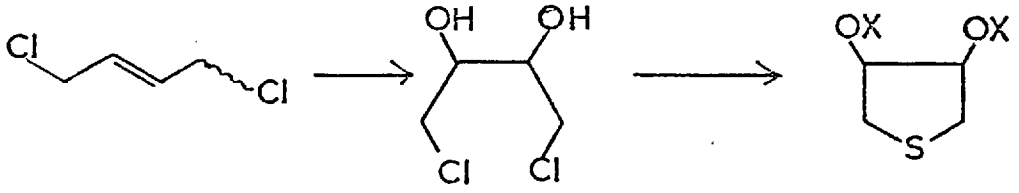
(64)

However, the corresponding sulphoxides might be expected to show an activation similar to, though weaker than, that in the sulphones.

The dibromide (52) proved inert to nucleophiles. It was oxidised to a crystalline sulphoxide with hydrogen peroxide. This also gave no amino-compounds on reaction with amine nucleophiles (see Section 4). The limited availability of the dibromide (52) led to a search for a more versatile thiolan synthesis.

1,4-dichlorobut-2-ene gave diols (65) and (66) when reacted with neutral potassium permanganate[31]. With sodium sulphide, the dihydroxythiolans (67) and (68) were formed in high yield. If the pH was allowed to fall below 6 on workup, much polymerization occurred. The crude diols were used as starting materials for the synthesis of a number of compounds,

both cis and trans; since dichlorobutenes of both configurations were readily available, the diols were easily made in yields of 60% overall (Scheme 12).



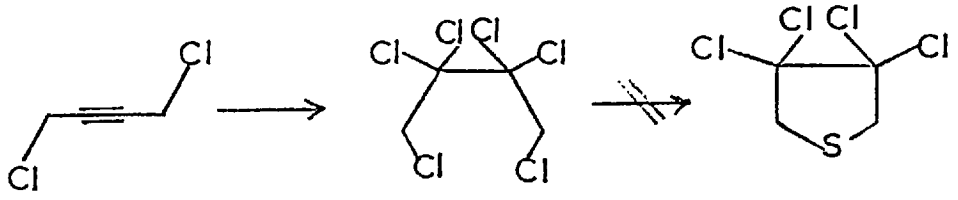
(27) cis
(20) trans

(65) meso
(66) DL

(67) cis, X=H
(68) trans, X=H
(69) cis, X=Ac
(70) trans, X=Ac
(71) cis, X=Ts
(72) trans, X=Ts

Scheme 12.

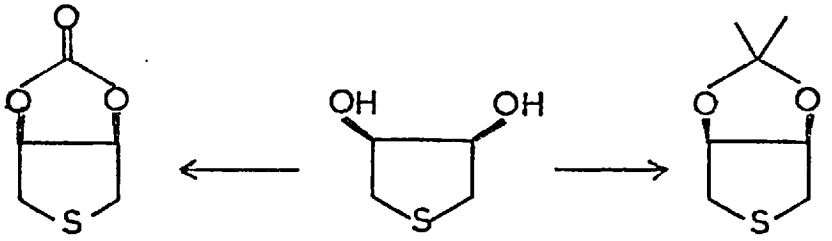
The more flexible structure of these saturated 1,4-dichlorobutanes completely eliminated any linear polymer formation, which had been a serious drawback in the preparation of dihydrothiophen. Chlorination of 1,4-dichlorobut-2-yne in boiling carbon tetrachloride gave the crystalline hexachloride (73). However, all attempts at effecting ring closure to the 3,3,4,4-tetrachlorothiolan (74) gave unchanged (73).



(73) (74)

The diols (67) and (68) gave diacetates (69) and (70) as oils on treatment with acetyl chloride. Both diols gave

stable crystalline ditosylates (71) and (72) with tosyl chloride and pyridine at 0°. Careful reaction of the cis-diol with phosgene and pyridine gave the cyclic carbonate ester (75) in fair yield. Reaction of cis-diol with 2,2-dimethoxypropane in acetone gave the acetonide (76). The trans-diol gave no cyclic products in either case, reflecting the lower stability (ca. 5kcal) of trans-fused 5-5 rings compared to the cis-fused isomers[31].



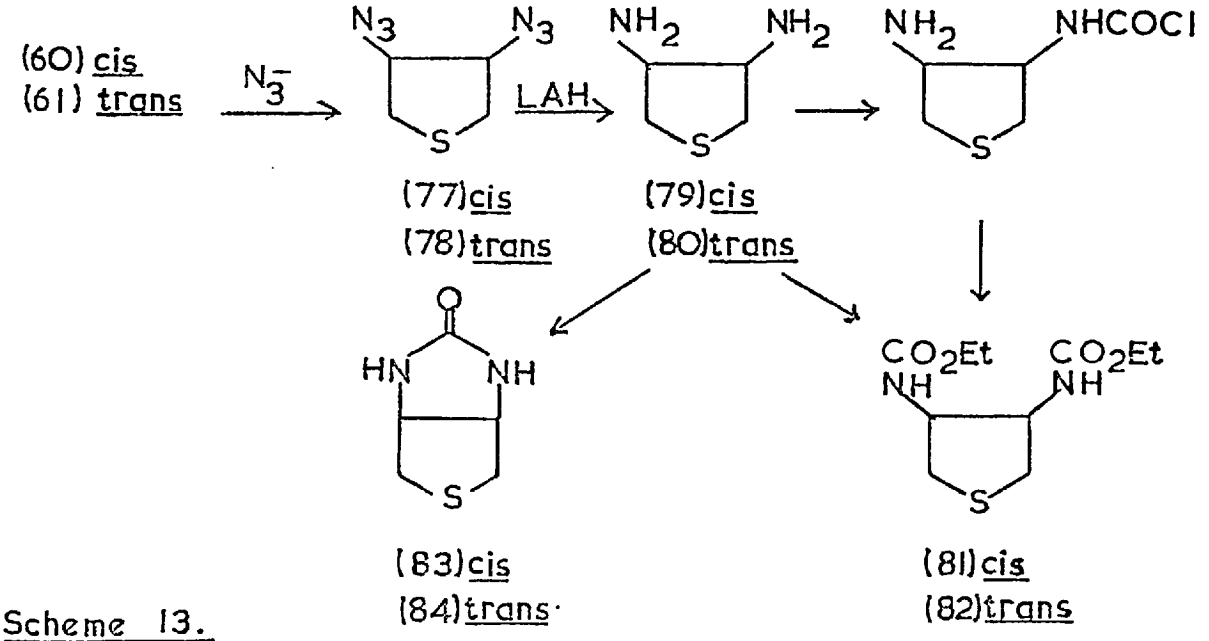
(75) (76)

The NMR spectra of all these derivatives were often very characteristic of their stereochemistry. The trans-dibromide (52), diol (68), diacetate (70) and ditosylate (72) showed the methine protons as a narrow, tightly-coupled multiplet, and the α-methylene protons as a distorted ABX eight-line system, where $J_{A,X}$ was generally different from $J_{B,X}$. The resonances of the spectra of the cis-compounds showed more variety, but were generally less complex. In the diol (67) and the diacetate (69), the methine protons formed a broad, more complex multiplet than the corresponding signal in the trans-isomers; the geminal coupling constants to the α-methylene protons were smaller, giving a narrower, more tightly coupled multiplet than the corresponding signals in the trans-isomers. In the ditosylate (71), the geminal

coupling constant is so small that the methylene and methine protons appear virtually as a doublet and triplet respectively; while in the bicyclic acetonide (76) the methylene-methine coupling is also very small, giving rise to two broadened singlet resonances. In cyclic carbonate (75), we have the opposite situation to the ditosylate (71); the geminal coupling is strong, but the vicinal coupling is weak, so the methylene and methine protons resonate as an AB quartet and a singlet respectively. For diagnostic purposes, the trans-isomers are unmistakeable, while the cis-isomers, albeit showing more individuality, give equally characteristic, less complex spectra.

Both ditosylates (71) and (72) were inert to displacement by amines. Cyclic carbonate esters have been reported to give epoxides with iodide ion and oxazolones with urea[32]. However, cyclic carbonate (75) proved extraordinarily unreactive, being recovered unchanged after refluxing with sodium iodide or urea in DMF or ethylene glycol. When ditosylates (71) and (72) were stirred with sodium azide in DMSO at 80°, the diazides (77) and (78) were obtained reasonably pure, as fairly stable oils, which gave a correct molecular ion (M^+=170) and showed loss of two molecules of hydrazoic acid in the mass spectrum. The infrared spectrum showed strong absorptions at ca. 2100cm^{-1}, highly characteristic of the azide group. That the relative stereochemistry had been preserved was shown by NMR. The methylene protons in the azide derived from the trans-ditosylate gave a broad distorted ABX-type spectrum; those in the azide derived from the cis-ditosylate resonated as a much sharper multiplet.

Addition of the azides to a stirred suspension of LAH in ether at room temperature resulted in a vigorous reaction with evolution of nitrogen after a short induction period. After a basic workup, the diamines (79) and (80) were obtained. NMR was of less diagnostic value here, as the methylene and methine resonances approached each other in chemical shift, or overlapped, giving a complex spectrum in both cases. Both showed a four-proton singlet at high field, exchangeable with D_2O. In chloroform/pyridine, cis-diamine (79) gave the urethane (81) with phosgene, resulting from reaction of the intermediate carbamoyl chloride with the ethanol stabilizer; the trans-diamine (80) gave the corresponding trans-urethane (82) when reacted with an excess of ethyl chloroformate and pyridine. It has a typical trans-3,4-disubstituted thiolan spectrum in the NMR. This gives an indication of the very slow rate of cyclization of the intermediate carbamoyl chloride (Scheme 13).



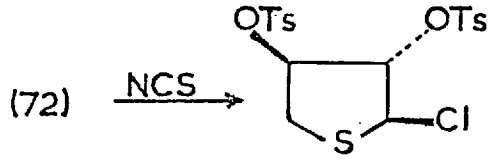
Scheme 13.

Instead, the diamines were cyclized in sodium carbonate solution with an excess of phosgene, under which conditions

any uncyclized carbamoyl chloride is readily hydrolysed to the diamine, suppressing polymerization. A moderate yield of cis-fused cyclic urea (83) was readily obtained in this fashion. Similar treatment of the trans-diamine gave much linear polymer, as detected by a strong amide II band in the infrared spectrum of the crude product. The trans-urea (84) was separated by crystallization from chloroform.

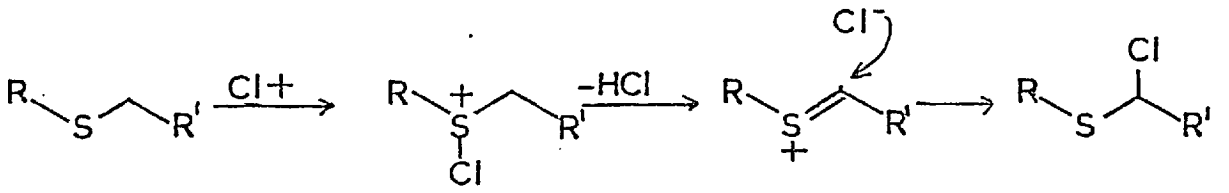
Both ureas are highly insoluble in all solvents. The cis-isomer shows a single carbonyl stretch at 1690cm^{-1}; the trans-isomer shows two carbonyl frequencies (1690 and 1715cm^{-1}). There is precedent for this observation in the corresponding sulphone series[3].

A 2,3,4-trisubstituted thiolan was made by chlorination of the trans-ditosylate (72) with N-chlorosuccinimide in dichloromethane at 0°. The all-trans-2-chloro-3,4-di-tosyloxythiolan (85) was obtained cleanly and separated from succinimide by column chromatography, from which it was obtained as large colourless cubic crystals.



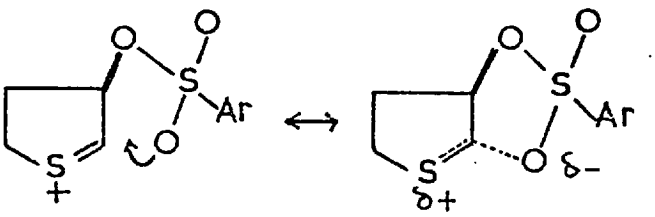
(85)

Mechanistically, this chlorination may be viewed as occurring via a chlorosulphonium intermediate followed by elimination, and addition at the 2-position, i.e. a Pummerer-type process (Scheme 14).



Scheme 14.

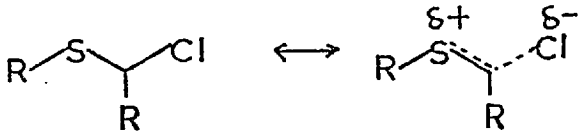
Evidence for this mechanism is provided by the well-known oxidation of sulphides to sulphoxides by N-chlorosuccinimide in aqueous media, by hydrolysis of the intermediate chlorosulphonium ion[25]. Since the product (85) is chromatographically homogeneous, the stereospecificity of its formation can be rationalized in two ways. One can invoke either (a) steric approach control, i.e. steric hindrance by the bulky tosyloxy group to the cis approach of Cl^-; or (b) the possibility of anchimeric assistance by the sulphonyl group.



Evidence for participation of sulphonyl groups in halogenation; reactions of ß-hydroxysulphones has already been discussed in the Review (p. 24).

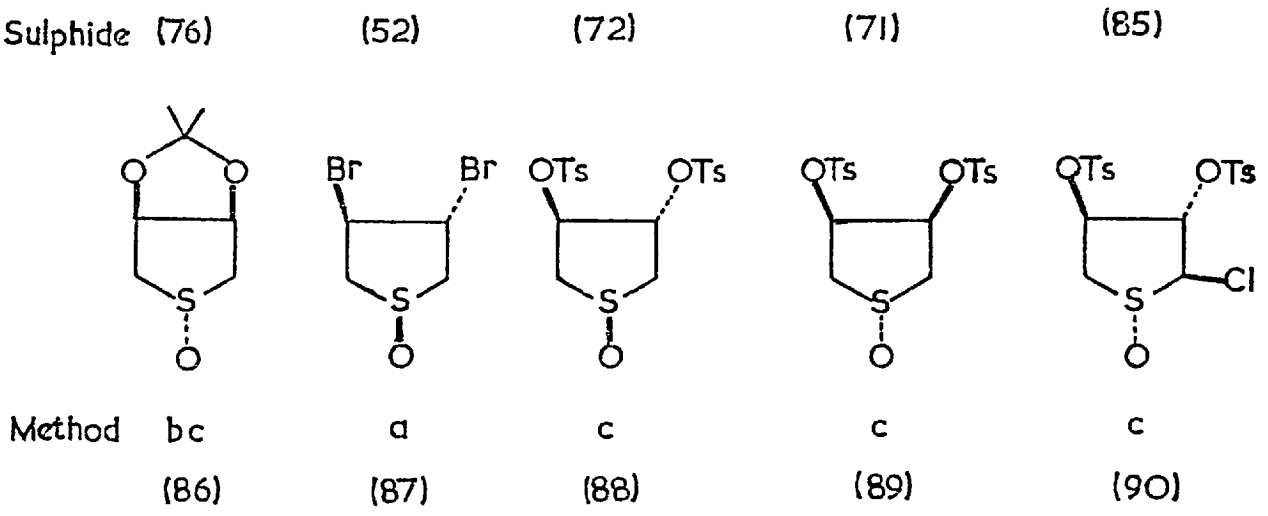
Surprisingly, all three leaving groups in compound (85) proved unreactive towards Grignard reagents. Because of the highly dipolar character of α-chlorosulphides, and the consequent weakness of the C-Cl bond, these compounds usually

react readily with nucleophiles.



Unreactivity in nucleophilic displacements appears to be a characteristic of all such substituted thiolans.

The sulphoxide derivatives of the thiolans were next studied, reasoning that they might be more reactive towards nucleophiles than the sulphides. Oxidation of the respective sulphides with (a) hydrogen peroxide in acetone, (b) sodium metaperiodate, or (c) m-chloroperbenzoic acid, gave the following sulphoxides (Scheme 15) as crystalline solids in good yield.

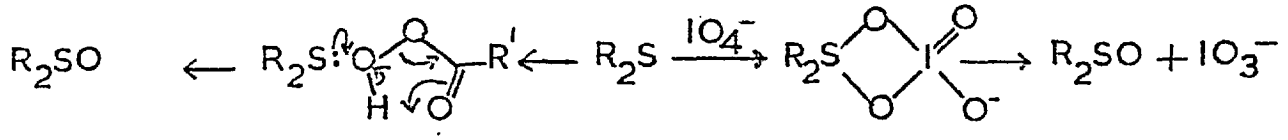


Scheme 15.

All these sulphoxides showed a strong absorption at ca. 1050cm^{-1} in their infrared spectra. There were no strong bands in the region 1300-1350cm^{-1} indicating absence of sulphones.

The stereochemistry of the oxidation is of some interest. With trans-3,4-disubstituted sulphides, only one product is

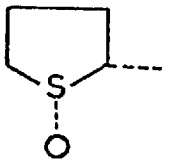
possible. Studies with various cis-3,4-disubstituted derivatives[35] have shown that the most stable product (with the S-O bond trans to the substituents) is formed with periodate, peracid and hydrogen peroxide. Only with t-butyl hypochlorite was less than 90% specificity observed. Johnson[36] has shown that the product distribution may be controlled by (a) steric approach control, or attack of the oxidising agent from the least hindered side; (b) product development control, or stabilization of the transition state by the same factors which stabilize the product; or (c) thermodynamic control. Since conditions suitable for the equilibration of sulphoxide isomers were not employed, we may discount (c). It has been suggested that periodate reacts via a cyclic transition state, while peracid oxidations involve nucleophilic attack by the sulphur atom on the electrophilic -OH group of the peracid. The product distribution in periodate oxidations is thus affected by product development control, while that for peracid oxidations is governed by steric approach control (Scheme 16).



Scheme 16.

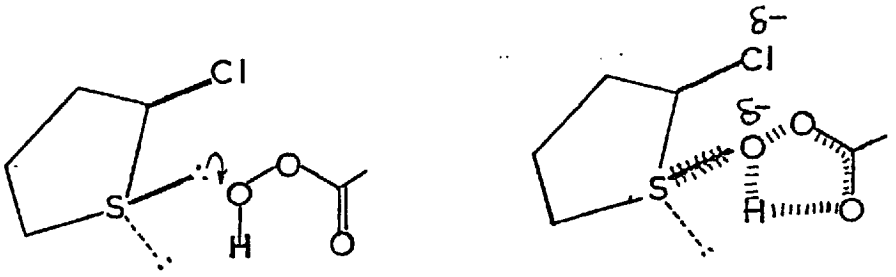
In the case of sulphides (71) and (76), attack from the least hindered side (i.e. using the axial lone pair on sulphur) also leads to the most stable product, so the observed specificity of oxidation of the cis-disubstituted sulphides

with a variety of oxidising agents is not surprising. The course of oxidation of the chlorosulphide (85) is more complex. Recent work[37] has shown that cis-2-methylthiolan-1-oxide (91) is more stable than the trans-isomer; also that the oxidation of 2-methylthiolan proceeds with little or no specificity with peracids.



(91)

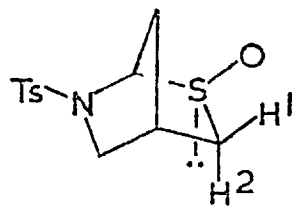
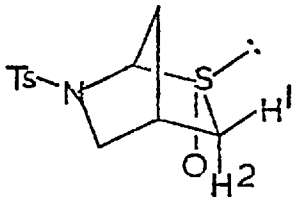
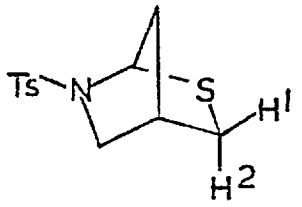
However, oxidation of chlorosulphide (85) with peracid gives, with high specificity, one product only. If steric approach control operates, we would expect at least a preponderance of the trans-isomer (90). However if we apply product development arguments in this case, we can find a rationalization of the high specificity. Although in the case of (91), the cis-isomer is more stable, it would be reasonable to suppose that the trans-isomer of 2-chlorothiolan-1-oxide would be more thermodynamically stable due to minimization of dipole-dipole effects; other evidence for this assertion will be discussed below. In this situation, attack of the peracid cis to the C-Cl bond results in the development of an electrostatically unfavourable dipole-dipole repulsion, such as would destabilize the transition state and the product; hence formation of the trans-activated complex leading to the all-trans sulphoxide would be highly favoured.



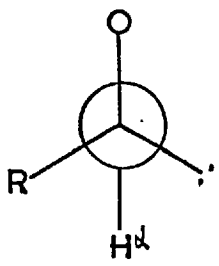
The operation of both steric and product development factors would be a powerful driving force for the formation of the all-trans-isomer (90).

The NMR spectra of sulphoxides are of great value in making structural assignments, and can be of considerable theoretical interest. Comparisons of the anisotropic magnetic influence of the sulphinyl group with that of the carbonyl group[38] or the acetylenic triple bond[39] are erroneous, as they fail to account for any effects of the sulphur lone pair. Empirically[40] it is found that an α-proton is strongly shielded if it bears a syn-axial relationship to the S-O bond, and less strongly if it is syn-equatorial. If the α-proton is syn-axial to the sulphur lone pair, then it is strongly deshielded, and less strongly if it is syn-equatorial. The results for a rigid system[40] are summarized in Table 2 below. The measure $\Delta\delta = \delta_S - \delta_{S-O}$ indicates the degree of shielding or deshielding relative to the parent sulphide; the more positive the value of $\Delta\delta$, the stronger is the shielding; the more negative, the stronger the deshielding.

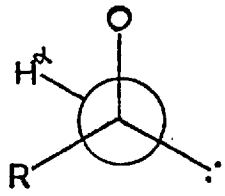
TABLE 2.

Compound	H^1	H^2
	δ 2.33 Δδ +0.55 syn-eq to S-O	δ 3.57 Δδ -0.51 syn-ax to L.P.
	δ 3.05 Δδ -0.17 syn-eq to L.P.	δ 2.29 Δδ +0.77 syn-ax to S-O
	δ 2.88	δ 3.06

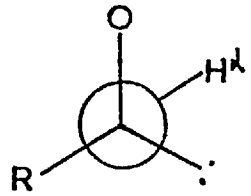
In non-rigid cis-3,4-disubstituted thiolan-1-oxides[41,42], where two isomeric sulphoxides can result upon oxidation of the sulphides, three conformations of an α-proton are possible.



(A)

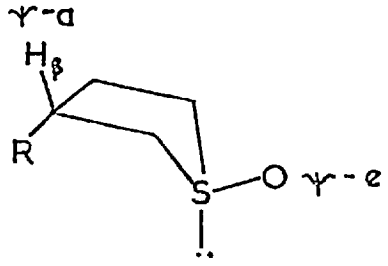


(B)

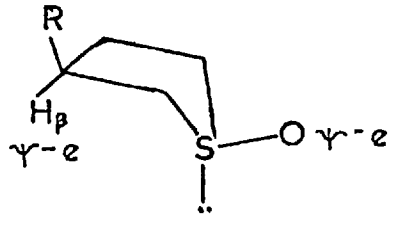


(C)

For an equatorial or pseudoequatorial α-proton, it is established that it is most deshielded in conformation (C)[42]. Finally, we may note that a proton ß- to the sulphinyl group are deshielded by up to 0.5ppm if they are oriented 1,3-diaxial with respect to the S-O bond[43]. In a five-ring system with pseudoequatorial and pseudoaxial protons, the following interactions are also important. In case I below, H_β is deshielded by ca. 0.4ppm by a pseudo-(equatorial-axial) interaction, or perhaps a trans-diaxial lone pair effect. In case II, H_β is shielded by ca. 0.1ppm by a pseudo-(equatorial-equatorial) interaction. In general, the strength of the interactions in these rings follows the order diaxial>axial-equatorial>diequatorial[42].



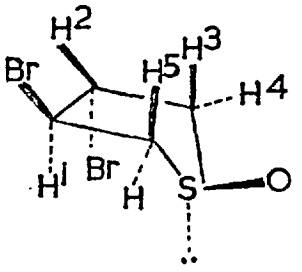
Case I



Case II

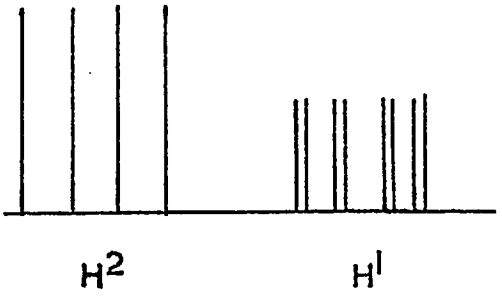
The above findings can be applied to the NMR data on the sulphoxides prepared above. The cis-sulphoxides (86) and

(89) posess an ABX-type pattern as the methylene resonance, i.e. the geminal and vicinal couplings were considerably enhanced over those for the sulphides, in which the two methylene protons are nearly equivalent. In the trans-sulphoxides (87) and (88), the methine protons are no longer equivalent, which gives a more complex set of methine resonances, which in sulphoxide (87) is fairly well resolved. Assuming (92) to be the most stable conformer of (87), then proton H^1 is shifted upfield by 0.1ppm to overlap with a complex methylene multiplet; the proton H^2 is shifted downfield by 0.5ppm and appears as a one-proton quartet, presumably coupled to H^1 and H^3, with a very small ($<$1Hz) coupling to H^4 or long-range to H^5.



(92)

Most interesting of all is the case of chlorosulphoxide (90). The structure with the stereochemistry shown is fairly well established from the discussion on p.99. In this compound, the methylene protons resonate as a quartet and as an eight-line system of one proton each, as illustrated below. The assignments are set out in Table 3.



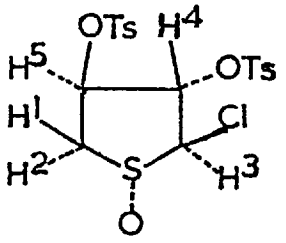


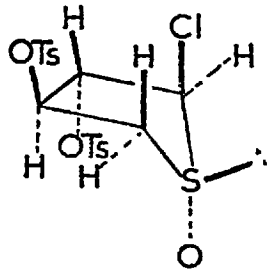
TABLE 3.

No.	Shift, δ	Rel. Area and Multiplicity	Assignments and Coupling Consts.
(1)	7.70	8H, m	Aromatic
(2)	5.78	1H, dd	H^4; $J_{3,4}$=14Hz, $J_{4,5}$=7Hz
(3)	5.33	2H, m	H^3, H^5
(4)	3.97	1H, dd	H^2; $J_{1,2}$=16Hz, $J_{2,4}$=9Hz
(5)	2.93	1H, dq	H^1; $J_{1,4}$=1.5Hz, $J_{1,5}$=6.5Hz
(6)	2.56	6H, s	Ar-CH_3

The reasoning behind the assignments is as follows. The downfield methylene proton is more strongly coupled to the vicinal methine proton H^5 than is the upfield methylene proton; from the usual dihedral angle considerations, H^2 is the downfield proton and H^1 is the upfield proton. Long-range couplings of protons α to a sulphoxide in cyclic systems are well known[44] and are of the order of 1-2Hz. Moreover, a W-type conformation is usual when such coupling is observed, which is in fact the relative configuration of H^1 and H^4. Long-range coupling across the C-S-C system

does not apparently occur.

We may thus assign a conformation to the molecule. Since we have seen the more deshielded proton is that in conformation (C) above (p.102), the conformation of (90) which meets this requirement is shown as (93).



(93)

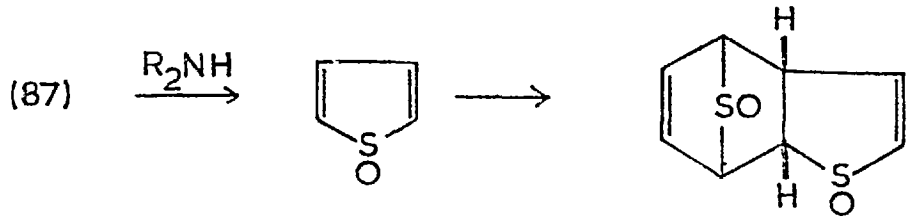
It is known that the most stable conformer of a cyclic sulphoxide is frequently that in which the S-O bond is axial[37]. In this case, preference for an axial S-O bond may well be ascribed to the necessity of avoiding any unfavourable dipole-dipole interactions. The well known preference for halogen substituents α to a carbonyl group in cyclic ketones to adopt the axial conformation, provides a clear analogy. In conformation (93), the C-Cl and S-O dihedral angle is maximised. We have more evidence (see next Section) in support of this theory.

If conformation (93) is adopted, one would expect H^5 to be more deshielded than H^4, as diaxial interactions effect greater changes in chemical shift than equatorial-axial interactions (p.102). However, as the most deshielded proton in fact appears as a quartet whose coupling constants do not match those already estimated from the splitting of H^1 and H^2, this cannot be H^5, so we must conclude that

perhaps the combination of diequatorial lone pair interaction and the presence of the C-Cl bond deshields H^4 to a greater extent. Therefore this leaves this assignment in some doubt.

4. THIOPHEN-1-OXIDE CHEMISTRY.

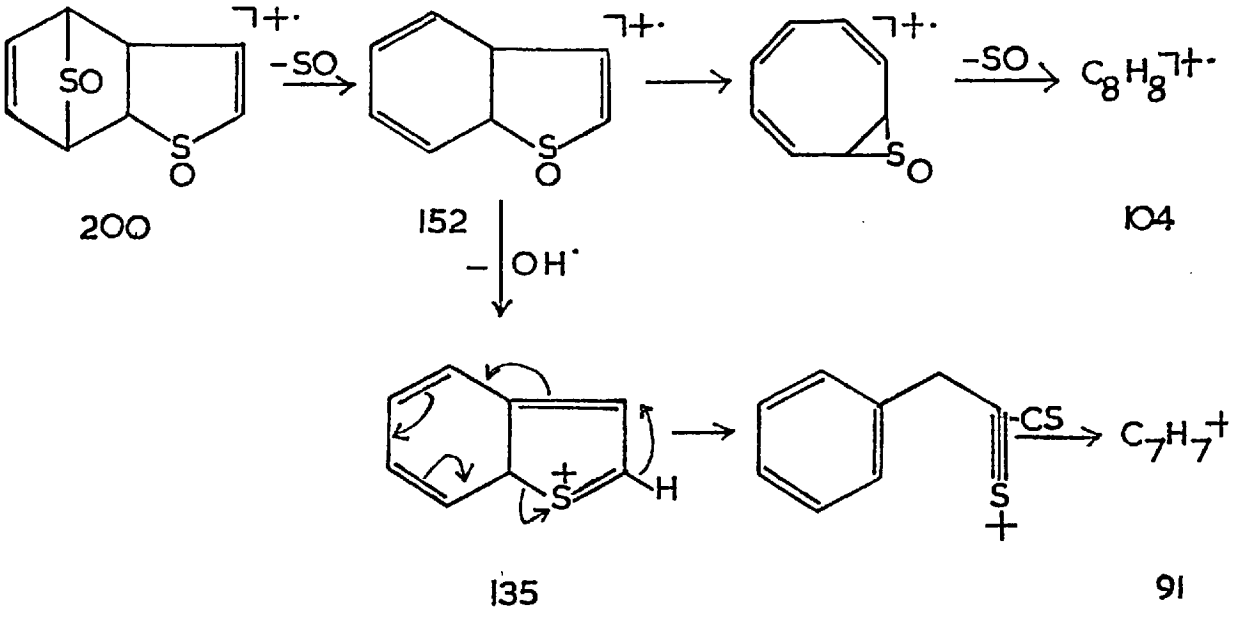
The sulphoxide (87) was treated with amine nucleophiles (ammonia, methylamine, benzylamine, piperidine) under various conditions (e.g. in aqueous, protic, aprotic or buffered solution; with free amines or their hydrochlorides; or in liquid ammonia) but no amino-compounds were ever obtained. When reaction did occur, a compound, identified as the dimer (95) of thiophen-1-oxide (94), was obtained.



(94) (95)

The compound analysed properly for $C_8H_8O_2S_2$; its mass spectrum gave a correct molecular ion (M^+=200) and also fragments at m/e 152, 135, 123, 104, 91, 77. An abundance of metastable peaks at m/e 115.5, 71.2, and 61.3 allowed the transitions 200→152, 152→104, and 135→91 to be assigned unambiguously. The fragmentation can thus be set out as in Scheme 17. The loss of the CS fragment from the ion m/e 135 is an unusual process.

Scheme 17.



The NMR data enables us to establish the stereochemistry of the adduct and are summarized in Table 4.

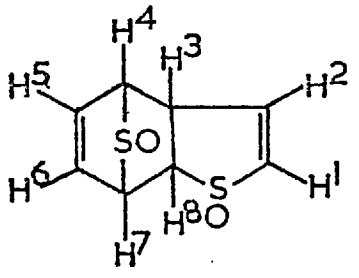


TABLE 4.

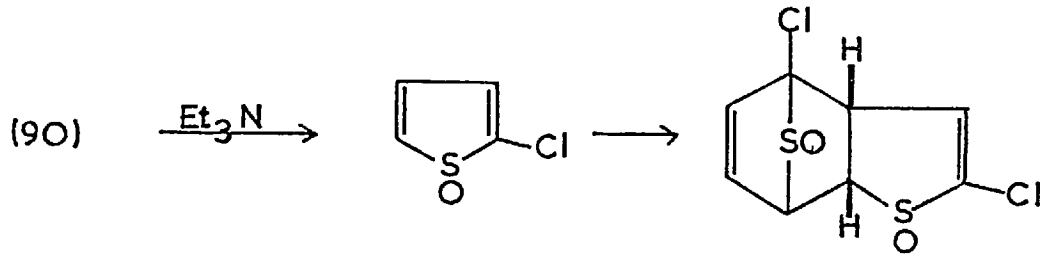
No.	Shift, δ	Rel. Area and Multiplicity	Assignments and Coupling Consts.
(1)	6.20-6.52	3H, m	H^1, H^5, H^6
(2)	5.81-5.94	1H, m	H^2
(3)	4.77	1H, dd	H^8; $J_{3,8}$=14Hz, $J_{7,8}$=7Hz
(4)	4.36-4.48	1H, m	H^7
(5)	3.92-4.10	2H, m	H^1, H^4

Decoupling experiments show that irradiation of signal (2) causes some simplification of signal (5); irradiation of signal (5) causes collapse of multiplet (2) to a doublet, thus assigning H^2 and H^3 unambiguously. Irradiation of signal (1) resulted in a collapse of signal (4) to a double doublet, which leaves unresolved the assignment of H^4 or H^7 to this signal. The stereochemistry of the S-O bond in the fused five-membered ring is not certainly known; if it were pointing downwards, we might expect H^7 to experience strong deshielding. This effect would probably be weaker were the S-O bond directed upwards. On balance, the combination of the ß-effect of the sulphinyl group, together with its probable through-space effects, the assignment of signal (4) to H^7 seems likely.

The magnitude of the coupling constants $J_{7,8}$ and $J_{3,8}$ supports the assignment of cis,-endo stereochemistry. If the dimer were trans, $J_{3,8}$ would be very small; if it were exo, the dihedral angle between H^7 and H^8 would be nearly 90°, hence $J_{7,8}$ would be nearly zero. Also, if the adduct were exo, a much less complex splitting pattern for H^5 and H^6 would be observed.

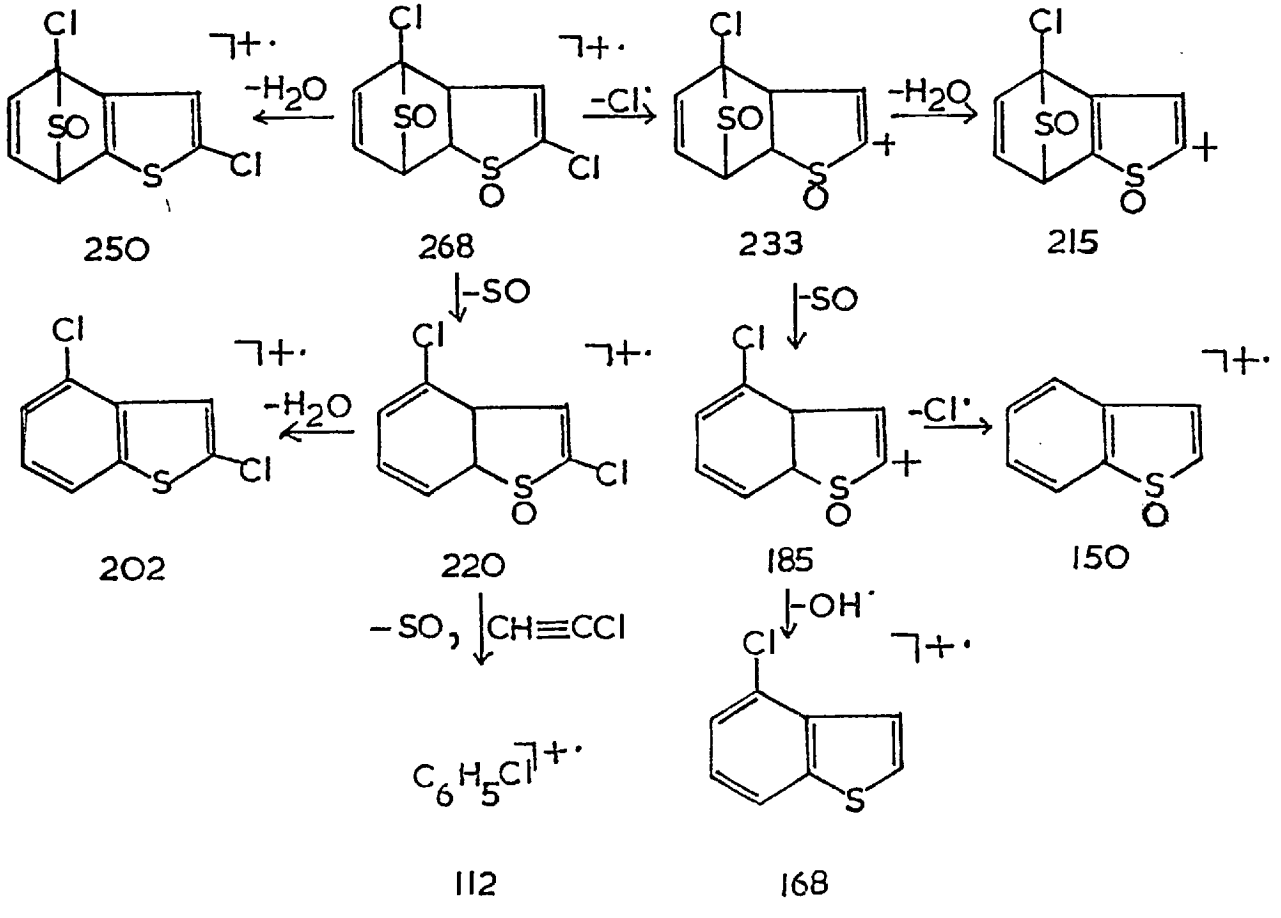
The sulphoxides (87) and (88) give the same dimer on treatment with base. A better preparative method was found by using basic ion-exchange resin in methanol as base; this gave a much cleaner product than amine or metallic bases.

The 2-chlorosulphoxide (90) gave a good yield of the dimer (97) of 2-chlorothiophen-1-oxide (96) with triethylamine.



(96) (97)

As before, the structure of (97) was established by elemental analysis and mass spectroscopy. The latter gave a correct molecular ion (M^+=268, with an appropriate M+2 ion for two chlorine atoms) of very low intensity. The fragmentation pattern was highly complex compared to dimer (95); initial loss of H_2O, or Cl·, or SO from the molecular ion constitute the chief fragmentation patterns (Scheme 18).



Scheme 18.

The structure of dimer (97) was finally established by NMR, the data being displayed in Table 5.

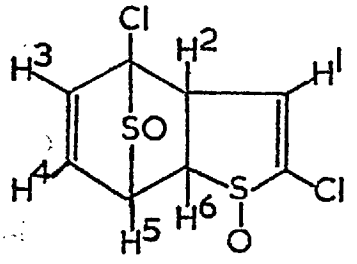
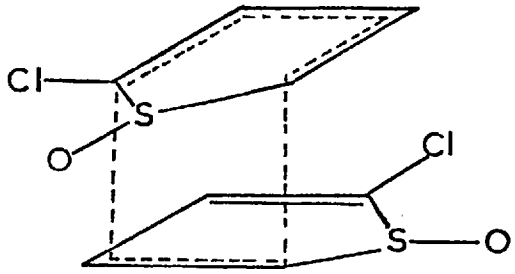


TABLE 5.

No.	Shift, δ	Rel. Area and Multiplicities	Assignments and Coupling Consts.
(1)	6.53	2H, m	H^3, H^4
(2)	6.06	1H, d	H^1; $J_{1,2}$=8Hz
(3)	4.97	1H, dd	H^6; $J_{2,6}$=14Hz, $J_{5,6}$=7Hz
(4)	4.30	2H, two superimposed dd's	H^2, H^5

The appearance of H^6 as a double doublet unambiguously establishes the gross structure as (97); obviously, none of the other three structural possibilities can give rise to this splitting pattern. Since the coupling constants for this double doublet are virtually the same as those for the corresponding proton in the unsubstituted dimer (95), the cis-endo structure is similarly established for (97).

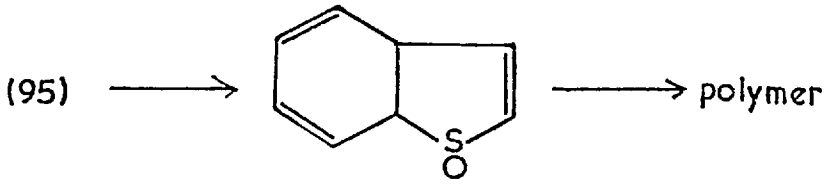
Since the dimerization can, in principle, give rise to four regioisomers, then, assuming an electrocyclic reaction, a clue to the source of this regiospecificity can be found by examining the transition state (98) leading to dimer (97).



(98)

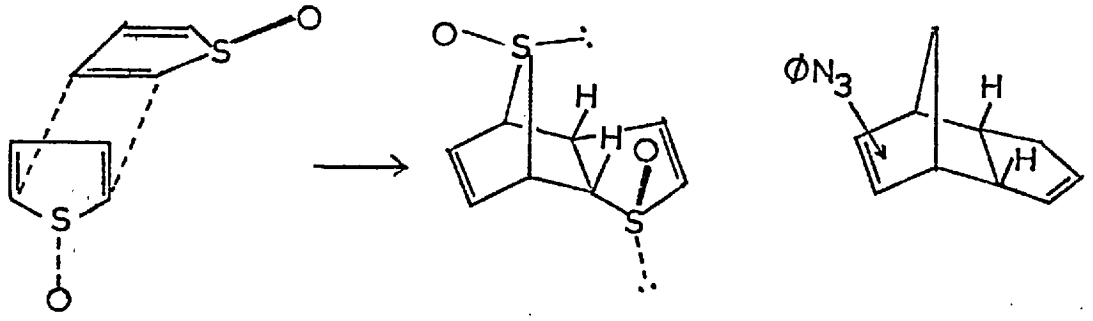
This transition state is the only possible one in which all the dipole-dipole C-Cl and S-O bond interactions are eliminated; the transition states for all the other isomers involve eclipsing of at least one S-O bond by a C-Cl dipole, which, as we have seen (p.99), may be energetically disfavoured.

The dimers (95) and (97) were white crystalline solids; on heating to their respective melting points, rapid gas evolution and polymerization occurred, presumably by loss of sulphur monoxide and further reaction of the cyclohexadiene (99).



(99)

The data presented so far are insufficient to determine the stereochemistry of the S-O bonds in the dimers. From steric approach control arguments, we might expect the least hindered transition state to be (100), giving a dimer of configuration (101). The thiophen-1-oxide itself does, in all probability, possess a tetrahedrally hybridised sulphur atom with a high energy barrier to inversion[45].

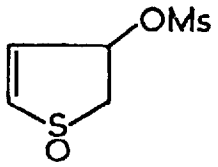


(100) (101) (102)

The only chemical evidence to support this hypothesis is a comparison of the reactivities of the strained double bonds in dimer (101) and dicyclopentadiene (102). Dicyclopentadiene reacts rapidly with phenyl azide to give an adduct resulting from addition of the azide at the least hindered exo-face of (102), as shown above. In dimer (101), both sides of the strained double bond are hindered; and no adduct is formed when phenyl azide was added to dimer (95), which suggests that the configuration of the S-O bond may be as shown in (101). It is also possible that the deshielding of H^7 in the dimer (95) may be due to the "upwards" orientation of the S-O bond in the five-membered ring in (101), but this is very uncertain. In view of the homogeneity of dimers (95) and (97) on t.l.c., it seems probable that only one of the possible stereoisomers is formed.

The reactivity of the monomeric thiophen-1-oxides is not surprising in view of their likely anti-aromatic character, similar to the cyclopentadienones[46]. Thiophen-1-oxide has been supposedly observed in the UV[47], but the absorption observed at 250nm which initially increased and then decreased

as the thiophen-1-oxide ceased to be generated, is more likely attributable to the intermediate (103)[46]. In view of the very facile dimerization of (94), this contention is very probably correct.



(103)

Thiophen-1-oxide would not yield any products resulting from Michael addition, even when generated in the presence of excess amine; nor was it trapped as a diene by dienophiles such as acetylene dicarboxylic ester or ethyl vinyl ether. One might have naively expected the latter to be a good dienophile for thiophen-1-oxide, which, being an electron deficient diene, might participate in Diels-Alder reactions with inverse electron demand[48]. In all these cases, the dimer (95) is the sole product, and one must conclude that dimerization is extremely rapid compared to Michael addition or trapping with dienophiles. The 2-chlorothiophen-1-oxide (96) was expected to be more stable, by analogy with halogenated thiophen dioxides which are considerably more stable than the parent compound[49], presumably due to the +M effect of the halogen substituents. However, like the unsubstituted compound, (96) could not be trapped and was thus not appreciably more stable.

There seems to be no obvious explanation for the fact that the α,β-unsaturated sulphoxide moiety in the dimers is

likewise inert to attack by amine nucleophiles.

At this point, the behaviour of thiophen oxides and dioxides might be contrasted. First, the latter are much more stable; the parent compound can be kept for long periods in solution at 0°[30]. Second, the dimers of the dioxides are less stable than those of the monoxides, as they often lose sulphur dioxide at room temperature[30,48]. This may be attributed to the greater driving force provided by the loss of the more stable SO_2 fragment. Third, the dioxides are readily trapped by olefins. Usually the sulphonyl group bridge of the initial adduct is lost rapidly giving secondary products. The dioxides also undergo Michael addition with nucleophiles[30].

A stable 2-chlorothiophen-1-oxide was reported in the patent literature[50], as being the product of the oxidation of 2-chlorothiophen with peracid. We were not able to repeat this experiment, the only products being obtained were highly coloured non-polar materials. In the light of our above findings, it would have been surprising indeed to have isolated any monomeric (96). The following thiophens were treated with peracid under various conditions; 2-chloro-, 2,5-dichloro-, 3,4-dibromo-, and 2,3,4,5-tetrabromo-. In all cases, mainly starting material with a little polymeric material was recovered. The oxidation of thiophens with electron-withdrawing (-I) substituents is difficult[51], unless alkyl or similar electron-donating groups are also present.

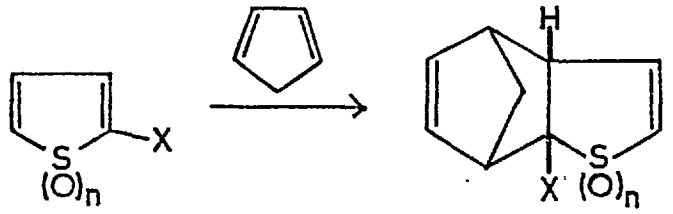
The dimerization reaction should be examined critically in the light of known studies[52] on dimerization of the cyclopentadienones ("cyclones"). Admittedly, although the

symmetry point group of cyclones (C_{2v} point group) is different from that of the thiophen-1-oxides (C_s point group), some qualitative correlations are of interest. It is generally recognized that the dominant interaction in a Diels-Alder reaction is that between the highest occupied and lowest unoccupied molecular orbitals (HOMO and LUMO respectively) of the reactants. Second-order perturbation theory leads to an equation which enables us to calculate the net change in π-electronic energy ($\triangle E_\pi$) in going to the transition state, due to HOMO-LUMO interactions. From the value of $\triangle E_\pi$, we can obtain rate data for various cycloadditions.

In the special case of a Diels-Alder dimerization, the HOMO and LUMO of the monomer must be close in energy to ensure effective mixing of these orbitals in the transition state, giving a large negative $\triangle E_\pi$, hence a fast reaction rate. For cyclones, the energy gap is very small, and the rate of dimerization is virtually encounter-controlled; it has a half life of ca. 10^{-8} sec. HOMO-LUMO calculations, considering cyclone as a diene and a dienophile, conclude that it should be efficiently trapped by cyclopentadiene, but as a dienophile, not as a diene. This is in fact observed. However, a discrepancy occurs in the case of maleic anhydride, which, it was predicted, would also trap cyclone, this time as a diene; no reaction is in fact observed. Like thiophen-1-oxide, it is totally unreactive towards both electron-rich and electron-poor dienophiles[53].

It is thus hardly necessary to emphasize the similarities between thiophen-1-oxide and cyclopentadienone chemistry. The same rapid dimerization, and the same reluctance to trap

with olefins is notable. It was, then, proposed to attempt to trap thiophen-1-oxide with cyclopentadiene. 2,3-dimethylbutadiene gave no adduct, but when generated in the presence of an excess of cyclopentadiene, thiophen-1-oxide gave the adduct (104), exactly as for cyclones.. 2-Chlorothiophen-1-oxide (96) similarly gave an adduct (105).

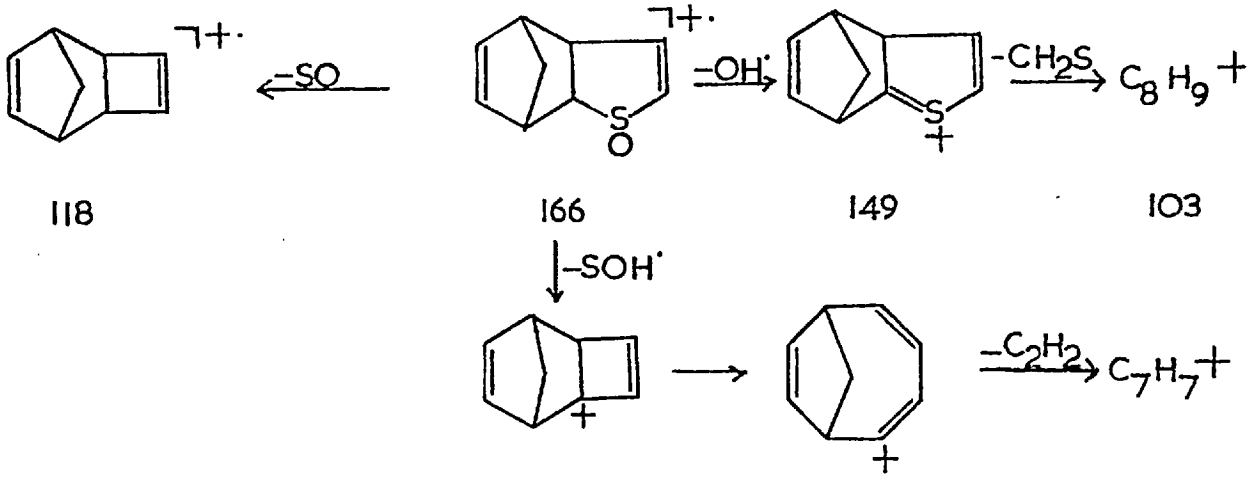


(104) n = 1 X = H
(105) n = 1 X = Cl
(106) n = 2 X = H

The failure of 2,3-dimethylbutadiene to give any adduct, like the failure of cyclone to trap with anthracene[53], reaffirms the essential complementarity of such cycloadditions; that is, from its ready dimerization, we might naively conclude that thiophen-1-oxide is a "powerful" diene or dienophile, yet we find that, like cyclone, it is quite selective in its reactions. The truth is, of course, that in any reaction, the energies of the relevant molecular orbitals in the components of the reaction must be of a similar order for any bond-forming or bond-breaking process to occur, and other criteria of reactivity are often of secondary importance.

Evidence for the structure of the adducts (104) and (105) is provided in the usual way by microanalysis and mass spectroscopy, which establish the gross structure. NMR

did not establish the stereochemistry of the adducts. The sulphone adduct (106) was prepared for comparison purposes by addition of piperidine to a cooled stirred suspension of 3,4-dichlorosulpholan in benzene and cyclopentadiene. All these adducts had a four-proton multiplet in the olefinic region, in two groups of two-proton signals, except in (106), where the olefinic resonance of the proton β to the sulphonyl group was observed as a double doublet, the other three vinylic protons resonating as a complex multiplet. All the adducts had a characteristic four-line two proton signal at high field (δ 2.0-2.5) assigned to the methylene bridge. The remaining signals occurred at δ 3.0-4.0 as a complex pattern. The bridgehead methine proton α to the sulphur function in the fused five-ring was buried in this band. However, from the above assignments and by analogy with dimers (95) and (97), a cis-endo configuration can be expected for the adducts. The existence of the four-proton olefinic signal for (105) unambiguously establishes that this regioisomer is exclusively formed. The reason for this specificity is not clear, but it may be a combination of steric effects and the fact that the chlorine-substituted double bond is the more electron-deficient. The mass spectra of the three adducts are quite similar; possible fragmentation pathways are given for (104) (Scheme 19). The fragmentation pattern of sulphone (106) closely resembled that for (104); loss of $SO_2H^{\cdot}$ and elimination of C_2H_2 to give ions of m/e 117 and 91 were the principal pathways observed for (106).

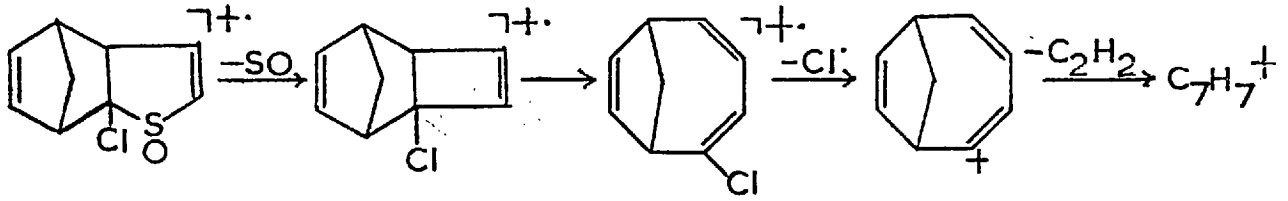


118 166 149 103

117 91

Scheme 19.

The fragmentation pattern for adduct (105) is indicated briefly in Scheme 20.

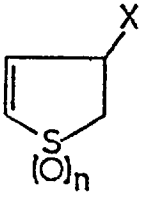


200 152 117 91

Scheme 20.

The absence of a pathway involving OH· loss from (105) is perhaps confirmatory of the absence of the α-bridgehead methine proton.

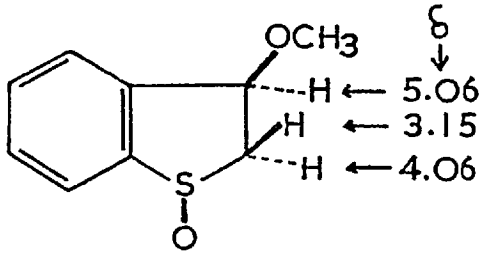
One other possible route to the adducts (104)-(106) can be ruled out; the intermediates, e.g. (107), in the formation of thiophen oxides and dioxides are not involved in the trapping reactions with cyclopentadiene under the conditions employed to make the adducts.



(107) n=1 X=OTs
(108) n=2 X=H
(109) n=2 X=Cl

While the adducts (104)-(106) were formed at room temperature, 2-sulpholene (108) only gives an adduct with cyclopentadiene at elevated temperatures[54]. The intermediate (109) in the formation of (106) was inert to cyclopentadiene for extended periods at room temperature.

Finally, an anomalous reaction may be noted. Thiophen-1-oxide was generated in the usual way from ditosylate (88) and ion-exchange resins in methanol, and in the presence of norbornadiene. No adduct was formed, neither was any dimer (95) observed. A compound was isolated in low yield with a molecular weight of 182; the NMR showed a methoxy singlet, three one-proton double doublets at δ 5.06, 4.06 and 3.15, and a four-proton aromatic multiplet. The only structure which fits these facts is (110), though it was not observed in subsequent reactions. The reason for its formation in this particular case is obscure.



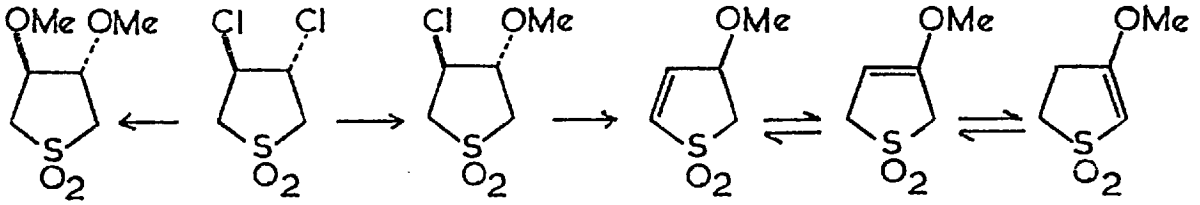
(110)

5. SULPHOLAN CHEMISTRY.

When considering possible starting materials for thiolan synthesis, the vast number of substituted sulpholans, in many cases prepared from 3-sulpholene, seemed ideal for this purpose. Reduction of a sulphonyl group to a sulphide is notoriously difficult, various rather obscure reagents being cited in the older literature, e.g. sulphur[55], phosphorus

pentachloride[56], and hydrogen sulphide[56].

Lithium aluminium hydride seems the reagent of choice[57], though a recent report states that di-isobutylaluminium hydride (Dibal-H) is more effective. Sulpholan itself gives thiolan in 73% yield[58]. Trials with various derivatives of 3,4-diaminosulpholan and LAH gave only complex mixtures. An attempt was made to prepare the bis-methyl ether (111) by reaction of 3,4-dichlorosulpholan (112) with an excess of sodium methoxide. The crystalline enol ether (113) was obtained instead, probably via the equilibria indicated in Scheme 21, all of which are well-documented[59].

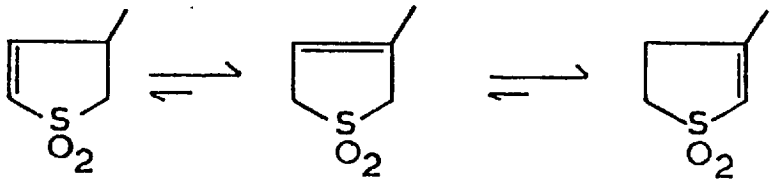


(111) (112) (113)

Scheme 21.

It is worth noting that in small-ring sulphones, various constraints operate which might alter the relative thermodynamic stabilities of the α,β- and β,γ-unsaturated isomers, e.g. ring strain effects or hybridisation changes[60]. The overwhelming evidence that the latter isomer is the more stable in acyclic systems has been discussed in the Review section (p.14); in five-membered cyclic systems, equilibration of the 2- and 3-sulpholenes gives a 6:4 predominance of the former[61]. Allowing for statistical effects, this implies that 3-sulpholene is stabilized by about 0.2kcal. over the 2-isomer. In the six-membered cyclic series, the β,γ-isomer is by far the most stable[62]. In five-membered rings, β-

substitution of alkyl or electron-donating +M substituents favours the α,ß-isomer very strongly, as shown in the equilibration of isoprene sulphone (3-methyl-3-sulpholene) (114).



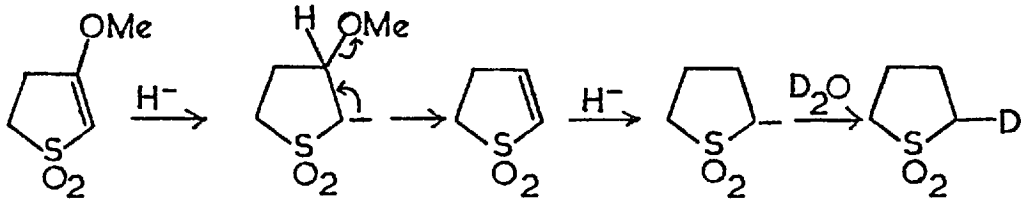
(114)

~0% 9% 91%

The enol ether (113) was reacted with a large excess of LAH in ether. The principal reaction product after aqueous workup was found to be sulpholan, with a very small amount of thiolan, isolated as its mercuric chloride derivative. This was curious, as sulpholan is readily reduced by LAH under these conditions to thiolan. In order to explain this, the mechanism of reduction of sulphones by LAH has to be considered.

The reaction pathway is highly dependent upon the structure of the substrate. With acyclic sulphones, the α-monoanion is involved; labelling studies[64] show that with sulpholan, no proton abstraction occurs on reduction, the most likely mechanism being coordination of the sulphone oxygen and the aluminium centre, followed by nucleophilic attack of hydride ion on sulphur, displacing oxygen. It is tempting, though illogical, to extrapolate this observation and conclude that since reduction does not involve the α-anion, then the anion is not reduced. Hence if the α-anion of sulpholan (115) is formed during the reduction of (113), then it may be stable to further reduction, and thus

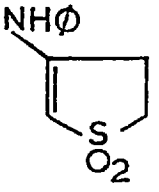
sulpholan is isolated upon protonation, even in the presence of excess LAH. We can thus propose the mechanism of Scheme 22, invoking consecutive Michael addition of hydride ion, with intermediate elimination of methoxide ion.



(115) (116)

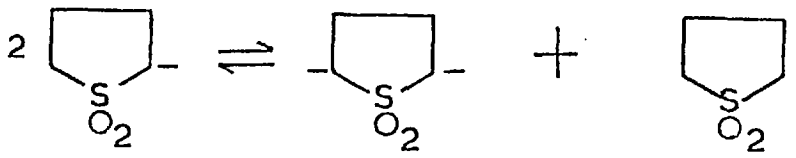
Scheme 22.

This theory was tested by showing that under the same conditions, 2-sulpholene also was reduced to sulpholan, and also that workup in D_2O, gave exclusively monodeuterated sulpholan (116), identified by mass spectroscopy (M^+=121). NMR shows that the label is in the 2-position, from the relative areas of the α- and ß-proton signals. It was also shown that the enamine (117) was reduced in the same way to aniline and sulpholan.



(117)

The small amount of thiolan isolated might arise during workup where sulpholan might be liberated before all the LAH had been destroyed; or quite probably, the transient 2-sulpholene or even a second molecule of (115) could act as a proton source (Scheme 23).

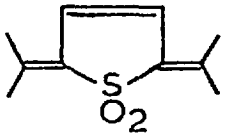


(118)

Scheme 23.

The dianion (118) would give rise to dideuterated sulpholan (M^+=122) which is observed in very low intensity, though this could be due to slight scrambling of deuterium under the conditions of workup.

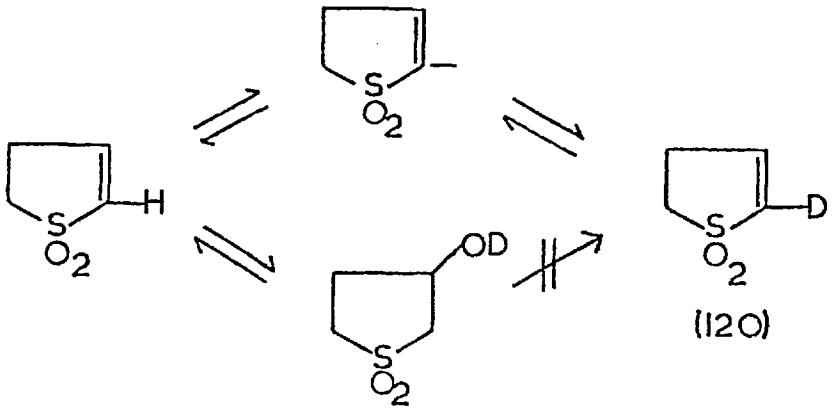
Also of interest to us was the alkylation of sulpholenes, both as a useful reaction in biotin synthesis, and as a route to terminally substituted butadienes (by loss of sulphur dioxide from the alkylated sulpholene). It is known that 3-sulpholene can form a diisopropylidene derivative (119) with acetone in aqueous base[3].



(119)

It is also reported that the α-vinyl proton in 2-sulpholene exchanges rapidly in $NaOD/D_2O$ to give (120), without the intervention of Michael adducts such as (121) (Scheme 24)[63].

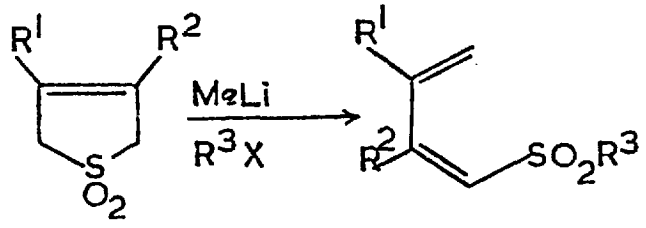
Scheme 24.



(120)

(121)

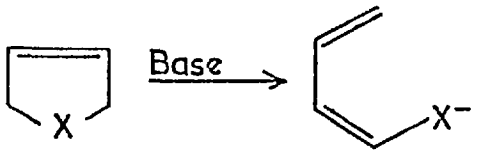
2-Sulpholene showed no tendency to form an α-anion with various bases. 3-Sulpholene, whose α-protons were expected to be highly acidic, only formed an anion with sodium hydride in DMF at 60°, when much decomposition occurred. On workup with methyl iodide, no α-alkylated product was found, but instead the butadienyl sulphone (124) was isolated.



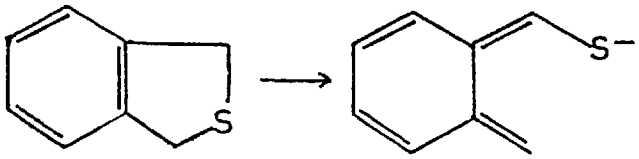
(122) R^1= H, R^2=Me
(123) R^1=R^2=Me

	R^1	R^2	R^3
(124)	H	H	Me
(125)	H	H	ϕCH_2
(126)	H	Me	Me
(127)	H	Me	ϕCH_2
(128)	Me	Me	ϕCH_2
(129)	H	H	Bu^n
(130a)	H	H	Li
(130b)	Me	Me	Li

We now have a complete family of reactions which are the formal analogues of the electrocyclic elimination of sulphur dioxide from 3-sulpholenes. The base-catalysed ring-opening of compounds (131) is known for X=O[16], X=S[16], $X=\overset{+}{S}R$, SO and SO_2, and also the benzothiophen (132)[65].



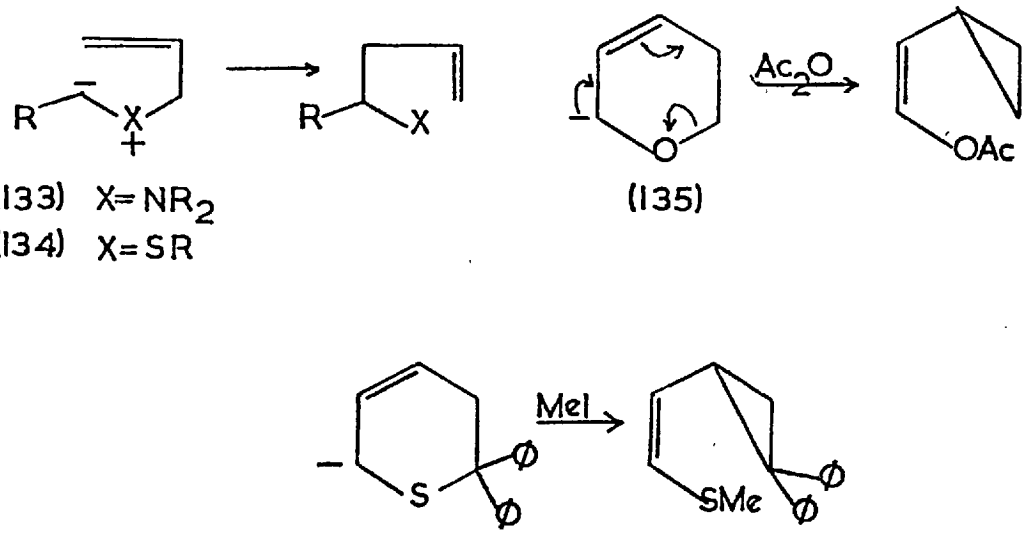
(131)



(132)

The analogous reaction for the acyclic compounds (133)[66] and (134)[67] has been discussed by Rautenstrauch. The homocyclic dihydropyran case (135)[68] and dihydrothiopyran (136)[69] have

also been documented (Scheme 25).



(133) X=NR_2
(134) X=SR

(135)

(136)

Scheme 25.

These reactions have not been rigorously shown to be concerted, though a high degree of stereospecificity is observed in all cases, only the Z isomer being formed.

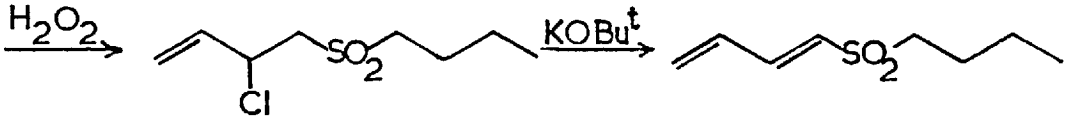
A milder method of ring-opening of sulpholenes was developed, in which a solution of the sulpholene in ether was treated with methyl-lithium at room temperature. An exothermic reaction occurred, and a white precipitate was obtained which was filtered off. This was the lithium salt of the butadienylsulphinic acid, e.g. (130), in quantitative yield. This was a white solid, stable to air and moisture.

Reaction of isoprene[70] and 2,3-dimethylbutadiene[71] with sulphur dioxide gave the crystalline sulphones (122) and (123) respectively. These gave lithium salts in the same fashion as 3-sulpholene when treated with methyl-lithium. These salts were not alkylated in ether by alkyl halides, but when stirred in DMF with an alkyl halide, an excellent yield of the sulphones (124)-(129) was obtained. The

structures followed from the NMR spectra, which are set out in Table 6, where the butadiene skeleton is numbered as shown (see next page).

It is clear from this table that the relative shifts of H^2 and H^3 are highly dependent upon the nature of the alkyl group R^3 and upon the substitution of the diene system. The assignments are all consistent with the assignment of the cis-configuration about the sulphonyl-substituted double bond. Though analysis of some spectra was difficult, the highly characteristic signal at ca. δ 5.6 due to the terminal methylene group established the structures at once.

A sample of the trans-sulphone (138) was made for the purposes of comparison by oxidation of the chlorosulphide (42) to sulphone (137) followed by elimination to (138). Its spectrum is listed in Table 6.

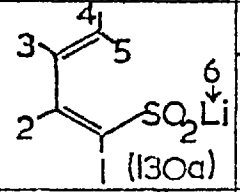
(42) 

(137) (138)

The vinylic assignments of (138) are not strikingly different from those of (124) or (129). A slightly higher value of $J_{1,2}$ is expected and the signal attributed to H^2 in both cases is unaltered.

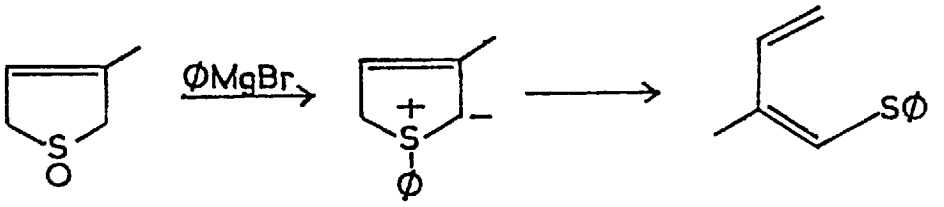
Of related interest is the rather specific ring-opening of the non-symmetrical isoprene sulphone (122). The crude lithium sulphinate salt from the reaction with methyl-lithium showed numerous olefinic signals in the NMR that were not

TABLE 6.

Compound	Shifts, (δ), Assignments and Multiplicities*							Coupling Consts., Hz			
	(1)	(2)	(3)	(4)	(5)	(6)	Other	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
 (130a)	5.90, d	6.43, dd	7.00, oct	5.41, 2H, m		-	-	10	10	6	18
(124)	6.53, d	7.28, dd	6.57, oct	5.72, 2H, m		3.00, 3H, s	-	13	10	8	8
(125)	5.93, d	6.40 - 7.30, 2H, m		5.53, 2H, m		4.16, 2H, s	7.35, 5H, aromatic m	11	-	-	-
(126)	6.16, bs	2.00, 3H, bs	7.53, dd	5.57, 2H, m		3.00, 3H, s	-	-	-	10	17
(127)	5.93, bs	2.00, 3H, bs	7.23, dd	5.50, 2H, m		4.26, 2H, s	7.36, 5H, aromatic m	-	-	8	18
(128)	6.06, bs	2.00, 3H, bs	2.07, 3H, bs	4.77, bs	5.10, bs	4.30, 2H, s	-	-	-	-	-
(138)	6.40, d	7.21, dd	6.53, oct	5.75, 2H, m		3.06, 2H, t	0.85-2.15, 7H, m	15	10	11	19

*All are one-proton signals unless otherwise stated; the term "octet" is applied to the 8-line pattern of the M proton in an ABMX spin system.

attributable to exclusive attack of the base at either α-position. However, on alkylating with benzyl bromide to give (127), the small amount of isomeric sulphone (15-20%) was removed completely by recrystallization of the major product. Attempted isolation of the minor product from the mother liquors appeared to lead to decomposition of the minor component on t.l.c. This specificity of attack (ca. 80% in the 2-position) has been observed in the ring-opening of the sulphoxide (139) with Grignard reagents to give, it was claimed, exclusively sulphide (140)[70].

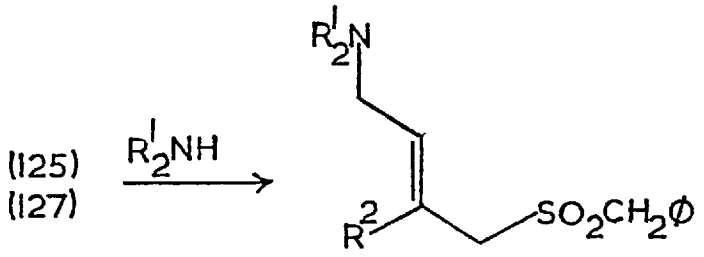


(139) (140)

This was attributed to an electronic effect of the 3-methyl group which increases the acidity of the 2-methylene group over that of the 5-methylene, and a similar, though weaker, effect may operate in the sulphone series, in which specificity of reaction is good, though apparently not so pronounced as in the case of the sulphoxide.

The dienyl sulphones were unstable oils [(124), (126), (129)], or crystalline solids [(125), (127), (128)], which were much more stable than the oils; the latter readily polymerized on storage at 0°. Unfortunately, these sulphones do not readily form Diels-Alder adducts, being unreactive towards 2,3-dimethylbutadiene and ethyl vinyl ether at 110°.

The action of nucleophiles on such systems was of interest because of their availability, the sulphone (127) being prepared rapidly and specifically from the readily available isoprene sulphone in high yield; and because of their obvious potential uses as an activated isoprene unit or "synthon". This would effectively be an electrophilic synthon, to compliment the nucleophilic synthons developed by Julia (see p.18). There are, however, two possible modes of addition of nucleophiles to the dienyl sulphones; (a) addition at the 2-position or (b) addition at the 4-position, of which only the latter would be of interest in isoprenoid work. Time did not permit investigation of carbon nucleophiles, but secondary amine nucleophiles gave exclusively 1,4-products with (125) or (127). Use of an excess of amine gave only the monoadduct.

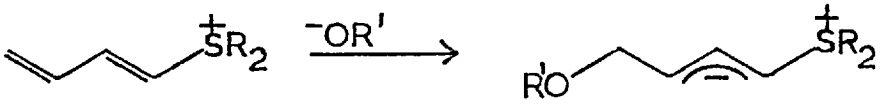


	R^1	R^2
(141)	$-(CH_2)_5-$	H
(142)	Me	H
(143)	Me	Me

Compound (141) had an unremarkable mass spectrum, showing, besides the molecular ion (M^+=293), a benzylsulphonyl fragment corresponding to C_1-S bond fission. Its structure followed from NMR spectroscopy. The olefinic protons appeared as an overlapping pair of triplets at δ 5.87 and 5.76; the two methylene signals resonated at δ 3.03 (C_2) and 3.60 (C_4) as doublets. The multiplet at δ 5.6, characteristic of a

terminal methylene group, had completely disappeared. These observations are only accounted for by the structures shown. The adduct of (125) with dimethylamine, (142), was similar in properties. The reaction between dimethylamine and sulphone (127) was sluggish and incomplete, but a singlet methylene at $\delta 3.63$ (C_1) and a doublet methylene resonance at $\delta 3.03$ (C_4) and a singlet methyl signal at $\delta 2.27$ proved the formation of the 1,4-adduct (143).

There is a literature precedent for this type of addition; the analogous sulphonium salts (144) prefer to add alkoxides in the 4-position to give the ylids (145)[71].



(144) (145)

EXPERIMENTAL

I counted two-and-seventy stenches,
All well-defined, and several stinks!

(S.T. Coleridge)

All melting—points were recorded on a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were obtained on a Unicam SP200 spectrophotometer. Ultraviolet spectra were recorded on a Unicam SP800 instrument. Proton NMR spectra were recorded on a Varian T60 or HA100 spectrometer, using deuterochloroform solutions with tetramethylsilane as internal reference, unless otherwise stated. Mass spectra were obtained on a MS9 instrument.

All organic extracts from an aqueous phase were dried with sodium sulphate prior to removal of solvent on a rotary evaporator.

Solvents used were GPR grade. Ether and benzene were dried over sodium. THF was distilled immediately before use from LAH. Petrol refers to petroleum ether, the cuts being referred to by boiling range.

Thin-layer chromatography used silica gel prepared according to Stahl.

NOTE. When quoting chemical shifts (in δ, ppm from tetramethylsilane) of complex resonances, the following convention is used. For a complex group of superimposed resonances, the shift is quoted as a range, e.g. δ 1.74-2.30 (4H, m). For a single resonance with a spin-spin coupling pattern too complex for analysis, the shift is given as the centre of the multiplet, e.g. δ 2.02 (4H, m).

4-(2-Thenoyl)-butyric acid (5).- Aluminium chloride (36g) was added during 1h. to a stirred mixture of glutaric anhydride (12.5g) and thiophen (10g, 0.12M) and nitrobenzene (120ml), kept at 0-5°. Stirring was continued for 4h. at room temperature and the resulting complex was decomposed by 2N hydrochloric acid. The nitrobenzene was removed by steam distillation and the hot aqueous solution decanted from residual tars. The acid (5) crystallized from the aqueous phase on cooling. Extraction of the tarry material with boiling sodium carbonate solution yielded a further crop of acid. Overall yield was 11.7g (47%), m.p. 92-94°, (lit.[72] 92-94°); ν_{max} (Nujol) 1694, 1653, 1293, 1197, 750, 740cm^{-1}; λ_{max} (EtOH) 267nm (ε 62,000), 283nm (ε 50,000); δ 10.70 (1H, s), 7.33 (2H, m), 7.21 (1H, m), 2.96 (2H, t), 2.00-2.64 (4H, m).

5-(2-Thienyl)-valeric acid (6).- The acid (5) (7.5g, 38mM), 85% aqueous hydrazine (7.5ml) and ethylene glycol (30ml) were refluxed for 1h. and cooled to 60° when potassium hydroxide pellets (15g) were added. After the reaction had subsided, acidification of the mixture gave crude acid (6) (6.8g, 91%). Recrystallized material had a m.p. 41-42° (lit.[72] 40-41°); ν_{max} (Nujol) 1712, 935, 852, 693cm^{-1}; λ_{max} (EtOH) 241nm (ε 4,200); δ 10.88 (1H, s), 7.02 (3H, m), 2.88 (2H, t), 2.44 (2H, t), 2.07 (4H, m).

Reduction of acid (6).- The acid (6) (5g) and methanol (25ml) were stirred in liquid ammonia (25ml) and lithium metal (0.5g) added in small portions over 1h. After stirring for 6h., the ammonia was allowed to evaporate off and the residue acidified, and extracted with ether. NMR analysis of the

product showed a complete absence of olefinic signals; some starting material was present.

6-Bromo-hexa-2,4-dienoic acid, methyl ester (10).- Methyl sorbate (10g, 79mM) was heated to 120° with N-bromosuccinimide (13.5g, 79mM) and stirred at this temperature until all solids had dissolved, and then for a further 30 min. The cooled reaction mixture was diluted with carbon tetrachloride (20ml) and the succinimide filtered off and washed with carbon tetrachloride. The filtrate was poured into petrol (40-60°) (500ml) and the precipitate of red tar filtered off. Evaporation of the solvents gave a yellow liquid which gave the bromoester (10) upon fractionation through a spinning band column as a colourless oil (1.9g, 12%); b.p. 75-82°/0.5mm (lit.[8] 73-77°/0.1mm); ν_{max} (neat) 2980, 1720, 1640, 1615, 1440, 1340, 1275, 1250, 1200, 1150, 1115, 1000, 860, 830, 720cm^{-1}; δ 7.33 (1H, m), 6.20-6.50 (2H, m), 5.97 (1H, d), 4.10 (2H, d), 3.80 (3H, s).

6-Thiolacetoxy-hexa-2,4-dienoic acid, methyl ester (11).- Bromide (10) (1.0g, 4.7mM) in DMF (5ml) was treated with potassium thiolacetate (0.6g, 5.2mM) in DMF (2ml). An exothermic reaction occurred; after 30min, water was added and the oil extracted with ether, and the ether layer was washed well with water. The oil obtained on removal of solvent was chromatographed on a short silica column (20g SiO_2) and eluted with ether/petrol (40-60°) (3:7). The thiolacetate so obtained was distilled in a ball-oven to give a yellowish oil (0.31g, 32%); ν_{max} (neat) 2920, 1680, 1610, 1430, 1250, 1125, 1000cm^{-1}; δ 7.30 (1H, m), 5.90-6.63 (2H, m), 5.89 (1H, d), 3.79 (3H, s), 3.37 (2H, d),

2.33 (3H, s).

When a sample of thiolacetate (11) was refluxed with 5% methanolic hydrogen chloride, a complex mixture (t.l.c.) was observed to be formed. NMR analysis showed a triplet at δ 1.58, exchangeable with D_2O, indicating the presence of the unstable thiol (12).

(5,5-Diethoxy-3-thiapent-1-yl)triphenylphosphonium bromide (17).- Mercaptoacetal (0.75g, 5mM) and vinyltriphenylphosphonium bromide (1.84g, 5mM) were dissolved in dichloromethane (20ml) and triethylamine (2 drops) added. An immediate slightly exothermic reaction occurred and removal of solvent gave an orange syrup which would not crystallize.

A small portion of this syrup (100mg) was dissolved in water and a solution of tetraphenylboron sodium (100mg) in water was added. The white tetraphenylborate complex was filtered off and recrystallized from ethanol; m.p. 126.5-128.5°.

(Found: C, 78.08%; H, 6.78%. $C_{50}H_{52}BPSO_2$ requires C, 79.14%; H, 6.91%.)

(4-Formyl-3-thiabut-1-yl)triphenylphosphonium bromide (18).- The crude adduct (17)(from 5mM of each reactant) was dissolved in THF (20ml) and 2N hydrochloric acid (10ml) added. The mixture was boiled and allowed to cool over 2h. The THF was removed and the aqueous phase extracted with methylene chloride (100ml) to give (18) as a syrup. The tetraphenylborate complex was prepared as above and recrystallized from acetone-water; m.p. 169-173°.

(Found: C, 79.14%; H, 6.46%. $C_{42}H_{42}BPSO$ requires C, 79.23%; H, 6.65%.)

The crude aldehyde (5mM) was dissolved in pyridine (5ml)

and triethylamine (5ml) and left overnight at room temperature. After acidification and ether extraction, NMR analysis of the product showed that extensive decomposition had occurred, but that a trace of dihydrothiophen was also present.

Trans-1-chloro-4-butylthiobut-2-ene (21).- Butanethiol (9.0g, 0.1M) in methanol (20ml) and potassium hydroxide (5.6g, 0.1M) was added dropwise to a cooled stirred solution of trans-1,4-dichlorobut-2-ene (12.5g, 0.1M) in methanol (20ml). Potassium chloride was precipitated, the mixture warmed for 30 min at 60°, and then poured into water. The oil was extracted with ether. The sulphide (21) was obtained as an oil after distillation in a ball-oven (13.1g, 70%); ν_{max} (neat) 1660, 1445, 1250, 965cm^{-1}; δ 5.76 (2H, m), 4.06 (2H, d), 3.10 (2H, d), 2.47 (2H, t), 0.8-1.7 (7H, m).

The benzyl derivative (22) was prepared similarly from benzyl mercaptan (12.4g, 0.1M) in 95% yield (20.2g); ν_{max} (neat) 1660, 1600, 1500, 1070, 960, 765cm^{-1}; δ 7.25 (5H, s), 5.63 (2H, m), 3.98 (2H, d), 3.62 (2H, s), 2.97 (2H, d).

A sample of (21) was converted to its isothiuronium picrate which formed yellow rhombs, m.p. 135-137° (from ethanol-water). (Found: C, 40.45%; H, 4.72%; N, 15.67%. $C_{15}H_{22}N_5O_7S_2$ requires C, 40.26%; H, 4.73%; N, 15.65%.)

Trans-1-chloro-4-thiolacetoxybut-2-ene (23).- A solution of potassium thiolacetate (1.14g, 10mM) in DMF (3ml) was added dropwise to a solution of trans-1,4-dichlorobut-2-ene (1.25g, 10mM) in DMF (3ml). The reaction mixture was poured into water after 30 min and the oil extracted with ether. The crude product was distilled in a ball-oven to give the

thiolacetate as a colourless oil (1.30g, 79%); δ 5.83 (2H, m), 4.06 (2H, m), 3.50 (2H, m), 2.27 (3H, s).

The isothiuronium picrate was prepared and recrystallized from ethanol-water as yellow rhombs, m.p. 136-138°. (Found: C, 36.14%; H, 3.49%; N, 16.20%; S, 15.02%. $C_{13}H_{15}N_5O_8S_2$ requires C, 36.02%; H, 3.49%; N, 16.16%; S, 14.80%.)

When the thiolacetate (23) (0.5g) was hydrolysed with 1N methanolic hydrogen chloride under reflux for 30 min, the reaction mixture was poured into water and ether-extracted to give the thiol (24) as a malodorous unstable oil (0.15g, 40%); δ 5.77 (2H, m), 4.03 (2H, m), 3.12 (2H, m), 1.47 (1H, t, exch. with D_2O).

Pyrolysis experiments.

(a) Sulphide (21) (0.5g) was heated neat in a sealed tube with a few crystals of iodine at 155° in boiling bromobenzene for 2h. NMR examination of the product showed that the only products were thiophen (δ 7.30, 7.10) and n-butyl chloride (δ 3.53, t). No reaction was observed in boiling chlorobenzene (b.p. 135°).

(b) Pyrolysis of (21) under the same conditions, only substituting galvinoxyl or diphenylpicrylhydrazide for iodine, gave starting material only.

(c) Sulphide (22) (0.5g) was pyrolysed in toluene solution (3ml) at 150° with an iodine crystal. NMR analysis of the product showed that (22) had decomposed completely, and that dihydrothiophen and benzyl chloride were amongst the products.

In the case of (a) and (b), considerable darkening of the reaction mixture occurred.

Cis-but-2-ene-1,4-diol[73] and cis-1,4-dichlorobut-2-ene[74] were prepared by literature methods.

1-butyl-2,5-dihydrothiophenium chloride (33) and its 1-ethyl analogue (34).- The chlorosulphide (28) was made by reaction of butanethiol (2.88g, 32mM), potassium hydroxide (1.80g, 32mM) and cis-1,4-dichlorobut-2-ene (4.0g, 32mM) in methanol (20ml) as detailed for the trans-isomer (21). The potassium chloride was filtered off and removal of the methanol gave an oil which crystallized on trituration with ether. The deliquescent crystals of salt (33) (2.57g, 45%) were stored in a desiccator and had $\delta(CDCl_3)$ 6.07 (2H, bs), 4.60 (4H, ABq, J=16Hz), 3.56 (2H, t), 0.8-2.1 (7H, m). In D_2O, this changed to δ 6.12 (2H, bs), 4.30 (4H, m), 3.20 (2H, t), 0.77-2.10 (7H, m).

Using ethanethiol (2.48g, 3.0ml, 40mM), cis-1,4-dichlorobut-2-ene (6.0g, 40mM) and potassium hydroxide (2.53g) in methanol (20ml) gave the 1-ethyl-2,5-dihydrothiophenium chloride (34), (4.2g, 70%). Its tetraphenylborate salt was recrystallized from acetone-water and had an m.p. 219-221°. (Found: C, 82.73%; H, 7.12%. $C_{30}H_{31}BS$ requires C, 82.93%; H, 7.19%.)

Cis-1-chloro-4-thiolacetoxybut-2-ene (31).- This was made in the same fashion as the trans isomer (23) in 93% yield and had ν_{max} (neat) 1690, 1350, 1250, 1130, 960, 785cm^{-1}; δ (neat liquid) 5.82 (2H, m), 4.17 (2H, d), 3.57 (2H, d), 2.30 (3H, s).

The isothiuronium picrate was prepared and recrystallized from ethanol-water as needles, m.p. 119-121°.

(Found: C, 35.93%; H, 3.64%; N, 15.94%. $C_{13}H_{15}N_5O_8S_2$ requires C, 36.02%; H, 3.49%; N, 16.16%.)

When thiolacetate (31) was hydrolysed as described for the trans-isomer (23), the thiol (32) was obtained as an unstable oil on workup in 59% yield; δ 5.63 (2H, t), 4.13 (2H, d), 3.30 (2H, dd), 1.67 (1H, t, exch. D_2O). Treatment of this thiol with an equivalent of triethylamine or pyridine produced a polymer.

1-Butyl-3,4-dibromotetrahydrothiophenium chloride (35).- The sulphonium salt (33) (1.0g, 5.6mM) was dissolved in chloroform (50ml) and a solution of bromine (1.0g, 0.3ml, 5.6mM) in chloroform (5ml) added dropwise with stirring. Evaporation of the solvent gave a reddish oil which, when triturated with acetone, gave white crystals of dibromide (35) (0.93g, 49%); δ 5.83 (2H, m), 4.36 (4H, m), 3.60 (2H, t), 0.77-1.90 (7H, m). The tetraphenylborate salt gave consistently incorrect microanalysis results, which was attributed to decomposition by HBr elimination; its m.p. was depressed by further recrystallization, a maximum m.p. of 161-162° being observed.

Cis-1-butylthiobutadiene (40).- Dowex 1X-8 ion exchange resin in the OH^- form (10g in methanol) was added to a solution of the sulphonium salt (33) (1.0g) in methanol (20ml). The mixture was stirred for 2h. under nitrogen, when t.l.c. indicated the disappearance of the starting material, and the appearance of a single non-polar compound. The resin was then filtered off and the oil obtained when the solvent was removed was triturated with petrol (40-60°) and the solution was

decanted from a small amount of tar. The petrol was removed and the resulting oil distilled in a ball-oven to give the dienyl sulphide (40) as a colourless oil (0.90g, 90%); ν_{max} (neat) 3040, 2980, 2960, 2955, 1620, 1520, 1460, 1380, 1330, 1290, 1270, 1220, 1160, 990, 900, 755cm^{-1}; λ_{max} (EtOH) 286nm (ε 17,000); NMR data are presented in Table 1 (p.83).

3-Chloro-4-butylthiobut-1-ene (42).- A solution of n-butylsulphenyl chloride (29.4mM; from dibutyl disulphide and sulphuryl chloride at -20°) in dichloromethane (50ml) was added dropwise to a solution of a large excess of butadiene in dichloromethane (50ml) stirred at -10°. The orange colour of the sulphenyl halide was rapidly discharged; removal of excess diene and solvent at room temperature gave crude chlorosulphide as a colourless oil (10.2g, 97%). A portion was distilled from a ball-oven and gave δ5.93 (1H, dq), 5.10-5.47 (2H, m), 4.44 (1H, dt), 2.90 (2H, m), 2.57 (2H, t), 0.70-1.80 (7H, m); m/e 178 (M^+; 21), 140 (77), 129 (16), 88 (100), 61 (74), 57 (52), 56 (36), 55 (55), 53 (65).

Trans-1-butylthiobutadiene (43).- The chlorosulphide (42) (6.0g, 33.6mM) was dissolved in dry THF (10ml) and added to a stirred suspension of potassium t-butoxide (4.78g, 41.8mM) in THF (20ml) at 0°. After 1h. at room temperature, water was added and organic material extracted with ether. As much coloured impurity as possible was removed by washing the ethereal extracts with 2N sodium hydroxide solution. Evaporation of the ether and distillation of the residue in a ball-oven gave the sulphide (3.26g, 68%); ν_{max} (neat) 3040, 2980, 2960, 2955, 1620, 1520, 1460, 1380, 1330, 1290, 1270, 1220, 1120, 1110, 990, 900, 890, 755cm^{-1}; λ_{max} 281nm

(ε 19,500); NMR data are presented in Table 1 (p.83).

2,5-Dihydrothiophen (19).- Cis-1,4-dichlorobut-2-ene (25g, 0.2M) in DMF (80ml) and a solution of sodium sulphide (Na_2S, $9H_2O$; 54g, 0.225M) in water (90ml) were added simultaneously at the same rate to stirred and cooled DMF (200ml). When the exothermic reaction was complete, water (250ml) was added and the reaction mixture distilled under water-pump vacuum until no more oily drops were collected. The distillate was then extracted with ether (2 x 100ml) and the extracts washed well with water. On evaporation of solvent at room temperature, dihydrothiophen is obtained as a colourless oil (5.04g, 30%); δ 5.88 (2H, s), 3.77 (4H, s)[75].

2,5,7,10-Tetrahydrodithiecin (45).- If the steam-distillation in the above preparation was continued after all the dihydrothiophen was collected, white crystals were observed in the condenser, which were collected and recrystallized from benzene-petrol ether (60-80°) to give the sulphide (258mg); m.p. ca. 136° accompanied by sublimation; δ 5.46 (4H, t), 3.12 (8H, d).

(Found: C, 55.8%; H, 7.0%; S, 36.9%. $C_8H_{12}S_2$ requires C, 55.7%; H, 7.0%; S, 37.2%.)

2,5-dihydrothiophen-1-oxide (49)[24].- 2,5-Dihydrothiophen (6.96g, 81mM), was dissolved in acetone (A.R.; 40ml) and cooled to 0°. Hydrogen peroxide (30%; 9.8ml, 83mM) was added dropwise with stirring so that the temperature of the reaction mixture was kept below 6°. The temperature was allowed to rise to 20° overnight, a small amount of solid was filtered off and the acetone removed. The sulphoxide was taken up in

dichloromethane, dried and the solvent evaporated to give the sulphoxide as an oil (5.23g, 65%). It could be distilled at $55°/10^{-4}$ torr with ca. 70% recovery to give the pure material; ν_{max} 3330, 2980, 2955, 1625, 1400, 1335, 1245, 1135, 1030, 890, 700cm^{-1}; δ 6.03 (2H, s), 3.76 (4H, ABq, J=19Hz).

Cis-1-methylsulphinylbutadiene (51).- 2,5-dihydrothiophen-1-oxide (100mg, 9.8mM) in THF (3ml) was added dropwise to a stirred suspension of sodium hydride (60% dispersion in oil; 40mg, 9.8mM) in THF (10ml) under nitrogen at 0°. After 1h. methyl iodide (200mg) was added and the reaction mixture allowed to warm up overnight. It was then diluted with dichloromethane (30ml) and the inorganic salts filtered off. When the solvents were removed, the sulphoxide (51) was obtained as an oil (85mg, 82%); ν_{max} 3000, 2960, 1630, 1575, 1420, 1310, 1290, 1135, 1040, 960, 940, 800, 780, 755, 640cm^{-1}; λ_{max} 248nm (ε 12,500); δ 6.1-7.5 (3H, m), 5.3-5.8 (2H, m), 2.70 (3H, s).

Trans-3,4-dibromotetrahydrothiophen (52).- 2,5-Dihydrothiophen-1-oxide (0.5g, 49mM) was dissolved in carbon tetrachloride (10ml) and a rapid stream of anhydrous hydrogen bromide passed through the solution for 30 min. A red oil precipitated, and stirring was continued overnight. The solution was then decanted from tars and evaporated; the resulting oil was triturated with petrol (40-60°) and the solution filtered through Celite. Evaporation of the filtrate gave nearly pure dibromide (660mg, 62%); ν_{max} 2950, 1430, 1295, 1230, 1170, 890cm^{-1}; δ 5.60-4.86 (2H, m), 3.10-3.96 (4H, m).

It was better obtained from dihydrothiophen. 2,5-Dihydro-

thiophen (4.3g, 50mM), was dissolved in chloroform (100ml) and cooled to ca. 3°. Bromine (16.0g, 5.5ml, 100mM) in chloroform (50ml) was added over 2h. while the temperature was maintained below 5°. A bright orange solid (the bromosulphonium bromide) was precipitated towards the end of the addition. The solution was decanted from the solid and shaken with dilute sodium bisulphite solution. The solid was extracted with chloroform and the extracts similarly decolourized. The combined colourless extracts were dried and evaporated and the oil thus obtained was treated with petrol (40-60°) and the solution decanted from tars. Removal of the solvent gave the pure dibromide (10.4g, 84%).

Oxidation of two samples of these dibromides with excess hydrogen peroxide in acetic acid gave the sulphone (54), identical to authentic material; m.p. 141-142°:(lit.[30] 141-142°); ν_{max} (Nujol) 1410, 1330, 1320, 1295, 1265, 1240, 1210, 1180, 1145, 1120, 910, 840, 730cm^{-1}. A mixed m.p. showed no depression.

Phenyl azide and its p-nitro- and p-methoxy-derivatives were prepared from aniline, p-nitroaniline, and p-anisidine by a literature procedure[76].

1-Phenyl-4,5-bischloromethyl-1H-1,2,3-triazole (56).- 1,4-Dichlorobut-2-yne (7.0g, 57mM) and phenyl azide (7.0g, 59mM) were refluxed in benzene (20ml) for 48h. the benzene was then evaporated and the black oil dissolved in acetone (30ml) and treated with charcoal (1g) for 2h. at room temperature. The filtered solution was evaporated, and the resulting oil was triturated with five 10ml portions of

petrol (40-60°) to give the triazole as a light yellow crystalline powder (6.8g, 49%). A sample recrystallized from petrol (60-80°) had m.p. 50-52°; δ 7.57 (5H, s), 4.36 (2H, s), 4.10 (2H, s).

(Found: C, 48.51%; H, 3.83%; N, 17.04%. $C_{10}H_9Cl_2N_3$ requires C, 49.60%; H, 3.75%; N, 17.36%).

1-(4-Methoxyphenyl)-4,5-bischloromethyl-1H-1,2,3-triazole (57).- This was prepared similarly, using p-methoxyphenyl azide, in 71% yield, and recrystallized from petrol (60-80°) to give pure triazole; m.p. 75-77°; δ 7.33 (4H, m), 4.90 (2H, s), 4.66 (2H, s), 3.93 (3H, s).

(Found: C, 48.78%; H, 4.07%; N, 15.39%. $C_{11}H_{11}Cl_2N_3O$ requires C, 48.55%; H, 4.07%; N, 15.44%).

1-(4-Nitrophenyl)-4,5-bischloromethyl-1H-1,2,3-triazole (58).- This was made similarly from p-nitrophenyl azide in 63% yield. The triazole was recrystallized from petrol (60-80°) and analytical material had a m.p. 135-137°; δ 8.52 (2H, d), 7.88 (2H, d), 4.88 (2H, s), 4.75 (2H, s).

(Found: C, 41.93%; H, 2.85%; N, 19.50%. $C_{10}H_8Cl_2N_4O_2$ requires C, 41.88%; H, 2.81%; N, 19.52%).

1-(4-Methoxyphenyl)-4,6-dihydrothieno[3,4-d]-1H-1,2,3-triazole (60).- Triazole (57) (272mg, 1mM) in ethanol (15ml) was treated with a solution of sodium sulphide (Na_2S, $9H_2O$; 270mg, 1mM) in ethanol-water (5:1; 10ml). After 1h. starting material had disappeared (t.l.c.) and the reaction mixture was diluted with water. Extraction of the aqueous phase with methylene chloride gave the product as a crystalline foam (300mg). This was chromatographed on a 1mm silica plate and eluted with a 6% solution of methanol in dichloromethane.

The band of R_f 0.2-0.6 was removed to give the thienotriazole (60) (190mg, 81%) as a crystalline foam, m.p. 84-91°; δ 7.23 (4H, m), 3.91 (7H, m); m/e 233 (M^+; 47), 159 (100), 147 (55), 133 (66), 121 (37), 86 (100).

Cis-3,4-dihydroxytetrahydrothiophen (67)[48,77].- A solution of potassium permanganate (30.3g, 0.19M) and anhydrous magnesium sulphate (23g) in water (400ml) was added to a well-stirred solution of cis-1,4-dichlorobut-2-ene (30g, 0.19M) in ethanol (300ml) at -50° at such a rate that the temperature was kept below -25°. When addition was complete, the reaction mixture was acidified with concentrated sulphuric acid and sodium bisulphite (30g) added to dissolve the brown precipitate of manganese dioxide. The clear aqueous solution was then continuously extracted with ether for 48h. to give the crude meso-1,4-dichloro-2,3-butanediol (65) as a white solid (26.2g, 69%); ν_{max} (Nujol) 3300, 1420, 1335, 1300, 1260, 1235, 1160, 990, 860, 705cm^{-1}; δ ($CDCl_3$/TFA) 4.12 (2H, m), 3.87 (4H, m). A portion of this dichloro-compound (20g, 0.13M) in ethanol (100ml) was treated with a solution of sodium sulphide (ca. Na_2S, $2H_2O$; 20.8g, 0.18M) in water (50ml). The mixture was refluxed for 2h. and the ethanol distilled off. The residue was adjusted to pH 5 with concentrated hydrochloric acid and filtered. The filtrate was continuously extracted with ether for at least 72h. to give cis-dihydroxythiolan as a white solid (10.2g, 66%); ν_{max} (Nujol) 3300, 1350, 1315, 1275, 1260, 1220, 1170, 1075, 1025, 980, 920, 850cm^{-1}; δ 4.30 (2H, m), 3.73 (2H, bs, exch. with D_2O), 2.91 (4H, m).

Trans-3,4-dihydroxytetrahydrothiophen (68).- This was made

on the same scale by oxidation of trans-1,4-dichlorobut-2-ene to the (±)-DL-1,4-dichloro-2,3-butanediol (66) in 71% yield; ν_{max} (Nujol) 3200, 1390, 1375, 1240, 1155, 1120, 1060, 915, 860, 780, 720, 660cm^{-1}; δ 3.94 (2H, m), 3.58 (4H, m), 3.26 (2H, bs, exch. D_2O). This was cyclized to trans-dihydroxythiolan in 72% yield using the same method as before; ν_{max} 3250, 1305, 1280, 1215, 1145, 1020, 960, 910, 875, 835, 800, 710cm^{-1}; δ 4.30 (2H, m), 3.58 (4H, m), 3.26 (2H, bs, exch. D_2O).

The respective acetates were made by treatment of the diols with excess acetyl chloride. Cis-3,4-diacetoxytetrahydrothiophen (69) had δ 5.43 (2H, m), 3.26 (4H, m), 2.08 (6H, s). Trans-3,4-diacetoxytetrahydrothiophen (70) had δ 5.34 (2H, m), 3.06 (4H, m), 2.06 (6H, s).

Cis-3,4-ditosyloxytetrahydrothiophen (71).- This was prepared from p-toluenesulphonyl chloride and the diol (67) in pyridine by a standard method[78]. Recrystallization from chloroform-petrol (60-80°) gave the tosylate, m.p. 113-115°; δ 7.53 (8H, m), 4.93 (2H, m), 2.95 (4H, m), 2.40 (6H, s). (Found: C, 50.28%; H, 4.88%; S, 22.28%. $C_{18}H_{20}O_6S_3$ requires C, 50.45%; H, 4.70%; S, 22.45%).

Trans-3,4-ditosyloxytetrahydrothiophen (72) was prepared similarly. When recrystallized from chloroform-petrol (60-80°) the tosylate had an m.p. 80-81°; ν_{max} (Nujol) 1600, 1530, 1220, 1190, 1175, 1140, 1100, 980, 960, 885, 855, 820, 760cm^{-1}; δ 7.59 (8H, m), 5.00 (2H, m), 2.96 (4H, m), 2.49 (6H, s). (Found: C, 50.39%; H, 4.95%; S, 22.16%. $C_{18}H_{20}O_6S_3$ requires C, 50.45%; H, 4.70%; S, 22.45%).

Cis-tetrahydrothieno[3,4-d]-1,3-dioxolan-2-one (75).- Cis-diol (67) (600mg, 5mM) was stirred in ether (50ml) with triethylamine (1.50g, 15mM) at room temperature. A solution of phosgene (ca. 1.50g) in benzene (10ml) was added over 30min; a precipitate of amine hydrochloride formed. The reaction was stirred for a further 2h., after which an excess of phosgene was present. The amine salt was filtered off and the ether solution washed well with water. Evaporation gave the cyclic carbonate as a white solid (254mg, 36%). Recrystallization of a sample from chloroform-petrol (60-80°) gave analytical material, m.p. 81-82°; ν_{max} (Nujol) 1780, 1430, 1325, 1235, 1225, 1165, 1055, 1040, 890, 855, 825, 765, 735, 690cm^{-1}; δ 5.37 (2H, m), 3.06 (4H, m). (Found: C, 41.06%; H, 4.16%; S, 22.13%. $C_5H_6O_3S$ requires C, 41.08%; H, 4.14%; S, 21.94%).

2,2-Dimethyl-cis-tetrahydrothieno[3,4-d]-1,3-dioxolan (76)[79].- Cis-diol (67) (3.0g, 25mM) was refluxed with 2,2-dimethoxypropane (12g) in acetone (150ml) with p-toluenesulphonic acid (100mg) as catalyst, for 10h. The acetone was then removed, the residue dissolved in ether, and the ether extract washed with sodium bicarbonate solution. Evaporation of the ether gave crystals of the acetonide (76) (2.55g, 64%); m.p.52-54°; ν_{max} (Nujol) 1430, 1350, 1300, 1255, 1210, 1170, 1055, 975, 900, 820, 725cm^{-1}; δ 4.86 (2H, m), 2.87 (4H, m), 1.52 (3H, s), 1.35 (3H, s).

Cis-3,4-diazidotetrahydrothiophen (77).- The ditosylate (71) (8.62g, 20mM) was dissolved in DMSO (70ml) and sodium azide (3.42g, 52mM) added. The mixture was stirred at 85°

for 72h., when the reaction mixture was poured into water and extracted with petrol (40-60°) (150ml). The extracts were washed well with water and evaporated; the brown oil thus obtained was dissolved in a small quantity of petrol (40-60°) and the solution decanted from the solid residue. Evaporation gave the diazide as a yellow oil (2.65g, 78%); δ 4.10 (2H, m), 3.04 (4H, m).

Trans-3,4-diazidotetrahydrothiophen (78) was prepared in a similar fashion; reaction time necessary was only 36h. in this case. The product was an oil which had ν_{max} (neat) 2700, 2100, 1410, 1260, 930cm^{-1}; δ 4.07 (2H, m), 3.03 (4H, m); m/e 170 (M^+; 32), 121 (3), 119 (5), 99 (3), 86 (71), 84 (100), 60 (26).

Cis-3,4-diaminotetrahydrothiophen (79).- The diazide (77) (2.65g, 15.6mM) in ether (10ml) was added to a stirred suspension of lithium aluminium hydride (1g) in ether (50ml). After a few seconds, a vigorous reaction set in and nitrogen was evolved. After stirring the suspension for 1h., water was cautiously added to decompose excess LAH, and the ether solution decanted from inorganic salts. The salts were stirred with dichloromethane (50ml) and the solution filtered. The combined organic extracts were dried and evaporated to give the diamine (79) as a colourless oil [1.73g, 73% based on ditosylate (71)]; δ 2.40-3.53 (6H, m), 1.60 (4H, s, exch. D_2O).

Trans-3,4-diaminotetrahydrothiophen (80) was similarly obtained in 75% overall yield from ditosylate (72); it had δ 3.05 (2H, m), 2.58 (4H, m), 1.42 (4H, s, exch. D_2O).

Tetrahydrothiophen-cis-3,4-dicarbamic acid, diethyl ester (81).- The diamine (79) (51mg, 0.44mM) was dissolved in chloroform (5ml) and pyridine (120mg) added. Phosgene was bubbled through the stirred solution for 30min at room temperature and then the mixture was allowed to stir overnight. The chloroform was removed and the residue washed with water; the resulting white solid was dissolved in dichloromethane and the solution dried and evaporated to give crude product (72mg, 82%); sublimes at ca. 150°; δ 5.39 (2H, m), 4.21 (4H, q, overlapping 2H, bs), 2.93 (4H, m), 1.25 (6H, t); m/e 262 (M^+; 0.5), 217 (12), 173 (100), 147 (57), 144 (25), 112 (26), 110 (46), 100 (7), 85 (20), 84 (91).

Tetrahydrothiophen-trans-3,4-dicarbamic acid. diethyl ester (82).- This was made from the diamine (80) and an excess of ethyl chloroformate and pyridine. The ester was obtained as a crystalline solid which was recrystallized from chloroform-petrol (60-80°); sublimes at ca. 150°; δ 5.00 (2H, m), 4.16 (4H, q, overlapping 2H, bs), 2.91 (4H, m), 1.27 (6H, t).

(Found: C, 45.87%; H, 6.92%; N, 10.42%; S, 12.43%. $C_{10}H_{18}N_2O_4S$ requiresC, 45.78%; H, 6.93%; N, 10.68%; S, 12.23%).

Cis-hexahydrothieno[3,4-d]imidazol-2-one (83).- The cis-diamine (79) (500mg, 4.2mM) was dissolved in a solution of sodium carbonate (4g) in water (20ml) and stirred at 0° while a solution of phosgene (2g) in benzene (10ml) was added. The mixture was stirred for 24h. and then filtered. The urea thus obtained was almost insoluble in all common solvents but could be recrystallized from a large volume of chloroform. The yield was 169mg (28%); sublimes at ca. 200°; ν_{max} (Nujol)

3280, 1690, 1420, 1340, 1320, 1220, 1165, 1090, 910, 890cm^{-1}; m/e 144 (M^+; 71), 101 (50), 97 (100), 84 (24), 60 (52). (Found: C, 41.63%; H, 5.43%; N, 19.31%; S, 21.86%. $C_5H_8N_2OS$ requires C, 41.64%; H, 5.59%; N, 19.43%; S, 21.24%).

Trans-hexahydrothieno[3,4-d]imidazol-2-one (84) was similarly made from the diamine (81). IR analysis of the crude product showed an amide II band at 1550cm^{-1}, indicating linear polymer formation. Recrystallization from chloroform, in which the polymer was insoluble, gave the urea as a microcrystalline powder (32mg from 200mg of the diamine; 13%); sublimes at ca. 200°; ν_{max} (Nujol) 3280, 1715, 1690, 1400, 1345, 1220, 1170, 1140, 1055, 1020, 990, 900cm^{-1}; m/e 144 (M^+; 45), 97 (100), 84 (5), 74 (14), 60 (9).
(Found: C, 41.28%; H, 5.42%; N, 19.64%. $C_5H_8N_2OS$ requires C, 41.64%; H, 5.59%; N, 19.43%).

2-Chloro-3,4-ditosyloxytetrahydrothiophen (85).- The ditosylate (72) (2.14g, 50mM) was stirred in dichloromethane (100ml) with N-chlorosuccinimide (660mg, 50mM) at room temperature until the solution gave a negative starch/iodide test (ca. 6h.). Silica gel (4g) was added and the solvent removed. The adsorbed product was slurried onto a silica gel column (100g SiO_2) and eluted with ether-petrol (30-40°) (1:1) until no more non-polar material was collected. The eluates were evaporated and the product recrystallized from chloroform-petrol (60-80°) to give cubic crystals of the chlorosulphide (85) (2.22g, 94%). Three recrystallizations from the same solvent gave material which had an m.p. 126-127°; ν_{max} (Nujol) 1595, 1310, 1195, 1180, 1095, 1045, 1000, 855, 820, 765, 670cm^{-1}; δ 7.53 (8H, m), 5.40 (1H, d), 5.01

(2H, m), 3.12 (2H, m), 2.47 (6H, s).

(Found: C, 46.49%; H, 4.40%; Cl, 7.62%; S, 20.73%. $C_{18}H_{19}ClO_6S_3$ requires C, 46.69%; H, 4.14%; Cl, 7.66%; S, 20.78%).

Trans-3,4-dibromotetrahydrothiophen-1-oxide (87).- The dibromosulphide (52) (2.46g, 10mM) was dissolved in acetone (A.R.; 20ml) and hydrogen peroxide (30%; 1.2ml, 10mM) added slowly to the stirred and cooled solution at such a rate that the temperature was kept below 5°. The mixture was stirred for 24h. at room temperature and the acetone evaporated. The residue was taken up in dichloromethane and the solution dried and evaporated, which yielded a red oil. This was centrifuged to remove oily impurity, leaving crystalline sulphoxide which was recrystallized from chloroform-petrol (60-80°) to give pure material (1.93g, 74%); m.p. 68-70°; ν_{max} (Nujol) 1425, 1400, 1325, 1295, 1220, 1200, 1170, 1115, 1055, 1015, 965, 865, 780, 730cm^{-1}; δ 4.35 - 5.18 (2H, m), 3.06 - 4.35 (4H, m). (Found: C, 18.32%; H, 2.33%; Br, 61.03%, S, 12.44%. $C_4H_6Br_2OS$ requires C, 18.34%, H, 2.33%, Br, 61.01%, S, 12.24%).

2,2-Dimethyl-cis-tetrahydrothieno[3,4-d]-1,3-dioxolan-5-oxide (86).- The acetonide (76) (1.60g, 10mM) was dissolved in methanol (100ml) and water (25ml) added. A solution of sodium metaperiodate (2.32g, 10.8mM) in water (25ml) was added at such a rate that the temperature of the stirred cooled solution was kept below 5°. The suspension was stirred for 24h. when t.l.c. showed reaction was complete. The inorganic salts were filtered off and methanol and water were removed under vacuum. The residue was extracted with dichloromethane (2 x 20ml) and the extracts evaporated to

give a crystalline solid which was recrystallized from chloroform-petrol (60-80°) to give pure material (1.22g, 70%); m.p. 110-112° (lit.[42] 125°); ν_{max} (Nujol) 1350, 1310, 1295, 1270, 1160, 1120, 1000, 900, 860, 830, 720cm^{-1}; δ 5.16 (2H, m), 3.20 (4H, m), 1.46 (3H, s), 1.33 (3H, s). T.l.c. showed a trace of more polar material, presumably the isomeric sulphoxide.

Trans-3,4-ditosyloxytetrahydrothiophen-1-oxide (88).- The sulphide (72) (1.18g, 2.7mM) was dissolved in dichloromethane (10ml) and m-chloroperbenzoic acid (85%; 550mg, 2.7mM) in dichloromethane (5ml) added so that the temperature did not exceed 5°. The solution was allowed to warm up overnight and was then shaken with saturated sodium bicarbonate solution until effervescence ceased. The organic layer was dried and evaporated to give almost pure sulphoxide (1.15g, 94%). Recrystallization from chloroform-petrol (60-80°) gave pure material, m.p. 147-149°; ν_{max} (Nujol) 1590, 1305, 1230, 1190, 1180, 1095, 1060, 1015, 980, 870, 850, 670cm^{-1}; δ 7.56 (8H, m), 5.36 (2H, m), 3.32 (4H, m), 2.46 (6H, s).

(Found: C, 48.36%; H, 4.56%; S, 21.35%. $C_{18}H_{20}O_7S_3$ requires C, 48.63%; H, 4.54%; S, 21.64%).

Cis-3,4-ditosyloxytetrahydrothiophen-1-oxide (89) was similarly made from sulphide (71) (1.50g, 3.5mM) and m-chloroperbenzoic acid (85%; 720mg, 3.5mM) to give the sulphoxide (1.50g, 97%). Recrystallization from chloroform-petrol (60-80°) gave pure material, m.p. 150-155°; δ 7.63 (8H, m), 5.32 (2H, m), 3.20 (4H, m), 2.50 (6H, s).

(Found: C, 48.44%; H, 4.54%; S, 21.15%. $C_{18}H_{20}O_7S_2$ requires C, 48.63%; H, 4.54%; S, 21.64%).

2-Chloro-3,4-ditosyloxytetrahydrothiophen-1-oxide (90) was made from sulphide (85) (1.0g, 2.17mM) and m-chloroperbenzoic acid (85%; 443mg, 2.17mM) in the same way, giving the sulphoxide (1.02g, 99%). Recrystallization from chloroform-petrol (60-80°) gave analytical material, m.p. 129-131°; ν_{max} (Nujol) 1595, 1195, 1180, 1095, 1070, 1030, 985, 965, 865, 835, 820, 790, 750, 735, 670cm^{-1}; NMR data collected in Table 3.

(Found: C, 44.96%; H, 4.19%; S, 20.43%. $C_{18}H_{19}ClO_7S_3$ requires C, 45.13%; H, 4.00%; S, 20.08%).

Endo-3a,4,7,7a-tetrahydro-4,7-epithiobenzo[b]thiophen-1,8-dioxide (95).- Methylamine gas was bubbled slowly through a stirred cooled solution of dibromosulphoxide (87) (52mg, 0.2mM) in chloroform (10ml) for 20min. The solution was stirred overnight and the chloroform evaporated. Sodium hydroxide solution (2N; 5ml) was added to the residue which was then extracted with dichloromethane (3 x 15ml). The extracts yielded brown needles which were boiled in methanol with decolourizing carbon (50mg) for 30min. and then recrystallized from chloroform-petrol (60-80°) to give the dioxide (15mg, 76%); m.p. ca. 120° (dec.); ν_{max} (Nujol) 1590, 1350, 1310, 1295, 1255, 1230, 1170, 1140, 1080, 1060, 1050, 1030, 795, 780, 740, 720cm^{-1}; NMR data are set out in Table 4; m/e 200 (M^+; 11), 152 (81), 135 (100), 104 (81), 91 (59), 78 (37), 77 (33), 51 (33).

(Found: C, 48.05%; H, 4.15%; S, 32.32%. $C_8H_8O_2S_2$ requires C, 47.98%; H, 4.02%; S, 32.02%).

An improved method of preparation involved stirring the ditosylate (88) with Dowex 1X-8 ion exchange resin (OH^- form)

(10g to 1mM of sulphoxide) in methanol for 24h. After filtration and decolourization of the solution with charcoal, an almost quantitative yield of dimer (95) was obtained.

2,5-Dichloro-endo-3a,4,7,7a-tetrahydro-4,7-epithiobenzo[b]thiophen-1,8-dioxide (97).- Sulphoxide (90) (240mg, 0.5mM) in dichloromethane (15ml) was stirred with triethylamine (200mg, 2mM) at room temperature for 3h. when reaction was complete (t.l.c.). The solution was washed well with water, dried and stirred with charcoal for 2h., filtered and evaporated to give a crystalline solid (103mg, 80%). This was recrystallized from chloroform-petrol (60-80°) to give the dioxide, m.p. ca. 130° (dec.); NMR data are recorded in Table 5; m/e 268 (M^+; 0.7), 250 (0.7), 233 (6), 215 (33), 202 (35), 185 (100), 168 (92), 150 (21), 136 (11), 121 (10), 112 (19), 102 (8), 101 (8), 77 (24).
(Found: C, 35.51%; H, 2.19%; Cl, 26.15%; S, 24.03%. $C_8H_6Cl_2O_2S_2$ requires C, 35.69%; H, 2.25%; Cl, 26.34%; S, 23.83%).

Endo-3a,4,7,7a-tetrahydro-4,7-methanobenzo[b]thiophen-1-oxide (104).- Ditosylate (88) (220mg, 0.5mM) was added to a stirred mixture of Dowex 1X-8 ion exchange resin (OH^- form) (5g), methanol (15ml) and cyclopentadiene (2g). After 24h., reaction was complete (t.l.c.) and the solution was filtered and evaporated to give a brown gum. This was chromatographed on 1mm silica plates and eluted with 2% methanol-dichloromethane. The band of R_f 0.2 was collected and recrystallized from petrol (60-80°) to give colourless crystals of the sulphoxide (52mg, 28%); m.p. 54-56°; δ 6.07 (2H, m), 5.60 (2H, m), 3.87 (4H, m), 2.06 (2H, m); m/e 166 (M^+; 20), 117 (100), 118 (60), 103 (10), 91 (23), 77 (6), 66 (3), 65 (5), 58 (13).

(Found: C, 65.02%; H, 6.06%. $C_9H_{10}OS$ requires C, 64.91%; H, 5.94%).

7a-Chloro-endo-3a,4,7,7a-tetrahydro-4,7-methanobenzo[b]-thiophen-1-oxide (105).- The sulphoxide (90) (240mg, 0.5mM) in dichloromethane (10ml) and cyclopentadiene (200mg) was treated with triethylamine (200mg, 2mM). When reaction was complete (2h., by t.l.c.) the solution was washed well with water, dried and evaporated. The resulting oil was then chromatographed on 1mm silica plates and eluted with 2% methanol-dichloromethane. The band of R_f 0.5 was collected to furnish the adduct (105) as an unstable oil (43mg, 43%); δ 6.20 (2H, m), 5.73 (1H, m), 5.59 (1H, m), 3.83 (3H, m), 1.70-2.83 (2H, m); m/e 200 (M^+; 4), 152 (29), 117 (100), 91 (9).

Endo-3a,4,7,7a-tetrahydro-4,7-methanobenzo[b]thiophen-1,1-dioxide (106).- 3,4-Dichlorosulpholan (380mg, 2mM) was dissolved in benzene (5ml) and piperidine (344mg, 4mM) and cyclopentadiene (2g) added with stirring. An exothermic reaction occurred and the amine hydrochloride was precipitated. After 1h., this was filtered off and the benzene solution washed well with water. The benzene solution gave a crystalline solid on evaporation (347mg, 96%). Recrystallization from chloroform-petrol (60-80°) gave the pure sulphone, m.p. 108-111°; δ 6.40 (3H, m), 5.94 (1H, dd), 3.56 (2H, m), 3.41 (1H, m), 3.15 (1H, m), 1.72 (2H, m); m/e 182 (M^+; 30), 133 (13), 117 (100), 116 (50), 115 (50), 105 (27), 91 (37), 79 (23), 66 (87).

(Found: C, 59.47%; H, 5.68%; S, 17.56%. $C_9H_{10}O_2S$ requires C, 59.33%; H, 5.53%; S, 17.59%).

3-Methoxy-2,3-dihydrobenzo[b]thiophen-1-oxide (110).- This compound was obtained when thiophen-1-oxide was generated in the presence of norbornadiene, using tosylate (88) and Dowex 1X-8 ion exchange resin in the usual way. Chromatography of the oil, obtained from the reaction mixture after removal of solvents, on 1mm silica plates eluted with 4% methanol-dichloromethane gave (110) in 20% yield; it had δ 7.66 (4H, m), 5.06 (1H, dd; J_1=6Hz, J_2=5Hz), 4.06 (1H, dd; J_1=12Hz, J_2=6Hz), 3.50 (3H, s), 3.15 (1H, dd; J_1=12Hz, J_2=5Hz); m/e 182 (M^+; 19), 165 (71), 152 (76), 135 (95), 121 (24), 106 (62), 91 (29), 77 (24), 58 (100).

4-Methoxy-2,3-dihydrothiophen-1,1-dioxide (113).- 3,4-Dichlorosulpholan (3.80g, 20mM) in methanol (50ml) was added slowly to a solution of sodium methoxide (2.08g, 40mM) in methanol (20ml). The reaction mixture was then refluxed for 1h. and the solvent removed. The solid residue was acidified with 2N hydrochloric acid, and the aqueous phase extracted with dichloromethane (2 x 40ml). The extracts yielded the crude enol ether (1.83g, 67%), which was recrystallized from chloroform-petrol (60-80°) to give material with m.p. 131-132° (lit.[80] 134.5°); δ 5.76 (1H, bs), 3.80 (3H, s), 3.47 (2H, m), 2.94 (2H, m).

Reduction experiments: general technique.- The sulphones were reduced by addition of the sulphone, either as a solid or in ether solution, to a stirred suspension of lithium aluminium hydride (in four-fold excess) in ether or THF. When reaction was complete by t.l.c., water was carefully added and the organic solvent decanted from inorganic material. The salts were washed well with dichloromethane and the combined

organic extracts dried and evaporated to give the product, which was then analysed by NMR spectroscopy.

(a) Reduction of the enol ether (113) (0.5g) gave sulpholan as the principal product. On repeating the reduction, an ethanolic solution of mercuric chloride was added to a solution of the product in ethanol, when a small quantity of the mercuric chloride complex of thiolan (m.p. 122-123°; lit.[81] 123.5-124.5°) was precipitated.

(b) Reduction of 2-sulpholene (0.5g) gave sulpholan after workup.. Workup in D_2O gave monodeuterated sulpholan (116); δ 3.01 (3H, m), 2.21 (4H, m); m/e 121 (M^+; 22), 57 (73), 42 (100).

Lithium butadiene-1-sulphinate (130a).- 3-Sulpholene (6.0g, 50mM) in ether (250ml) was stirred at room temperature under nitrogen while methyl-lithium (2.3M; 22ml, 50mM) was added slowly. An exothermic reaction occurred and a white precipitate was formed. This was filtered off and the ether removed under vacuum to give the lithium salt (6.16g, 100%).

Note. The NMR spectral data of this, and all subsequently described compounds, are in Table 6, unless otherwise stated.

Lithium 2,3-dimethylbutadiene-1-sulphinate (130b) was similarly made from 3,4-dimethyl-3-sulpholene (300mg, 2mM) in ether (50ml) and methyl-lithium (2.3M; 1.7ml, 2mM); yield, 296mg (97%); δ (D_2O/CH_3OH) 5.95 (1H, bs), 5.21 (1H, m), 2.00 (3H, s), 1.95 (3H, s).

Lithium 2-methylbutadiene-1-sulphinate mixed with the 3-methyl isomer was made in the same fashion as (130a) from 3-methyl-3-sulpholene (122) (6.60g, 50mM) in ether (200ml) and methyl-lithium (2.3M; 22ml, 50mM).

Cis-1-benzylsulphonylbutadiene (125).- The lithium salt (130a) (248mg, 2mM) and benzyl bromide (342mg, 2mM) were stirred in DMF (5ml) at room temperature for 24h. Reaction was then complete by t.l.c. The mixture was diluted with water and the aqueous phase extracted with dichloromethane. The extracts were washed well with water and dried and evaporated to give an oil, which was stirred under vacuum to remove DMF. The resulting oil slowly crystallized at 0° (310mg, 78%). A sample was chromatographed to give the sulphone by elution with dichloromethane on 1mm silica plates.

(Found: C, 63.22%; H, 5.77%. $C_{11}H_{12}O_2S$ requires C, 63.43%; H, 5.81%).

Cis-1-butylsulphonylbutadiene (129).- This was similarly prepared using the lithium salt (250mg, 2mM) and n-butyl bromide (274mg, 2mM). Removal of DMF gave an oil which was triturated with petrol (40-60°) and insoluble material was rejected. Evaporation of the petrol gave the product as a light yellow oil which was chromatographed as in the preceding case to give the pure sulphone.

(Found: C, 55.06%; H, 7.88%. $C_8H_{14}O_2S$ requires C, 55.14%; H, 8.10%).

Cis-1-benzylsulphonyl-2-methylbutadiene (127) was made by the same method from the mixture of lithium salts from 3-methyl-3-sulpholene (2.74g, 20mM) and benzyl bromide (3.42g, 20mM) in DMF (25ml). The solid obtained was a mixture from which pure crystals of the sulphone (127) were isolated after recrystallization from chloroform-petrol (60-80°) (2.63g, 59%); m.p. 82-84°; ν_{max} (Nujol) 1615, 1590, 1555, 1310, 1280, 1195, 1155, 1140, 1110, 1060, 980, 920, 910, 890, 850, 790,

780, 690cm^{-1}.

(Found: C, 64.57%; H, 6.37%. $C_{11}H_{12}O_2S$ requires C, 64.83%; H, 6.35%).

Cis-1-benzylsulphonyl-2,3-dimethylbutadiene (128) was similarly made from lithium salt (130b) (296mg, 2mM) and benzyl bromide (342mg, 2mM). The product crystallized after trituration with petrol (40-60°) and was recrystallized from petrol (60-80°) to give pure sulphone (219mg, 46%); m.p. 63-65°; ν_{max} (Nujol) 1640, 1600, 1310, 1290, 1260, 1190, 1160, 1150, 1120, 890, 830, 780, 700cm^{-1}.

(Found: C, 66.15%; H, 6.85%. $C_{13}H_{16}O_2S$ requires C, 66.06%; H, 6.83%).

3-Chloro-4-butylsulphonylbut-1-ene (137).- The sulphide (42) (357mg, 2mM) in glacial acetic acid (2ml) was mixed with hydrogen peroxide (30%; 0.5ml) at room temperature. The reaction mixture was allowed to stand overnight, and the acetic acid removed under vacuum. The product had m/e 202 (M^+) and was used immediately in the next step.

Trans-1-butylsulphonylbutadiene (138).- The sulphone (137) from the previous experiment was dissolved in ether (10ml) and potassium t-butoxide (250mg, 2.23mM) added with stirring at 0°. The mixture was allowed to warm up overnight when the reaction was acidified with 2N hydrochloric acid. Then dichloromethane (10ml) was added, and the organic layer dried and evaporated to yield a dark brown oil. This was triturated with petrol (40-60°) and the tarry matter rejected. Removal of the petrol gave the sulphone as a light yellow oil which was chromatographed to give a sample of pure material (169mg, 48%).

(Found: C, 54.99%; H, 8.05%. $C_8H_{14}O_2S$ requires C, 55.14%; H, 8.10%).

1-Piperidino-4-benzylsulphonylbut-2-ene (141).- The sulphone (125) (208mg, 1mM) was mixed with piperidine (170mg, 2mM) in dichloromethane (5ml) for 24h. The solution was then washed with water, dried and evaporated to give an oil (273mg). Using 10% methanol-dichloromethane with a few drops of acetic acid a solvent, t.l.c. showed it to be a single compound; δ 7.42 (5H, s), 5.87 (1H, t), 5.76 (1H, t), 4.20 (2H, s), 3.55 (2H, d), 3.03 (2H, d), 2.35 (4H, m), 1.47 (6H, m); m/e 293 (M^+; 6), 138 (100), 98 (19), 91 (19), 84 (22), 55 (17).

1-Benzylsulphonyl-4-dimethylaminobut-2-ene (142).- This was made using the same conditions with the sulphone (127) (222mg, 1mM) and dimethylamine in ether (2.17M; 0.5ml, 1.1mM) in dichloromethane (5ml). After 24h., reaction was incomplete, but the NMR had new signals at δ 3.63 (2H, s), 3.03 (2H, d), and 2.27 (6H, s) thus proving the presence of adduct (143).

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